Stem Cell and Development Research Literatures

Mark Herbert

Brooklyn, New York 11212, USA, Ms10012002@gmail.com

Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.

[Mark Herbert. **Stem Cell and Development Research Literatures.** *Stem Cell* 2018;9(2):39-73]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 6. doi:10.7537/marsscj090218.06.

Key words: stem cell; life; development; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Akamatsu, W., et al. (2009). "Suppression of Oct4 by germ cell nuclear factor restricts pluripotency and promotes neural stem cell development in the early neural lineage." J Neurosci **29**(7): 2113-2124.

The earliest murine neural stem cells are leukemia inhibitory factor (LIF)-dependent, primitive neural stem cells, which can be isolated from embryonic stem cells or early embryos. These primitive neural stem cells have the ability to differentiate to non-neural tissues and transition into FGF2-dependent, definitive neural stem cells between embryonic day 7.5 and 8.5 in vivo, accompanied by a decrease in non-neural competency. We found that Oct4 is expressed in LIF-dependent primitive neural stem cells and suppressed in FGF-dependent definitive neural stem cells. In mice lacking germ cell nuclear factor (GCNF), a transcriptional repressor of Oct4, generation of definitive neural stem cells was dramatically suppressed, accompanied by a sustained expression of Oct4 in the early neuroectoderm. Knockdown of Oct4 in GCNF (-/-) neural stem cells rescued the GCNF (-/-) phenotype. Overexpression of Oct4 blocked the differentiation of primitive to definitive neural stem cells, but did not induce the dedifferentiation of definitive to primitive neural stem cells. These results suggested that primitive neural stem cells develop into definitive neural stem cells by means of GCNF induced suppression of Oct4. The Oct4 promoter was methylated during the development from primitive neural stem cell to definitive neural stem cell, while these neural stem cells lose their pluripotency through a GCNF dependent mechanism. Thus, the suppression of Oct4 by GCNF is important for the transition from primitive to definitive neural stem cells and restriction of the non-neural competency in the early neural stem cell lineage.

Batsivari, A., et al. (2017). "Understanding Hematopoietic Stem Cell Development through Functional Correlation of Their Proliferative Status with the Intra-aortic Cluster Architecture." Stem Cell Reports **8**(6): 1549-1562.

During development, hematopoietic stem cells (HSCs) emerge in the aorta-gonad-mesonephros (AGM) region through a process of multi-step maturation and expansion. While proliferation of adult HSCs is implicated in the balance between self-renewal and differentiation, very little is known about the proliferation status of nascent HSCs in the AGM region. Using Fucci reporter mice that enable in vivo visualization of cell-cycle status, we detect increased proliferation during pre-HSC expansion followed by a slowing down of cycling once cells start to acquire a definitive HSC state, similar to fetal liver HSCs. We observe time-specific changes in intra-aortic hematopoietic clusters corresponding to HSC

maturation stages. The proliferative architecture of the clusters is maintained in an orderly anatomical manner with slowly cycling cells at the base and more actively proliferating cells at the more apical part of the cluster, which correlates with c-KIT expression levels, thus providing an anatomical basis for the role of SCF in HSC maturation.

Behre, G., et al. (2002). "Proteomic analysis of transcription factor interactions in myeloid stem cell development and leukaemia." Expert Opin Ther Targets **6**(4): 491-495.

Recent results indicate that interactions of transcription factors with other nuclear proteins play an important role in stem cell development, lineage commitment and differentiation in the haematopoietic system, and the pathogenesis of myeloid leukaemias. High-throughput proteomics by mass spectrometric analysis of gel-separated proteins can identify multi-protein complexes and changes in the expression of multiple proteins simultaneously. This review describes an application of proteomic methods (2D gel electrophoresis (GE) and mass spectrometry (MS)), which can be used to identify regulated protein targets of transcription factors important in myeloid differentiation and leukaemia. This global high-throughput functional proteomics approach could lead to new insights into the network of protein-protein interactions and target proteins involved in myeloid stem cell development and leukaemia as well as provide new targets for rational pathogenesis-based therapies of leukaemia and cancer.

Bertrand, J. Y., et al. (2005). "Hematopoietic stem cell development during mouse embryogenesis." Methods Mol Med **105**: 273-288.

The progress of the last few years in the understanding of hematopoietic cell development during embryogenesis resulted from a combination of experimental approaches used in hematology and developmental biology. This methodology has been particularly powerful for the analysis of the earliest steps of hematopoietic ontogeny because it allows for the first time the demonstration of the existence of two independent sites of hematopoietic cell generation. Here, we describe the methods used in our laboratories to characterize the phenotype and differentiation potential of the primordial hematopoietic precursors as well as their localization in the mouse embryo. This multidisciplinary approach is required to explore the mechanisms of hematopoietic cell generation.

Brashem-Stein, C., et al. (1993). "Ontogeny of hematopoietic stem cell development: reciprocal expression of CD33 and a novel molecule by maturing myeloid and erythroid progenitors." Blood **82**(3): 792-799.

We have identified a molecule expressed by human marrow granulocyte/monocyte colony-forming cells (CFU-GM), erythroid colony-forming cells (CFU-E), and erythroid burst-forming units (BFU-E), but not their precursors detectable in long-term bone marrow culture. This antigen, detected by flow microfluorimetry using monoclonal antibody 7B9, is coexpressed with CD33 on many CD34+ CFCs, although only the 7B9 antigen was detected on a portion of BFU-E and CFU-E, whereas only CD33 was found on a portion of CFU-GM. Antibody 7B9 appears to be useful for isolating subsets of progenitors based on their common or selective expression of 7B9 antigen and CD33.

Burnstock, G. and H. Ulrich (2011). "Purinergic signaling in embryonic and stem cell development." Cell Mol Life Sci **68**(8): 1369-1394.

Nucleotides are of crucial importance as carriers of energy in all organisms. However, the concept that in addition to their intracellular roles, nucleotides act as extracellular ligands specifically on receptors of the plasma membrane took longer to be accepted. Purinergic signaling exerted by purines and pyrimidines, principally ATP and adenosine, occurs throughout embryologic development in a wide variety of organisms, including amphibians, birds, and mammals. Cellular signaling, mediated by ATP, is present in development at very early stages, e.g., gastrulation of Xenopus and germ layer definition of chick embryo cells. Purinergic receptor expression and functions have been studied in the development of many organs, including the heart, eye, skeletal muscle and the nervous system. In vitro studies with stem cells revealed that purinergic receptors are involved in the processes of proliferation, differentiation, and phenotype determination of differentiated cells. Thus, nucleotides are able to induce various intracellular signaling pathways via crosstalk with other bioactive molecules acting on growth factor and neurotransmitter receptors. Since normal development is disturbed by dysfunction of purinergic signaling in animal models, further studies are needed to elucidate the functions of purinoceptor subtypes in developmental processes.

Busch, H., et al. (2013). "Network theory inspired analysis of time-resolved expression data reveals key players guiding P. patens stem cell development." PLoS One **8**(4): e60494.

Transcription factors (TFs) often trigger developmental decisions, yet, their transcripts are often only moderately regulated and thus not easily detected by conventional statistics on expression data.

Here we present a method that allows to determine such genes based on trajectory analysis of time-resolved transcriptome data. As a proof of principle, we have analysed apical stem cells of filamentous moss (P. patens) protonemata that develop from leaflets upon their detachment from the plant. By our novel correlation analysis of the post detachment transcriptome kinetics we predict five out of 1,058 TFs to be involved in the signaling leading to the establishment of pluripotency. Among the predicted regulators is the basic helix loop helix TF PpRSL1, which we show to be involved in the establishment of apical stem cells in P. patens. Our methodology is expected to aid analysis of key players of developmental decisions in complex plant and animal systems.

Chanda, B., et al. (2013). "Retinoic acid signaling is essential for embryonic hematopoietic stem cell development." Cell **155**(1): 215-227.

Hematopoietic stem cells (HSCs) develop from a specialized subpopulation of endothelial cells known as hemogenic endothelium (HE). Although the HE origin of HSCs is now well established in different species, the signaling pathways that control this transition remain poorly understood. Here, we show that activation of retinoic acid (RA) signaling in aorta-gonad-mesonephros-derived HE ex vivo dramatically enhanced its HSC potential, whereas conditional inactivation of the RA metabolizing enzyme retinal dehydrogenase 2 in VE-cadherin expressing endothelial cells in vivo abrogated HSC development. Wnt signaling completely blocked the HSC inductive effects of RA modulators, whereas inhibition of the pathway promoted the development of HSCs in the absence of RA signaling. Collectively, these findings position RA and Wnt signaling as key regulators of HSC development and in doing so provide molecular insights that will aid in developing strategies for their generation from pluripotent stem cells.

Chen, J. (2011). "Hematopoietic stem cell development, aging and functional failure." Int J Hematol **94**(1): 3-10.

Hematopoietic stem cells (HSCs) are found in yolk sac, fetal liver, umbilical cord blood, placenta, and amniotic fluid during mammalian embryonic development. In adults, HSCs reside in marrow cavity of long bones where they self-renew and differentiate to replenish short-lived mature blood cells. HSCs exist in very low frequencies within specific "niches" where they interact with the surrounding environment through molecular associations. Overall HSC function can last much longer than a normal lifetime, but HSCs do show functional senescence with characteristic features of decreased self-renewal, reduced clonal stability, reduced homing and engraftment, and biased lineage commitment. The progressive shortening of telomeres with increasing age, especially under conditions with specific mutations in the telomerase gene complex, could predispose patients to HSC dysfunction and bone marrow failure diseases. Continuous investigation into HSC biology should facilitate the utilization of HSCs as a therapeutic modality and helps to prevent HSC malfunction.

Chen, J., et al. (2016). "Cyp2aa9 regulates haematopoietic stem cell development in zebrafish." Sci Rep **6**: 26608.

Definitive haematopoiesis occurs during the lifetime of an individual, which continuously replenishes all blood and immune cells. During embryonic development, haematopoietic stem cell (HSC) formation is tightly controlled by growth factors, signalling molecules and transcription factors. But little is known about roles of the cytochrome P450 (CYP) 2 family member in the haematopoiesis. Here we report characterization and functional studies of Cyp2aa9, a novel zebrafish Cyp2 family member. And demonstrate that the cyp2aa9 is required for the HSC formation and homeostasis. Knockdown of cyp2aa9 by antisense morpholino oligos resulted the definitive HSC development is defective and the Wnt/beta-catenin activity becomes reduced. The impaired HSC formation caused by cyp2aa9 morpholino can be rescued by administration of PGE2 through the cAMP/PKA pathway. Furthermore, the in vivo PGE2 level decreases in the cyp2aa9 morphants, and none of the PGE2 precursors is able to rescue phenotypes in the Cyp2aa9-deficient embryos. Taken together, these data indicate that Cyp2aa9 is functional in the step of PGE2 synthesis from PGH2, thus promoting Wnt activation and definitive HSC development.

Chotinantakul, K. and W. Leeanansaksiri (2012). "Hematopoietic stem cell development, niches, and signaling pathways." Bone Marrow Res **2012**: 270425.

Hematopoietic stem cells (HSCs) play a key role in hematopoietic system that functions mainly in homeostasis and immune response. HSCs transplantation has been applied for the treatment of several diseases. However, HSCs persist in the small quantity within the body, mostly in the quiescent state. Understanding the basic knowledge of HSCs is useful for stem cell biology research and therapeutic medicine development. Thus, this paper emphasizes on HSC origin, source, development, the niche, and signaling pathways which support HSC maintenance and balance between self-renewal and proliferation which will be useful for the advancement of HSC expansion and transplantation in the future.

Chu, L. F., et al. (2011). "Blimp1 expression predicts embryonic stem cell development in vitro." Curr Biol **21**(20): 1759-1765.

Despite recent critical insights into the pluripotent state of embryonic stem cells (ESCs), there is little agreement over the inaugural and subsequent steps leading to its generation [1-4]. Here we show that inner cell mass (ICM)-generated cells expressing Blimp1, a key transcriptional repressor of the somatic program during germ cell specification [5, 6], emerge on day 2 of blastocyst culture. Single-cell gene expression profiling indicated that many of these Blimp1-positive cells coexpress other genes typically associated with early germ cell specification. When genetically traced in vitro, these cells acquired properties normally associated with primordial germ cells. Importantly, fate-mapping experiments revealed that ESCs commonly arise from Blimp1-positive precursors; indeed, prospective sorting of such cells from ICM outgrowths increased the rate of ESC derivation more than 9-fold. Finally, using genetic ablation or distinct small molecules [7, 8], we show that epiblast cells can become ESCs without first acquiring Blimp1 positivity. Our findings suggest that the germ cell-like state is facultative for the stabilization of pluripotency in vitro. Thus, the association of Blimp1 expression with ESC development furthers understanding of how the pluripotent state of these cells is established in vitro and suggests a means to enhance the generation of new stem cell lines from blastocysts.

Ciau-Uitz, A., et al. (2013). "ETS transcription factors in hematopoietic stem cell development." Blood Cells Mol Dis **51**(4): 248-255.

Hematopoietic stem cells (HSCs) are essential for the maintenance of the hematopoietic system. However, these cells cannot be maintained or created in vitro, and very little is known about their generation during embryogenesis. Many transcription factors and signaling pathways play essential roles at various stages of HSC development. Members of the ETS ('E twenty-six') family of transcription factors are recognized as key regulators within the gene regulatory networks governing hematopoiesis, including the ontogeny of HSCs. Remarkably, although all ETS transcription factors bind the same DNA consensus sequence and overlapping tissue expression is observed, individual ETS transcription factors play unique roles in the development of HSCs. Also, these transcription factors are recurrently used throughout development and their functions are context-dependent, increasing the challenge of studying their mechanism of action. Critically, ETS factors also play roles under pathological conditions, such as leukemia and, therefore, deciphering their mechanism of action will not only enhance our knowledge of normal hematopoiesis, but also inform protocols for their creation in vitro from pluripotent stem cells and the design of new therapeutic approaches for the treatment of malignant blood cell diseases. In this review, we summarize the key findings on the roles of ETS transcription factors in HSC development and discuss novel mechanisms by which they could control hematopoiesis.

Couture, L. A. and M. K. Carpenter (2015). "2005 Donor Eligibility Requirements: Unintended Consequences for Stem Cell Development." Stem Cells Transl Med **4**(10): 1097-1100.

UNLABELLED: Several human embryonic stem cell (hESC)-derived cell therapeutics have entered clinical testing and more are in various stages of preclinical development. The U.S. Food and Drug Administration (FDA) regulates these products under existing regulations and has stated that these products do not constitute a new class of biologic. However, as human tissue, hESCs are subject to regulations that were developed before hESCs were first described. The regulations have not been revised since 2005, well before the first hESC-derived product entered clinical studies. The current regulations require donors of hESCs to be tested in the same manner as donors of tissues intended for transplantation. However, because hESC-derived cell products are more than minimally manipulated, they are also subject to the same end-of-production release testing as most other biologic agents. In effect, this makes hESC products subject to redundant testing. No other biologic is subject to a similar testing requirement. Furthermore, the regulations that require donor testing are specifically applicable to hESC cells harvested from donors after a date in 2005. It is unclear which regulations cover hESCs harvested before 2005. Ambiguity in the guidelines and redundant testing requirements have unintentionally created a burdensome regulatory paradigm for these products and reluctance on the part of developers to invest in these promising therapeutics. We propose a simple solution that would address FDA safety concerns, eliminate regulatory uncertainty and risk, and provide flexibility for the FDA in the regulation of hESC-derived cell therapies. SIGNIFICANCE: Regulatory ambiguity concerning donor eligibility screening and testing requirements for human embryonic stem cell lines, in particular those lines created before 2005, are causing significant concern for drug developers. Technically, most of these lines fail to meet eligibility under U.S. Food and Drug Administration (FDA) rules for product licensure, and many developers are unaware that FDA approval to begin trials under an exemption is not an assurance that the FDA will grant licensure of the product. This

Perspective outlines the ambiguity and the problem it has caused and proposes a workable solution. The intent is to generate stakeholder and FDA discussion on this issue.

Cullen, S. M., et al. (2014). "Hematopoietic stem cell development: an epigenetic journey." Curr Top Dev Biol **107**: 39-75.

Hematopoietic development and homeostasis are based on hematopoietic stem cells (HSCs), a pool of ancestor cells characterized by the unique combination of self-renewal and multilineage potential. These two opposing forces are finely orchestrated by several regulatory mechanisms, comprising both extrinsic and intrinsic factors. Over the past decades, several studies have contributed to dissect the key role of niche factors, signaling transduction pathways, and transcription factors in HSC development and maintenance. Accumulating evidence, however, suggests that a higher level of intrinsic regulation exists; epigenetic marks, by controlling chromatin accessibility, directly shape HSC developmental cascades, including their emergence during embryonic development, maintenance of self-renewal, lineage commitment, and aging. In addition, aberrant epigenetic marks have been found in several hematological malignancies, consistent with clinical findings that mutations targeting epigenetic regulators promote leukemogenesis. In this review, we will focus on both normal and malignant hematopoiesis, covering recent findings that illuminate the epigenetic life of HSCs.

Cumano, A. and I. Godin (2001). "Pluripotent hematopoietic stem cell development during embryogenesis." Curr Opin Immunol **13**(2): 166-171.

Significant progress has been made towards a better understanding of the establishment of hematopoiesis in the embryo. Hematopoietic precursors have been shown to arise independently in the yolk sac and in the intra-embryonic mesoderm. From the combined analysis of differentiation potentials, expression patterns and mutant phenotypes, a picture has emerged: definitive hematopoietic precursors are transiently generated in a specific environment close to the endothelium of the main arteries.

Dang, L. and V. Tropepe (2006). "Neural induction and neural stem cell development." Regen Med **1**(5): 635-652.

Embryonic stem (ES) cells are a pluripotent and renewable cellular resource with tremendous potential for broad applications in regenerative medicine. Arguably the most important consideration for stem cell-based therapies is the ability to precisely direct the differentiation of stem cells along a preferred cellular lineage. During development, lineage commitment is a multistep process requiring the activation and repression of sets of genes at various stages, from an ES cell identity to a tissue-specific stem cell identity and beyond. Thus, the challenge is to ensure that the pattern of genomic regulation is recapitulated during the in vitro differentiation of ES cells into stem/progenitor cells of the appropriate tissue in a robust, predictable and stable manner. To address this issue, we must understand the ontogeny of tissue-specific stem cells during normal embryogenesis and compare the ontogeny of tissue-specific stem cells in ES cell models. Here, we discuss the issue of directed differentiation of pluripotent ES cells into neural stem cells, which is fundamentally linked to two early events in the development of the mammalian nervous system: the 'decision' of the ectoderm to acquire a neural identity (neural determination) and the origin of neural stem cells within this neural-committed population of cells. A clearer understanding of the molecular and cellular mechanisms that govern mammalian neural cell fate determination will lead to improved ES technology applications in neural regeneration.

Deshpande, A. J. and C. Buske (2007). "Knocking the Wnt out of the sails of leukemia stem cell development." Cell Stem Cell **1**(6): 597-598.

Tumor propagation by cancer stem cells (CSCs) requires their ability to self-renew, and yet the signal pathways involved in this process remain poorly defined. In the December issue of Cancer Cell, Zhao et al. (2007) provide compelling evidence that Wnt/beta-catenin signaling is crucial for the maintenance of chronic myelogenous leukemia (CML) stem cells.

