Oligopotent Stem Cell Research Literatures

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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.
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Key words: stem cell; oligopotent; life; 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. Oligopotent stem cells can differentiate into only a few cell types, such as lymphoid or myeloid stem cells.

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

Allen, R. D., 3rd, et al. (1999). "c-Myb is essential for early T cell development." Genes Dev **13**(9): 1073-1078.

The c-Myb transcription factor is important for fetal hematopoiesis and has been proposed to mediate later stages of lymphocyte development. Using homozygous null c-Myb/Rag1 chimeric mice, we have determined that c-Myb plays an important role in the differentiation of macrophages and lymphocytes from precursor stem cells. We also determine that deletion of c-Myb leads to a complete block in early T cell development just before the oligopotent thymocyte matures into the definitive T cell precursor. These data indicate that c-Myb plays an important role at multiple stages of hematopoiesis and is required at an early stage of T cell development.

Benz, C. and C. C. Bleul (2005). "A multipotent precursor in the thymus maps to the branching point of the T versus B lineage decision." J Exp Med **202**(1): 21-31.

Hematopoietic precursors continuously colonize the thymus where they give rise mainly to T cells, but also to B and dendritic cells. The lineage relationship between these three cell types is unclear, and it remains to be determined if precursors in the thymus are multipotent, oligopotent, or lineage restricted. Resolution of this question necessitates the determination of the clonal differentiation potential of the most immature precursors in the thymus. Using a CC chemokine receptor 9-enhanced green fluorescent protein knock-in allele like a surface marker of unknown function, we identify a multipotent precursor present in bone marrow, blood, and thymus. Single cells of this precursor give rise to T, B, and dendritic cells. A more differentiated stage of this multipotent precursor in the thymus has lost the capacity to generate B but not T, dendritic, and myeloid cells. Thus, the newly identified precursor maps to the branching point of the T versus B lineage decision in the hematopoietic lineage hierarchy.

Billia, F., et al. (2001). "Resolution of pluripotential intermediates in murine hematopoietic differentiation by global complementary DNA amplification from single cells: confirmation of assignments by expression profiling of cytokine receptor transcripts." Blood **97**(8): 2257-2268.

Although hematopoiesis is known to proceed from stem cells through a graded series of multipotent, oligopotent, and unipotent precursor cells, it has been difficult to resolve these cells physically one from

another. There is, therefore, corresponding uncertainty about the exact distribution and timing of the expression of genes known to be important in hematopoietic differentiation. In earlier work, the generation of a set of amplified complementary DNAs (cDNAs) from single precursor cells was described, whose biologic potential was determined by the outcome of cultured sibling cells. In this study, the new acquisition of cDNA from multipotent myeloid precursor cells is described, as is the mapping of RNA-level expression of 17 distinct cytokine receptors (c-kit, Flk-1, Flk-2/Flt-3, c-fms, gp130, erythropoietin receptor, GM-CSFRalpha, G-CSFR, TNFR1, IL-1RI, IL-1RII, IL-2Rbeta, IL-3-specific beta receptor, IL-4R, IL-6Ralpha, IL-7Ralpha, and IL-11Ralpha) to the enlarged sample set, spanning stages from pentapotent precursors through oligopotent intermediates to committed and maturing cells in the myeloid and lymphoid lineages. Although the enhanced scope and resolving power of the analysis yielded previously unreported observations, there was overall agreement with known biologic responsiveness at individual stages, and major contradictions did not arise. Moreover, each precursor category displayed a unique overall pattern of hybridization to the matrix of 17 receptor probes, supporting the notion that each sample pool indeed reflected a unique precursor stage. Collectively, the results provide supportive evidence for the validity of the cDNA assignments to particular stages, the depth of the information captured, and the unique capacity of the sample matrix to resolve individual stages in the hematopoietic hierarchy.

Boussaad, I., et al. (2011). "Wild-type measles virus interferes with short-term engraftment of human CD34+ hematopoietic progenitor cells." J Virol **85**(15): 7710-7718.

Transient lymphopenia is a hallmark of measles virus (MV)-induced immunosuppression. To address to what extent replenishment of the peripheral lymphocyte compartment from bone marrow (BM) progenitor/stem cells might be affected, we analyzed the interaction of wild-type MV with hematopoietic stem and progenitor cells (HS/PCs) and stroma cells in vitro. Infection of human CD34(+) HS/PCs or stroma cells with wild-type MV is highly inefficient yet noncytolytic. It occurs independently of CD150 in stroma cells but also in HS/PCs, where infection is established in CD34(+) CD150(-) and CD34(+) CD150(+) (in humans representing HS/PC oligopotent precursors) subsets. Stroma cells and HS/PCs can mutually transmit MV and may thereby create a possible niche for continuous viral exchange in the BM. Infected lymphocytes homing to this compartment may serve as sources for HS/PC or stroma cell infection, as reflected by highly efficient transmission of MV from both populations in cocultures with MV-infected B or T cells. Though MV exposure does not detectably affect the viability, expansion, and colony-forming activity of either CD150(+) or CD150(-) HS/PCs in vitro, it efficiently interferes with short- but not long-term hematopoietic reconstitution in NOD/SCID mice. Altogether, these findings support the hypothesis that MV accession of the BM compartment by infected lymphocytes may contribute to peripheral blood mononuclear cell lymphopenia at the level of BM suppression.

Bradley, H. L., et al. (2004). "Hematopoietic-repopulating defects from STAT5-deficient bone marrow are not fully accounted for by loss of thrombopoietin responsiveness." Blood **103**(8): 2965-2972.

Signal transducer and activator of transcription-5 (STAT5) plays an important role in repopulating activity of hematopoietic stem cells (HSCs). However, the relationship of STAT5 activation with early acting cytokine receptors is not well established. We have directly compared bone marrow (BM) from mice mutant for STAT5a and STAT5b (STAT5ab (-/-)) with that from mice lacking c-Mpl (c-Mpl (-/-)), the thrombopoietin receptor. Both STAT5 and c-Mpl deficiency only mildly affected committed myeloid progenitors assayed in vitro, but STAT5ab (-/-) BM showed lower Gr-1+ (4.4-fold), B220+ (23-fold), CD4+ (20-fold), and Ter119+ (17-fold) peripheral blood repopulating activity than c-Mpl (-/-) BM against wild-type competitor in long-term repopulating assays in vivo. Direct head-to-head competitions of STAT5ab (-/-) BM and c-Mpl (-/-) BM showed up to a 25-fold reduction in STAT5ab (-/-) contribution. Differences affecting reconstitution of primitive c-Kit+Lin-Sca-1+ multipotent progenitor (MPP)/HSC (1.8-fold) and c-Kit+Lin-Sca-1- oligopotent progenitor BM fractions (3.3-fold) were more modest. In serial transplantation experiments, STAT5ab (-/-) and c-Mpl (-/-) BM both failed to provide consistent engraftment in tertiary hosts and could not radioprotect lethally irradiated quaternary recipients. These results indicate substantial overlap in c-Mpl-STAT5 signaling defects at the MPP/HSC level but indicate that STAT5 is activated independent of c-Mpl to promote multilineage hematopoietic differentiation.

Carrelha, J., et al. (2018). "Hierarchically related lineage-restricted fates of multipotent haematopoietic stem cells." Nature **554**(7690): 106-111.

Rare multipotent haematopoietic stem cells (HSCs) in adult bone marrow with extensive self-renewal potential can efficiently replenish all myeloid and lymphoid blood cells, securing long-term multilineage reconstitution after physiological and

clinical challenges such as chemotherapy and haematopoietic transplantations. HSC transplantation remains the only curative treatment for many haematological malignancies, but inefficient blood-lineage replenishment remains a major cause of morbidity and mortality. Single-cell transplantation has uncovered considerable heterogeneity among reconstituting HSCs, a finding that is supported by studies of unperturbed haematopoiesis and may reflect different propensities for lineage-fate decisions by distinct myeloid-, lymphoid- and platelet-biased HSCs. Other studies suggested that such lineage bias might reflect generation of unipotent or oligopotent self-renewing progenitors within the phenotypic HSC compartment, and implicated uncoupling of the defining HSC properties of self-renewal and multipotency. Here we use highly sensitive tracking of progenitors and mature cells of the megakaryocyte/platelet, erythroid, myeloid and B and T cell lineages, produced from singly transplanted HSCs, to reveal a highly organized, predictable and stable framework for lineage-restricted fates of long-term self-renewing HSCs. Most notably, a distinct class of HSCs adopts a fate towards effective and stable replenishment of a megakaryocyte/platelet-lineage tree but not of other blood cell lineages, despite sustained multipotency. No HSCs contribute exclusively to any other single blood-cell lineage. Single multipotent HSCs can also fully restrict towards simultaneous replenishment of megakaryocyte, erythroid and myeloid lineages without executing their sustained lymphoid lineage potential. Genetic lineage-tracing analysis also provides evidence for an important role of platelet-biased HSCs in unperturbed adult haematopoiesis. These findings uncover a limited repertoire of distinct HSC subsets, defined by a predictable and hierarchical propensity to adopt a fate towards replenishment of a restricted set of blood lineages, before loss of self-renewal and multipotency.

Chao, M. P., et al. (2008). "Establishment of a normal hematopoietic and leukemia stem cell hierarchy." Cold Spring Harb Symp Quant Biol **73**: 439-449.

