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Stem Cell

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Stem Cell and Immortality 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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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.

Bell, R. J., et al. (2016). "Understanding TERT Promoter Mutations: A Common Path to Immortality." Mol Cancer Res **14**(4): 315-323.

Telomerase (TERT) activation is a fundamental step in tumorigenesis. By maintaining telomere length, telomerase relieves a main barrier on cellular lifespan, enabling limitless proliferation driven by oncogenes. The recently discovered, highly recurrent mutations in the promoter of TERT are found in over 50 cancer types, and are the most common mutation in many cancers. Transcriptional activation of TERT, via promoter mutation or other mechanisms, is the rate-limiting step in production of active telomerase. Although TERT is expressed in stem cells, it is naturally silenced upon differentiation. Thus, the presence of TERT promoter mutations may shed light on whether a particular tumor arose from a stem cell or more differentiated cell type. It is becoming clear that TERT mutations occur early during cellular transformation, and activate the TERT promoter by recruiting transcription factors that do not normally regulate TERT gene expression. This review highlights the fundamental and widespread role of TERT promoter mutations in tumorigenesis, including recent progress on their mechanism of transcriptional activation. These somatic promoter mutations, along with germline variation in the TERT locus also appear to have significant value as biomarkers of patient outcome. Understanding the precise molecular mechanism of TERT activation by promoter mutation and germline variation may inspire novel cancer cell-specific targeted therapies for a large number of cancer patients.

Carruba, G. and J. E. Trosko (2017). "The Long Evolutionary Journey of Cancer from Ancestor to Modern Humans." Crit Rev Oncog **22**(3-4): 323-352.

In this article, we review various key issues in cancer development and progression that have important implications for both cancer prevention and treatment: (1) evolutionary aspects of cancer appearance; (2) evidence of organ-specific adult stem cells as cancer-initiating cells; (3) the immortality of cancer-initiating cells; (4) cancer cell loss of growth control, contact inhibition, terminal differentiation, and apoptosis; (5) stem-cell versus de-differentiation theory of carcinogenesis; (6) mutations in cancer; (7) oncogenes and tumor suppressor genes; (8) epigenetics as the rate-limiting step in carcinogenesis; (9) the

potential role of cultural, lifestyle, and nutritional behaviors in oncology; and (10) changes of commensal microbial community and its metagenome in carcinogenesis and tumor progression. Relevant, combined evidence is discussed from a standpoint whereby cancer is considered a multifaceted disease requiring integrated biomolecular and clinico-pathological information to design and implement strategies for either primary prevention or therapy.

Chen, M., et al. (2010). "Emerging role of the MORF/MRG gene family in various biological processes, including aging." Ann N Y Acad Sci **1197**: 134-141.

Cellular senescence is the dominant phenotype over immortality. In our studies to identify senescence-related genes, we cloned Morf4, which induced senescence in a subset of tumor cells. Morf4 is a member of a family of seven genes, and Morf-related genes (Mrg) on chromosomes 15 (Mrg15) and X (MrgX) are also expressed. In contrast to MORF4, MRG15 and MRGX are positive regulators of cell division. All three proteins interact with histone deacetylases and acetyltransferases, suggesting that they function in regulation of chromatin dynamics. Mrg15 knockout mice are embryonic lethal, and mouse embryonic fibroblasts derived from Mrg15 null embryos proliferate poorly, enter senescence rapidly, and have impaired DNA repair compared to the wild type. Mrg15 null embryonic neural stem and progenitor cells also have a decreased capacity for proliferation and differentiation. Further studies are needed to determine the function of this gene family in various biological processes, including neural stem and progenitor cell aging.

Danko, M. J., et al. (2015). "Unraveling the non-senescence phenomenon in Hydra." J Theor Biol **382**: 137-149.

Unlike other metazoans, Hydra does not experience the distinctive rise in mortality with age known as senescence, which results from an increasing imbalance between cell damage and cell repair. We propose that the Hydra controls damage accumulation mainly through damage-dependent cell selection and cell sloughing. We examine our hypothesis with a model that combines cellular damage with stem cell renewal, differentiation, and elimination. The Hydra individual can be seen as a large single pool of three types of stem cells with some features of differentiated cells. This large stem cell community prevents "cellular damage drift," which is inevitable in complex conglomerate (differentiated) metazoans with numerous and generally isolated pools of stem cells. The process of cellular damage drift is based on changes in the distribution of damage among cells due to random events, and is thus similar to Muller's ratchet in asexual populations. Events in the model that are sources of randomness include budding, cellular death, and cellular damage and repair. Our results suggest that non-senescence is possible only in simple Hydra-like organisms which have a high proportion and number of stem cells, continuous cell divisions, an effective cell selection mechanism, and stem cells with the ability to undertake some roles of differentiated cells.