Drummond, B. E. and R. A. Wingert (2016). "Insights into kidney stem cell development and regeneration using zebrafish." World J Stem Cells **8**(2): 22-31.

Kidney disease is an escalating global health problem, for which the formulation of therapeutic approaches using stem cells has received increasing research attention. The complexity of kidney anatomy and function, which includes the diversity of renal cell types, poses formidable challenges in the identification of methods to generate replacement structures. Recent work using the zebrafish has revealed their high capacity to regenerate the integral working units of the kidney, known as nephrons, following acute injury. Here, we discuss these findings and explore the ways that zebrafish can be further utilized to gain a deeper molecular appreciation of renal stem cell biology, which may uncover important clues for regenerative medicine.

Dzierzak, E. and E. de Pater (2016). "Regulation of Blood Stem Cell Development." Curr Top Dev Biol **118**: 1-20.

Understanding how the blood system is formed is an ongoing fundamental research challenge. Developmental biology has provided many insights into the molecules and processes that affect the formation of the blood tissues, both in health and disease. It is of particular interest for clinical transplantation therapies to understand how hematopoietic stem cells (HSCs)-the self-renewing purveyors of the adult blood system that produce over 10 different functionally specialized cell lineages and over 10(11) cells daily-are generated during embryonic stages. Recent successes to reprogram the fate of adult differentiated cells to pluripotency and to other cell lineages now highlight the importance of identifying the cells and molecules that affect the in vivo developmental initiation of rare and robust transplantable HSCs. The close association of the developing hematopoietic and vascular system, hematopoietic cell mobility through the circulation, and the essential role of the embryonic hematopoietic system in adult hematopoietic cell development make this a formidable study. This chapter reviews the advances, controversies, and current state of our knowledge of the growing field of hematopoietic development, with a special focus on the regulation of the natural transdifferentiation of endothelial cells to HSCs within the developing embryo.

English, D. (2006). "Biochemical events involved in stem cell development." Stem Cells Dev **15**(6): 751-752.

Esain, V., et al. (2015). "Cannabinoid Receptor-2 Regulates Embryonic Hematopoietic Stem Cell Development via Prostaglandin E2 and P-Selectin Activity." Stem Cells **33**(8): 2596-2612.

Cannabinoids (CB) modulate adult hematopoietic stem and progenitor cell (HSPCs) function, however, impact on the production, expansion, or migration of embryonic HSCs is currently uncharacterized. Here, using chemical and genetic approaches targeting CB-signaling in zebrafish, we show that CB receptor (CNR) 2, but not CNR1, regulates embryonic HSC development. During HSC specification in the aorta-gonad-mesonephros (AGM) region, CNR2 stimulation by AM1241 increased runx1; cmyb (+) HSPCs, through heightened proliferation, whereas CNR2 antagonism decreased HSPC number; FACS analysis and absolute HSC counts confirmed and quantified these effects. Epistatic investigations showed AM1241 significantly upregulated PGE2 synthesis in a Ptgs2-dependent manner to increase AGM HSCs. During the phases of HSC production and colonization of secondary niches, AM1241 accelerated migration to the caudal hematopoietic tissue (CHT), the site of embryonic HSC expansion, and the thymus; however these effects occurred independently of PGE2. Using a candidate approach for HSC migration and retention factors, P-selectin was identified as the functional target of CNR2 regulation. Epistatic analyses confirmed migration of HSCs into the CHT and thymus was dependent on CNR2-regulated P-selectin activity. Together, these data suggest CNR2-signaling optimizes the production, expansion, and migration of embryonic HSCs by modulating multiple downstream signaling pathways.

Frame, J. M., et al. (2017). "Hematopoietic stem cell development: Using the zebrafish to identify extrinsic and intrinsic mechanisms regulating hematopoiesis." Methods Cell Biol **138**: 165-192.

Hematopoietic stem cells (HSCs) reside at the apex of the hematopoietic hierarchy, giving rise to each of the blood lineages found throughout the lifetime of the organism. Since the genetic programs regulating HSC development are highly conserved between vertebrate species, experimental studies in zebrafish have not only complemented observations reported in mammals but have also yielded important discoveries that continue to influence our understanding of HSC biology and homeostasis. Here, we summarize findings that have established zebrafish as an important conserved model for the study of hematopoiesis, and describe methods that can be utilized for future investigations of zebrafish HSC biology.

Fujimoto, K., et al. (2012). "Thyroid hormone activates protein arginine methyltransferase 1 expression by directly inducing c-Myc transcription during Xenopus intestinal stem cell development." J Biol Chem **287**(13): 10039-10050.

Adult organ-specific stem cells are essential for organ homeostasis and tissue repair and regeneration. The formation of such stem cells during vertebrate development is poorly understood. Intestinal remodeling during thyroid hormone (T3)-dependent Xenopus metamorphosis resembles postembryonic intestinal maturation in mammals. During metamorphosis, the intestine is remodeled de novo via a yet unknown mechanism. Protein arginine methyltransferase 1 (PRMT1) is up-regulated in and required for adult intestinal stem cells during metamorphosis. PRMT1 up-regulation is the earliest known molecular event for the developing stem cells and is also conserved during zebrafish and mouse intestinal development. To analyze how PRMT1 is specifically up-regulated during the formation of the

adult intestinal stem cells, we cloned the Xenopus PRMT1 promoter and characterized it in CaCo-2 cells, a human cell line with intestinal stem cell characteristics. Through a series deletion and mutational analyses, we showed that the stem cell-associated transcription factor c-Myc could bind to a conserved site in the first intron to activate the promoter. Furthermore, we demonstrated that during metamorphosis, both c-Myc and PRMT1 were highly up-regulated, specifically in the remodeling intestine but not the resorbing tail, and that c-Myc was induced by T3 prior to PRMT1 up-regulation. In addition, we showed that T3 directly activated the c-Myc gene during metamorphosis in the intestine via binding of the T3 receptor to the c-Myc promoter. These results suggest that T3 induces c-Myc transcription directly in the intestine, that c-Myc, in turn, activates PRMT1 expression, and that this is an important gene regulation cascade controlling intestinal stem cell development.

Gangloff, Y. G., et al. (2004). "Disruption of the mouse mTOR gene leads to early postimplantation lethality and prohibits embryonic stem cell development." Mol Cell Biol **24**(21): 9508-9516.

The mammalian target of rapamycin (mTOR) is a key component of a signaling pathway which integrates inputs from nutrients and growth factors to regulate cell growth. Recent studies demonstrated that mice harboring an ethylnitrosourea-induced mutation in the gene encoding mTOR die at embryonic day 12.5 (E12.5). However, others have shown that the treatment of E4.5 blastocysts with rapamycin blocks trophoblast outgrowth, suggesting that the absence of mTOR should lead to embryonic lethality at an earlier stage. To resolve this discrepancy, we set out to disrupt the mTOR gene and analyze the outcome in both heterozygous and homozygous settings. Heterozygous mTOR (mTOR (+/-)) mice do not display any overt phenotype, although mouse embryonic fibroblasts derived from these mice show a 50% reduction in mTOR protein levels and phosphorylation of S6 kinase 1 T389, a site whose phosphorylation is directly mediated by mTOR. However, S6 phosphorylation, raptor levels, cell size, and cell cycle transit times are not diminished in these cells. In contrast to the situation in mTOR (+/-) mice, embryonic development of homozygous mTOR (-/-) mice appears to be arrested at E5.5; such embryos are severely runted and display an aberrant developmental phenotype. The ability of these embryos to implant corresponds to a limited level of trophoblast outgrowth in vitro, reflecting a maternal mRNA contribution, which has been shown to persist during preimplantation development. Moreover, mTOR (-/-) embryos display a lesion in inner cell mass proliferation, consistent with the inability to establish embryonic stem cells from mTOR (-/-) embryos.

Garcion, E., et al. (2004). "Generation of an environmental niche for neural stem cell development by the extracellular matrix molecule tenascin C." Development **131**(14): 3423-3432.

Stem cells in the embryonic mammalian CNS are initially responsive to fibroblast growth factor 2 (FGF2). They then undergo a developmental programme in which they acquire epidermal growth factor (EGF) responsiveness, switch from the production of neuronal to glial precursors and become localized in specialized germinal zones such as the subventricular zone (SVZ). Here we show that extracellular matrix molecules act as regulators of this programme. Tenascin C is highly expressed in the SVZ, and transgenic mice lacking tenascin C show delayed acquisition of the EGF receptor. This results from alterations in the response of the stem cells to the growth factors FGF2 and bone morphogenic protein 4 (BMP4), which normally promote and inhibit acquisition of the EGF receptor, respectively. Tenascin C-deficient mice also have altered numbers of CNS stem cells and these stem cells have an increased probability of generating neurones when grown in cell culture. We conclude that tenascin C contributes to the generation of a stem cell 'niche' within the SVZ, acting to orchestrate growth factor signalling so as to accelerate neural stem cell development.

Gekas, C., et al. (2010). "Hematopoietic stem cell development in the placenta." Int J Dev Biol **54**(6-7): 1089-1098.

The placenta is a highly vascularized organ that mediates fetal-maternal exchange during pregnancy and is thereby vital for the survival and growth of the developing embryo. In addition to having this well-established role in supporting pregnancy, the placenta was recently shown to function as a hematopoietic organ. The placenta is unique among other fetal hematopoietic organs, as it is capable of both generating multipotential hematopoietic cells de novo and establishing a major hematopoietic stem cell (HSC) pool in the conceptus, while protecting HSCs from premature differentiation. The mouse placenta contains two distinct vascular regions that support hematopoiesis: the large vessels in the chorionic plate where HSCs/progenitors are thought to emerge and the labyrinth vasculature where nascent HSCs/progenitors may colonize for expansion and possible functional maturation. Defining how this cytokine- and growth factor rich organ supports HSC generation, maturation and expansion may ultimately help to establish culture protocols for HSC expansion or de novo generation from pluripotent cells.

Glauche, I., et al. (2009). "A novel view on stem cell development: analysing the shape of cellular genealogies." Cell Prolif **42**(2): 248-263.

OBJECTIVES: The analysis of individual cell fates within a population of stem and progenitor cells is still a major experimental challenge in stem cell biology. However, new monitoring techniques, such as high-resolution time-lapse video microscopy, facilitate tracking and quantitative analysis of single cells and their progeny. Information on cellular development, divisional history and differentiation are naturally comprised into a pedigree-like structure, denoted as cellular genealogy. To extract reliable information concerning effecting variables and control mechanisms underlying cell fate decisions, it is necessary to analyse a large number of cellular genealogies. MATERIALS AND METHODS: Here, we propose a set of statistical measures that are specifically tailored for the analysis of cellular genealogies. These measures address the degree and symmetry of cellular expansion, as well as occurrence and correlation of characteristic events such as cell death. Furthermore, we discuss two different methods for reconstruction of lineage fate decisions and show their impact on the interpretation of asymmetric developments. In order to illustrate these techniques, and to circumvent the present shortage of available experimental data, we obtain cellular genealogies from a single-cell-based mathematical model of haematopoietic stem cell organization. RESULTS AND CONCLUSIONS: Based on statistical analysis of cellular genealogies, we conclude that effects of external variables, such as growth conditions, are imprinted in their topology. Moreover, we demonstrate that it is essential to analyse timing of cell fate-specific changes and of occurrence of cell death events in the divisional context in order to understand the mechanisms of lineage commitment.

Godin, I. and A. Cumano (2005). "Of birds and mice: hematopoietic stem cell development." Int J Dev Biol **49**(2-3): 251-257.

For many years it has been assumed that the ontogeny of the mammalian hematopoietic system involves sequential transfers of hematopoietic stem cells (HSCs) generated in the yolk sac blood islands, to successive hematopoietic organs as these become active in the embryo (fetal liver, thymus, spleen and eventually bone marrow). Very little was known about early events related to hematopoiesis that could take place during the 4.5 day gap separating the appearance of the yolk sac blood islands and the stage of a fully active fetal liver. Experiments performed in birds documented that the yolk sac only produce erythro-myeloid precursors that become extinct after the emergence of a second wave of intra-embryonic HSCs from the region neighbouring the dorsal aorta. The experimental approaches undertaken over the last ten years in the murine model, which are reviewed here, led to the conclusion that the rules governing avian hematopoietic development basically apply to higher vertebrates.

Goessling, W. and T. E. North (2011). "Hematopoietic stem cell development: using the zebrafish to identify the signaling networks and physical forces regulating hematopoiesis." Methods Cell Biol **105**: 117-136.

Hematopoietic stem cells (HSC) form the basis of the hematopoietic hierarchy, giving rise to each of the blood lineages found throughout the lifetime of the organism. The genetic programs regulating HSC development are highly conserved between vertebrate species. The zebrafish has proven to be an excellent model for discovering and characterizing the signaling networks and physical forces regulating vertebrate hematopoietic development.

Gonzalez-Garcia, M. P., et al. (2015). "Single-cell telomere-length quantification couples telomere length to meristem activity and stem cell development in Arabidopsis." Cell Rep **11**(6): 977-989.

Telomeres are specialized nucleoprotein caps that protect chromosome ends assuring cell division. Single-cell telomere quantification in animals established a critical role for telomerase in stem cells, yet, in plants, telomere-length quantification has been reported only at the organ level. Here, a quantitative analysis of telomere length of single cells in Arabidopsis root apex uncovered a heterogeneous telomere-length distribution of different cell lineages showing the longest telomeres at the stem cells. The defects in meristem and stem cell renewal observed in tert mutants demonstrate that telomere lengthening by TERT sets a replicative limit in the root meristem. Conversely, the long telomeres of the columella cells and the premature stem cell differentiation plt1,2 mutants suggest that differentiation can prevent telomere erosion. Overall, our results indicate that telomere dynamics are coupled to meristem activity and continuous growth, disclosing a critical association between telomere length, stem cell function, and the extended lifespan of plants.

Guiu, J., et al. (2013). "Hes repressors are essential regulators of hematopoietic stem cell development downstream of Notch signaling." J Exp Med **210**(1): 71-84.

Previous studies have identified Notch as a key regulator of hematopoietic stem cell (HSC) development, but the underlying downstream

mechanisms remain unknown. The Notch target Hes1 is widely expressed in the aortic endothelium and hematopoietic clusters, though Hes1-deficient mice show no overt hematopoietic abnormalities. We now demonstrate that Hes is required for the development of HSC in the mouse embryo, a function previously undetected as the result of functional compensation by de novo expression of Hes5 in the aorta/gonad/mesonephros (AGM) region of Hes1 mutants. Analysis of embryos deficient for Hes1 and Hes5 reveals an intact arterial program with overproduction of nonfunctional hematopoietic precursors and total absence of HSC activity. These alterations were associated with increased expression of the hematopoietic regulators Runx1, c-myb, and the previously identified Notch target Gata2. By analyzing the Gata2 locus, we have identified functional RBPJ-binding sites, which mutation results in loss of Gata2 reporter expression in transgenic embryos, and functional Hes-binding sites, which mutation leads to specific Gata2 up-regulation in the hematopoietic precursors. Together, our findings show that Notch activation in the AGM triggers Gata2 and Hes1 transcription, and next HES-1 protein represses Gata2, creating an incoherent feed-forward loop required to restrict Gata2 expression in the emerging HSCs.

Guo, J., et al. (2017). "Chromatin and Single-Cell RNA-Seq Profiling Reveal Dynamic Signaling and Metabolic Transitions during Human Spermatogonial Stem Cell Development." Cell Stem Cell **21**(4): 533-546.e536.

Human adult spermatogonial stem cells (hSSCs) must balance self-renewal and differentiation. To understand how this is achieved, we profiled DNA methylation and open chromatin (ATAC-seq) in SSEA4(+) hSSCs, analyzed bulk and single-cell RNA transcriptomes (RNA-seq) in SSEA4(+) hSSCs and differentiating c-KIT (+) spermatogonia, and performed validation studies via immunofluorescence. First, DNA hypomethylation at embryonic developmental genes supports their epigenetic "poising" in hSSCs for future/embryonic expression, while core pluripotency genes (OCT4 and NANOG) were transcriptionally and epigenetically repressed. Interestingly, open chromatin in hSSCs was strikingly enriched in binding sites for pioneer factors (NFYA/B, DMRT1, and hormone receptors). Remarkably, single-cell RNA-seq clustering analysis identified four cellular/developmental states during hSSC differentiation, involving major transitions in cell-cycle and transcriptional regulators, splicing and signaling factors, and glucose/mitochondria regulators. Overall, our results outline the dynamic chromatin/transcription landscape operating in hSSCs and identify crucial molecular pathways that accompany the transition from quiescence to proliferation and differentiation.

Han, T., et al. (2016). "Identification of novel genes and networks governing hematopoietic stem cell development." EMBO Rep **17**(12): 1814-1828.

Hematopoietic stem cells (HSCs) are capable of giving rise to all blood cell lineages throughout adulthood, and the generation of engraftable HSCs from human pluripotent stem cells is a major goal for regenerative medicine. Here, we describe a functional genome-wide RNAi screen to identify genes required for the differentiation of embryonic stem cell (ESC) into hematopoietic stem/progenitor cells (HSPCs) in vitro We report the discovery of novel genes important for the endothelial-to-hematopoietic transition and subsequently for HSPC specification. High-throughput sequencing and bioinformatic analyses identified twelve groups of genes, including a set of 351 novel genes required for HSPC specification. As in vivo proof of concept, four of these genes, Ap2a1, Mettl22, Lrsam1, and Hal, are selected for validation, confirmed to be essential for HSPC development in zebrafish and for maintenance of human HSCs. Taken together, our results not only identify a number of novel regulatory genes and pathways essential for HSPC development but also serve as valuable resource for directed differentiation of therapy grade HSPCs using human pluripotent stem cells.

Hasebe, T., et al. (2011). "Epithelial-connective tissue interactions induced by thyroid hormone receptor are essential for adult stem cell development in the Xenopus laevis intestine." Stem Cells **29**(1): 154-161.

In the amphibian intestine during metamorphosis, stem cells appear and generate the adult absorptive epithelium, analogous to the mammalian one, under the control of thyroid hormone (TH). We have previously shown that the adult stem cells originate from differentiated larval epithelial cells in the Xenopus laevis intestine. To clarify whether TH signaling in the epithelium alone is sufficient for inducing the stem cells, we have now performed tissue recombinant culture experiments using transgenic X. laevis tadpoles that express a dominant-positive TH receptor (dpTR) under a control of heat shock promoter. Wild-type (Wt) or dpTR transgenic (Tg) larval epithelium (Ep) was isolated from the tadpole intestine, recombined with homologous or heterologous nonepithelial tissues (non-Ep), and then cultivated in the absence of TH with daily heat shocks to induce transgenic dpTR expression. Adult epithelial progenitor cells expressing sonic hedgehog became detectable on day 5 in both the recombinant intestine of Tg Ep and Tg non-Ep (Tg/Tg) and that of Tg Ep

and Wt non-Ep (Tg/Wt). However, in Tg/Wt intestine, they did not express other stem cell markers such as Musashi-1 and never generated the adult epithelium expressing a marker for absorptive epithelial cells. Our results indicate that, while it is unclear why some larval epithelial cells dedifferentiate into adult progenitor/stem cells, TR-mediated gene expression in the surrounding tissues other than the epithelium is required for them to develop into adult stem cells, suggesting the importance of TH-inducible epithelial-connective tissue interactions in establishment of the stem cell niche in the amphibian intestine.