Many types of adult tissues, especially for high turnover tissues such as the blood and intestinal system, stand on a hierarchical tissue-specific stem cell system. Tissue-specific stem cells concurrently have self-renewal capacity and potential to give rise to all types of mature cells in their tissue. The differentiation process of the tissue-specific stem cell is successive restriction of these capacities. The first progeny of tissue-specific stem cells are multipotent progenitors (MPPs) that lose long-term self-renewal capacity yet have full lineage potential. MPPs in turn give rise to oligopotent progenitors, which then commit into lineage-restricted progenitors. This hierarchical system enables a lifelong supply of matured functional cells that generally have a short life span and a relatively high turnover rate. In this chapter, we review our findings and other key experiments that have led to the establishment of the current cellular stem and progenitor hierarchy in the blood-forming systems of mice and humans for both normal and leukemic hematopoiesis. We also review select signaling pathways intrinsic to normal hematopoietic and leukemic stem cell populations as well our recent findings elucidating the possible origin of the leukemia stem cell.

Costa-Silva, B., et al. (2009). "Fibronectin promotes differentiation of neural crest progenitors endowed with smooth muscle cell potential." Exp Cell Res **315**(6): 955-967.

The neural crest (NC) is a model system used to investigate multipotency during vertebrate development. Environmental factors control NC cell fate decisions. Despite the well-known influence of extracellular matrix molecules in NC cell migration, the issue of whether they also influence NC cell differentiation has not been addressed at the single cell level. By analyzing mass and clonal cultures of mouse cephalic and quail trunk NC cells, we show for the first time that fibronectin (FN) promotes differentiation into the smooth muscle cell phenotype without affecting differentiation into glia, neurons, and melanocytes. Time course analysis indicated that the FN-induced effect was not related to massive cell death or proliferation of smooth muscle cells. Finally, by comparing clonal cultures of quail trunk NC cells grown on FN and collagen type IV (CLIV), we found that FN strongly increased both NC cell survival and the proportion of unipotent and oligopotent NC progenitors endowed with smooth muscle potential. In contrast, melanocytic progenitors were prominent in clonogenic NC cells grown on CLIV. Taken together, these results show that FN promotes NC cell differentiation along the smooth muscle lineage, and therefore plays an important role in fate decisions of NC progenitor cells.

Dygai, A. M. and E. G. Skurikhin (2011). "Monoaminergic regulation of hemopoiesis under extreme conditions." Bull Exp Biol Med **151**(2): 171-178.

The role of the adrenergic, dopaminergic, and serotoninergic systems in the regulation of hemopoiesis was evaluated on various models of pathological processes (restraint stress, experimental neurosis, and cytostatic treatment). The proliferation, differentiation, and maturation of polypotent, multipotent, partially determined, and oligopotent

hemopoietic precursors and functional activity of microenvironmental cells (stromal cells, macrophages, and Thy1,2(+) cells) were shown to be under the control of a complex system of monoaminergic regulation. Central monoamines have a direct or indirect (mediated by microenvironmental cells) regulatory effect on hemopoietic precursors of various classes, which is realized via specific receptors. The system of colony-stimulating factors is characterized by selective sensitivity to catecholamines. It should be emphasized that the effects of erythropoietin are mainly associated with serotonin. Irrespective of experimental conditions (hyperplasia of hemopoiesis, myelosuppression, and dysregulation of precursor cell proliferation and differentiation), the erythroid hemopoietic stem is more sensitive to serotoninergic influences. Granulocytopoiesis was revealed to be more sensitive to central catecholamines.

Dygai, A. M., et al. (2016). "Role of Hematopoietic Stem Cells in Inflammation of the Pancreas during Diabetes Mellitus." Bull Exp Biol Med **160**(4): 474-479.

The model of streptozotocin-induced diabetes mellitus in C57Bl/6 mice was employed to study the role of precursors of insulin-producing beta-cells, hematopoietic stem cells, and progenitor hematopoietic cells in inflammation. In addition to provoking hyperglycemia, streptozotocin elevated serum levels of IL-1beta and hyaluronic acid, induced edema in the pancreatic insular tissue and its infiltration by inflammatory cells (neutrophils, lymphocytes, and macrophages) and fibroblasts. Inflammation in pancreatic islets was accompanied by necrotic processes and decreasing counts of multipotent progenitor beta-cells (CD45(-), TER119(-), c-kit-1(-), and Flk-1(-)), oligopotent progenitor beta-cells (CD45(-), TER119(-), CD133(+), and CD49f (low)), and insulinproducing beta-cells (Pdx1(+)). Pancreatic infl ammation was preceded by elevation of the number of short-term hematopoietic stem cells (Lin-Sca-1(+)c-kit (+)CD34(+)) relative to long-term cells (Lin (-)Sca-1(+)c-kit (+)CD34(-)) in the bone marrow as well as recruitment of hematopoietic stem and progenitor cells into circulation. Transplantation of bone marrow hematopoietic stem and progenitor cells from diabetic C57Bl/6 donor mice to recipient CBA mice with 5-fluorouracilinduced leukopenia accelerated regeneration of granulocytopoiesis in recipient mice.

Ficara, F., et al. (2013). "Pbx1 restrains myeloid maturation while preserving lymphoid potential in hematopoietic progenitors." J Cell Sci **126**(Pt 14): 3181-3191.

The capacity of the hematopoietic system to promptly respond to peripheral demands relies on adequate pools of progenitors able to transiently proliferate and differentiate in a regulated manner. However, little is known about factors that may restrain progenitor maturation to maintain their reservoirs. Conditional knockout mice for the Pbx1 proto-oncogene have a significant reduction in lineage-restricted progenitors in addition to a profound defect in hematopoietic stem cell (HSC) self-renewal. Through analysis of purified progenitor proliferation, differentiation capacity and transcriptional profiling, we demonstrate that Pbx1 regulates the lineage-specific output of multipotent and oligopotent progenitors. In the absence of Pbx1 multipotent progenitor (MPP) and common myeloid progenitor (CMP) pools are reduced due to aberrantly rapid myeloid maturation. This is associated with premature expression of myeloid differentiation genes and decreased maintenance of proto-oncogene transcriptional pathways, including reduced expression of Meis1, a Pbx1 dimerization partner, and its subordinate transcriptional program. Conversely, Pbx1 maintains the lymphoid differentiation potential of lymphoid-primed MPPs (LMPPs) and common lymphoid progenitors (CLPs), whose reduction in the absence of Pbx1 is associated with a defect in lymphoid priming that is also present in CMPs, which persistently express lymphoid and HSC genes underlying a previously unappreciated lineage promiscuity that is maintained by Pbx1. These results demonstrate a role for Pbx1 in restraining myeloid maturation while maintaining lymphoid potential to appropriately regulate progenitor reservoirs.

Francis, W. R., et al. (2012). "Altered leucocyte progenitor profile in human bone marrow from patients with major trauma during the recovery phase." Br J Surg **99**(11): 1591-1599.

BACKGROUND: Changes in human bone marrow associated with the systemic inflammatory response to injury are little understood. It was hypothesized that major trauma results in an altered bone marrow leucocyte progenitor profile, with either uniform depletion or the balance between multipotent and committed progenitors varying, depending on whether self-renewal is favoured over differentiation. METHODS: Bone marrow aspirate and peripheral blood samples were obtained at definitive surgery in adults with pelvic fractures from blunt trauma (major trauma with Injury Severity Score (ISS) at least 18, or isolated fractures) and control patients undergoing iliac crest bone grafting. ISS, interval to surgery and transfusion in the first 24 h were recorded. Bone marrow aspirate flow cytometry was used to identify haemopoietic progenitor cells (CD34(+)), multipotent

cells (CD34(+) CD45(+) CD38(-)) and oligopotent cells (CD34(+) CD45(+) CD38(lo/+) and CD34(+) CD45(+) CD38(BRIGHT (++ +)) subsets). Peripheral blood levels of inflammatory markers were measured, and the ratio of immature to mature (CD35(-) /CD35(+)) granulocytes was determined. RESULTS: The median (range) interval between injury and sampling was 7 (1-21) and 5 (1-21) days in the major trauma and isolated fracture groups respectively. The CD34(+) pool was significantly depleted in the major trauma group (P = 0.017), particularly the CD34(+) CD45(+) CD38(BRIGHT (++ +)) oligopotent pool (P = 0.003). Immature CD35(-) granulocytes increased in bone marrow with increasing injury severity (P = 0.024) and massive transfusion (P = 0.019), and in peripheral blood with increasing interval to surgery (P = 0.005). CONCLUSION: Major blunt trauma resulted in changes in the bone marrow CD34(+) progenitor pool. At the point in recovery when these samples were obtained, oligopotent progenitors were lost from the bone marrow, with continued release of immature cells.

Galy, A. H., et al. (1995). "Delineation of T-progenitor cell activity within the CD34+ compartment of adult bone marrow." Blood **85**(10): 2770-2778.