Dewhirst, M. W., et al. (2016). "The future of biology in driving the field of hyperthermia." Int J Hyperthermia **32**(1): 4-13.

In 2011 Hanahan and Weinberg updated their well-established paper 'The hallmarks of cancer'. The rationale for that review and its predecessor was to produce a conceptual framework for future research in cancer. The original Hallmarks included: cell signalling to enhance tumour cell proliferation, acquisition of ability to evade growth suppressors, developing mechanisms to resist cell death, enabling replicative immortality, initiating angiogenesis and activating processes to enable invasion and metastasis. In the more recent paper, Hanahan and Weinberg added important new features to this composite paradigm. The new features were: (1) altered metabolism, (2) evasion of immune destruction, (3) tumour promoting inflammation, and (4) the cellular microenvironment. These four new features are the main focus of this review. Hanahan and Weinberg did not specifically include the physiological microenvironment which is dominated by hypoxia and acidosis. In this review we will consider these features in addition to the cellular and metabolic components of the microenvironment. The purpose of this review is to present a vision of emerging fields of study in hyperthermia biology over the next decade and beyond. As such, we are focusing our attention on pre-clinical studies, primarily using mice. The application of hyperthermia in human patients has been thoroughly reviewed elsewhere.

Dogan, F. and C. Biray Avci (2018). "Correlation between telomerase and mTOR pathway in cancer stem cells." Gene **641**: 235-239.

Cancer stem cells (CSCs), which are defined as a subset of tumor cells, are able to self-renew, proliferate, differentiate similar to normal stem cells. Therefore, targeting CSCs has been considered as a new approach in cancer therapy. The mammalian target of rapamycin (mTOR) is a receptor tyrosine kinase which plays an important role in regulating cell proliferation, differentiation, cell growth, self-renewal in CSCs. On the other hand, hTERT overactivation provides replicative feature and immortality to CSCs, so the stemness and replicative properties of CSCs depend on telomerase activity. Therefore

hTERT/telomerase activity may become a universal biomarker for anticancer therapy and it is an attractive therapeutic target for CSCs. It is known that mTOR regulates telomerase activity at the translational and post-translational level. Researchers show that mTOR inhibitor rapamycin reduces telomerase activity without changing hTERT mRNA activity. Correlation between mTOR and hTERT is important for survival and immortality of cancer cells. In addition, the PI3K/AKT/mTOR signaling pathway and hTERT up-regulation are related with cancer stemness features and drug resistance. mTOR inhibitor and TERT inhibitor combination may construct a novel strategy in cancer stem cells and it can make a double effect on telomerase enzyme. Consequently, inhibition of PI3K/AKT/mTOR signaling pathway components and hTERT activation may prohibit CSC self-renewal and surpass CSC-mediated resistance in order to develop new cancer therapeutics.

Drosos, I. and G. Kolios (2013). "Stem cells in liver regeneration and their potential clinical applications." Stem Cell Rev Rep **9**(5): 668-684.

Stem cells constitute a population of "primitive cells" with the ability to divide indefinitely and give rise to specialized cells under special conditions. Because of these two characteristics they have received particular attention in recent decades. These cells are the primarily responsible factors for the regeneration of tissues and organs and for the healing of lesions, a feature that makes them a central key in the development of cell-based medicine, called Regenerative Medicine. The idea of wound and organ repair and body regeneration is as old as the mankind, reflecting the human desire for inhibiting aging and immortality and it is first described in the ancient Greek myth of Prometheus. It is of interest that the myth refers to liver, an organ with remarkable regenerative ability after loss of mass and function caused by liver injury or surgical resection. Over the last decade there has been an important progress in understanding liver physiology and the mechanisms underlying hepatic development and regeneration. As liver transplantation, despite its difficulties, remains the only effective therapy for advanced liver disease so far, scientific interest has nowadays been orientated towards Regenerative Medicine and the use of stem cells to repair damaged liver. This review is focused on the available literature concerning the role of stem cells in liver regeneration. It summarizes the results of studies concerning endogenous liver regeneration and stem cell experimental protocols. Moreover, this review discusses the clinical studies that have been conducted in humans so far.

Duleba, M., et al. (2019). "Unlimited expansion of intestinal stem cells from a wide range of ages." Integr Mol Med **6**(4).

The recent technical advance in cloning and culturing ground-state intestinal stem cells (ISC) provides us an opportunity of accurate assessment of age-related impact on the function of highly proliferative intestinal stem cells. Our ability of indefinitely and robustly expanding single-stem-cell derived pedigrees in vitro allows us to study intestinal stem cells at the clonal level. Interestingly, comparable number of ISC clones was yielded from 1mm endoscopic biopsy of all donors despite the age. They were passaged in vitro as pedigrees and expanded to 1 billion cells in approximately sixty days without changes in stemness demonstrated by clonogenicity and multipotency. Therefore, our study shows that ISCs from a wide range of ages can be cloned and expanded to unlimited number in vitro with similar efficiency and stability. These patient-derived ISCs harbor intrinsic immortality and are ideal for autologous transplantation, supporting the promise of adult-stem-cell based personalized medicine.