Hasebe, T., et al. (2017). "Thyroid Hormone-Induced Activation of Notch Signaling is Required for Adult Intestinal Stem Cell Development During Xenopus Laevis Metamorphosis." Stem Cells **35**(4): 1028-1039.

In Xenopus laevis intestine during metamorphosis, the larval epithelial cells are removed by apoptosis, and the adult epithelial stem (AE) cells appear concomitantly. They proliferate and differentiate to form the adult epithelium (Ep). Thyroid hormone (TH) is well established to trigger this remodeling by regulating the expression of various genes including Notch receptor. To study the role of Notch signaling, we have analyzed the expression of its components, including the ligands (DLL and Jag), receptor (Notch), and targets (Hairy), in the metamorphosing intestine by real-time reverse transcription-polymerase chain reaction and in situ hybridization or immunohistochemistry. We show that they are up-regulated during both natural and TH-induced metamorphosis in a tissue-specific manner. Particularly, Hairy1 is specifically expressed in the AE cells. Moreover, up-regulation of Hairy1 and Hairy2b by TH was prevented by treating tadpoles with a gamma-secretase inhibitor (GSI), which inhibits Notch signaling. More importantly, TH-induced up-regulation of LGR5, an adult intestinal stem cell marker, was suppressed by GSI treatment. Our results suggest that Notch signaling plays a role in stem cell development by regulating the expression of Hairy genes during intestinal remodeling. Furthermore, we show with organ culture experiments that prolonged exposure of tadpole intestine to TH plus GSI leads to hyperplasia of secretory cells and reduction of absorptive cells. Our findings here thus provide evidence for evolutionarily conserved role of Notch signaling in intestinal cell fate determination but more importantly reveal, for the first time, an important role of Notch pathway in the formation of adult intestinal stem cells during vertebrate development. Stem Cells 2017;35:1028-1039.

Hasebe, T., et al. (2017). "Essential Roles of Thyroid Hormone-Regulated Hyaluronan/CD44 Signaling in Adult Stem Cell Development During Xenopus laevis Intestinal Remodeling." Stem Cells **35**(10): 2175-2183.

In the amphibian intestine during metamorphosis, thyroid hormone (TH) induces some larval epithelial cells to dedifferentiate into stem cells, which generate the adult epithelium analogous to the mammalian intestinal epithelium. We have previously shown that the canonical Wnt signaling pathway is involved in adult epithelial development in the Xenopus laevis intestine. To understand the function of this pathway more precisely, we here focused on CD44, a major Wnt target, which has been identified as a TH response gene in the X. laevis intestine. Our in situ hybridization analysis indicated that CD44 mRNA is detectable in adult epithelial primordia consisting of the adult stem/progenitor cells and is strongly expressed in the connective tissue (CT) cells surrounding them. Interestingly, when the expression of CD44 mRNA is the highest, hyaluronan (HA), a principle ligand of CD44, is newly synthesized and becomes most abundantly distributed in the CT just beneath the adult epithelial primordia that are actively proliferating. Thereafter, as the adult primordia differentiate into the simple columnar epithelium, the expression of CD44 mRNA is gradually downregulated. More importantly, using organ cultures of the X. laevis tadpole intestine in the presence of TH, we have experimentally shown that inhibition of HA synthesis by 4-methylumbelliferone suppresses development of not only the CT but also the epithelial stem cells, resulting in failure to generate the AE. Our findings strongly suggest that TH-upregulated HA/CD44 signaling plays an essential role in formation of the intestinal stem cell niche during vertebrate postembryonic development. Stem Cells 2017;35:2175-2183.

He, Q. and F. Liu (2016). "Unexpected role of inflammatory signaling in hematopoietic stem cell development: its role beyond inflammation." Curr Opin Hematol **23**(1): 18-22.

PURPOSE OF REVIEW: Inflammatory signaling under pathological conditions like infection and inflammation has been extensively studied. Whether inflammatory signaling plays a role in physiology and development remains elusive. The review summarizes recent advances in inflammatory signaling with particular focus on how distinct inflammatory signaling regulates hematopoietic stem cell (HSC) development. Understanding the underlying mechanism of inflammatory signaling on HSC development may help to generate and/or expand a large number of functional HSCs for clinical

application. RECENT FINDINGS: Like the hematopoietic progenitors, HSCs can be the first responders to infection. An unexpected observation is that genes involved in innate immunity and inflammatory signaling are enriched in emerging HSCs and their niche during embryogenesis. Thus, inflammatory signaling may also play a role in HSC development in the absence of infection and inflammation. SUMMARY: Inflammatory signaling is not only an important regulator of HSCs in response to infection, but also plays a previously unrecognized role in HSC development in the absence of infection and inflammation. The baseline inflammatory signaling can be activated to promote HSC development in cell autonomous and noncell autonomous manners. However, direct response of HSCs to inflammatory stimuli is not always advantageous and excessive chronic signaling can have negative effects on HSC regulation and function.

Hearn, J. P. (2001). "Embryo implantation and embryonic stem cell development in primates." Reprod Fertil Dev **13**(7-8): 517-522.

The endocrine dialogue that results in implantation and the successful establishment of pregnancy in primates relies on embryonic secretion of chorionic gonadotrophin (CG). This hormone is a signal of embryo viability and capacity to support the corpus luteum. The expression of CG is apparently restricted to primates. Active or passive immunization of marmoset monkeys against the beta subunit of CG prevented implantation and early pregnancy, without disrupting the ovarian cycle. Studies of individual embryos cultured in vitro showed that CG is secreted at low levels by the blastocyst from before attachment, with secretion increasing exponentially after attachment. Gonadotrophin releasing hormone (GnRH) was also secreted, from mid-blastocyst stages, before the detection of CG. The secretion of GnRH by the embryo continued through the attachment and outgrowth stages of embryonic differentiation in vitro. The hypothetical role of GnRH in regulating CG release during implantation was tested in recently completed experiments. Individual embryos cultured with GnRH, or with agonist or antagonist to GnRH, showed significant variations in their secretion of CG and in their survival in culture, suggesting a causal relationship between these hormones. Embryos cultured with natural GnRH showed enhanced growth and development. Embryonic stem cells, from the inner cell mass of marmoset and rhesus monkeys, were the first primate embryonic stem cells to be isolated and characterized, enabling the subsequent isolation of human embryonic stem cells.

Hsia, N. and L. I. Zon (2005). "Transcriptional regulation of hematopoietic stem cell development in zebrafish." Exp Hematol **33**(9): 1007-1014.

The zebrafish (Danio rerio) is a well-established vertebrate model for studying hematopoiesis. The major advantages of this system include robust experimental techniques in both genetics and embryology, which have been utilized to model many aspects of human development and disease. Although much is known about the transcription factors involved in the terminal differentiation of peripheral blood lineages, little is known about the development and maintenance of the hematopoietic stem cell (HSC). This review will focus on the current knowledge of the transcriptional regulation of the HSC in the context of the zebrafish. Future studies using new technologies in the zebrafish model will enhance our understanding of the molecular networks regulating HSC pluripotency and differentiation.

Huang, B. Y., et al. (2012). "Polycomb group proteins and their roles in regulating stem cell development." Zhongguo Yi Xue Ke Xue Yuan Xue Bao **34**(3): 281-285.

Polycomb group (PcG) proteins are a family of epigenetic regulators responsible for the repression of genes in proliferation and differentiation of stem cells. PcG protein complex consists of two important epigenetic regulators: PRC1 (polycomb repressive complex 1) and PRC2 (polycomb repressive complex 2). In order to further understand the functions of PcG proteins in stem cell growth and differentiation, we review the PcG protein composition, PcG protein localization in the target gene, PcG protein recruitment, and the functions of PcG proteins in the development of stem cells.

Imanirad, P., et al. (2014). "HIF1alpha is a regulator of hematopoietic progenitor and stem cell development in hypoxic sites of the mouse embryo." Stem Cell Res **12**(1): 24-35.

Hypoxia affects many physiologic processes during early stages of mammalian ontogeny, particularly placental and vascular development. In the adult, the hypoxic bone marrow microenvironment plays a role in regulating hematopoietic stem cell (HSC) function. HSCs are generated from the major vasculature of the embryo, but whether the hypoxic response affects the generation of these HSCs is as yet unknown. Here we examined whether Hypoxia Inducible Factor1-alpha (HIF1alpha), a key modulator of the response to hypoxia, is essential for HSC development. We found hypoxic cells in embryonic tissues that generate and expand hematopoietic cells (aorta, placenta and fetal liver), and specifically aortic endothelial and hematopoietic cluster cells. A Cre/loxP

conditional knockout (cKO) approach was taken to delete HIF1alpha in Vascular Endothelial-Cadherin expressing endothelial cells, the precursors to definitive hematopoietic cells. Functional assays show that HSC and hematopoietic progenitor cells (HPCs) are significantly reduced in cKO aorta and placenta. Moreover, decreases in phenotypic aortic hematopoietic cluster cells in cKO embryos indicate that HIF1alpha is necessary for generation and/or expansion of HPCs and HSCs. cKO adult BM HSCs are also affected under transplantation conditions. Thus, HIF1alpha is a regulator of HSC generation and function beginning at the earliest embryonic stages.

Ishizuya-Oka, A. and Y. B. Shi (2007). "Regulation of adult intestinal epithelial stem cell development by thyroid hormone during Xenopus laevis metamorphosis." Dev Dyn **236**(12): 3358-3368.

During amphibian metamorphosis, most or all of the larval intestinal epithelial cells undergo apoptosis. In contrast, stem cells of yet-unknown origin actively proliferate and, under the influence of the connective tissue, differentiate into the adult epithelium analogous to the mammalian counterpart. Thus, amphibian intestinal remodeling is useful for studying the stem cell niche, the clarification of which is urgently needed for regenerative therapies. This review highlights the molecular aspects of the niche using the Xenopus laevis intestine as a model. Because amphibian metamorphosis is completely controlled by thyroid hormone (TH), the analysis of TH response genes serves as a powerful means for clarifying its molecular mechanisms. Although functional analysis of the genes is still on the way, recent progresses in organ culture and transgenic studies have gradually uncovered important roles of cell-cell and cell-extracellular matrix interactions through stromelysin-3 and sonic hedgehog/bone morphogenetic protein-4 signaling pathway in the epithelial stem cell development.

Ishizuya-Oka, A. and Y. B. Shi (2008). "Thyroid hormone regulation of stem cell development during intestinal remodeling." Mol Cell Endocrinol **288**(1-2): 71-78.

During amphibian metamorphosis the small intestine is remodeled from larval to adult form, analogous to the mammalian intestine. The larval epithelium mostly undergoes apoptosis, while a small number of stem cells appear, actively proliferate, and differentiate into the adult epithelium possessing a cell-renewal system. Because amphibian intestinal remodeling is completely controlled by thyroid hormone (T3) through T3 receptors (TRs), it serves as an excellent model for studying the molecular mechanism of the mammalian intestinal development. TRs bind T3 response elements in target genes and have dual functions by interacting with coactivators or corepressors in a T3-dependent manner. A number of T3 response genes have been isolated from the Xenopus laevis intestine. They include signaling molecules, matrix metalloproteinases, and transcription factors. Functional studies have been carried out on many such genes in vitro and in vivo by using transgenic and culture technologies. Here we will review recent findings from such studies with a special emphasis on the adult intestinal stem cells, and discuss the evolutionarily conserved roles of T3 in the epithelial cell-renewal in the vertebrate intestine.

Ivanovs, A., et al. (2017). "Human haematopoietic stem cell development: from the embryo to the dish." Development **144**(13): 2323-2337.

Haematopoietic stem cells (HSCs) emerge during embryogenesis and give rise to the adult haematopoietic system. Understanding how early haematopoietic development occurs is of fundamental importance for basic biology and medical sciences, but our knowledge is still limited compared with what we know of adult HSCs and their microenvironment. This is particularly true for human haematopoiesis, and is reflected in our current inability to recapitulate the development of HSCs from pluripotent stem cells in vitro In this Review, we discuss what is known of human haematopoietic development: the anatomical sites at which it occurs, the different temporal waves of haematopoiesis, the emergence of the first HSCs and the signalling landscape of the haematopoietic niche. We also discuss the extent to which in vitro differentiation of human pluripotent stem cells recapitulates bona fide human developmental haematopoiesis, and outline some future directions in the field.

Kaimakis, P., et al. (2013). "The biochemistry of hematopoietic stem cell development." Biochim Biophys Acta **1830**(2): 2395-2403.

BACKGROUND: The cornerstone of the adult hematopoietic system and clinical treatments for blood-related disease is the cohort of hematopoietic stem cells (HSC) that is harbored in the adult bone marrow microenvironment. Interestingly, this cohort of HSCs is generated only during a short window of developmental time. In mammalian embryos, hematopoietic progenitor and HSC generation occurs within several extra- and intraembryonic microenvironments, most notably from 'hemogenic' endothelial cells lining the major vasculature. HSCs are made through a remarkable transdifferentiation of endothelial cells to a hematopoietic fate that is long-lived and self-renewable. Recent studies are beginning to provide an understanding of the biochemical signaling pathways and transcription

factors/complexes that promote their generation. SCOPE OF REVIEW: The focus of this review is on the biochemistry behind the generation of these potent long-lived self-renewing stem cells of the blood system. Both the intrinsic (master transcription factors) and extrinsic regulators (morphogens and growth factors) that affect the generation, maintenance and expansion of HSCs in the embryo will be discussed. MAJOR CONCLUSIONS: The generation of HSCs is a stepwise process involving many developmental signaling pathways, morphogens and cytokines. Pivotal hematopoietic transcription factors are required for their generation. Interestingly, whereas these factors are necessary for HSC generation, their expression in adult bone marrow HSCs is oftentimes not required. Thus, the biochemistry and molecular regulation of HSC development in the embryo are overlapping, but differ significantly from the regulation of HSCs in the adult. GENERAL SIGNIFICANCE: HSC numbers for clinical use are limiting, and despite much research into the molecular basis of HSC regulation in the adult bone marrow, no panel of growth factors, interleukins and/or morphogens has been found to sufficiently increase the number of these important stem cells. An understanding of the biochemistry of HSC generation in the developing embryo provides important new knowledge on how these complex stem cells are made, sustained and expanded in the embryo to give rise to the complete adult hematopoietic system, thus stimulating novel strategies for producing increased numbers of clinically useful HSCs. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

Katebi, M., et al. (2009). "Adenosine A2A receptors play an active role in mouse bone marrow-derived mesenchymal stem cell development." J Leukoc Biol **85**(3): 438-444.

Bone marrow-derived mesenchymal stem cells (BM-MSCs) play a role in wound healing and tissue repair and may also be useful for organ regeneration. As we have demonstrated previously that A (2A) adenosine receptors (A (2A)R) promote tissue repair and wound healing by stimulating local repair mechanisms and enhancing accumulation of endothelial progenitor cells, we investigated whether A (2A)R activation modulates BM-MSC proliferation and differentiation. BM-MSCs were isolated and cultured from A (2A)-deficient and ecto-5'nucleotidase (CD73)-deficient female mice; the MSCs were identified and quantified by a CFU-fibroblast (CFU-F) assay. Procollagen alpha2 type I expression was determined by Western blotting and immunocytochemistry. MSC-specific markers were examined in primary cells and third-passage cells by cytofluorography. PCR and real time-PCR were used to quantitate adenosine receptor and CD73 expression. There were significantly fewer CFU-Fs in cultures of BM-MSCs from A (2A)R knockout (KO) mice or BM-MSCs treated with the A (2A)R antagonist ZM241385, 1 microM. Similarly, there were significantly fewer procollagen alpha2 type I-positive MSCs in cultures from A (2A)R KO and antagonist-treated cultures as well. In late passage cells, there were significantly fewer MSCs from A (2A) KO mice expressing CD90, CD105, and procollagen type I ($P<0.05$ for all; $n=3$). These findings indicate that adenosine and adenosine A (2A)R play a critical role in promoting the proliferation and differentiation of mouse BM-MSCs.

Kaushansky, K. (1999). "Thrombopoietin and hematopoietic stem cell development." Ann N Y Acad Sci **872**: 314-319.

Thrombopoietin, the long sought primary regulator of thrombopoiesis, was cloned four years ago. In addition to its fulfilling most, if not all, of the expected biological activities relating to megakaryocyte and platelet development, the availability of the recombinant hormone and reagents to characterize its receptor have allowed detailed investigation of additional biological activities. In cultures of purified populations of candidate stem cells, thrombopoietin supports the survival, and augments the proliferation of hematopoietic stem cells when present together with interleukin-3 or steel factor. The progeny of such cultures are not skewed in their developmental potential; colony-forming cells of all lineages arise from thrombopoietin-stimulated stem cells. Evidence for an important effect of thrombopoietin on stem cell physiology in vivo are equally compelling. Genetic elimination of thrombopoietin or its receptor leads to a profound reduction not only of megakaryocytes and platelets, but also of committed myeloid progenitors of all types, primitive progenitors and hematopoietic stem cells. When administered to animals, thrombopoietin profoundly stimulates thrombopoiesis and enhances the number of hematopoietic progenitor cells of all lineages, and when used in most animal models of myelosuppressive therapy, accelerates the recovery of platelet, erythrocyte and leukocyte production. Thus, thrombopoietin appears to be more than a lineage-restricted growth factor.

Kaushansky, K. and H. M. Ranney (2009). "Thrombopoietin in normal and neoplastic stem cell development." Best Pract Res Clin Haematol **22**(4): 495-499.

It has been known for sometime that thrombopoietin acts on megakaryocytic progenitor cells to stimulate platelet production. It has recently

been discovered that it also stimulates the self-renewal and expansion of normal murine and human haematopoietic stem cells (HSCs) by acting on its cognate receptor, the product of the myeloproliferative leukaemia (c-MPL) proto-oncogene. The c-MPL receptor may also play an important role in the development of human myeloproliferative disorders, essential thrombocythemia, myelofibrosis and polycythemia vera, cooperating with the dysregulated Janus kinase JAK2V (617)F.

Kauts, M. L., et al. (2016). "Hematopoietic (stem) cell development - how divergent are the roads taken?" FEBS Lett **590**(22): 3975-3986.

The development of the hematopoietic system during early embryonic stages occurs in spatially and temporally distinct waves. Hematopoietic stem cells (HSC), the most potent and self-renewing cells of this system, are produced in the final 'definitive' wave of hematopoietic cell generation. In contrast to HSCs in the adult, which differentiate via intermediate progenitor populations to produce functional blood cells, the generation of hematopoietic cells in the embryo prior to HSC generation occurs in the early waves by producing blood cells without intermediate progenitors (such as the 'primitive' hematopoietic cells). The lineage relationship between the early hematopoietic cells and the cells giving rise to HSCs, the genetic networks controlling their emergence, and the precise temporal determination of HSC fate remain topics of intense research and debate. This Review article discusses the current knowledge on the step-wise embryonic establishment of the adult hematopoietic system, examines the roles of pivotal intrinsic regulators in this process, and raises questions concerning the temporal onset of HSC fate determination.