T-cell production is largely dependent on the presence of a thymus gland where CD34+ precursors mature into T lymphocytes. Prethymic stages of T-cell development are less defined. Therefore, this study aims to delineate T-progenitor cell potential within the CD34+ Lineage--(Lin-) cell compartment of adult bone marrow (ABM). Fractionation of CD34+ Lin- ABM cells with CD45RA, Thy-1, CD38, and HLA-DR failed to absolutely segregate T-cell reconstituting ability, indicating broad distribution of T-progenitor cell potential. Titration experiments showed that low numbers of CD34+ Lin- CD45RA+ (RA+) cells had greater thymus repopulating ability than CD34+ Lin- CD45RA- cells (RA-). The great majority (> 95%) of RA+ cells expressed CD38, HLA-DR and 70% to 90% of RA+ cells lacked Thy-1 surface expression. RA+ cells contained colony-forming unit granulocyte-macrophage (CFU-GM) progenitor cells but were depleted of erythroid potential, did not provide hematopoietic reconstitution of human bone fragments implanted into SCID mice, and did not efficiently maintain CD34+ cells with secondary clonogenic potential in bone marrow cultures. Thus, RA+ cells are oligopotent (nonprimitive) CD34+ progenitors with T-cell reconstituting ability. In contrast, these same assays indicated that CD34+ Lin- CD45RA- cells (RA- cells) comprised hematopoietic stem cells (HSC) with primitive multilineage (T, B, myeloid, and erythroid) hematopoietic potential. It was confirmed that HSC-containing populations, such as CD34+ Lin- CD45RA- Thy-1+ cells had thymus repopulating ability. Culture of RA- cells on murine bone marrow stromal cells in the presence of interleukin (IL)-3, IL-6, and leukemia inhibitory factor (LIF) generated CD34+ CD45RA+ progeny engrafting in a secondary severe combined immunodeficiency (SCID)-hu thymus assay. Altogether, our results underscore the fact that T-cell reconstituting potential can be dissociated from HSC activity. Furthermore, we speculate that HSC might develop into the T lineage indirectly, via differentiation into an intermediate oligopotent CD34+ CD45RA+ stage. Finally, T-progenitor cells can be cultured in vitro.

Geng, Y. J., et al. (2006). "Vascular stem cells: a new concept in the pathogenesis of atherosclerosis and interventions for coronary heart disease." Future Cardiol **2**(5): 585-592.

Vascular stem cells are undifferentiated, oligopotent progenitor cells that are capable of giving rise to mature, functional cells in the vascular wall. Several types of vascular progenitor cells have been identified and characterized from embryonic and adult tissues, including progenitors with the potential to differentiate into endothelial and smooth muscle cells. The progenitors for endothelial and smooth muscle cells reside in atherosclerotic or restenotic lesions and circulate in the bloodstream. These stem cells may malfunction under the influence of the risk factors for atherosclerosis, as well as by medical interventions. The biological activities of these stem cells contribute to the regeneration, repair and remodeling of arterial walls injured by atherosclerosis. Hypercholesterolemia, inflammation, mechanical stress and genetic defects may interact in regulating the vascular stem cell response to atherogenic stimulation. Stem cell production, potency, growth and differentiation may decline as people age. Clarifying the cellular and molecular pathways that govern stem cell growth, differentiation and apoptosis should help clinical scientists to understand the pathogenesis of atherosclerosis and to develop novel therapeutic strategies for coronary heart disease. Recent clinical trials demonstrate encouraging outcomes of stem cell therapies.

Giladi, A., et al. (2018). "Single-cell characterization of haematopoietic progenitors and their trajectories in homeostasis and perturbed haematopoiesis." Nat Cell Biol **20**(7): 836-846.

The dynamics of haematopoietic stem cell differentiation and the hierarchy of oligopotent stem cells in the bone marrow remain controversial. Here we dissect haematopoietic progenitor populations at single cell resolution, deriving an unbiased reference

model of transcriptional states in normal and perturbed murine bone marrow. We define the signature of the naive haematopoietic stem cell and find a continuum of core progenitor states. Core cell populations mix transcription of pre-myeloid and pre-lymphoid programs, but do not mix erythroid or megakaryocyte programs with other fates. CRISP-seq perturbation analysis confirms our models and reveals that Cebpa regulates entry into all myeloid fates, while Irf8 and PU.1 deficiency block later differentiation towards monocyte or granulocyte fates. Our transcriptional map defines a reference network model for blood progenitors and their differentiation trajectories during normal and perturbed haematopoiesis.

Hagglund, A. C., et al. (2011). "Lhx2 is required for patterning and expansion of a distinct progenitor cell population committed to eye development." PLoS One **6**(8): e23387.

Progenitor cells committed to eye development become specified in the prospective forebrain and develop subsequently into the optic vesicle and the optic cup. The optic vesicle induces formation of the lens placode in surface ectoderm from which the lens develops. Numerous transcription factors are involved in this process, including the eye-field transcription factors. However, many of these transcription factors also regulate the patterning of the anterior neural plate and their specific role in eye development is difficult to discern since eye-committed progenitor cells are poorly defined. By using a specific part of the Lhx2 promoter to regulate Cre recombinase expression in transgenic mice we have been able to define a distinct progenitor cell population in the forebrain solely committed to eye development. Conditional inactivation of Lhx2 in these progenitor cells causes an arrest in eye development at the stage when the optic vesicle induces lens placode formation in the surface ectoderm. The eye-committed progenitor cell population is present in the Lhx2(-/-) embryonic forebrain suggesting that commitment to eye development is Lhx2-independent. However, re-expression of Lhx2 in Lhx2(-/-) progenitor cells only promotes development of retinal pigment epithelium cells, indicating that Lhx2 promotes the acquisition of the oligopotent fate of these progenitor cells. This approach also allowed us to identify genes that distinguish Lhx2 function in eye development from that in the forebrain. Thus, we have defined a distinct progenitor cell population in the forebrain committed to eye development and identified genes linked to Lhx2's function in the expansion and patterning of these progenitor cells.

Hamilton, P. W. and J. J. Henry (2016). "The lens regenerative competency of limbal vs. central regions of mature Xenopus cornea epithelium." Exp Eye Res **152**: 94-99.

The frog, Xenopus laevis, is capable of completely regenerating a lens from the cornea epithelium. Because this ability appears to be limited to the larval stages of Xenopus, virtually all the work to understand the mechanisms regulating this process has been limited to pre-metamorphic tadpoles. It has been reported that the post-metamorphic cornea is competent to regenerate under experimental conditions, despite the fact that the in vivo capacity to regenerate is lost; however, that work didn't examine the regenerative potential of different regions of the cornea. A new model suggests that cornea-lens regeneration in Xenopus may be driven by oligopotent stem cells, and not by transdifferentiation of mature cornea cells. We investigated the regenerative potential of the limbal region in post-metamorphic cornea, where the stem cells of the cornea are thought to reside. Using EdU (5-Ethynyl-2'-deoxyuridine), we identified long-term label retaining cells in the basal cells of peripheral post-metamorphic Xenopus cornea, consistent with slow-cycling stem cells of the limbus that have been described in other vertebrates. Using this data to identify putative stem cells of the limbal region in Xenopus, we tested the regenerative competency of limbal regions and central cornea. These regions showed a similarly high ability for the cells of the basal epithelium to express lens proteins when cultured in proximity to larval retina. Thus, the regenerative competency in the post-metamorphic cornea is not restricted to stem cells of the limbal region, but also occurs in the transit amplifying cells throughout the basal layer of the cornea epithelium.

Herbst, B., et al. (1998). "GM-CSF promotes differentiation of a precursor cell of monocytes and Langerhans-type dendritic cells from CD34+ haemopoietic progenitor cells." Br J Haematol **101**(2): 231-241.

Epithelia-associated dendritic cells (DC) including Langerhans cells in the skin (LC) are precursors of lymph node located interdigitating DC (iDC). CD1a+ LC are known to be derived from CD34+ haemopoietic progenitor cells (HPC); however, cells of an intermediate differentiation state that are CD34- and CD1a- have not been identified. Monitoring the differentiation pathway of HPC in the presence of GM-CSF+IL-4, we observed the emergence of a distinct LC precursor population that was CD33+ CD13+ CD4+ CD38+ CD44+ CD34- CD14- CD1a-. The cells could be separated by FACS due to a unique CD44/CD38 expression pattern or by CD44 expression in conjunction with the SSC profile. It was found that they were similarly generated in the presence of GM-CSF alone and were detectable in

culture for at least a week. Irrespective of being generated in the presence of GM-CSF+IL-4 or GM-CSF alone, CD44/SSC-sorted precursor cells matured to MHC class II compartments (MIIC) and Birbeck granules (BG) expressing LC, when subsequently cultured in the presence of GM-CSF+IL-4. When IL-4 was omitted, however, the same cells matured to phagocytically active adherent macrophages (Mphi). These culture conditions were associated with a > 4-fold increase in the concentration of IL-6 when compared to those used for LC differentiation. The identification of a distinct oligopotent precursor cell population that can deliberately be induced to give rise to BG+ MIIC+ CD1a+ CD14- LC or to adherent CD14+ Mk further substantiates the close relationship of monocytes and DC and may help to identify its in vivo equivalent.

Hodgkinson, K. M., et al. (2017). "Intersecting Worlds of Transfusion and Transplantation Medicine: An International Symposium Organized by the Canadian Blood Services Centre for Innovation." Transfus Med Rev **31**(3): 183-192.