Kos, O., et al. (2018). "Regulation of fetal hemoglobin expression during hematopoietic stem cell development and its importance in bone metabolism and osteoporosis." Int Immunopharmacol **57**: 112-120.

We have shown that an altered tissue redox environment in mice lacking either murine beta Hemoglobin major (HgbbetamaKO) or minor (HgbbetamiKO) regulates inflammation. The REDOX environment in marrow stem cell niches also control differentiation pathways. We investigated osteoclastogenesis (OC)/osteoblastogenesis (OB), in bone cultures derived from untreated or FSLE-treated WT, HgbbetamaKO or HgbbetamiKO mice. Marrow mesenchymal cells from 10d pre-cultures were incubated on an osteogenic matrix for 21d prior to analysis of inflammatory cytokine release into culture supernatants, and relative OC:OB using (TRAP:BSP, RANKL:OPG) mRNA expression ratios and TRAP or Von Kossa staining. Cells from WT and HgbbetamaKO mice show decreased IL-1beta, TNFalpha and IL-6 production and enhanced osteoblastogenesis with altered mRNA expression ratios and increased bone nodules (Von Kossa staining) in vitro after in vivo stimulation of mRNA expression of fetal Hgb genes (Hgbepsilon and Hgbbetami) by a fetal liver extract (FSLE). Marrow from HgbbetamiKO showed enhanced cytokine release and preferential enhanced osteoclastogenesis relative to similar cells from WT or HgbbetamaKO mice, with no increased osteoblastogenesis after mouse treatment with FSLE. Pre-treatment of WT or HgbbetamaKO, but not HgbbetamiKO mice, with other molecules (rapamycin; hydroxyurea) which increase expression of fetal Hgb genes also augmented osteoblastogenesis and decreased cytokine production in cells differentiating in vitro. Infusion of rabbit anti-Hgbepsilon or anti- Hgbbetami, but not anti-Hgbalpha or anti- Hgbbetama into WT mice from day 13 gestation for 3weeks led to attenuated osteoblastogenesis in cultured cells. We conclude that increased fetal hemoglobin expression, or use of agents which improve fetal hemoglobin expression, increases osteoblast bone differentiation in association with decreased inflammatory cytokine release.

Krivtsov, A. V. and S. A. Armstrong (2007). "MLL translocations, histone modifications and leukaemia stem-cell development." Nat Rev Cancer **7**(11): 823-833.

Translocations that involve the mixed lineage leukaemia (MLL) gene identify a unique group of acute leukaemias, and often predict a poor prognosis. The MLL gene encodes a DNA-binding protein that methylates histone H3 lysine 4 (H3K4), and positively regulates gene expression including multiple Hox genes. Leukaemogenic MLL translocations encode MLL fusion proteins that have lost H3K4 methyltransferase activity. A key feature of MLL fusion proteins is their ability to efficiently transform haematopoietic cells into leukaemia stem cells. The link between a chromatin modulator and leukaemia stem cells provides support for epigenetic landscapes as an important part of leukaemia and normal stem-cell development.

Lee, S., et al. (2016). "Polo Kinase Phosphorylates Miro to Control ER-Mitochondria Contact Sites and Mitochondrial Ca (2+) Homeostasis in Neural Stem Cell Development." Dev Cell **37**(2): 174-189.

Mitochondria play central roles in buffering intracellular Ca (2) (+) transients. While basal mitochondrial Ca (2) (+) (Ca (2) (+) mito) is needed to maintain organellar physiology, Ca (2) (+) mito

overload can lead to cell death. How Ca (2) (+) mito homeostasis is regulated is not well understood. Here we show that Miro, a known component of the mitochondrial transport machinery, regulates Drosophila neural stem cell (NSC) development through Ca (2) (+) mito homeostasis control, independent of its role in mitochondrial transport. Miro interacts with Ca (2) (+) transporters at the ER-mitochondria contact site (ERMCS). Its inactivation causes Ca (2) (+) mito depletion and metabolic impairment, whereas its overexpression results in Ca (2) (+) mito overload, mitochondrial morphology change, and apoptotic response. Both conditions impaired NSC lineage progression. Ca (2) (+) mito homeostasis is influenced by Polo-mediated phosphorylation of a conserved residue in Miro, which positively regulates Miro localization to, and the integrity of, ERMCS. Our results elucidate a regulatory mechanism underlying Ca (2) (+) mito homeostasis and how its dysregulation may affect NSC metabolism/development and contribute to disease.

Leiderman, L. J., et al. (1986). "Altered hematopoietic stem cell development in male B6C3F1 mice following exposure to 1,3-butadiene." Exp Mol Pathol **44**(1): 50-56.

The effects of the murine lymphomagen, 1,3-butadiene (BD), on the proliferation and differentiation of hematopoietic stem cells were examined in male B6C3F1 mice. Exposure to 1250 ppm BD for 6 weeks resulted in no demonstrable alteration in the frequency of spleen colony-forming units (CFU-S); however, colonies derived from treated animals were smaller than those from controls. The absence of any difference in the frequency of CFU-GM after 6 weeks exposure suggests that BD produces an alteration in the relative proportion of immature to mature pluripotent stem cells in BD-exposed animals. This was confirmed by the examination of the effects of BD on stem cell development in long-term bone marrow culture. After 14 days, the number of CFU-GM derived from cultures of animals exposed for 6 weeks was reduced compared to controls. However, at 28 days an increase relative to controls was observed. This shift in the course of differentiation of the granulocyte/macrophage precursor cell, as assessed by the CFU-GM, provides further evidence that there is an increase in the relative frequency of primitive or immature stem cells in BD-treated mice. After a 30-31 week exposure to BD, a decrease in the numbers of both CFU-S and CFU-GM was observed. These findings indicate that BD causes alterations in stem cell development and suggest that alterations in bone marrow stem cells may play an essential role in the pathogenesis of BD-induced thymic lymphoma.

Leng, J., et al. (2009). "Brain-derived neurotrophic factor and electrophysiological properties of voltage-gated ion channels during neuronal stem cell development." Brain Res **1272**: 14-24.

Brain-derived neurotrophic factor (BDNF) has been reported to play a critical role in modulating a variety of neural functions such as membrane excitability, synaptic transmission, and activity-dependent synaptic plasticity. BDNF has also been found to enhance neurogenesis. Although consensus is found on the general trophic effected by BDNF on subpopulations of neurons, little information appears concerning the effects of BDNF on ion currents during the development of these newborn cells. Here, we report that BDNF plays an essential role in the development of neural stem cells during a plastic period in vitro. We found that chronic stimulation of neural stem cells with bath application of 40 ng/ml BDNF during differentiation promoted the functional development of passive membrane, evoked biphasic changes in Na (+) currents, regulated the expression of K (+) channels and the outward K (+) especially at the early developmental stage. In conclusion, our findings indicate that BDNF principally regulates the electrical properties of neural stem cell (NSC) especially in the early developmental stage.

Li, C., et al. (2016). "Epigenetic regulation of hematopoietic stem cell development." Methods Cell Biol **135**: 431-448.

Hematopoietic stem cells (HSCs) are multipotent self-renewing precursors with the capacity to differentiate into all adult blood cell lineages. HSC development is a highly orchestrated process regulated by multiple transcription factors and signaling pathways. Emerging evidence suggests that epigenetic regulation is an additional essential component of HSC development. Powerful genetic and imaging approaches, combined with conservation of mammalian programs, have made zebrafish a prominent model for the study of HSC production. This chapter summarizes approaches that have been used to identify epigenetic regulators of HSC development in zebrafish and highlights additional strategies that are likely to facilitate progress in this promising field.

Li, Z., et al. (2012). "Mouse embryonic head as a site for hematopoietic stem cell development." Cell Stem Cell **11**(5): 663-675.

In the mouse embryo, the aorta-gonad-mesonephros (AGM) region is considered to be the sole location for intraembryonic emergence of hematopoietic stem cells (HSCs). Here we report that, in parallel to the AGM region, the E10.5-E11.5 mouse

head harbors bona fide HSCs, as defined by long-term, high-level, multilineage reconstitution and self-renewal capacity in adult recipients, before HSCs enter the circulation. The presence of hemogenesis in the midgestation head is indicated by the appearance of intravascular cluster cells and the blood-forming capacity of a sorted endothelial cell population. In addition, lineage tracing via an inducible VE-cadherin-Cre transgene demonstrates the hemogenic capacity of head endothelium. Most importantly, a spatially restricted lineage labeling system reveals the physiological contribution of cerebrovascular endothelium to postnatal HSCs and multilineage hematopoiesis. We conclude that the mouse embryonic head is a previously unappreciated site for HSC emergence within the developing embryo.

Liu, D. Z., et al. (2015). "MIR-150 promotes prostate cancer stem cell development via suppressing p27Kip1." Eur Rev Med Pharmacol Sci **19**(22): 4344-4352.

OBJECTIVE: Our previous study found that high miR-150 expression was positively correlated with prostate tumor recurrence or metastasis. In this work, we investigated the expression of miR-150 in prostate cancer stem cells (CSCs) and explored its regulation over p27 in the development of CSCs. MATERIALS AND METHODS: MiR-150 expression in CD144 or CD44 positive primary prostate cells and in DU145 cell line was measured. It regulation over CSCs was measured using tumor sphere assay and qRT-PCR analysis of CSC related Oct4, Nestin and Nanog genes. The direct binding between miR-150 and 3'UTR of p27 mRNA was verified using dual luciferase, qRT-PCR and western blot assay. The influence of miR-150-p27 axis on prostate CSC properties was further investigated. RESULTS: Findings of this study found miR-150 expression was significantly upregulated in CD44+ or CD133+ subgroups of prostate cancer cells. MiR-150 could directly target 3'UTR of p27 and decrease its expression, through which it increased the number and volume of tumor sphere formed by DU145 cells, as well as the expression of CSC related Oct4, Nestin and Nanog genes. CONCLUSIONS: Increased miR-150 expression might participate in the development and progression of human prostate CSC by suppressing p27. This supported our previous study which found miR-150 was positively correlated with prostate tumor recurrence or metastasis.

Lodge, E. J., et al. (2016). "Expression Analysis of the Hippo Cascade Indicates a Role in Pituitary Stem Cell Development." Front Physiol **7**: 114.

The pituitary gland is a primary endocrine organ that controls major physiological processes. Abnormal development or homeostatic disruptions can lead to human disorders such as hypopituitarism or tumors. Multiple signaling pathways, including WNT, BMP, FGF, and SHH regulate pituitary development but the role of the Hippo-YAP1/TAZ cascade is currently unknown. In multiple tissues, the Hippo kinase cascade underlies neoplasias; it influences organ size through the regulation of proliferation and apoptosis, and has roles in determining stem cell potential. We have used a sensitive mRNA in situ hybridization method (RNAscope) to determine the expression patterns of the Hippo pathway components during mouse pituitary development. We have also carried out immunolocalisation studies to determine when YAP1 and TAZ, the transcriptional effectors of the Hippo pathway, are active. We find that YAP1/TAZ are active in the stem/progenitor cell population throughout development and at postnatal stages, consistent with their role in promoting the stem cell state. Our results demonstrate for the first time the collective expression of major components of the Hippo pathway during normal embryonic and postnatal development of the pituitary gland.

Logan, C. M., et al. (2007). "Prostaglandin E2: at the crossroads between stem cell development, inflammation and cancer." Cancer Biol Ther **6**(10): 1517-1520.

Stem cells have tremendous therapeutic potential for a series of pathologies ranging from cancer to genetic diseases. The obstacles to exploiting their potential reside mainly in their limited numbers or potency. Prostaglandins are known to be involved in many physiological and pathological processes. Among these, their importance in stem cell development is just starting to emerge. The recent findings by North and colleagues (Nature, 2007; 447:1007-1011) uncover a crucial role for PGE2 in hematopoietic stem cell growth and development not only in embryonic, but also in adult stem cell homeostasis in both simple and complex vertebrate systems. This new information adds to recent advances in the study of PGE2's role in many diseases and in the reaction to various cellular stress conditions. This is the perfect time to improve our knowledge of stem cell regulation, which hopefully will lead to improved stem cell-based therapeutic options and also to better understand and manage current anti-inflammatory and immuno-suppressive drugs in the therapy of cancer and other diseases.

Lovasco, L. A., et al. (2015). "TAF4b is required for mouse spermatogonial stem cell development." Stem Cells **33**(4): 1267-1276.

Long-term mammalian spermatogenesis requires proper development of spermatogonial stem cells (SSCs) that replenish the testis with germ cell

progenitors during adult life. TAF4b is a gonadal-enriched component of the general transcription factor complex, TFIID, which is required for the maintenance of spermatogenesis in the mouse. Successful germ cell transplantation assays into adult TAF4b-deficient host testes suggested that TAF4b performs an essential germ cell autonomous function in SSC establishment and/or maintenance. To elucidate the SSC function of TAF4b, we characterized the initial gonocyte pool and rounds of spermatogenic differentiation in the context of the Taf4b-deficient mouse testis. Here, we demonstrate a significant reduction in the late embryonic gonocyte pool and a deficient expansion of this pool soon after birth. Resulting from this reduction of germ cell progenitors is a developmental delay in meiosis initiation, as compared to age-matched controls. While GFRalpha1+ spermatogonia are appropriately present as Asingle and Apaired in wild-type testes, TAF4b-deficient testes display an increased proportion of long and clustered chains of GFRalpha1+ cells. In the absence of TAF4b, seminiferous tubules in the adult testis either lack germ cells altogether or are found to have missing generations of spermatogenic progenitor cells. Together these data indicate that TAF4b-deficient spermatogenic progenitor cells display a tendency for differentiation at the expense of self-renewal and a renewing pool of SSCs fail to establish during the critical window of SSC development.

Lu, K., et al. (2012). "A cell state splitter and differentiation wave working-model for embryonic stem cell development and somatic cell epigenetic reprogramming." Biosystems **109**(3): 390-396.

Cell fate determination and development is a biology question that has yet to be fully answered. During embryogenesis and in vivo stem cell differentiation, cells/tissues deploy epigenetic mechanisms to accomplish differentiation and give rise to the fully developed organism. Although a biochemistry description of cellular genetics and epigenetics is important, additional mechanisms are necessary to completely solve the problem of embryogenesis, especially differentiation and the spatiotemporal coordination of cells/tissues during morphogenesis. The cell state splitter and differentiation wave working-model was initially proposed to explain the homeostatic primary neural induction in amphibian embryos. Here the model is adopted to explain experimental findings on in vitro embryonic stem cell, pluripotency and differentiation. Moreover, since somatic cells can be reverted to a stem-cell-like pluripotent state through the laboratory procedure called epigenetic reprogramming, erection of a cell state splitter could be a key event in their successful reprogramming. Overall, the cell state splitter working-model introduces a bistable cytoskeletal mechanism that partially explains cell fate determination and biological development. It offers an interdisciplinary framework that bridges the gap between molecular epigenetics and embryogenesis.

Ma, D. K., et al. (2005). "Glial influences on neural stem cell development: cellular niches for adult neurogenesis." Curr Opin Neurobiol **15**(5): 514-520.

Neural stem cells continually generate new neurons in very limited regions of the adult mammalian central nervous system. In the neurogenic regions there are unique and highly specialized microenvironments (niches) that tightly regulate the neuronal development of adult neural stem cells. Emerging evidence suggests that glia, particularly astrocytes, have key roles in controlling multiple steps of adult neurogenesis within the niches, from proliferation and fate specification of neural progenitors to migration and integration of the neuronal progeny into pre-existing neuronal circuits in the adult brain. Identification of specific niche signals that regulate these sequential steps during adult neurogenesis might lead to strategies to induce functional neurogenesis in other brain regions after injury or degenerative neurological diseases.

Madras, N., et al. (2002). "Modeling stem cell development by retrospective analysis of gene expression profiles in single progenitor-derived colonies." Stem Cells **20**(3): 230-240.

The process of development of various cell types is often based on a linear or deterministic paradigm. This is true, for example, for osteoblast development, a process that occurs through the differentiation of a subset of primitive fibroblast progenitors called colony-forming unit-osteoblasts (CFU-Os). CFU-O differentiation has been subdivided into three stages: proliferation, extracellular matrix development and maturation, and mineralization, with characteristic changes in gene expression at each stage. Few analyses have asked whether CFU-O differentiation, or indeed stem cell differentiation in general, may follow more complex and nondeterministic paths, a possibility that may underlie the substantial number of discrepancies in published reports of progenitor cell developmental sequences. We analyzed 99 single colonies of osteoblast stem/primitive progenitor cells cultured under identical conditions. The colonies were analyzed by global amplification poly (A) polymerase chain reaction to determine which of nine genes had been expressed. We used the expression profiles to develop a statistically rigorous map of the cell fate decisions that occur during osteoprogenitor differentiation and show that different developmental routes can be taken to achieve the same end point

phenotype. These routes appear to involve both developmental "dead ends" (leading to the expression of genes not correlated with osteoblast-associated genes or the mature osteoblast phenotype) and developmental flexibility (the existence of multiple gene expression routes to the same developmental end point). Our results provide new insight into the biology of primitive progenitor cell differentiation and introduce a powerful new quantitative method for stem cell lineage analysis that should be applicable to a wide variety of stem cell systems.

Magnusson, P., et al. (2004). "Deregulation of Flk-1/vascular endothelial growth factor receptor-2 in fibroblast growth factor receptor-1-deficient vascular stem cell development." J Cell Sci **117**(Pt 8): 1513-1523.

We have employed embryoid bodies derived from murine embryonal stem cells to study effects on vascular development induced by fibroblast growth factor (FGF)-2 and FGF receptor-1, in comparison to the established angiogenic factor vascular endothelial growth factor (VEGF)-A and its receptor VEGF receptor-2. Exogenous FGF-2 promoted formation of morphologically distinct, long slender vessels in the embryoid bodies, whereas VEGF-A-treated bodies displayed a compact plexus of capillaries. FGF-2 stimulation of embryonal stem cells under conditions where VEGF-A/VEGFR-2 function was blocked, led to formation of endothelial cell clusters, which failed to develop into vessels. FGFR-1(-/-) embryoid bodies responded to VEGF-A by establishment of the characteristic vascular plexus, but FGF-2 had no effect on vascular development in the absence of FGFR-1. The FGFR-1(-/-) embryoid bodies displayed considerably increased basal level of vessel formation, detected by immunohistochemical staining for platelet-endothelial cell adhesion molecule (PECAM)/CD31. This basal vascularization was blocked by neutralizing antibodies against VEGFR-2 or VEGF-A and biochemical analyses indicated changes in regulation of VEGFR-2 in the absence of FGFR-1 expression. We conclude that VEGF-A/VEGFR-2-dependent vessel formation occurs in the absence of FGF-2/FGFR-1, which, however, serve to modulate vascular development.

Mahmud, N., et al. (1996). "A possible change in doubling time of haemopoietic progenitor cells with stem cell development." Br J Haematol **94**(2): 242-249.

We separated haemopoietic progenitors derived from marrow cells of 5-fluorouracil (5-FU)-treated mice into three groups, based on the stages of stem cell development and studied doubling time, using a serum-free clonal culture system. Stage I progenitors were those present in primary marrow cells from 5-FU-treated mice. Stages II and III progenitors were early and late progenies in culture of stage I progenitors respectively. The morphological analysis of colonies derived from stage I, II and III progenitors demonstrated an association of progression of stages with loss of multipotentiality. The doubling time of haemopoietic progenitors was estimated by sequential analysis of colony formation and studies of growth fraction. The time required for haemopoietic progenitors to double shortened as their stage of development progressed. Alteration in one doubling time of haemopoietic progenitors at progressive stages of stem cell development was seen in cultures supported by various combinations of growth factors, including interleukin-3 (IL-3), IL-11. and steel factor (SF), Cell-cycle analysis suggested that reduction of the doubling time of haemopoietic progenitors is probably due to a decrease in the time spent in the G1 phase of the cell cycle. Our results suggest that in early haemopoiesis the doubling time of haemopoietic progenitors may change with stem cell development.

Mascarenhas, M. I., et al. (2009). "Identification of novel regulators of hematopoietic stem cell development through refinement of stem cell localization and expression profiling." Blood **114**(21): 4645-4653.

The first adult-repopulating hematopoietic stem cells (HSCs) are detected starting at day 10.5 of gestation in the aorta-gonads-mesonephros (AGM) region of the mouse embryo. Despite the importance of the AGM in initiating HSC production, very little is currently known about the regulators that control HSC emergence in this region. We have therefore further defined the location of HSCs in the AGM and incorporated this information into a spatial and temporal comparative gene expression analysis of the AGM. The comparisons included gene expression profiling (1) in the newly identified HSC-containing region compared with the region devoid of HSCs, (2) before and after HSC emergence in the AGM microenvironment, and (3) on populations enriched for HSCs and their putative precursors. Two genes found to be up-regulated at the time and place where HSCs are first detected, the cyclin-dependent kinase inhibitor p57Kip2/Cdkn1c and the insulin-like growth factor 2, were chosen for further analysis. We demonstrate here that they play a novel role in AGM hematopoiesis. Interestingly, many genes involved in the development of the tissues surrounding the dorsal aorta are also up-regulated during HSC emergence, suggesting that the regulation of HSC generation occurs in coordination with the development of other organs.

Matsuura, K., et al. (2012). "Liganded thyroid hormone receptor induces nucleosome removal and

histone modifications to activate transcription during larval intestinal cell death and adult stem cell development." Endocrinology **153**(2): 961-972.

Thyroid hormone (T (3)) plays an important role in regulating multiple cellular and metabolic processes, including cell proliferation, cell death, and energy metabolism, in vertebrates. Dysregulation of T (3) signaling results in developmental abnormalities, metabolic defects, and even cancer. We used T (3)-dependent Xenopus metamorphosis as a model to study how T (3) regulates transcription during vertebrate development. T (3) exerts its metamorphic effects through T (3) receptors (TR). TR recruits, in a T (3)-dependent manner, cofactor complexes that can carry out chromatin remodeling/histone modifications. Whether and how histone modifications change upon gene regulation by TR during vertebrate development is largely unknown. Here we analyzed histone modifications at T (3) target genes during intestinal metamorphosis, a process that involves essentially total apoptotic degeneration of the simple larval epithelium and de novo development of the adult epithelial stem cells, followed by their proliferation and differentiation into the complex adult epithelium. We demonstrated for the first time in vivo during vertebrate development that TR induces the removal of core histones at the promoter region and the recruitment of RNA polymerase. Furthermore, a number of histone activation and repression marks have been defined based on correlations with mRNA levels in cell cultures. Most but not all correlate with gene expression induced by liganded TR during development, suggesting that tissue and developmental context influences the roles of histone modifications in gene regulation. Our findings provide important mechanistic insights on how chromatin remodeling affects developmental gene regulation in vivo.

Mikkola, H. K., et al. (2005). "Placenta as a site for hematopoietic stem cell development." Exp Hematol **33**(9): 1048-1054.

The discovery of a major hematopoietic stem cell (HSC) pool in mid-gestation mouse placenta has defined the placenta as yet another important anatomical site that participates in HSC development. Placental HSC activity starts in parallel with the AGM region, before HSCs are found in circulation or have colonized the fetal liver. Moreover, placental hematopoietic activity culminates in a rapid expansion of the definitive HSC pool, which occurs during the time when the fetal liver HSC reservoir begins to grow. Furthermore, hematopoietic cells in mid-gestation mouse placenta are not instructed for differentiation along the myeloerythroid lineage, as in the fetal liver. These findings suggest that the placenta provides a supportive niche where the definitive hematopoietic stem cell pool can be temporarily established during development. Future studies are needed to characterize the developmental events that lead to the establishment of placental HSC pool, and to define the microenvironmental signals that support this process. Furthermore, if the stem cell-promoting properties of the placental niche can be harnessed in vitro to support HSC formation, maturation, and/or expansion in culture, these assets may greatly improve hematopoietic stem cell-based therapies in the future.

Mizuno, S., et al. (2018). "Notch1 expression is regulated at the post-transcriptional level by the 3' untranslated region in hematopoietic stem cell development." Int J Hematol **107**(3): 311-319.

In hematopoiesis, the expression of critical genes is regulated in a stage-specific manner to maintain normal hematopoiesis. Notch1 is an essential gene involved in the commitment and development of the T-cell lineage. However, the regulation of Notch1 in hematopoiesis is controversial, particularly at the level of hematopoietic stem cell (HSC). Here, we found that the expression of Notch1 is controlled at the post-transcriptional level in HSCs. HSCs express a considerable level of Notch1 mRNA, but its protein level is very low, suggesting a post-transcriptional suppression for Notch1. Using a retroviral sensor vector expressing a fusion mRNA of GFP and 3' untranslated region (3'UTR) of a target gene, we demonstrated that the Notch1-3'UTR had a post-translational suppressive effect only at the HSC but not in the downstream progenitor stages. The sequence motif AUnA was required for this post-transcriptional regulation by the Notch1-3'UTR. Interestingly, this Notch1-3'UTR-mediated suppressive effect was relieved when HSCs were placed in the thymus, but not in the bone marrow. Thus, the expression of Notch1 in HSCs is regulated by microenvironment at the post-transcriptional level, which may control T lymphoid lineage commitment from HSCs.

Nikolsky, I. and T. V. Serebrovska (2009). "Role of hypoxia in stem cell development and functioning." Fiziol Zh **55**(4): 116-130.

The response of stem cells (SC) to hypoxia is one of the main mechanisms of an organism's adaptation to changing terms of external and internal environment. This review describes the role of hypoxia in functioning of various stem cell, types--embryonic, hematopoietic, nmesenchvmal and neural, paying special attention to the very limited data concerning intermittent hypoxia (IH) effects. All stem cells and their precursors exist in microenvironment named stem cell niches. The most crucial factor for their normal functioning is hypoxia. which contributes to maintaining the SC in quiescent state with necessary

rate of self-renewal. The key element qf these mechanisms is a complex of hypoxia-inducible transcription factors. An additional exogenous hypoxic impact leads to activation of SC system. Very scant information on IH effects on SC that was obtained generally in cell culture models, reveals that intermittent hypoxia at certain duration and intensity is a more potent trigger of transcription activation than constant hypoxia. In the future a method of IH training/treatment could be effectively used for correction of physiological changes and pathological disorders in art organism.

North, T. E., et al. (2009). "Hematopoietic stem cell development is dependent on blood flow." Cell **137**(4): 736-748.

During vertebrate embryogenesis, hematopoietic stem cells (HSCs) arise in the aorta-gonads-mesonephros (AGM) region. We report here that blood flow is a conserved regulator of HSC formation. In zebrafish, chemical blood flow modulators regulated HSC development, and silent heart (sih) embryos, lacking a heartbeat and blood circulation, exhibited severely reduced HSCs. Flow-modifying compounds primarily affected HSC induction after the onset of heartbeat; however, nitric oxide (NO) donors regulated HSC number even when treatment occurred before the initiation of circulation, and rescued HSCs in sih mutants. Morpholino knockdown of nos1 (nnos/enos) blocked HSC development, and its requirement was shown to be cell autonomous. In the mouse, Nos3 (eNos) was expressed in HSCs in the AGM. Intrauterine Nos inhibition or embryonic Nos3 deficiency resulted in a reduction of hematopoietic clusters and transplantable murine HSCs. This work links blood flow to AGM hematopoiesis and identifies NO as a conserved downstream regulator of HSC development.

Ohbo, K. and S. Tomizawa (2015). "Epigenetic regulation in stem cell development, cell fate conversion, and reprogramming." Biomol Concepts **6**(1): 1-9.

Stem cells are identified classically by an in vivo transplantation assay plus additional characterization, such as marker analysis, linage-tracing and in vitro/ex vivo differentiation assays. Stem cell lines have been derived, in vitro, from adult tissues, the inner cell mass (ICM), epiblast, and male germ stem cells, providing intriguing insight into stem cell biology, plasticity, heterogeneity, metastable state, and the pivotal point at which stem cells irreversibly differentiate to non-stem cells. During the past decade, strategies for manipulating cell fate have revolutionized our understanding about the basic concept of cell differentiation: stem cell lines can be established by introducing transcription factors, as with the case for iPSCs, revealing some of the molecular interplay of key factors during the course of phenotypic changes. In addition to de-differentiation approaches for establishing stem cells, another method has been developed whereby induced expression of certain transcription factors and/or micro RNAs artificially converts differentiated cells from one committed lineage to another; notably, these cells need not transit through a stem/progenitor state. The molecular cues guiding such cell fate conversion and reprogramming remain largely unknown. As differentiation and de-differentiation are directly linked to epigenetic changes, we overview cell fate decisions, and associated gene and epigenetic regulations.

Ohmura, M., et al. (2004). "Spatial analysis of germ stem cell development in Oct-4/EGFP transgenic mice." Arch Histol Cytol **67**(4): 285-296.

Questions persist regarding male germ stem cells and how they mature during the prespermatogenic period of testicular development. We successfully labeled the prespermatogonia with green fluorescence protein (GFP) by using Oct-4 enhancer/promoter. This study shows that GFP was specifically expressed in prespermatogonia, spermatogonia and spermatids that faithfully reproduce the endogenous expression of Oct-4. Histochemical analysis revealed that most of the TRA98-positive gonocytes are also positive for GFP. However, the frequency of GFP expressing cells out of TRA98 expressing cells decreased together with the maturation of gonocytes in the first week after birth. To compare the stem cell activity between GFP-positive and -negative populations, we performed a transplantation of sorted cells into testes from an individual population. Colonization efficiency of germ cells from a GFP-positive population resulted in a 30-fold increase in colonization compared with a GFP-negative population. Since the expression of Oct-4 in prespermtogonia correlates well with the stem activity, Oct-4 might be a crucial molecule in the stem cell property of spermatogonia but not in cell survival.

Okada, M., et al. (2017). "A balance of Mad and Myc expression dictates larval cell apoptosis and adult stem cell development during Xenopus intestinal metamorphosis." Cell Death Dis **8**(5): e2787.

The Myc/Mad/Max network has long been shown to be an important factor in regulating cell proliferation, death and differentiation in diverse cell types. In general, Myc-Max heterodimers activate target gene expression to promote cell proliferation, although excess of c-Myc can also induce apoptosis. In contrast, Mad competes against Myc to form Mad-Max heterodimers that bind to the same target genes to repress their expression and promote differentiation.

The role of the Myc/Mad/Max network during vertebrate development, especially, the so-called postembryonic development, a period around birth in mammals, is unclear. Using thyroid hormone (T3)-dependent Xenopus metamorphosis as a model, we show here that Mad1 is induced by T3 in the intestine during metamorphosis when larval epithelial cell death and adult epithelial stem cell development take place. More importantly, we demonstrate that Mad1 is expressed in the larval cells undergoing apoptosis, whereas c-Myc is expressed in the proliferating adult stem cells during intestinal metamorphosis, suggesting that Mad1 may have a role in cell death during development. By using transcription activator-like effector nuclease-mediated gene-editing technology, we have generated Mad1 knockout Xenopus animals. This has revealed that Mad1 is not essential for embryogenesis or metamorphosis. On the other hand, consistent with its spatiotemporal expression profile, Mad1 knockout leads to reduced larval epithelial apoptosis but surprisingly also results in increased adult stem cell proliferation. These findings not only reveal a novel role of Mad1 in regulating developmental cell death but also suggest that a balance of Mad and Myc controls cell fate determination during adult organ development.

Peeters, M., et al. (2009). "Ventral embryonic tissues and Hedgehog proteins induce early AGM hematopoietic stem cell development." Development **136**(15): 2613-2621.

Hematopoiesis is initiated in several distinct tissues in the mouse conceptus. The aorta-gonad-mesonephros (AGM) region is of particular interest, as it autonomously generates the first adult type hematopoietic stem cells (HSCs). The ventral position of hematopoietic clusters closely associated with the aorta of most vertebrate embryos suggests a polarity in the specification of AGM HSCs. Since positional information plays an important role in the embryonic development of several tissue systems, we tested whether AGM HSC induction is influenced by the surrounding dorsal and ventral tissues. Our explant culture results at early and late embryonic day 10 show that ventral tissues induce and increase AGM HSC activity, whereas dorsal tissues decrease it. Chimeric explant cultures with genetically distinguishable AGM and ventral tissues show that the increase in HSC activity is not from ventral tissue-derived HSCs, precursors or primordial germ cells (as was previously suggested). Rather, it is due to instructive signaling from ventral tissues. Furthermore, we identify Hedgehog protein (s) as an HSC inducing signal.

Peltz, L., et al. (2012). "Resveratrol exerts dosage and duration dependent effect on human mesenchymal stem cell development." PLoS One **7**(5): e37162.

Studies in the past have illuminated the potential benefit of resveratrol as an anticancer (pro-apoptosis) and life-extending (pro-survival) compound. However, these two different effects were observed at different concentration ranges. Studies of resveratrol in a wide range of concentrations on the same cell type are lacking, which is necessary to comprehend its diverse and sometimes contradictory cellular effects. In this study, we examined the effects of resveratrol on cell self-renewal and differentiation of human mesenchymal stem cells (hMSCs), a type of adult stem cells that reside in a number of tissues, at concentrations ranging from 0.1 to 10 microM after both short- and long-term exposure. Our results reveal that at 0.1 microM, resveratrol promotes cell self-renewal by inhibiting cellular senescence, whereas at 5 microM or above, resveratrol inhibits cell self-renewal by increasing senescence rate, cell doubling time and S-phase cell cycle arrest. At 1 microM, its effect on cell self-renewal is minimal but after long-term exposure it exerts an inhibitory effect, accompanied with increased senescence rate. At all concentrations, resveratrol promotes osteogenic differentiation in a dosage dependent manner, which is offset by its inhibitory effect on cell self-renewal at high concentrations. On the contrary, resveratrol suppresses adipogenic differentiation during short-term exposure but promotes this process after long-term exposure. Our study implicates that resveratrol is the most beneficial to stem cell development at 0.1 microM and caution should be taken in applying resveratrol as an anticancer therapeutic agent or nutraceutical supplement due to its dosage dependent effect on hMSCs.

Pimanda, J. E. and B. Gottgens (2010). "Gene regulatory networks governing haematopoietic stem cell development and identity." Int J Dev Biol **54**(6-7): 1201-1211.

Development can be viewed as a dynamic progression through regulatory states which characterise the various cell types within a given differentiation cascade. To understand the progression of regulatory states that define the origin and subsequent development of haematopoietic stem cells, the first imperative is to understand the ontogeny of haematopoiesis. We are fortunate that the ontogeny of blood development is one of the best characterized mammalian developmental systems. However, the field is still in its infancy with regard to the reconstruction of gene regulatory networks and their interactions with cell signalling cascades that drive a mesodermal progenitor to adopt the identity of a

haematopoietic stem cell and beyond. Nevertheless, a framework to dissect these networks and comprehend the logic of its circuitry does exist and although they may not as yet be available, a sense for the tools that will be required to achieve this aim is also emerging. In this review we cover the fundamentals of network architecture, methods used to reconstruct networks, current knowledge of haematopoietic and related transcriptional networks, current challenges and future outlook.

Ponting, I. L. and T. M. Dexter (1988). "The role of colony stimulating factors, interleukin 1 and stromal extracellular matrix in the regulation of stem cell development." Behring Inst Mitt (83): 48-55.

In recent years increasing attention has been paid to elucidating the way in which stem cell development is regulated. There have been essentially two in vitro approaches to the problem. In the first approach, haemopoietic stem cells have been cultured on adherent bone marrow stroma (long-term bone marrow culture): this has revealed the importance of stromal-stem cell interactions. In the second approach haemopoietic cells have been cultured in short-term clonogenic systems: this has shown the importance of a group of growth factors, the colony stimulating factors (CSFs). Work carried out by our group has provided a link between these two systems, as heparan sulphate a component of the stromal extra-cellular matrix is able to bind CSFs and present them to the stem cells in an active form. Furthermore, we have shown that synergistic interactions between combinations of CSFs, or between CSFs and IL-1 have a potentially critical role to play in stem cell development, due to their ability to stimulate a proportion of IL-3 responsive, multi-potential cells. This provides a possible explanation for the growth and development of stem cells in association with stromal cells in the apparent absence of IL-3 production by stroma.

Prokopi, M., et al. (2014). "The Secret Role of microRNAs in Cancer Stem Cell Development and Potential Therapy: A Notch-Pathway Approach." Front Oncol **4**: 389.

MicroRNAs (miRNAs) have been implicated in the development of some if not all cancer types and have been identified as attractive targets for prognosis, diagnosis, and therapy of the disease. miRNAs are a class of small non-coding RNAs (20-22 nt in length) that bind imperfectly to the 3'-untranslated region of target mRNA regulating gene expression. Aberrantly expressed miRNAs in cancer, sometimes known as oncomiRNAs, have been shown to play a major role in oncogenesis, metastasis, and drug resistance. Amplification of oncomiRNAs during cancer development correlates with the silencing of tumor suppressor genes; on the other hand, down-regulation of miRNAs has also been observed in cancer and cancer stem cells (CSCs). In both cases, miRNA regulation is inversely correlated with cancer progression. Growing evidence indicates that miRNAs are also involved in the metastatic process by either suppressing or promoting metastasis-related genes leading to the reduction or activation of cancer cell migration and invasion processes. In particular, circulating miRNAs (vesicle-encapsulated or non-encapsulated) have significant effects on tumorigenesis: membrane-particles, apoptotic bodies, and exosomes have been described as providers of a cell-to-cell communication system transporting oncogenic miRNAs from tumors to neighboring cells and distant metastatic sites. It is hypothesized that miRNAs control cancer development in a traditional manner, by regulating signaling pathways and factors. In addition, recent developments indicate a non-conventional mechanism of cancer regulation by stem cell reprograming via a regulatory network consisting of miRNAs and Wnt/beta-catenin, Notch, and Hedgehog signaling pathways, all of which are involved in controlling stem cell functions of CSCs. In this review, we focus on the role of miRNAs in the Notch-pathway and how they regulate CSC self-renewal, differentiation and tumorigenesis by direct/indirect targeting of the Notch-pathway.

Ruiz-Herguido, C., et al. (2012). "Hematopoietic stem cell development requires transient Wnt/beta-catenin activity." J Exp Med **209**(8): 1457-1468.