The principal theme of the symposium was centered on how the world of regenerative medicine intersects with that of transfusion medicine, with a particular focus on hematopoietic stem cells (HSCs) and stem cell therapies. The symposium highlighted several exciting developments and identified areas where additional research is needed. A revised map of human hematopoietic hierarchy was presented based on the functional and phenotypic analysis of thousands of single stem and progenitor cells from adult bone marrow and fetal liver. These analyses revealed that multipotency is largely restricted to the HSC and multipotent progenitor compartments in adult bone marrow where most progenitors are unipotent, whereas fetal liver contains a large number of distinct oligopotent progenitors. Furthermore, unlike adult bone marrow, multipotency is extended in the downstream progenitors in the hierarchy in the fetal liver stage. Production of platelets ex vivo from HSCs is emerging as a potentially viable option because of advances in culture techniques that combine cytokine mixtures, small molecules, and shear stress. However, limited HSC expansion and low platelet yield from culture-derived megakaryocytes remain problematic. Evidence was presented to support stricter guidelines for transfusion of platelets and red blood cells practices in allogeneic HSC transplant patients, although evidence is often extrapolated from general indications. Basic principles of human leukocyte antigen testing in HSC transplant were described, emphasizing the need for a national (and global) stem cell donor registry. Ongoing research is aimed at improving cellular cryopreservation including the establishment of a new thawing protocol that improves viability of umbilical cord blood CD34+ cells. Umbilical cord blood transplantation practices have also been improved; recent studies suggest noninferior outcomes when patients are transplanted with umbilical cord blood vs a matched adult donor. Finally, mesenchymal stem cell infusion is an example of a cellular therapy useful for immunomodulation. Preclinical trials suggest that mesenchymal stem cells may be effective in managing sepsis. In conclusion, practices and research surrounding HSCs are continuing to evolve rapidly as new information is obtained.

Ji, H., et al. (2010). "Comprehensive methylome map of lineage commitment from haematopoietic progenitors." Nature **467**(7313): 338-342.

Epigenetic modifications must underlie lineage-specific differentiation as terminally differentiated cells express tissue-specific genes, but their DNA sequence is unchanged. Haematopoiesis provides a well-defined model to study epigenetic modifications during cell-fate decisions, as multipotent progenitors (MPPs) differentiate into progressively restricted myeloid or lymphoid progenitors. Although DNA methylation is critical for myeloid versus lymphoid differentiation, as demonstrated by the myeloerythroid bias in Dnmt1 hypomorphs, a comprehensive DNA methylation map of haematopoietic progenitors, or of any multipotent/oligopotent lineage, does not exist. Here we examined 4.6 million CpG sites throughout the genome for MPPs, common lymphoid progenitors (CLPs), common myeloid progenitors (CMPs), granulocyte/macrophage progenitors (GMPs), and thymocyte progenitors (DN1, DN2, DN3). Marked epigenetic plasticity accompanied both lymphoid and myeloid restriction. Myeloid commitment involved less global DNA methylation than lymphoid commitment, supported functionally by myeloid skewing of progenitors following treatment with a DNA methyltransferase inhibitor. Differential DNA methylation correlated with gene expression more strongly at CpG island shores than CpG islands. Many examples of genes and pathways not previously known to be involved in choice between lymphoid/myeloid differentiation have been identified, such as Arl4c and Jdp2. Several transcription factors, including Meis1, were methylated and silenced during differentiation, indicating a role in maintaining an undifferentiated state. Additionally, epigenetic modification of modifiers of the epigenome seems to be important in haematopoietic differentiation. Our results directly demonstrate that modulation of DNA methylation occurs during lineage-specific differentiation and defines a comprehensive map of the methylation and

transcriptional changes that accompany myeloid versus lymphoid fate decisions.

Jin, K. and M. Xiang (2017). "Transitional Progenitors during Vertebrate Retinogenesis." Mol Neurobiol **54**(5): 3565-3576.

The retina is a delicate neural tissue responsible for light signal capturing, modulating, and passing to mid-brain. The brain then translated the signals into three-dimensional vision. The mature retina is composed of more than 50 subtypes of cells, all of which are developed from a pool of early multipotent retinal progenitors, which pass through sequential statuses of oligopotent, bipotent, and unipotent progenitors, and finally become terminally differentiated retinal cells. A transitional progenitor model is proposed here to describe how intrinsic developmental programs, along with environmental cues, control the step-by-step differentiation during retinogenesis. The model could elegantly explain many current findings as well as predict roles of intrinsic factors during retinal development.

Karsunky, H., et al. (2008). "Flk2+ common lymphoid progenitors possess equivalent differentiation potential for the B and T lineages." Blood **111**(12): 5562-5570.

Mature blood cells develop from multipotent hematopoietic stem cells through a series of sequential intermediates in which the developmental potential for particular blood lineages is progressively extinguished. We previously reported the identification of one of these developmental intermediates, the common lymphoid progenitor (CLP), which can give rise to T cells, B cells, dendritic cells (DCs), and natural killer cells (NKs), but lacks myeloid and erythroid potential. Recently, several studies have suggested that the T-cell and DC potential of CLP is limited or absent, and/or that CLP contains significant myeloid potential. Here, we show that the originally identified CLP population can be divided into functionally distinct subsets based on the expression of the tyrosine kinase receptor, Flk2. The Flk2(+) subset contains robust in vivo and in vitro T-cell, B-cell, DC, and NK potential, but lacks myeloid potential and, therefore, represents an oligopotent, lymphoid-restricted progenitor. This population of cells does not appear to be B cell-biased and robustly reconstitutes both B and T lineages in vivo, consistent with its being a physiologic progenitor of both of these subsets. Thus, Flk2 expression defines a homogeneous, readily obtainable subset of bone marrow CLP that is completely lymphoid-committed and can differentiate equivalently well into both B and T lineages.

Kolios, G. and Y. Moodley (2013). "Introduction to stem cells and regenerative medicine." Respiration **85**(1): 3-10.

Stem cells are a population of undifferentiated cells characterized by the ability to extensively proliferate (self-renewal), usually arise from a single cell (clonal), and differentiate into different types of cells and tissue (potent). There are several sources of stem cells with varying potencies. Pluripotent cells are embryonic stem cells derived from the inner cell mass of the embryo and induced pluripotent cells are formed following reprogramming of somatic cells. Pluripotent cells can differentiate into tissue from all 3 germ layers (endoderm, mesoderm, and ectoderm). Multipotent stem cells may differentiate into tissue derived from a single germ layer such as mesenchymal stem cells which form adipose tissue, bone, and cartilage. Tissue-resident stem cells are oligopotent since they can form terminally differentiated cells of a specific tissue. Stem cells can be used in cellular therapy to replace damaged cells or to regenerate organs. In addition, stem cells have expanded our understanding of development as well as the pathogenesis of disease. Disease-specific cell lines can also be propagated and used in drug development. Despite the significant advances in stem cell biology, issues such as ethical controversies with embryonic stem cells, tumor formation, and rejection limit their utility. However, many of these limitations are being bypassed and this could lead to major advances in the management of disease. This review is an introduction to the world of stem cells and discusses their definition, origin, and classification, as well as applications of these cells in regenerative medicine.

Koya, T., et al. (1999). "Enrichment of c-kit+ Lin- haemopoietic progenitor cells that commit themselves to extrathymic T cells in in vitro culture of appendix mononuclear cells." Immunology **96**(3): 447-456.

The appendix as well as the small intestine have recently been found to carry c-kit+ stem cells which give rise to extrathymic T cells. In this study, the properties of c-kit+ stem cells in the appendix of mice were further characterized. When appendix mononuclear cells (MNC) were cultured in the presence of stem cell factor, interleukin-3, interleukin-6 and erythropoietin on a methylcellulose culture plate, the population of c-kitdull Lin- and that of c-kithi Lin- cells expanded. Morphological study revealed that these c-kithi Lin- cells were basophilic granular cells (possibly mast cells). Both populations of cultured appendix MNC were then injected into severe combined immunodeficient mice or cultured with Tst-4 thymic stroma cells. These in vivo and in vitro studies demonstrated that c-kitdull Lin- cells were

oligopotent haemopoietic progenitor cells which gave rise to extrathymic T cells, while c-kithi Lin- cells lacked haemopoietic progenitor cell activity. In contrast to c-kit+ stem cells in the bone marrow, those in the appendix did not give rise to myeloid cells and conventional thymic T cells under any of the conditions tested. The present results suggest that the appendix primarily comprises c-kit+ cells which give rise to basophilic granular cells and extrathymic T cells and that such c-kit+ cells have the ability to replicate themselves in culture in vitro.

Lin, K. Y., et al. (2015). "Engraftment of mouse amniotic fluid-derived progenitor cells after in utero transplantation in mice." J Formos Med Assoc **114**(11): 1105-1115.

BACKGROUND/PURPOSE: Amniotic fluid-derived progenitor cells (AFPCs) are oligopotent and shed from the fetus into the amniotic fluid. It was reported that AFPCs express stem cell-like markers and are capable of differentiating into specific cell type in in vitro experiments. However, no study has fully investigated the potentiality and destiny of these cells in in vivo experiments. METHODS: Ds-red transgenic mice (on Day 13.5 of pregnancy) were transplanted in utero with enhanced green fluorescent protein-labeled mouse AFPC (EGFP-mAFPCs). After birth, baby mice were euthanized at 3-week intervals beginning 3 weeks postnatally, and the specimens were examined by polymerase chain reaction, histology, and flow cytometry. RESULTS: Our results demonstrate the transplantability of mAFPCs into all three germ layers and the potential of mAFPCs in the study of progenitor cell homing, differentiation, and function. Engraftment of EGFP-mAFPCs was detected in the intestine, kidney, muscle, skin, bladder, heart, stomach, etc., at 3 weeks after delivery. CONCLUSION: This model using EGFP-mAFPCs injected in utero may provide an ideal method for determining the fate of transplanted cells in recipients and these findings may justify a clinical trial of in utero transplantation during gestation for patients who have inherited genetic disorders.