Understanding how hematopoietic stem cells (HSCs) are generated and the signals that control this process is a crucial issue for regenerative medicine applications that require in vitro production of HSC. HSCs emerge during embryonic life from an endothelial-like cell population that resides in the aorta-gonad-mesonephros (AGM) region. We show here that beta-catenin is nuclear and active in few endothelial nonhematopoietic cells closely associated with the emerging hematopoietic clusters of the embryonic aorta during mouse development. Importantly, Wnt/beta-catenin activity is transiently required in the AGM to generate long-term HSCs and to produce hematopoietic cells in vitro from AGM endothelial precursors. Genetic deletion of beta-catenin from the embryonic endothelium stage (using VE-cadherin-Cre recombinase), but not from embryonic hematopoietic cells (using Vav1-Cre), precludes progression of mutant cells toward the hematopoietic lineage; however, these mutant cells still contribute to the adult endothelium. Together, those findings indicate that Wnt/beta-catenin activity

is needed for the emergence but not the maintenance of HSCs in mouse embryos.

Schlaeger, T. M., et al. (2005). "Tie2Cre-mediated gene ablation defines the stem-cell leukemia gene (SCL/tal1)-dependent window during hematopoietic stem-cell development." Blood **105**(10): 3871-3874.

The stem-cell leukemia gene (SCL/tal1) is essential for the formation of all blood lineages. SCL is first expressed in mesodermal cells that give rise to embryonic blood cells, and continues to be expressed in fetal and adult hematopoietic stem cells (HSCs). However, SCL is not required for the maintenance of established long-term repopulating (LTR) HSCs in the adult. The time point at which HSC development becomes SCL independent has not been defined. Tyrosine kinase with immunoglobulin and epidermal growth factor homology domains-2 (Tie2) expression appears in hemogenic and vasculogenic sites shortly after SCL. We therefore used the Tie2Cre mouse to inactivate SCL early during embryonic and fetal hematopoiesis. Tie2Cre completely inactivated SCL in yolk sac, the aortagonad-mesonephros (AGM) region, and fetal liver hematopoietic cells and circulating blood cells. However, the fetal liver was colonized by functional LTR-HSCs. Yet SCL remained crucial for proper differentiation of both primitive and definitive red cells and megakaryocytes. These results indicate that the SCL-dependent phase of HSC development ends before Tie2Cre-mediated gene ablation becomes effective.

Schutte, J., et al. (2012). "Establishing the stem cell state: insights from regulatory network analysis of blood stem cell development." Wiley Interdiscip Rev Syst Biol Med **4**(3): 285-295.

Transcription factors (TFs) have long been recognized as powerful regulators of cell-type identity and differentiation. As TFs function as constituents of regulatory networks, identification and functional characterization of key interactions within these wider networks will be required to understand how TFs exert their powerful biological functions. The formation of blood cells (hematopoiesis) represents a widely used model system for the study of cellular differentiation. Moreover, specific TFs or groups of TFs have been identified to control the various cell fate choices that must be made when blood stem cells differentiate into more than a dozen distinct mature blood lineages. Because of the relative ease of accessibility, the hematopoietic system represents an attractive experimental system for the development of regulatory network models. Here, we review the modeling efforts carried out to date, which have already provided new insights into the molecular control of blood cell development. We also explore potential areas of future study such as the need for new high-throughput technologies and a focus on studying dynamic cellular systems. Many leukemias arise as the result of mutations that cause transcriptional dysregulation, thus suggesting that a better understanding of transcriptional control mechanisms in hematopoiesis is of substantial biomedical relevance. Moreover, lessons learned from regulatory network analysis in the hematopoietic system are likely to inform research on less experimentally tractable tissues.

Sengupta, D. and S. Kar (2018). "Deciphering the Dynamical Origin of Mixed Population during Neural Stem Cell Development." Biophys J **114**(4): 992-1004.

Neural stem cells (NSCs) often give rise to a mixed population of cells during differentiation. However, the dynamical origin of these mixed states is poorly understood. In this article, our mathematical modeling study demonstrates that the bone morphogenetic protein 2 (BMP2) mediated disparate differentiation dynamics of NSCs in central and peripheral nervous systems essentially function through two distinct bistable switches that are mutually interconnected via a mushroom-like bifurcation. Stochastic simulations of the model reveal that the mixed population originates due to the existence of these bistable switching regulations and that the maintenance of such mixed states depends on the level of stochastic fluctuations of the system. It further demonstrates that due to extrinsic variability, cells in an NSC population can dynamically transit from mushroom to a unique isola kind of bifurcation state, which essentially extends the range of the BMP2-driven mixed population state during differentiation. Importantly, the model predicts that by individually altering the expression level of key regulatory proteins, the NSCs can be converted entirely to a preferred phenotype for BMP2 doses that previously resulted in a mixed population. Our findings show that efficient neuronal regeneration can be achieved by systematically maneuvering the differentiation dynamics.

Shearman, M. S., et al. (1993). "Haemopoietic stem cell development to neutrophils is associated with subcellular redistribution and differential expression of protein kinase C subspecies." J Cell Sci **104 (Pt 1)**: 173-180.

Multipotential FDCP-Mix A4 (A4) cells can be induced either to self-renew or to differentiate and develop into mature neutrophils in liquid culture, depending on the haemopoietic growth factors with which they are cultured. When cultured in low concentrations of interleukin 3 (IL-3, 1 unit/ml)) plus Granulocyte Macrophage Colony Stimulating Factor

(GM-CSF) and Granulocyte-CSF (G-CSF), A4 cells proliferate with accompanying development to form cells which resemble mature, postmitotic neutrophils. The presence of high concentrations of IL-3 (100 units/ml) blocks the development of A4 cells even in the presence of GM-CSF plus G-CSF. A4 cell development to neutrophils is accompanied by major changes in the expression of protein kinase C (PKC) subspecies in these cells. The predominant subspecies present in multipotent A4 cells, as judged by direct chromatographic analysis, was the type III enzyme (alpha) subspecies, whereas in mature A4 cell neutrophils, the type II (beta I + beta II) enzymes were predominant. Phorbol esters added to immature A4 cells resulted in a proliferative response, but when added to postmitotic A4 cells resembling neutrophils they elicited a large increase in reactive oxygen intermediate production. This suggests that the type III (alpha) subspecies may mediate proliferative responses in stem cells, whilst the type II (beta I + beta II) enzymes are more important for the mature cell functions of postmitotic neutrophils. In cultures containing IL-3 (100 units/ml) both the type III, and also the type II subspecies were predominantly membrane-associated for prolonged periods (> 24 hours). (ABSTRACT TRUNCATED AT 250 WORDS)

Shinde, V., et al. (2017). "Definition of transcriptome-based indices for quantitative characterization of chemically disturbed stem cell development: introduction of the STOP-Toxukn and STOP-Toxukk tests." Arch Toxicol **91**(2): 839-864.

Stem cell-based in vitro test systems can recapitulate specific phases of human development. In the UKK test system, human pluripotent stem cells (hPSCs) randomly differentiate into cells of the three germ layers and their derivatives. In the UKN1 test system, hPSCs differentiate into early neural precursor cells. During the normal differentiation period (14 days) of the UKK system, 570 genes [849 probe sets (PSs)] were regulated >fivefold; in the UKN1 system (6 days), 879 genes (1238 PSs) were regulated. We refer to these genes as 'developmental genes'. In the present study, we used genome-wide expression data of 12 test substances in the UKK and UKN1 test systems to understand the basic principles of how chemicals interfere with the spontaneous transcriptional development in both test systems. The set of test compounds included six histone deacetylase inhibitors (HDACis), six mercury-containing compounds ('mercurials') and thalidomide. All compounds were tested at the maximum non-cytotoxic concentration, while valproic acid and thalidomide were additionally tested over a wide range of concentrations. In total, 242 genes (252 PSs) in the UKK test system and 793 genes (1092 PSs) in the UKN1 test system were deregulated by the 12 test compounds. We identified sets of 'diagnostic genes' appropriate for the identification of the influence of HDACis or mercurials. Test compounds that interfered with the expression of developmental genes usually antagonized their spontaneous development, meaning that up-regulated developmental genes were suppressed and developmental genes whose expression normally decreases were induced. The fraction of compromised developmental genes varied widely between the test compounds, and it reached up to 60 %. To quantitatively describe disturbed development on a genome-wide basis, we recommend a concept of two indices, 'developmental potency' (D p) and 'developmental index' (D i), whereby D p is the fraction of all developmental genes that are up- or down-regulated by a test compound, and D i is the ratio of overrepresentation of developmental genes among all genes deregulated by a test compound. The use of D i makes hazard identification more sensitive because some compounds compromise the expression of only a relatively small number of genes but have a high propensity to deregulate developmental genes specifically, resulting in a low D p but a high D i. In conclusion, the concept based on the indices D p and D i offers the possibility to quantitatively express the propensity of test compounds to interfere with normal development.

Sinden, D., et al. (2012). "Jak-STAT regulation of cyst stem cell development in the Drosophila testis." Dev Biol **372**(1): 5-16.

Establishment and maintenance of functional stem cells is critical for organ development and tissue homeostasis. Little is known about the mechanisms underlying stem establishment during organogenesis. Drosophila testes are among the most thoroughly characterized systems for studying stem cell behavior, with germline stem cells (GSCs) and somatic cyst stem cells (CySCs) cohabiting a discrete stem cell niche at the testis apex. GSCs and CySCs are arrayed around hub cells that also comprise the niche and communication between hub cells, GSCs, and CySCs regulates the balance between stem cell maintenance and differentiation. Recent data has shown that functional, asymmetrically dividing GSCs are first established at approximately 23 h after egg laying during Drosophila testis morphogenesis (Sheng et al., 2009). This process correlates with coalescence of the hub, but development of CySCs from somatic gonadal precursors (SGPs) was not examined. Here, we show that functional CySCs are present at the time of GSC establishment, and that Jak-STAT signaling is necessary and sufficient for CySC maintenance shortly thereafter. Furthermore, hyper-activation of Jak in

CySCs promotes expansion of the GSC population, while ectopic Jak activation in the germline induces GSC gene expression in GSC daughter cells but does not prevent spermatogenic differentiation. Together, these observations indicate that, similar to adult testes, Jak-STAT signaling from the hub acts on both GSCs and CySC to regulate their development and differentiation, and that additional signaling from CySCs to the GSCs play a dominant role in controlling GSC maintenance during niche formation.

Slaidina, M. and R. Lehmann (2014). "Translational control in germline stem cell development." J Cell Biol **207**(1): 13-21.

Stem cells give rise to tissues and organs during development and maintain their integrity during adulthood. They have the potential to self-renew or differentiate at each division. To ensure proper organ growth and homeostasis, self-renewal versus differentiation decisions need to be tightly controlled. Systematic genetic studies in Drosophila melanogaster are revealing extensive regulatory networks that control the switch between stem cell self-renewal and differentiation in the germline. These networks, which are based primarily on mutual translational repression, act via interlocked feedback loops to provide robustness to this important fate decision.

Small, D. H., et al. (2014). "beta-Amyloid precursor protein: function in stem cell development and Alzheimer's disease brain." Neurodegener Dis **13**(2-3): 96-98.

Stem cell therapy may be a suitable approach for the treatment of many neurodegenerative diseases. However, one major impediment to the development of successful cell-based therapies is our limited understanding of the mechanisms that instruct neural stem cell behaviour, such as proliferation and cell fate specification. The beta-amyloid precursor protein (APP) of Alzheimer's disease (AD) may play an important role in neural stem cell proliferation and differentiation. Our recent work shows that in vitro, APP stimulates neural stem or progenitor cell proliferation and neuronal differentiation. The effect on proliferation is mediated by an autocrine factor that we have identified as cystatin C. As cystatin C expression is also reported to inhibit the development of amyloid pathology in APP transgenic mice, our finding has implications for the possible use of cystatin C for the therapy of AD.

Sommer, L. (2005). "Checkpoints of melanocyte stem cell development." Sci STKE **2005**(298): pe42.

The bulge region of the adult hair follicle contains the niches for both epithelial and melanocyte stem cells. Recent evidence suggests that the development of melanocyte stem cells is controlled by a complex network of transcription factors, including Pax3, Sox10, and Mitf, and of regulatory extracellular cues such as Wnt. However, additional players are likely to be involved. It will be intriguing to identify these signals and to elucidate whether and how neighboring epithelial stem cells influence the balance between melanocyte stem cell maintenance and differentiation.

Stubbs, M. C. and S. A. Armstrong (2007). "Therapeutic implications of leukemia stem cell development." Clin Cancer Res **13**(12): 3439-3442.

Acute myelogenous leukemias, and perhaps many other cancers, are maintained by a population of cancer stem cells that can regenerate themselves as well as give rise to more differentiated and less proliferative cells that constitute the bulk of the disease. Recent discoveries have shed light on both the nature of leukemia stem cells (LSC) and their cells of origin. Here, we review which hematopoietic cells could give rise to LSC, and the phenotype of fully developed LSC. The perturbed developmental pathways and cellular context of LSC development have implications for the development of new therapeutic approaches.

Sun, G., et al. (2014). "Epigenetic regulation of thyroid hormone-induced adult intestinal stem cell development during anuran metamorphosis." Cell Biosci **4**: 73.

Epigenetic modifications of histones are emerging as key factors in gene regulation by diverse transcription factors. Their roles during vertebrate development and pathogenesis are less clear. The causative effect of thyroid hormone (T3) on amphibian metamorphosis and the ability to manipulate this process for molecular and genetic studies have led to the demonstration that T3 receptor (TR) is necessary and sufficient for Xenopus metamorphosis, a process that resembles the postembryonic development (around birth) in mammals. Importantly, analyses during metamorphosis have provided some of the first in vivo evidence for the involvement of histone modifications in gene regulation by TR during vertebrate development. Furthermore, expression and functional studies suggest that various histone modifying epigenetic enzymes likely participate in multiple steps during the formation of adult intestinal stem cells during metamorphosis. The similarity between intestinal remodeling and the maturation of the mammalian intestine around birth when T3 levels are high suggests conserved roles for the epigenetic enzymes in mammalian adult intestinal stem cell development and/or proliferation.

Sun, G., et al. (2013). "Expression profiling of intestinal tissues implicates tissue-specific genes and pathways essential for thyroid hormone-induced adult stem cell development." Endocrinology **154**(11): 4396-4407.

The study of the epithelium during development in the vertebrate intestine touches upon many contemporary aspects of biology: to name a few, the formation of the adult stem cells (ASCs) essential for the life-long self-renewal and the balance of stem cell activity for renewal vs cancer development. Although extensive analyses have been carried out on the property and functions of the adult intestinal stem cells in mammals, little is known about their formation during development due to the difficulty of manipulating late-stage, uterus-enclosed embryos. The gastrointestinal tract of the amphibian Xenopus laevis is an excellent model system for the study of mammalian ASC formation, cell proliferation, and differentiation. During T3-dependent amphibian metamorphosis, the digestive tract is extensively remodeled from the larval to the adult form for the adaptation of the amphibian from its aquatic herbivorous lifestyle to that of a terrestrial carnivorous frog. This involves de novo formation of ASCs that requires T3 signaling in both the larval epithelium and nonepithelial tissues. To understand the underlying molecular mechanisms, we have characterized the gene expression profiles in the epithelium and nonepithelial tissues by using cDNA microarrays. Our results revealed that T3 induces distinct tissue-specific gene regulation programs associated with the remodeling of the intestine, particularly the formation of the ASCs, and further suggested the existence of potentially many novel stem cell-associated genes, at least in the intestine during development.

Sun, G. and Y. B. Shi (2012). "Thyroid hormone regulation of adult intestinal stem cell development: mechanisms and evolutionary conservations." Int J Biol Sci **8**(8): 1217-1224.

The adult mammalian intestine has long been used as a model to study adult stem cell function and tissue renewal as the intestinal epithelium is constantly undergoing self-renewal throughout adult life. This is accomplished through the proliferation and subsequent differentiation of the adult stem cells located in the crypt. The development of this self-renewal system is, however, poorly understood. A number of studies suggest that the formation/maturation of the adult intestine is conserved in vertebrates and depends on endogenous thyroid hormone (T3). In amphibians such as Xenopus laevis, the process takes place during metamorphosis, which is totally dependent upon T3 and resembles postembryonic development in mammals when T3 levels are also high. During metamorphosis, the larval epithelial cells in the tadpole intestine undergo apoptosis and concurrently, adult epithelial stem/progenitor cells are formed de novo, which subsequently lead to the formation of a trough-crest axis of the epithelial fold in the frog, resembling the crypt-villus axis in the adult mammalian intestine. Here we will review some recent molecular and genetic studies that support the conservation of the development of the adult intestinal stem cells in vertebrates. We will discuss the mechanisms by which T3 regulates this process via its nuclear receptors.

Takakura, N. (1999). "[The molecular mechanism of hematopoietic stem cell development in the AGM region]." Rinsho Ketsueki **40**(4): 262-267.

Teif, V. B., et al. (2014). "Nucleosome repositioning links DNA (de)methylation and differential CTCF binding during stem cell development." Genome Res **24**(8): 1285-1295.

During differentiation of embryonic stem cells, chromatin reorganizes to establish cell type-specific expression programs. Here, we have dissected the linkages between DNA methylation (5mC), hydroxymethylation (5hmC), nucleosome repositioning, and binding of the transcription factor CTCF during this process. By integrating MNase-seq and ChIP-seq experiments in mouse embryonic stem cells (ESC) and their differentiated counterparts with biophysical modeling, we found that the interplay between these factors depends on their genomic context. The mostly unmethylated CpG islands have reduced nucleosome occupancy and are enriched in cell type-independent binding sites for CTCF. The few remaining methylated CpG dinucleotides are preferentially associated with nucleosomes. In contrast, outside of CpG islands most CpGs are methylated, and the average methylation density oscillates so that it is highest in the linker region between nucleosomes. Outside CpG islands, binding of TET1, an enzyme that converts 5mC to 5hmC, is associated with labile, MNase-sensitive nucleosomes. Such nucleosomes are poised for eviction in ESCs and become stably bound in differentiated cells where the TET1 and 5hmC levels go down. This process regulates a class of CTCF binding sites outside CpG islands that are occupied by CTCF in ESCs but lose the protein during differentiation. We rationalize this cell type-dependent targeting of CTCF with a quantitative biophysical model of competitive binding with the histone octamer, depending on the TET1, 5hmC, and 5mC state.

Teif, V. B., et al. (2012). "Genome-wide nucleosome positioning during embryonic stem cell development." Nat Struct Mol Biol **19**(11): 1185-1192.

We determined genome-wide nucleosome occupancies in mouse embryonic stem cells and their neural progenitor and embryonic fibroblast counterparts to assess features associated with nucleosome positioning during lineage commitment. Cell-type- and protein-specific binding preferences of transcription factors to sites with either low (Myc, Klf4 and Zfx) or high (Nanog, Oct4 and Sox2) nucleosome occupancy as well as complex patterns for CTCF were identified. Nucleosome-depleted regions around transcription start and transcription termination sites were broad and more pronounced for active genes, with distinct patterns for promoters classified according to CpG content or histone methylation marks. Throughout the genome, nucleosome occupancy was correlated with certain histone methylation or acetylation modifications. In addition, the average nucleosome repeat length increased during differentiation by 5-7 base pairs, with local variations for specific regions. Our results reveal regulatory mechanisms of cell differentiation that involve nucleosome repositioning.

Teitell, M. A. and H. K. Mikkola (2006). "Transcriptional activators, repressors, and epigenetic modifiers controlling hematopoietic stem cell development." Pediatr Res **59**(4 Pt 2): 33r-39r.

Hematopoietic stem cells (HSCs) are pluripotent cells that give rise to all of the circulating blood cell types. Their unique ability to self-renew while generating differentiated daughter cells permits HSCs to sustain blood cell production throughout life. In mammals, the pool of HSCs shifts from early sites in the aorta-gonad-mesonephros region and the placenta to the fetal liver and ultimately bone marrow. During the past decade, a map of transcriptional activators and repressors that regulate gene expression in HSCs, their precursors and their progeny, at distinct stages of development has been drafted. These factors control a program that first establishes the pool of HSCs in the fetus, and later guides decisions between quiescence, self-renewal, and lineage commitment with progressive differentiation to maintain homeostasis. Continuing studies of the regulatory mechanisms that control HSC gene expression followed by the identification of specific loci that are activated or silenced during the life of an HSC will help to further elucidate longstanding issues in HSC decisions to self-renew or to differentiate, and to define the origins of and connections between distinct HSC pools and their precursors.

Thurmond, T. S., et al. (2000). "Role of estrogen receptor alpha in hematopoietic stem cell development and B lymphocyte maturation in the male mouse." Endocrinology **141**(7): 2309-2318.

Although estrogens and estrogen receptors (ERs) are known to function in the male brain and reproductive tract, few studies have evaluated their involvement in the male hematopoietic and immune systems. This study was undertaken to determine the role of ERalpha in hematopoietic progenitor and B lymphocyte maturation. ERalpha knockout (ER-/-), wild-type (ER+/+), and radiation chimeric (ERalpha positive or negative in either nonhematopoietic or hematopoietic elements, or both) male mice were used to determine target tissues. ER-/- and ER+/+ animals showed similar hematopoietic progenitor profiles, but the ER-/- animals had fewer cells in all bone marrow B lymphocyte subpopulations. Animals receiving a pharmacological dose (5 mg/kg BW) of 17beta-estradiol (E2) with both elements, ER+/+, had decreased early hematopoietic progenitors and a shift toward a mature B cell subpopulation, whereas animals with both elements, ER-/-, showed changes only in early hematopoietic progenitors. Hematopoietic element ER+/+ animals exhibited greater E2-induced hematopoietic progenitor and B lymphocyte alterations than those having only nonhematopoietic ERalpha. These data indicate that 1) ERalpha is not necessary for regulating male mouse normal hematopoietic progenitor cell proportions, but is involved in B cell regulation; and 2) ERalpha in hematopoietic elements is predominantly responsible for mediating E2-induced hematopoietic and B cell changes.

Tucker, M. R., et al. (2008). "Vascular signalling mediated by ZWILLE potentiates WUSCHEL function during shoot meristem stem cell development in the Arabidopsis embryo." Development **135**(17): 2839-2843.

Stem cells are maintained in an undifferentiated state by signals from their microenvironment, the stem cell niche. Despite its central role for organogenesis throughout the plant's life, little is known about how niche development is regulated in the Arabidopsis embryo. Here we show that, in the absence of functional ZWILLE (ZLL), which is a member of the ARGONAUTE (AGO) family, stem cell-specific expression of the signal peptide gene CLAVATA3 (CLV3) is not maintained despite increased levels of the homeodomain transcription factor WUSCHEL (WUS), which is expressed in the organising centre (OC) of the niche and normally promotes stem cell identity. Tissue-specific expression indicates that ZLL acts to maintain the stem cells from the neighbouring vascular primordium, providing direct evidence for a non-cell-autonomous mechanism. Furthermore, mutant and marker gene analyses suggest that during shoot meristem formation, ZLL functions in a similar manner but in a sequential order with its close

homologue AGO1, which mediates RNA interference. Thus, WUS-dependent OC signalling to the stem cells is promoted by AGO1 and subsequently maintained by a provascular ZLL-dependent signalling pathway.

Ungerer, P., et al. (2012). "Unravelling the evolution of neural stem cells in arthropods: notch signalling in neural stem cell development in the crustacean Daphnia magna." Dev Biol **371**(2): 302-311.

The genetic regulatory networks controlling major developmental processes seem to be conserved in bilaterians regardless of an independent or a common origin of the structures. This has been explained by the employment of a genetic toolkit that was repeatedly used during bilaterian evolution to build the various forms and body plans. However, it is not clear how genetic networks were incorporated into the formation of novel structures and how homologous genes can regulate the disparate morphological processes. Here we address this question by analysing the role of Notch signalling, which is part of the bilaterian toolkit, in neural stem cell evolution in arthropods. Within arthropods neural stem cells have evolved in the last common ancestor of insects and crustaceans (Tetraconata). We analyse here for the first time the role of Notch signalling in a crustacean, the branchiopod Daphnia magna, and show that it is required in neural stem cells for regulating the time of neural precursor production and for binary cell fate decisions in the ventral neuroectoderm. The function of Notch signalling has diverged in the ventral neuroectoderm of insects and crustaceans accompanied by changes in the morphogenetic processes. In the crustacean, Notch controlled mechanisms of neuroblast regulation have evolved that are surprisingly similar to vertebrates and thus present a remarkable case of parallel evolution. These new data on a representative of crustaceans complete the arthropod data set on Notch signalling in the nervous system and allow for reconstructing how the Notch signalling pathway has been co-opted from pre-existing structures to the development of the evolving neural stem cells in the Tetraconata ancestor.

Vadakke Madathil, S., et al. (2014). "Klotho deficiency disrupts hematopoietic stem cell development and erythropoiesis." Am J Pathol **184**(3): 827-841.

Klotho deficiency is a characteristic feature of chronic kidney disease in which anemia and cardiovascular complications are prevalent. Disruption of the Klotho gene in mice results in hypervitaminosis D and a syndrome resembling accelerated aging that includes osteopenia and vascular calcifications. Given that the bone microenvironment and its cellular components considerably influence hematopoiesis, in the present study, we addressed the in vivo role of klotho in blood cell formation and differentiation. Herein, we report that genetic ablation of Klotho in mice results in a significant increase in erythropoiesis and a decrease in the hematopoietic stem cell pool size in the bone marrow, leading to impaired hematopoietic stem cell homing in vivo. Our data also suggest that high vitamin D levels are only partially responsible for these hematopoietic changes in Klotho (-/-) mice. Importantly, we found similar hematopoietic abnormalities in Klotho (-/-) fetal liver cells, suggesting that the effects of klotho in hematopoietic stem cell development are independent of the bone microenvironment. Finally, injection of klotho protein results in hematopoietic changes opposite to the ones observed in Klotho (-/-) mice. These observations unveil a novel role for the antiaging hormone klotho in the regulation of prenatal and postnatal hematopoiesis and provide new insights for the development of therapeutic strategies targeting klotho to treat hematopoietic disorders associated with aging.

Vogel-Hopker, A., et al. (2012). "Co-opting functions of cholinesterases in neural, limb and stem cell development." Protein Pept Lett **19**(2): 155-164.

Acetylcholinesterase (AChE) is a most remarkable protein, not only because it is one of the fastest enzymes in nature, but also since it appears in many molecular forms and is regulated by elaborate genetic networks. As revealed by sensitive histochemical procedures, AChE is expressed specifically in many tissues during development and in many mature organisms, as well as in healthy and diseased states. Therefore it is not surprising that there has been a long-standing search for additional, "non-classical" functions of cholinesterases (ChEs). In principle, AChE could either act nonenzymatically, e.g. exerting cell adhesive roles, or, alternatively, it could work within the frame of classic cholinergic systems, but in non-neural tissues. AChE might be considered a highly co-opting protein, since possibly it combines such various functions within one molecule. By presenting four different developmental cases, we here review i) the expression of ChEs in the neural tube and their close relation to cell proliferation and differentiation, ii) that AChE expression reflects a polycentric brain development, iii) the retina as a model for AChE functioning in neural network formation, and iv) nonneural ChEs in limb development and mature bones. Also, possible roles of AChE in neuritic growth and of cholinergic regulations in stem cells are briefly outlined.

Wang, L., et al. (2013). "Fev regulates hematopoietic stem cell development via ERK signaling." Blood **122**(3): 367-375.

Reprogramming of somatic cells to desired cell types holds great promise in regenerative medicine. However, production of transplantable hematopoietic stem cells (HSCs) in vitro by defined factors has not yet been achieved. Therefore, it is critical to fully understand the molecular mechanisms of HSC development in vivo. Here, we show that Fev, an ETS transcription factor, is a pivotal regulator of HSC development in vertebrates. In fev-deficient zebrafish embryos, the first definitive HSC population was compromised and fewer T cells were found in the thymus. Genetic and chemical analyses support a mechanism whereby Fev regulates HSC through direct regulation of ERK signaling. Blastula transplant assay demonstrates that Fev regulation of HSC development is cell autonomous. Experiments performed with purified cord blood show that fev is expressed and functions in primitive HSCs in humans, indicating its conserved role in higher vertebrates. Our data indicate that Fev-ERK signaling is essential for hemogenic endothelium-based HSC development.

Whitmill, A., et al. (2017). "Tip110 Deletion Impaired Embryonic and Stem Cell Development Involving Downregulation of Stem Cell Factors Nanog, Oct4, and Sox2." Stem Cells **35**(7): 1674-1686.

HIV-1 Tat-interacting protein of 110 kDa, Tip110, plays important roles in multiple biological processes. In this study, we aimed to characterize the function of Tip110 in embryonic development. Transgenic mice lacking expression of a functional Tip110 gene (Tip110(-/-)) died post-implantation, and Tip110(-/-) embryos exhibited developmental arrest between 8.5 and 9.5 days post coitum. However, in vitro cultures of Tip110(-/-) embryos showed that Tip110 loss did not impair embryo growth from the zygote to the blastocyst. Extended in vitro cultures of Tip110(-/-) blastocysts showed that Tip110 loss impaired both blastocyst outgrowth and self-renewal and survival of blastocyst-derived embryonic stem cells. Microarray analysis of Tip110(-/-) embryonic stem cells revealed that Tip110 loss altered differentiation, pluripotency, and cycling of embryonic stem cells and was associated with downregulation of several major stem cell factors including Nanog, Oct4, and Sox2 through a complex network of signaling pathways. Taken together, these findings document for the first time the lethal effects of complete loss of Tip110 on mammalian embryonic development and suggest that Tip110 is an important regulator of not only embryonic development but also stem cell factors. Stem Cells 2017;35:1674-1686.

Wiles, M. V. and B. M. Johansson (1999). "Embryonic stem cell development in a chemically defined medium." Exp Cell Res **247**(1): 241-248.

Vertebrate germ layer development is an intricately interwoven process with the organism operating as an integrated whole. To examine these processes we have used embryonic stem (ES) cell in vitro differentiation in a serum-free, chemically defined medium (CDM). In CDM, ES cells differentiate as embryoid bodies to neuroectoderm with upregulation of pax-6, without commensurate expression of Brachyury. In the presence of Activin A, pax-6 and Brachyury mRNAs are readily detectable, suggestive of both neuroectoderm and mesoderm formation, while in the presence of BMP-4 a process resembling primitive streak formation at the molecular level occurs. Neuroectoderm development in CDM alone is consistent with the view that this process can occur by default, as reported in Xenopus, due to the absence or sequestration of mesoderm-inducing factors. Additionally, these data show that BMP-4 alone is capable of instigating a process resembling primitive streak formation in ES cells and possibly in vivo.

Wolosin, J. M., et al. (2004). "Ocular surface epithelial and stem cell development." Int J Dev Biol **48**(8-9): 981-991.

Phenotypic features and developmental events involved in the genesis of the limbo-corneal and conjunctival epithelia are described. Together, these two epithelia define the ocular surface. They derive from a small cohort of optic vesicle-induced PAX6+ head ectodermal cells that remain on the surface following lens vesicle formation by the main PAX6+ cell cohort. Both epithelia are stratified, and display wet, non-keratinizing phenotypes. The most significant spatial feature of the limbo-corneal epithelium is the segregation of its supporting stem and early precursor cells to the limbus, the outer vascularized rim separating the cornea from the conjunctiva. These stem cells express ABCG2, a xenobiotic transporter present in stem cells from other organs. ABCG2 transport activity excludes the DNA dye Hoechst 33342, allowing the isolation of the ocular stem cells by flow cytometry, as a unique cohort known as a side 'side population'. Limbal stem cells do not form gap junctions and exist as metabolically isolated entities. Tracking of expression changes in Cx43, the main gap junction protein expressed in both the pre-epithelial ectoderm and in the mature central corneal epithelium, indicates that a limbal stem cell phenotype starts developing very soon after lens vesicle invagination, in advance of the appearance of any recognizable anatomical sub-epithelial limbal feature. Differences in Cx43 expression also reveal the very early nature of the divergence in limbo-corneal and conjunctival

lineages. The putative involvement of several early genes, including gradients of PAX6 and differences in expression patterns for members of the Id or msh gene expression regulators are reviewed.

Wu, X., et al. (2016). "Autophagy regulates Notch degradation and modulates stem cell development and neurogenesis." Nat Commun **7**: 10533.

Autophagy is a conserved, intracellular, lysosomal degradation pathway. While mechanistic aspects of this pathway are increasingly well defined, it remains unclear how autophagy modulation impacts normal physiology. It is, however, becoming clear that autophagy may play a key role in regulating developmental pathways. Here we describe for the first time how autophagy impacts stem cell differentiation by degrading Notch1. We define a novel route whereby this plasma membrane-resident receptor is degraded by autophagy, via uptake into ATG16L1-positive autophagosome-precursor vesicles. We extend our findings using a physiologically relevant mouse model with a hypomorphic mutation in Atg16L1, a crucial autophagy gene, which shows developmental retention of early-stage cells in various tissues where the differentiation of stem cells is retarded and thus reveal how modest changes in autophagy can impact stem cell fate. This may have relevance for diverse disease conditions, like Alzheimer's Disease or Crohn's Disease, associated with altered autophagy.

Yabut, O. R. and S. J. Pleasure (2016). "The Crossroads of Neural Stem Cell Development and Tumorigenesis." Opera Med Physiol **2**(3-4): 181-187.

Isolated brain tumors contain cells that exhibit stem cell features and a tissue microenvironment bearing remarkable similarities to the normal neurogenic niche. This supports the idea that neural stem (NSCs) or progenitor cells, and their progeny are the likely tumor cell (s) of origin. This prompted the investigation of the relationship between NSCs/progenitors and the initiation of tumorigenesis. These studies led to the identification of common signaling machineries underlying NSC development and tumor formation, particularly those with known roles in proliferation and cell fate determination. This review will explore the molecular mechanisms that regulate NSC behavior in the neurogenic niche of the forebrain, and how deregulation of the developmental potential of NSCs might contribute to tumorigenesis.

Zhang, C., et al. (2013). "Hematopoietic stem cell development and regulatory signaling in zebrafish." Biochim Biophys Acta **1830**(2): 2370-2374.

BACKGROUND: Hematopoietic stem cells (HSCs) are a population of multipotent cells that can self-renew and differentiate into all blood lineages. HSC development must be tightly controlled from cell fate determination to self-maintenance during adulthood. This involves a panel of important developmental signaling pathways and other factors which act synergistically within the HSC population and/or in the HSC niche. Genetically conserved processes of HSC development plus many other developmental advantages make the zebrafish an ideal model organism to elucidate the regulatory mechanisms underlying HSC programming. SCOPE OF REVIEW: This review summarizes recent progress on zebrafish HSCs with particular focus on how developmental signaling controls hemogenic endothelium-derived HSC development. We also describe the interaction of different signaling pathways during these processes. MAJOR CONCLUSIONS: The hematopoietic stem cell system is a paradigm for stem cell studies. Use of the zebrafish model to study signaling regulation of HSCs in vivo has resulted in a great deal of information concerning HSC biology in vertebrates. GENERAL SIGNIFICANCE: These new findings facilitate a better understanding of molecular mechanisms of HSC programming, and will provide possible new strategies for the treatment of HSC-related hematological diseases, such as leukemia. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

Zhang, P. and F. Liu (2011). "In vivo imaging of hematopoietic stem cell development in the zebrafish." Front Med **5**(3): 239-247.

In vivo imaging is crucial for developmental biology and can further help to follow cell development/ differentiation in normal and pathological conditions. Recent advances in optical imaging techniques has facilitated tracing of the developmental dynamics of a specific organ, tissue, or even a single cell. The zebrafish is an excellent model for imaging of hematopoiesis due to its transparent embryo at early stage; moreover, different zebrafish hematopoietic stem cells (HSCs) transgenic lines have been demonstrated as very useful tools for illustrating the details of the HSC developmental process. In this review, we summarize recent studies related to the non-invasive in vivo imaging of HSC transgenics, to show that zebrafish transgenic lines are powerful tools for developmental biology and disease. At the end of the review, the perspective and some open questions in this field will be discussed.

Zhang, Y., et al. (2008). "A Gata6-Wnt pathway required for epithelial stem cell development and airway regeneration." Nat Genet **40**(7): 862-870.