Majo, F., et al. (2008). "Oligopotent stem cells are distributed throughout the mammalian ocular surface." Nature **456**(7219): 250-254.

The integrity of the cornea, the most anterior part of the eye, is indispensable for vision. Forty-five million individuals worldwide are bilaterally blind and another 135 million have severely impaired vision in both eyes because of loss of corneal transparency; treatments range from local medications to corneal transplants, and more recently to stem cell therapy. The corneal epithelium is a squamous epithelium that is constantly renewing, with a vertical turnover of 7 to 14 days in many mammals. Identification of slow cycling cells (label-retaining cells) in the limbus of the mouse has led to the notion that the limbus is the niche for the stem cells responsible for the long-term renewal of the cornea; hence, the corneal epithelium is supposedly renewed by cells generated at and migrating from the limbus, in marked opposition to other squamous epithelia in which each resident stem cell has in charge a limited area of epithelium. Here we show that the corneal epithelium of the mouse can be serially transplanted, is self-maintained and contains oligopotent stem cells with the capacity to generate goblet cells if provided with a conjunctival environment. Furthermore, the entire ocular surface of the pig, including the cornea, contains oligopotent stem cells (holoclones) with the capacity to generate individual colonies of corneal and conjunctival cells. Therefore, the limbus is not the only niche for corneal stem cells and corneal renewal is not different from other squamous epithelia. We propose a model that unifies our observations with the literature and explains why the limbal region is enriched in stem cells.

Nakajima, H. (2011). "Role of transcription factors in differentiation and reprogramming of hematopoietic cells." Keio J Med **60**(2): 47-55.

Differentiation of hematopoietic cells is a sequential process of cell fate decision originating from hematopoietic stem cells (HSCs), allowing multi- or oligopotent progenitors to commit to certain lineages. HSCs are cells that are able to self-renew and repopulate the marrow for the long term. They first differentiate into multipotent progenitors (MPPs), which give rise to common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). CMPs then differentiate into granulocyte monocyte progenitors (GMPs) and megakaryocyte erythroid progenitors (MEPs), which are the precursors of granulocytes/monocytes and erythrocytes/megakaryocytes, respectively. Lineage specification at differentiation branch points is dictated by the activation of lineage-specific transcription factors such as C/EBPalpha, PU.1, and GATA-1. The role of these transcription factors is generally instructive, and the expression of a single factor can often determine cell fate. Differentiation was long regarded as an irreversible process, and it was believed that somatic cells would not change their fate once they were differentiated. This paradigm was first challenged by the finding that ectopic cytokine signals could change the fate of differentiation, probably through modulating internal transcription networks. Subsequently, we and others showed that virtually all progenitors, including CLPs, CMPs, GMPs, and MEPs, still retain differentiation plasticity, and they can be

converted into lineages other than their own by ectopic activation of only a single lineage-specific transcription factor. These findings established a novel paradigm for cellular differentiation and opened up an avenue for artificially manipulating cell fate for clinical use.

Narayanan, D. L. and S. R. Phadke (2018). "Concepts, Utility and Limitations of Cord Blood Banking: What Clinicians Need to Know." Indian J Pediatr.

Stem cell transplantation and cord blood banking have received much popularity among general public and medical professionals in the recent past. But information about the scientific aspects, its utility and limitations is incomplete amongst laypersons as well as many medical practitioners. Stem cells differ from all other types of cells in the human body because of their ability to multiply in order to self perpetuate and differentiate into specialized cells. Stems cells could be totipotent, multipotent, pluripotent, oligopotent or unipotent depending on the type of cells that can arise or differentiate from them. Umbilical cord blood serves as a potent source of hematopoeitic stem cells and is being used to treat various disorders like blood cancers, hemoglobinopathies and immunodeficiency disorders for which hematological stem cell transplantation is the standard of care. Cord blood can be collected at ease, without any major complications and has a lower incidence of graft vs. host reaction compared to bone marrow cells or peripheral blood cells. Both public and private banks have been established for collection and storage of umbilical cord blood. However, false claims and misleading commercial advertisements about the use of umbilical cord blood stem cells for the treatment of a variety of conditions ranging from neuromuscular disorders to cosmetic benefits are widespread and create unrealistic expectations in laypersons and clinicians. Many clinicians and laypersons are unaware of the limitations of cord blood banking, as in treating a genetic disorder by autologous cord blood transplant. Knowledge and awareness about the scientific indications of cord blood stem cell transplantation and realistic expectations about the utility of cord blood among medical practitioners are essential for providing accurate information to laypersons before they decide to preserve umbilical cord blood in private banks and thus prevent malpractice.

Notta, F., et al. (2016). "Distinct routes of lineage development reshape the human blood hierarchy across ontogeny." Science **351**(6269): aab2116.

In a classical view of hematopoiesis, the various blood cell lineages arise via a hierarchical scheme starting with multipotent stem cells that become increasingly restricted in their differentiation potential through oligopotent and then unipotent progenitors. We developed a cell-sorting scheme to resolve myeloid (My), erythroid (Er), and megakaryocytic (Mk) fates from single CD34(+) cells and then mapped the progenitor hierarchy across human development. Fetal liver contained large numbers of distinct oligopotent progenitors with intermingled My, Er, and Mk fates. However, few oligopotent progenitor intermediates were present in the adult bone marrow. Instead, only two progenitor classes predominate, multipotent and unipotent, with Er-Mk lineages emerging from multipotent cells. The developmental shift to an adult "two-tier" hierarchy challenges current dogma and provides a revised framework to understand normal and disease states of human hematopoiesis.

O'Neill, H. C., et al. (2014). "Spleen stroma maintains progenitors and supports long-term hematopoiesis." Curr Stem Cell Res Ther **9**(4): 354-363.

Hematopoietic stem/progenitor cells (HSPC) differentiate in the context of stromal niches producing cells of multiple lineages. Limited success has been achieved in the past with induction of hematopoiesis in vitro. Previously, spleen long-term stromal cultures (LTC) were shown to continuously support restricted hematopoiesis for production of novel dendritic-like cells (LTC-DC). An in vivo equivalent dendritic cell type was then described which is specific for spleen. The in vivo counterpart cell was termed 'L-DC' and represents a dendritic-like CD11c (lo)CD11b (hi)CD8alpha-MHC-II- cell which differs phenotypically and functionally from monocytes/macrophages and conventional and plasmacytoid DC. Splenic stroma is now shown to maintain HSPC and to support their restricted in vitro differentiation to give this 'L-DC' subset. In order to characterise progenitors of this distinct cell type, LTC were analysed for cell subsets produced, and these subsets sorted and assessed for hematopoietic potential in subsequent co-cultures over STX3 stroma. Progenitors were defined as a lineage (Lin) (-)ckit (lo) subset reflecting HSPC. Furthermore, when Lin (-)ckit (hi)Sca1(+)Flt3(-) HSPC were sorted from bone marrow, they colonised splenic stroma with long-term production of L-DC. The maintenance of HSPC by splenic stroma was confirmed when non-adherent cells collected from LTC showed oligopotent reconstitution of the hematopoietic compartment of lethally irradiated mice. All data support a model whereby spleen houses a niche for HSPC in the resting state, with production of progenitors, and their differentiation to give tissue-specific antigen presenting cells.

Paiushina, O. V. and E. I. Domaratskaia (2015). "[Heterogeneity and possible structure of mesenchymal stromal cell population]." Tsitologiia **57**(1): 31-38.

Mesenchymal stromal cells (MSC) represent a heterogeneous population of cells that differ in morphology, phenotype, ability to grow and differentiate, and other properties. Differences between MSC are related in part to the influence of their microenvironment. However, the heterogeneity of these cells also is due to their parent-progeny relationship. Hierarchical organization of the MSC population that comprises different categories of oligopotent and multipotent cells, is complicated and poorly understood. This review includes data on morphological, phenotypic and functional heterogeneity of MSC and its possible connection with the population structure.

Palii, C. G., et al. (2011). "Lentiviral-mediated knockdown during ex vivo erythropoiesis of human hematopoietic stem cells." J Vis Exp (53).

Erythropoiesis is a commonly used model system to study cell differentiation. During erythropoiesis, pluripotent adult human hematopoietic stem cells (HSCs) differentiate into oligopotent progenitors, committed precursors and mature red blood cells. This process is regulated for a large part at the level of gene expression, whereby specific transcription factors activate lineage-specific genes while concomitantly repressing genes that are specific to other cell types. Studies on transcription factors regulating erythropoiesis are often performed using human and murine cell lines that represent, to some extent, erythroid cells at given stages of differentiation. However transformed cell lines can only partially mimic erythroid cells and most importantly they do not allow one to comprehensibly study the dynamic changes that occur as cells progress through many stages towards their final erythroid fate. Therefore, a current challenge remains the development of a protocol to obtain relatively homogenous populations of primary HSCs and erythroid cells at various stages of differentiation in quantities that are sufficient to perform genomics and proteomics experiments. Here we describe an ex vivo cell culture protocol to induce erythroid differentiation from human hematopoietic stem/progenitor cells that have been isolated from either cord blood, bone marrow, or adult peripheral blood mobilized with G-CSF (leukapheresis). This culture system, initially developed by the Douay laboratory, uses cytokines and co-culture on mesenchymal cells to mimic the bone marrow microenvironment. Using this ex vivo differentiation protocol, we observe a strong amplification of erythroid progenitors, an induction of differentiation exclusively towards the erythroid lineage and a complete maturation to the stage of enucleated red blood cells. Thus, this system provides an opportunity to study the molecular mechanism of transcriptional regulation as hematopoietic stem cells progress along the erythroid lineage. Studying erythropoiesis at the transcriptional level also requires the ability to over-express or knockdown specific factors in primary erythroid cells. For this purpose, we use a lentivirus-mediated gene delivery system that allows for the efficient infection of both dividing and non-dividing cells. Here we show that we are able to efficiently knockdown the transcription factor TAL1 in primary human erythroid cells. In addition, GFP expression demonstrates an efficiency of lentiviral infection close to 90%. Thus, our protocol provides a highly useful system for characterization of the regulatory network of transcription factors that control erythropoiesis.

Papavasiliou, A. K., et al. (1996). "Microglial lineage species are expressed in mammalian epidermal growth factor-generated embryonic neurospheres." J Neurosci Res **46**(1): 49-57.

The epigenetic signals and progenitor cell species involved in progressive neural maturation in the mammalian brain are poorly understood. Although these complex developmental issues can be examined in cultures of generative zone progenitor cells, analysis of signaling relationships in complex progenitor cell systems requires the meticulous definition of the cellular complement at each developmental stage. The presence of microglia within the generative zone cultures would further complicate these developmental analyses. Utilizing the microglial markers Griffonia simplicifolia B4 isolectin, carbocyanine dye-acetylated low density lipoprotein, F4/80, and Mac-1 we now report the presence of microglia within cultures of late embryonic murine epidermal growth factor-derived generative zone progenitor cells. Cytokine treatment of serially passaged epidermal growth factor-generated neurospheres altered the phenotype of the microglia in culture. Macrophage colony-stimulating factor treatment promoted the expression of spindle-shaped microglia, whereas granulocytemacrophage colony-stimulating factor treatment promoted the elaboration of flat and amoeboid microglia. Treatment with microglial-conditioned medium or 10% non-heat inactivated fetal calf serum led to an increased complement of both phenotypes. Microglia could be generated from single isolated neurospheres, and there were differences in the number of microglial lineage species obtained from distinct oligopotent progenitor cells, raising the possibility that a complement of this cellular lineage may be derived from a progenitor cell present within the generative zones. These

observations indicate that microglia are present within the generative zone progenitor cell system, and this system thus represents an important experimental resource to examine the progenitor cell maturation and the origin of the microglial lineage.

Pathak, P., et al. (2017). "Synchronous Occurrence of Chronic Myeloid Leukemia and Mantle Cell Lymphoma." Case Rep Hematol **2017**: 7815095.

Chronic myeloid leukemia (CML) and mantle cell lymphoma (MCL) are hematologic malignancies that originate from different oligopotent progenitor stem cells, namely, common myeloid and lymphoid progenitor cells, respectively. Although blastic transformation of CML can occur in the lymphoid lineage and CML has been related to non-Hodgkin lymphoma on transformation, to our knowledge, de novo and synchronous occurrence of CML and MCL has not been reported. Herein, we report the first case of synchronous CML and MCL in an otherwise healthy 38-year-old man. Potential etiologies and pathological relationships between the two malignancies are explored, including the possibility that the downstream effects of BCR-ABL may link it to an overexpression of cyclin D1, which is inherent to the etiology of MCL.

Perez, S. A., et al. (2003). "A novel myeloid-like NK cell progenitor in human umbilical cord blood." Blood **101**(9): 3444-3450.

Natural killer (NK) cell differentiation from pluripotent CD34(+) human hematopoietic stem cells or oligopotent lymphoid progenitors has already been reported. In the present study, long-term cultures of the CD56(-)/CD34(-) myeloid-like adherent cell fraction (ACF) from umbilical cord blood (UCB), characterized by the expression of CD14(+) as well as other myeloid markers, were set up with flt3 ligand (FL) and interleukin-15 (IL-15). The UCB/ACF gradually expressed the CD56 marker, which reached fairly high levels (approximately 90% of the cells were CD56(+)) by day 15. FL plus IL-15-driven ACF/CD56(+) cells progressively expressed a mature NK functional program lysing both NK- and lymphokine-activate killer (LAK)-sensitive tumor targets and producing high levels of interferon-gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor, tumor necrosis factor alpha, and IL-10 upon stimulation with IL-12 and IL-18. Similar results were obtained when highly purified CD14(+) cells from UCB were cultured with FL and IL-15. In contrast, UCB/CD34(+) cells cultured under the same conditions showed a delayed expression of CD56 and behaved functionally differently in that they exhibited NK but not LAK cytotoxicity and produced significantly fewer cytokines. Kinetic studies on the phenotype of UCB/ACF or UCB/CD14(+) cells cultured in the presence of FL and IL-15 showed a rapid decrease in CD14 expression after day 5, which reached levels of zero by day 20. Approximately 60% of the CD56(+) derived from the UCB/ACF or the UCB/CD14(+) cells coexpressed CD14 by day 5. Taken together, our data support the role of CD14(+) myeloid-like cells within UCB as a novel progenitor for lymphoid NK cells.

Perry, K. J., et al. (2013). "Expression of pluripotency factors in larval epithelia of the frog Xenopus: evidence for the presence of cornea epithelial stem cells." Dev Biol **374**(2): 281-294.

Understanding the biology of somatic stem cells in self renewing tissues represents an exciting field of study, especially given the potential to harness these cells for tissue regeneration and repair in treating injury and disease. The mammalian cornea contains a population of basal epithelial stem cells involved in cornea homeostasis and repair. Research has been restricted to mammalian systems and little is known about the presence or function of these stem cells in other vertebrates. Therefore, we carried out studies to characterize frog cornea epithelium. Careful examination shows that the Xenopus larval cornea epithelium consists of three distinct layers that include an outer epithelial layer and underlying basal epithelium, in addition to a deeper fibrous layer that contains the main sensory nerve trunks that give rise to numerous branches that extend into these epithelia. These nerves convey sensory and presumably also autonomic innervation to those tissues. The sensory nerves are all derived as branches of the trigeminal nerve/ganglion similar to the situation encountered in mammals, though there appear to be some potentially interesting differences, which are detailed in this paper. We show further that numerous pluripotency genes are expressed by cells in the cornea epithelium, including: sox2, p63, various oct4 homologs, c-myc, klf4 and many others. Antibody localization revealed that p63, a well known mammalian epithelial stem cell marker, was localized strictly to all cells in the basal cornea epithelium. c-myc, was visualized in a smaller subset of basal epithelial cells and adjacent stromal tissue predominately at the periphery of the cornea (limbal zone). Finally, sox2 protein was found to be present throughout all cells of both the outer and basal epithelia, but was much more intensely expressed in a distinct subset of cells that appeared to be either multinucleate or possessed multi-lobed nuclei that are normally located at the periphery of the cornea. Using a thymidine analog (EdU), we were able to label mitotically active cells, which revealed that cell proliferation takes place throughout the cornea epithelium, predominantly in the basal epithelial layer.

Species of Xenopus and one other amphibian are unique in their ability to replace a missing lens from cells derived from the basal cornea epithelium. Using EdU we show, as others have previously, that proliferating cells within the cornea epithelium do contribute to the formation of these regenerated lenses. Furthermore, using qPCR we determined that representatives of various pluripotency genes (i.e., sox2, p63 and oct60) are upregulated early during the process of lens regeneration. Antibody labeling showed that the number of sox2 expressing cells increased dramatically within 4 h following lens removal and these cells were scattered throughout the basal layer of the cornea epithelium. Historically, the process of lens regeneration in Xenopus had been described as one involving transdifferentiation of cornea epithelial cells (i.e., one involving cellular dedifferentiation followed by redifferentiation). Our combined observations provide evidence that a population of stem cells exists within the Xenopus cornea. We hypothesize that the basal epithelium contains oligopotent epithelial stem cells that also represent the source of regenerated lenses in the frog. Future studies will be required to clearly identify the source of these lenses.

Pouzolles, M., et al. (2016). "Hematopoietic stem cell lineage specification." Curr Opin Hematol **23**(4): 311-317.

PURPOSE OF REVIEW: Hematopoietic stem cells (HSCs) possess two fundamental characteristics, the capacity for self-renewal and the sustained production of all blood cell lineages. The fine balance between HSC expansion and lineage specification is dynamically regulated by the interplay between external and internal stimuli. This review introduces recent advances in the roles played by the stem cell niche, regulatory transcriptional networks, and metabolic pathways in governing HSC self-renewal, commitment, and lineage differentiation. We will further focus on discoveries made by studying hematopoiesis at single-cell resolution. RECENT FINDINGS: HSCs require the support of an interactive milieu with their physical position within the perivascular niche dynamically regulating HSC behavior. In these microenvironments, transcription factor networks and nutrient-mediated regulation of energy resources, signaling pathways, and epigenetic status govern HSC quiescence and differentiation. Once HSCs begin their lineage specification, single-cell analyses show that they do not become oligopotent but rather, differentiate directly into committed unipotent progenitors. SUMMARY: The diversity of transcriptional networks and metabolic pathways in HSCs and their downstream progeny allows a high level of plasticity in blood differentiation. The intricate interactions between these pathways, within the perivascular niche, broaden the specification of HSCs in pathological and stressed conditions.