Epithelial organs, including the lung, are known to possess regenerative abilities through activation of endogenous stem cell populations, but the molecular pathways regulating stem cell expansion and regeneration are not well understood. Here we show that Gata6 regulates the temporal appearance and number of bronchioalveolar stem cells (BASCs) in the lung, its absence in Gata6-null lung epithelium leading to the precocious appearance of BASCs and concurrent loss in epithelial differentiation. This expansion of BASCs was the result of a pronounced increase in canonical Wnt signaling in lung epithelium upon loss of Gata6. Expression of the noncanonical Wnt receptor Fzd2 was downregulated in Gata6 mutants and increased Fzd2 or decreased beta-catenin expression rescued, in part, the lung epithelial defects in Gata6 mutants. During lung epithelial regeneration, canonical Wnt signaling was activated in the niche containing BASCs and forced activation of Wnt signaling led to a large increase in BASC numbers. Moreover, Gata6 was required for proper lung epithelial regeneration, and postnatal loss of Gata6 led to increased BASC expansion and decreased differentiation. Together, these data demonstrate that Gata6-regulated Wnt signaling controls the balance between progenitor expansion and epithelial differentiation required for both lung development and regeneration.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Akamatsu, W., et al. (2009). "Suppression of Oct4 by germ cell nuclear factor restricts pluripotency and promotes neural stem cell development in the early neural lineage." J Neurosci 29(7): 2113-2124.
2. Baidu. http://www.baidu.com. 2018.
3. Batsivari, A., et al. (2017). "Understanding Hematopoietic Stem Cell Development through Functional Correlation of Their Proliferative Status with the Intra-aortic Cluster Architecture." Stem Cell Reports 8(6): 1549-1562.
4. Behre, G., et al. (2002). "Proteomic analysis of transcription factor interactions in myeloid stem cell development and leukaemia." Expert Opin Ther Targets 6(4): 491-495.
5. Bertrand, J. Y., et al. (2005). "Hematopoietic stem cell development during mouse embryogenesis." Methods Mol Med 105: 273-288.
6. Brashem-Stein, C., et al. (1993). "Ontogeny of hematopoietic stem cell development: reciprocal expression of CD33 and a novel molecule by maturing myeloid and erythroid progenitors." Blood 82(3): 792-799.
7. Burnstock, G. and H. Ulrich (2011). "Purinergic signaling in embryonic and stem cell development." Cell Mol Life Sci 68(8): 1369-1394.
8. Busch, H., et al. (2013). "Network theory inspired analysis of time-resolved expression data reveals key players guiding P. patens stem cell development." PLoS One 8(4): e60494.
9. Chanda, B., et al. (2013). "Retinoic acid signaling is essential for embryonic hematopoietic stem cell development." Cell 155(1): 215-227.
10. Chen, J. (2011). "Hematopoietic stem cell development, aging and functional failure." Int J Hematol 94(1): 3-10.
11. Chen, J., et al. (2016). "Cyp2aa9 regulates haematopoietic stem cell development in zebrafish." Sci Rep 6: 26608.
12. Chotinantakul, K. and W. Leeanansaksiri (2012). "Hematopoietic stem cell development, niches, and signaling pathways." Bone Marrow Res 2012: 270425.
13. Chu, L. F., et al. (2011). "Blimp1 expression predicts embryonic stem cell development in vitro." Curr Biol 21(20): 1759-1765.
14. Ciau-Uitz, A., et al. (2013). "ETS transcription factors in hematopoietic stem cell development." Blood Cells Mol Dis 51(4): 248-255.
15. Couture, L. A. and M. K. Carpenter (2015). "2005 Donor Eligibility Requirements: Unintended Consequences for Stem Cell Development." Stem Cells Transl Med 4(10): 1097-1100.
16. Cullen, S. M., et al. (2014). "Hematopoietic stem cell development: an epigenetic journey." Curr Top Dev Biol 107: 39-75.
17. Cumano, A. and I. Godin (2001). "Pluripotent hematopoietic stem cell development during embryogenesis." Curr Opin Immunol 13(2): 166-171.
18. Dang, L. and V. Tropepe (2006). "Neural induction and neural stem cell development." Regen Med 1(5): 635-652.
19. Deshpande, A. J. and C. Buske (2007). "Knocking the Wnt out of the sails of leukemia stem cell development." Cell Stem Cell 1(6): 597-598.
20. Drummond, B. E. and R. A. Wingert (2016). "Insights into kidney stem cell development and regeneration using zebrafish." World J Stem Cells 8(2): 22-31.
21. Dzierzak, E. and E. de Pater (2016). "Regulation of Blood Stem Cell Development." Curr Top Dev Biol 118: 1-20.

22. English, D. (2006). "Biochemical events involved in stem cell development." Stem Cells Dev 15(6): 751-752.
23. Esain, V., et al. (2015). "Cannabinoid Receptor-2 Regulates Embryonic Hematopoietic Stem Cell Development via Prostaglandin E2 and P-Selectin Activity." Stem Cells 33(8): 2596-2612.
24. Frame, J. M., et al. (2017). "Hematopoietic stem cell development: Using the zebrafish to identify extrinsic and intrinsic mechanisms regulating hematopoiesis." Methods Cell Biol 138: 165-192.
25. Fujimoto, K., et al. (2012). "Thyroid hormone activates protein arginine methyltransferase 1 expression by directly inducing c-Myc transcription during Xenopus intestinal stem cell development." J Biol Chem 287(13): 10039-10050.
26. Gangloff, Y. G., et al. (2004). "Disruption of the mouse mTOR gene leads to early postimplantation lethality and prohibits embryonic stem cell development." Mol Cell Biol 24(21): 9508-9516.
27. Garcion, E., et al. (2004). "Generation of an environmental niche for neural stem cell development by the extracellular matrix molecule tenascin C." Development 131(14): 3423-3432.
28. Gekas, C., et al. (2010). "Hematopoietic stem cell development in the placenta." Int J Dev Biol 54(6-7): 1089-1098.
29. Glauche, I., et al. (2009). "A novel view on stem cell development: analysing the shape of cellular genealogies." Cell Prolif 42(2): 248-263.
30. Godin, I. and A. Cumano (2005). "Of birds and mice: hematopoietic stem cell development." Int J Dev Biol 49(2-3): 251-257.
31. Goessling, W. and T. E. North (2011). "Hematopoietic stem cell development: using the zebrafish to identify the signaling networks and physical forces regulating hematopoiesis." Methods Cell Biol 105: 117-136.
32. Gonzalez-Garcia, M. P., et al. (2015). "Single-cell telomere-length quantification couples telomere length to meristem activity and stem cell development in Arabidopsis." Cell Rep 11(6): 977-989.
33. Google. http://www.google.com. 2018.
34. Guiu, J., et al. (2013). "Hes repressors are essential regulators of hematopoietic stem cell development downstream of Notch signaling." J Exp Med 210(1): 71-84.
35. Guo, J., et al. (2017). "Chromatin and Single-Cell RNA-Seq Profiling Reveal Dynamic Signaling and Metabolic Transitions during Human Spermatogonial Stem Cell Development." Cell Stem Cell 21(4): 533-546.e536.
36. Han, T., et al. (2016). "Identification of novel genes and networks governing hematopoietic stem cell development." EMBO Rep 17(12): 1814-1828.
37. Hasebe, T., et al. (2011). "Epithelial-connective tissue interactions induced by thyroid hormone receptor are essential for adult stem cell development in the Xenopus laevis intestine." Stem Cells 29(1): 154-161.
38. Hasebe, T., et al. (2017). "Essential Roles of Thyroid Hormone-Regulated Hyaluronan/CD44 Signaling in Adult Stem Cell Development During Xenopus laevis Intestinal Remodeling." Stem Cells 35(10): 2175-2183.
39. Hasebe, T., et al. (2017). "Thyroid Hormone-Induced Activation of Notch Signaling is Required for Adult Intestinal Stem Cell Development During Xenopus Laevis Metamorphosis." Stem Cells 35(4): 1028-1039.
40. He, Q. and F. Liu (2016). "Unexpected role of inflammatory signaling in hematopoietic stem cell development: its role beyond inflammation." Curr Opin Hematol 23(1): 18-22.
41. Hearn, J. P. (2001). "Embryo implantation and embryonic stem cell development in primates." Reprod Fertil Dev 13(7-8): 517-522.
42. Hsia, N. and L. I. Zon (2005). "Transcriptional regulation of hematopoietic stem cell development in zebrafish." Exp Hematol 33(9): 1007-1014.
43. Huang, B. Y., et al. (2012). "Polycomb group proteins and their roles in regulating stem cell development." Zhongguo Yi Xue Ke Xue Yuan Xue Bao 34(3): 281-285.
44. Imanirad, P., et al. (2014). "HIF1alpha is a regulator of hematopoietic progenitor and stem cell development in hypoxic sites of the mouse embryo." Stem Cell Res 12(1): 24-35.
45. Ishizuya-Oka, A. and Y. B. Shi (2007). "Regulation of adult intestinal epithelial stem cell development by thyroid hormone during Xenopus laevis metamorphosis." Dev Dyn 236(12): 3358-3368.
46. Ishizuya-Oka, A. and Y. B. Shi (2008). "Thyroid hormone regulation of stem cell development during intestinal remodeling." Mol Cell Endocrinol 288(1-2): 71-78.
47. Ivanovs, A., et al. (2017). "Human haematopoietic stem cell development: from the embryo to the dish." Development 144(13): 2323-2337.
48. Kaimakis, P., et al. (2013). "The biochemistry of hematopoietic stem cell development." Biochim Biophys Acta 1830(2): 2395-2403.
49. Katebi, M., et al. (2009). "Adenosine A2A receptors play an active role in mouse bone

marrow-derived mesenchymal stem cell development." J Leukoc Biol 85(3): 438-444.
50. Kaushansky, K. (1999). "Thrombopoietin and hematopoietic stem cell development." Ann N Y Acad Sci 872: 314-319.
51. Kaushansky, K. and H. M. Ranney (2009). "Thrombopoietin in normal and neoplastic stem cell development." Best Pract Res Clin Haematol 22(4): 495-499.
52. Kauts, M. L., et al. (2016). "Hematopoietic (stem) cell development - how divergent are the roads taken?" FEBS Lett 590(22): 3975-3986.
53. Kos, O., et al. (2018). "Regulation of fetal hemoglobin expression during hematopoietic stem cell development and its importance in bone metabolism and osteoporosis." Int Immunopharmacol 57: 112-120.
54. Krivtsov, A. V. and S. A. Armstrong (2007). "MLL translocations, histone modifications and leukaemia stem-cell development." Nat Rev Cancer 7(11): 823-833.
55. Lee, S., et al. (2016). "Polo Kinase Phosphorylates Miro to Control ER-Mitochondria Contact Sites and Mitochondrial Ca (2+) Homeostasis in Neural Stem Cell Development." Dev Cell 37(2): 174-189.
56. Leiderman, L. J., et al. (1986). "Altered hematopoietic stem cell development in male B6C3F1 mice following exposure to 1,3-butadiene." Exp Mol Pathol 44(1): 50-56.
57. Leng, J., et al. (2009). "Brain-derived neurotrophic factor and electrophysiological properties of voltage-gated ion channels during neuronal stem cell development." Brain Res 1272: 14-24.
58. Li, C., et al. (2016). "Epigenetic regulation of hematopoietic stem cell development." Methods Cell Biol 135: 431-448.
59. Li, Z., et al. (2012). "Mouse embryonic head as a site for hematopoietic stem cell development." Cell Stem Cell 11(5): 663-675.
60. Liu, D. Z., et al. (2015). "MIR-150 promotes prostate cancer stem cell development via suppressing p27Kip1." Eur Rev Med Pharmacol Sci 19(22): 4344-4352.
61. Lodge, E. J., et al. (2016). "Expression Analysis of the Hippo Cascade Indicates a Role in Pituitary Stem Cell Development." Front Physiol 7: 114.
62. Logan, C. M., et al. (2007). "Prostaglandin E2: at the crossroads between stem cell development, inflammation and cancer." Cancer Biol Ther 6(10): 1517-1520.
63. Lovasco, L. A., et al. (2015). "TAF4b is required for mouse spermatogonial stem cell development." Stem Cells 33(4): 1267-1276.
64. Lu, K., et al. (2012). "A cell state splitter and differentiation wave working-model for embryonic stem cell development and somatic cell epigenetic reprogramming." Biosystems 109(3): 390-396.
65. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
66. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
67. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.
68. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
69. Ma, D. K., et al. (2005). "Glial influences on neural stem cell development: cellular niches for adult neurogenesis." Curr Opin Neurobiol 15(5): 514-520.
70. Madras, N., et al. (2002). "Modeling stem cell development by retrospective analysis of gene expression profiles in single progenitor-derived colonies." Stem Cells 20(3): 230-240.
71. Magnusson, P., et al. (2004). "Deregulation of Flk-1/vascular endothelial growth factor receptor-2 in fibroblast growth factor receptor-1-deficient vascular stem cell development." J Cell Sci 117(Pt 8): 1513-1523.
72. Mahmud, N., et al. (1996). "A possible change in doubling time of haemopoietic progenitor cells with stem cell development." Br J Haematol 94(2): 242-249.
73. Marsland Press. http://www.sciencepub.net. 2018.
74. Mascarenhas, M. I., et al. (2009). "Identification of novel regulators of hematopoietic stem cell development through refinement of stem cell localization and expression profiling." Blood 114(21): 4645-4653.
75. Matsuura, K., et al. (2012). "Liganded thyroid hormone receptor induces nucleosome removal and histone modifications to activate transcription during larval intestinal cell death and adult stem cell development." Endocrinology 153(2): 961-972.
76. Mikkola, H. K., et al. (2005). "Placenta as a site for hematopoietic stem cell development." Exp Hematol 33(9): 1048-1054.
77. Mizuno, S., et al. (2018). "Notch1 expression is regulated at the post-transcriptional level by the 3' untranslated region in hematopoietic stem cell development." Int J Hematol 107(3): 311-319.
78. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2018.

79. Nikolsky, I. and T. V. Serebrovska (2009). "Role of hypoxia in stem cell development and functioning." Fiziol Zh 55(4): 116-130.
80. North, T. E., et al. (2009). "Hematopoietic stem cell development is dependent on blood flow." Cell 137(4): 736-748.
81. Ohbo, K. and S. Tomizawa (2015). "Epigenetic regulation in stem cell development, cell fate conversion, and reprogramming." Biomol Concepts 6(1): 1-9.
82. Ohmura, M., et al. (2004). "Spatial analysis of germ stem cell development in Oct-4/EGFP transgenic mice." Arch Histol Cytol 67(4): 285-296.
83. Okada, M., et al. (2017). "A balance of Mad and Myc expression dictates larval cell apoptosis and adult stem cell development during Xenopus intestinal metamorphosis." Cell Death Dis 8(5): e2787.
84. Peeters, M., et al. (2009). "Ventral embryonic tissues and Hedgehog proteins induce early AGM hematopoietic stem cell development." Development 136(15): 2613-2621.
85. Peltz, L., et al. (2012). "Resveratrol exerts dosage and duration dependent effect on human mesenchymal stem cell development." PLoS One 7(5): e37162.
86. Pimanda, J. E. and B. Gottgens (2010). "Gene regulatory networks governing haematopoietic stem cell development and identity." Int J Dev Biol 54(6-7): 1201-1211.
87. Ponting, I. L. and T. M. Dexter (1988). "The role of colony stimulating factors, interleukin 1 and stromal extracellular matrix in the regulation of stem cell development." Behring Inst Mitt (83): 48-55.
88. Prokopi, M., et al. (2014). "The Secret Role of microRNAs in Cancer Stem Cell Development and Potential Therapy: A Notch-Pathway Approach." Front Oncol 4: 389.
89. Ruiz-Herguido, C., et al. (2012). "Hematopoietic stem cell development requires transient Wnt/beta-catenin activity." J Exp Med 209(8): 1457-1468.
90. Schlaeger, T. M., et al. (2005). "Tie2Cre-mediated gene ablation defines the stem-cell leukemia gene (SCL/tal1)-dependent window during hematopoietic stem-cell development." Blood 105(10): 3871-3874.
91. Schutte, J., et al. (2012). "Establishing the stem cell state: insights from regulatory network analysis of blood stem cell development." Wiley Interdiscip Rev Syst Biol Med 4(3): 285-295.
92. Sengupta, D. and S. Kar (2018). "Deciphering the Dynamical Origin of Mixed Population during Neural Stem Cell Development." Biophys J 114(4): 992-1004.
93. Shearman, M. S., et al. (1993). "Haemopoietic stem cell development to neutrophils is associated with subcellular redistribution and differential expression of protein kinase C subspecies." J Cell Sci 104 (Pt 1): 173-180.
94. Shinde, V., et al. (2017). "Definition of transcriptome-based indices for quantitative characterization of chemically disturbed stem cell development: introduction of the STOP-Toxukn and STOP-Toxukk tests." Arch Toxicol 91(2): 839-864.
95. Sinden, D., et al. (2012). "Jak-STAT regulation of cyst stem cell development in the Drosophila testis." Dev Biol 372(1): 5-16.
96. Slaidina, M. and R. Lehmann (2014). "Translational control in germline stem cell development." J Cell Biol 207(1): 13-21.
97. Small, D. H., et al. (2014). "beta-Amyloid precursor protein: function in stem cell development and Alzheimer's disease brain." Neurodegener Dis 13(2-3): 96-98.
98. Sommer, L. (2005). "Checkpoints of melanocyte stem cell development." Sci STKE 2005(298): pe42.
99. Stubbs, M. C. and S. A. Armstrong (2007). "Therapeutic implications of leukemia stem cell development." Clin Cancer Res 13(12): 3439-3442.
100. Sun, G. and Y. B. Shi (2012). "Thyroid hormone regulation of adult intestinal stem cell development: mechanisms and evolutionary conservations." Int J Biol Sci 8(8): 1217-1224.
101. Sun, G., et al. (2013). "Expression profiling of intestinal tissues implicates tissue-specific genes and pathways essential for thyroid hormone-induced adult stem cell development." Endocrinology 154(11): 4396-4407.
102. Sun, G., et al. (2014). "Epigenetic regulation of thyroid hormone-induced adult intestinal stem cell development during anuran metamorphosis." Cell Biosci 4: 73.
103. Takakura, N. (1999). "[The molecular mechanism of hematopoietic stem cell development in the AGM region]." Rinsho Ketsueki 40(4): 262-267.
104. Teif, V. B., et al. (2012). "Genome-wide nucleosome positioning during embryonic stem cell development." Nat Struct Mol Biol 19(11): 1185-1192.
105. Teif, V. B., et al. (2014). "Nucleosome repositioning links DNA (de)methylation and differential CTCF binding during stem cell development." Genome Res 24(8): 1285-1295.

106. Teitell, M. A. and H. K. Mikkola (2006). "Transcriptional activators, repressors, and epigenetic modifiers controlling hematopoietic stem cell development." Pediatr Res 59(4 Pt 2): 33r-39r.
107. Thurmond, T. S., et al. (2000). "Role of estrogen receptor alpha in hematopoietic stem cell development and B lymphocyte maturation in the male mouse." Endocrinology 141(7): 2309-2318.
108. Tucker, M. R., et al. (2008). "Vascular signalling mediated by ZWILLE potentiates WUSCHEL function during shoot meristem stem cell development in the Arabidopsis embryo." Development 135(17): 2839-2843.
109. Vadakke Madathil, S., et al. (2014). "Klotho deficiency disrupts hematopoietic stem cell development and erythropoiesis." Am J Pathol 184(3): 827-841.
110. Vogel-Hopker, A., et al. (2012). "Co-opting functions of cholinesterases in neural, limb and stem cell development." Protein Pept Lett 19(2): 155-164.
111. Wang, L., et al. (2013). "Fev regulates hematopoietic stem cell development via ERK signaling." Blood 122(3): 367-375.
112. Whitmill, A., et al. (2017). "Tip110 Deletion Impaired Embryonic and Stem Cell Development Involving Downregulation of Stem Cell Factors Nanog, Oct4, and Sox2." Stem Cells 35(7): 1674-1686.
113. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2018.
114. Wiles, M. V. and B. M. Johansson (1999). "Embryonic stem cell development in a chemically defined medium." Exp Cell Res 247(1): 241-248.
115. Wolosin, J. M., et al. (2004). "Ocular surface epithelial and stem cell development." Int J Dev Biol 48(8-9): 981-991.
116. Wu, X., et al. (2016). "Autophagy regulates Notch degradation and modulates stem cell development and neurogenesis." Nat Commun 7: 10533.
117. Yabut, O. R. and S. J. Pleasure (2016). "The Crossroads of Neural Stem Cell Development and Tumorigenesis." Opera Med Physiol 2(3-4): 181-187.
118. Zhang, C., et al. (2013). "Hematopoietic stem cell development and regulatory signaling in zebrafish." Biochim Biophys Acta 1830(2): 2370-2374.
119. Zhang, P. and F. Liu (2011). "In vivo imaging of hematopoietic stem cell development in the zebrafish." Front Med 5(3): 239-247.
120. Zhang, Y., et al. (2008). "A Gata6-Wnt pathway required for epithelial stem cell development and airway regeneration." Nat Genet 40(7): 862-870.

7/16/2018