Ronnerblad, M., et al. (2014). "Analysis of the DNA methylome and transcriptome in granulopoiesis reveals timed changes and dynamic enhancer methylation." Blood **123**(17): e79-89.

In development, epigenetic mechanisms such as DNA methylation have been suggested to provide a cellular memory to maintain multipotency but also stabilize cell fate decisions and direct lineage restriction. In this study, we set out to characterize changes in DNA methylation and gene expression during granulopoiesis using 4 distinct cell populations ranging from the oligopotent common myeloid progenitor stage to terminally differentiated neutrophils. We observed that differentially methylated sites (DMSs) generally show decreased methylation during granulopoiesis. Methylation appears to change at specific differentiation stages and overlap with changes in transcription and activity of key hematopoietic transcription factors. DMSs were preferentially located in areas distal to CpG islands and shores. Also, DMSs were overrepresented in enhancer elements and enriched in enhancers that become active during differentiation. Overall, this study depicts in detail the epigenetic and transcriptional changes that occur during granulopoiesis and supports the role of DNA methylation as a regulatory mechanism in blood cell differentiation.

Shostak, S. (2006). "(Re)defining stem cells." Bioessays **28**(3): 301-308.

Stem-cell nomenclature is in a muddle! So-called stem cells may be self-renewing or emergent, oligopotent (uni- and multipotent) or pluri- and totipotent, cells with perpetual embryonic features or cells that have changed irreversibly. Ambiguity probably seeped into stem cells from common usage, flukes in biology's history beginning with Weismann's divide between germ and soma and Haeckel's biogenic law and ending with contemporary issues over the therapeutic efficacy of adult versus embryonic cells. Confusion centers on tissue dynamics, whether stem cells are properly members of emerging or steady-state populations. Clarity might yet be achieved by codifying differences between cells in emergent populations, including embryonic stem and embryonic germ (ES and EG) cells in tissue culture as opposed to self-renewing (SR) cells in steady-state populations.

Skurikhin, E. G., et al. (2014). "Differentiation of pancreatic stem and progenitor beta-cells into insulin

secreting cells in mice with diabetes mellitus." Bull Exp Biol Med **156**(6): 726-730.

We studied in vitro differentiation of pancreatic stem and progenitor cells into insulin secreting cells in the model of streptozotocin-induced diabetes in C57Bl/6 mice. Streptozotocin was shown to increase the population of pancreatic oligopotent beta-cell precursors (CD45(-), TER119(-), CD133(+), and CD49f (low)) and did not affect multipotent (stem) progenitor cells (CD45(-), TER119(-), CD17(-), CD309(-)). During long-term culturing, diabetic multipotent progenitor cells showed high capacity for self-renewal. A population of dithizone-positive (insulin secreting cells) mononuclear cells was obtained releasing insulin after prolonged culturing in suspension enriched with diabetic CD45(-), TER119(-), CD17(-), and CD309(-) cells. The rate of generation of "new" insulin-producing cells and insulin release in the samples of experimental group considerably exceeded activity of the corresponding processes in the control group.

Skurikhin, E. G., et al. (2016). "Role of Tissue-Specific Stem and Progenitor Cells in the Regeneration of the Pancreas and Testicular Tissue in Diabetic Disorders." Bull Exp Biol Med **162**(1): 146-152.

Using the model of hypogonadism in C57Bl/6 male mice, we showed that injection of streptozotocin to newborn animals and high-fat diet induced serum IFN-gamma and IL-17 elevation, glucose metabolism disturbances, insulin resistance, destructive changes of the Langerhans islets (deficit of PDX1(+)beta cells), while the number of oligopotent beta cell precursors (CD45(-)TER119(-)CD133(+)CD49f (low)) increased. Diabetes played the role of an inducer of testicular tissue inflammation (pan-hemopoietic cell infiltration, increase of IL-2, IL-17, and IL-23 content) and reproductive system disturbances in mice (decrease in free testosterone concentration, suppression of spermatogenesis, and infertility). The development of hypogonadism was paralleled by an increase in the count of spermatogonial stem cells (CD117(+)CD29(+)CD90(+)), multipotent mesenchymal stromal cells (CD45(-)CD31(-)CD90(+)CD106(+)), hemangiogenesis precursors (CD45(-)CD117(+)Flk1(+)), and epithelial cells (CD45(-)CD31(-)CD49f (+)CD326(+)).

Suda, J., et al. (1984). "Analysis of differentiation of mouse hemopoietic stem cells in culture by sequential replating of paired progenitors." Blood **64**(2): 393-399.

Blast cell colonies seen in cultures of spleen cells from 5-fluorouracil-treated mice provide a highly enriched population of primitive hemopoietic progenitors. Our recent studies of the differentiation potentials of the paired daughter cells of these progenitors showed different patterns of differentiation in the colonies produced by the separated daughter cells. In this study, we carried out sequential micromanipulation of paired progenitors followed by cytologic examinations of the colonies derived from these progenitors. Of the total 94 evaluable cultures, consisting of three or more colonies, 52 consisted of macrophage colonies and one consisted of megakaryocyte colonies. In the remaining 41 cultures, diverse combinations of colonies revealing heterogeneous compositions of cell lineages were identified. Presumptive genealogic trees of the differentiation of hemopoietic progenitors constructed for the latter group of cultures suggested that monopotent progenitors may be derived from pluripotent progenitors in two ways: (1) directly during one cell division of pluripotent cells or (2) as a result of progressive lineage restriction during successive division of the pluripotent progenitors. The results also suggested that some of the oligopotent progenitors are capable of limited self-renewal.

Sun, T. T., et al. (2010). "Location of corneal epithelial stem cells." Nature **463**(7284): E10-11; discussion E11.

The longstanding concept that corneal epithelial stem cells reside mainly in the limbus is supported by the absence of major corneal epithelial differentiation markers, that is, K3 and K12 keratins, in limbal basal cells (these markers are expressed, however, in corneal basal cells, thus distinguishing the mode of keratin expression in corneal epithelium from that of all other stratified epithelia), the centripetal migration of corneal epithelial cells, the exclusive location of slow-cycling cells in the limbal basal layer, the superior in vitro proliferative potential of limbal epithelial cells, and the transplanted limbal cells' ability to reconstitute corneal epithelium in vivo (reviewed in refs 1-4). Moreover, previous data indicate that corneal and conjunctival epithelia represent two separate cell lineages (reviewed in refs 1-4). Majo et al. suggested, however, that corneal and conjunctival epithelia are equipotent, and that identical oligopotent stem cells are present throughout the corneal, limbal and conjunctival epithelia. We point out here that these suggestions are inconsistent with many known growth, differentiation and cell migration properties of the anterior ocular epithelia.

Tanabe, S., et al. (2008). "Gene expression profiling of human mesenchymal stem cells for identification of novel markers in early- and late-stage cell culture." J Biochem **144**(3): 399-408.

Human mesenchymal stem cells (hMSCs) are multipotent cells that differentiate into several cell types, and are expected to be a useful tool for cellular therapy. Although the hMSCs differentiate into osteogenic cells during early to middle stages, this differentiation capacity decreases during the late stages of cell culture. To test a hypothesis that there are biomarkers indicating the differentiation potential of hMSCs, we performed microarray analyses and profiled the gene expression in six batches of hMSCs (passages 4-28). At least four genes [necdin homolog (mouse) (NDN), EPH receptor A5 (EPHA5), nephroblastoma overexpressed gene (NOV) and runt-related transcription factor 2 (RUNX2)] were identified correlating with the passage numbers in all six batches. The results showed that the osteogenic differentiation capacity of hMSCs is down-regulated in the late stages of cell culture. It seemed that adipogenic differentiation capacity was also down-regulated in late stage of the culture. The cells in late stage are oligopotent and the genes identified in this study have the potential to act as quality-control markers of the osteogenic differentiation capacity of hMSCs.

Trentin, A., et al. (2004). "Self-renewal capacity is a widespread property of various types of neural crest precursor cells." Proc Natl Acad Sci U S A **101**(13): 4495-4500.

In vertebrates, trunk neural crest (NC) generates glia, neurons, and melanocytes. In addition, it yields mesectodermal derivatives (connective tissues, chondrocytes, and myofibroblasts lining the blood vessels) in the head. Previous in vitro clonal analyses of avian NC cells unraveled a hierarchical succession of highly pluripotent, followed by various intermediate, progenitors, suggesting a model of progressive restrictions in the multiple potentialities of a totipotent stem cell, as prevails in the hematopoietic system. However, which progenitors are able to self-renew within the hierarchy of the NC lineages is still undetermined. Here, we explored further the stem cell properties of quail NC cells by means of in vitro serial subcloning. We identified types of multipotent and oligopotent NC progenitors that differ in their developmental repertoire, ability to self-maintain, and response to exogenous endothelin 3 according to their truncal or cephalic origin. The most striking result is that bipotent progenitors are endowed with self-renewal properties. Thus glia-melanocyte and glia-myofibroblast progenitors behave like stem cells in that they are able both to self-renew and generate a restricted progeny. In our culture conditions, glia-myofibroblast precursors display a modest capacity to self-renew, whereas glia-melanocyte precursors respond to endothelin 3 by extensive self-renewal. These findings may explain the etiology of certain multiphenotypic NC-derived tumors in humans. Moreover, the presence of multiple stem cell phenotypes along the NC-derived lineages may account for the rarity of the "totipotent NC stem cell" and may be related to the large variety and widespread dispersion of NC derivatives throughout the body.

Wagers, A. J. and I. L. Weissman (2006). "Differential expression of alpha2 integrin separates long-term and short-term reconstituting Lin-/loThy1.1(lo)c-kit+ Sca-1+ hematopoietic stem cells." Stem Cells **24**(4): 1087-1094.

Self-renewing, multipotent hematopoietic stem cells are highly enriched within the Lin- Thy1.1(lo)c-kit+ Sca-1+ subset of mouse bone marrow. However, heterogeneous expression within this population of certain cell surface markers raises the possibility that it may be further fractionated phenotypically and perhaps functionally. We previously identified alpha2-integrin (CD49b) as a surface marker with heterogeneous expression on Lin (-/lo)Thy1.1(lo)c-kit+ Sca-1+ stem cells. To determine whether differences in alpha2 expression were indicative of differences in stem cell function, we purified alpha2- and alpha2hi stem cells by fluorescence-activated cell sorting and analyzed their function in long- and short-term hematopoietic reconstitution assays. Both alpha2- and alpha2hi cells could give rise to mature lymphoid and myeloid cells after transplantation into lethally irradiated congenic recipients. However, alpha2hi cells supported hematopoiesis for only a short time (<4 weeks), whereas alpha2- cells reproducibly yielded robust, long-term (>20 weeks) reconstitution, suggesting that alpha2- cells represent a more primitive population than do alpha2hi cells. Consistent with this idea, alpha2- Lin (-/lo)Thy1.1(lo)c-kit+ Sca-1+ cells exhibited an approximately sixfold decreased frequency of spleen colony-forming units (day 12) versus alpha2hi cells. Furthermore, bone marrow cells isolated from animals transplanted >20 weeks previously with 20 alpha2- Lin (-/lo)Thy1.1(lo)c-kit+ Sca-1+ cells included both alpha2- and alpha2hi stem cells of donor origin, indicating that alpha2hi cells are likely lineal descendents of alpha2- cells. Interestingly, alpha2 integrin expression is significantly reduced on lineage-restricted oligopotent progenitors in the marrow, suggesting that high level expression of alpha2 selectively marks a subset of primitive hematopoietic cells which retains multilineage reconstitution potential but exhibits reduced self-renewal capacity.

Wang, H., et al. (2014). "A reporter mouse reveals lineage-specific and heterogeneous expression

of IRF8 during lymphoid and myeloid cell differentiation." J Immunol **193**(4): 1766-1777.

The IFN regulatory factor family member 8 (IRF8) regulates differentiation of lymphoid and myeloid lineage cells by promoting or suppressing lineage-specific genes. How IRF8 promotes hematopoietic progenitors to commit to one lineage while preventing the development of alternative lineages is not known. In this study, we report an IRF8-EGFP fusion protein reporter mouse that revealed previously unrecognized patterns of IRF8 expression. Differentiation of hematopoietic stem cells into oligopotent progenitors is associated with progressive increases in IRF8-EGFP expression. However, significant induction of IRF8-EGFP is found in granulocyte-myeloid progenitors and the common lymphoid progenitors but not the megakaryocytic-erythroid progenitors. Surprisingly, IRF8-EGFP identifies three subsets of the seemingly homogeneous granulocyte-myeloid progenitors with an intermediate level of expression of EGFP defining bipotent progenitors that differentiation into either EGFP (hi) monocytic progenitors or EGFP (lo) granulocytic progenitors. Also surprisingly, IRF8-EGFP revealed a highly heterogeneous pre-pro-B population with a fluorescence intensity ranging from background to 4 orders above background. Interestingly, IRF8-EGFP readily distinguishes true B cell committed (EGFP (int)) from those that are noncommitted. Moreover, dendritic cell progenitors expressed extremely high levels of IRF8-EGFP. Taken together, the IRF8-EGFP reporter revealed previously unrecognized subsets with distinct developmental potentials in phenotypically well-defined oligopotent progenitors, providing new insights into the dynamic heterogeneity of developing hematopoietic progenitors.

Xiao, Y., et al. (2017). "Macrophages and osteoclasts stem from a bipotent progenitor downstream of a macrophage/osteoclast/dendritic cell progenitor." Blood Adv **1**(23): 1993-2006.

Monocytes/macrophages (MPhis), osteoclasts (OCs), and dendritic cells (DCs) are closely related cell types of high clinical significance, but the exact steps in their lineage commitment are unclear. In studies on MPhi and DC development, OC development is generally not addressed. Furthermore, findings on DC development are confusing, because monocytes can also differentiate into DC-like cells. To resolve these issues, we have examined the development of monocytes/MPhis, OCs, and DCs from common progenitors, using the homeostatic driver cytokines macrophage colony-stimulating factor, RANK ligand (L), and Flt3L. In mouse bone marrow, B220(-)CD11b (low/-)c-Kit (+)c-Fms (+) cells could be dissected into a CD27(+)Flt3(+) population that proved oligopotent for MPhi/OC/DC development (MODP) and a CD27(low/-)Flt3(-) population that proved bipotent for MPhi/OC development (MOP). Developmental potential and relationship of MODP and downstream MOP populations are demonstrated by differentiation cultures, functional analysis of MPhi/OC/DC offspring, and genome-wide messenger RNA expression analysis. A common DC progenitor (CDP) has been described as committed to plasmacytoid and conventional DC development. However, the human CDP proved identical to the MODP population, whereas the mouse CDP largely overlapped with the MODP population and was accordingly oligopotent for MPhi, OC, and DC development. The CX3CR1(+) MPhi/DC progenitor (MDP) population described in the mouse generated MPhis and OCs but not DCs. Thus, monocytes/MPhis, OCs, and DCs share a common progenitor that gives rise to a bipotent MPhi/OC progenitor, but a dedicated DC progenitor is currently undefined. The definition of these progenitor populations may serve diagnostics and interventions in diseases with pathogenic activity of MPhis, OCs, or DCs.

Xie, L. X. (2010). "[Advances in basic and clinical corneal research]." Zhonghua Yan Ke Za Zhi **46**(10): 883-887.

It is well known that corneal epithelial stem cells reside in the limbal basal layer. Recently, it has been found that oligopotent stem cells, located in the basal layer of corneal epithelium, can repair epithelial cell damage. Although corneal endothelial cells usually could not regenerate in vivo, stem cells have been detected in the endothelial cell layer and can convert into endothelial cells under certain circumstances. Stem cells are also present in corneal stroma. The heterogeneous stromal cells manifest features of neural crest progenitor cells in some situations, which make latent herpes simplex virus-1 infection possible. Moreover, the finding that the hyphal growth of different fungal pathogens shows different patterns in the cornea. This finding significantly promotes the surgical treatment of fungal keratitis. The major risk factor of acanthamoeba keratitis in China is trauma caused by plants or soil, which is different from developed countries, in which the major risk factor is contact lens wear. This finding provides important new information for clinical diagnosis of this disorder. Advances in basic and clinical corneal research in the last five years are reviewed in this article.

Yoon, J. J., et al. (2014). "Limbal stem cells: Central concepts of corneal epithelial homeostasis." World J Stem Cells **6**(4): 391-403.

A strong cohort of evidence exists that supports the localisation of corneal stem cells at the limbus. The

distinguishing characteristics of limbal cells as stem cells include slow cycling properties, high proliferative potential when required, clonogenicity, absence of differentiation marker expression coupled with positive expression of progenitor markers, multipotency, centripetal migration, requirement for a distinct niche environment and the ability of transplanted limbal cells to regenerate the entire corneal epithelium. The existence of limbal stem cells supports the prevailing theory of corneal homeostasis, known as the XYZ hypothesis where X represents proliferation and stratification of limbal basal cells, Y centripetal migration of basal cells and Z desquamation of superficial cells. To maintain the mass of cornea, the sum of X and Y must equal Z and very elegant cell tracking experiments provide strong evidence in support of this theory. However, several recent studies have suggested the existence of oligopotent stem cells capable of corneal maintenance outside of the limbus. This review presents a summary of data which led to the current concepts of corneal epithelial homeostasis and discusses areas of controversy surrounding the existence of a secondary stem cell reservoir on the corneal surface.

Yoshida, K., et al. (2007). "Oligopotent mesenchymal stem cell-like clone becomes multinucleated following phorbol ester, TPA stimulation." Anat Rec (Hoboken) **290**(10): 1256-1267.

We established a mesenchymal stem cell clone, 5F9A, from rat bone marrow substrate adherent cells by repeated limiting dilutions. The cells have a fibroblastic shape and form intimate contacts with adjacent cells with interdigitations and junctions similar to adherence and tight junctions in a semi-confluent culture. Analysis of the phenotypes of these cells by RT-PCR and FACS demonstrated that they resembled mesenchymal stem cells, and the cells could differentiate into adiopocytes and osteoblasts under appropriate conditions in vitro showing their oligopotency. Furthermore, the cells were induced to become multinuclear cells by TPA (12-o-tetradecanoylphorbol 13-acetate) stimulation.

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