Erenpreisa, J., et al. (2015). "The "virgin birth", polyploidy, and the origin of cancer." Oncoscience **2**(1): 3-14.

Recently, it has become clear that the complexity of cancer biology cannot fully be explained by somatic mutation and clonal selection. Meanwhile, data have accumulated on how cancer stem cells or stemloids bestow immortality on tumour cells and how reversible polyploidy is involved. Most recently, single polyploid tumour cells were shown capable of forming spheroids, releasing EMT-like descendents and inducing tumours in vivo. These data refocus attention on the centuries-old embryological theory of cancer. This review attempts to reconcile seemingly conflicting data by viewing cancer as a pre-programmed phylogenetic life-cycle-like process. This cycle is apparently initiated by a meiosis-like process and driven as an alternative to accelerated senescence at the DNA damage checkpoint, followed by an asexual syngamy event and endopolyploid-type embryonal cleavage to provide germ-cell-like (EMT) cells. This cycle is augmented by genotoxic treatments, explaining why chemotherapy is rarely curative and drives resistance. The logical outcome of this viewpoint is that alternative treatments may be more efficacious - either those that suppress the endopolyploidy-associated 'life cycle' or, those that cause reversion of embryonal malignant cells into benign counterparts. Targets for these opposing strategies are components of the same molecular pathways and interact with regulators of accelerated senescence.

Fahey, M. C. and E. M. Wallace (2011). "Stem cells: research tools and clinical treatments." J Paediatr Child Health **47**(9): 672-675.

The term 'stem cell' most commonly refers to embryonic stem cells, particularly in the lay media; however, it also describes other cell types. A stem cell represents a cell of multi-lineage potential with the ability for self-renewal. It is now clear that the plasticity and immortality of a given stem cell will depend on what type of stem cell it is, whether an embryonic stem cell, a fetal-placental stem cell or an adult stem cell. Stem cells offer great promise as cell-based therapies for the future. With evolving technology, much of the socio-political debate regarding stem cells can now be avoided.

Floor, S., et al. (2011). "Cancer cells in epithelial-to-mesenchymal transition and tumor-propagating-cancer stem cells: distinct, overlapping or same populations." Oncogene **30**(46): 4609-4621.

Cell populations of solid cancers and their distant models, the cancer cell lines, have been categorized in sub-populations: cancer stem-tumor-propagating cells (CSC-TPC) versus derived cells, epithelial- versus mesenchymal-type cells, dormant versus actively proliferating cells and so on. CSC-TPC are minimally defined by their operational properties: immortality and the ability to regenerate in vivo or in vitro the whole panel of cancer cells. The epithelial-to-mesenchymal transition (EMT), mostly observed in vitro, generates mesenchymal-type from epithelial-type cells. The converse transition is mesenchymal-to-epithelial transition. In vitro work suggests that CSC-TPC and EMT cell phenotypes overlap. An analysis of the properties of these sub-populations, as studied in vitro, shows that indeed these two phenotypes may be linked to some extent. However, the in vivo counterpart of this relation in human tumors has barely been investigated. A model in which among the EMT cells released from the tumor only the most competent CSC-TPC will succeed to metastasize is proposed. It is suggested that in the Darwinian evolution of cancer cells, many phenotypes reflecting the expression of various programs, reversible to irreversible, exclusive, overlapping or linked coexist and compete with each other.

Florea, M. (2017). "Aging and immortality in unicellular species." Mech Ageing Dev **167**: 5-15.

It has been historically thought that in conditions that permit growth, most unicellular species do not to age. This was particularly thought to be the case for symmetrically dividing species, as such species lack a clear distinction between the soma and the germline. Despite this, studies of the symmetrically dividing species Escherichia coli and Schizosaccharomyces pombe have recently started to challenge this notion. They indicate that E. coli and S. pombe do age, but only when subjected to environmental stress. If true, this suggests that aging may be widespread among microbial species in general, and that studying aging in microbes may inform other long-standing questions in aging. This review examines the recent evidence for and against replicative aging in symmetrically dividing unicellular organisms, the mechanisms that underlie aging, why aging evolved in these species, and how microbial aging fits into the context of other questions in aging.

Forster, P., et al. (2015). "Elevated germline mutation rate in teenage fathers." Proc Biol Sci **282**(1803): 20142898.

Men age and die, while cells in their germline are programmed to be immortal. To elucidate how germ cells maintain viable DNA despite increasing parental age, we analysed DNA from 24 097 parents and their children, from Europe, the Middle East and Africa. We chose repetitive microsatellite DNA that mutates (unlike point mutations) only as a result of cellular replication, providing us with a natural 'cell-cycle counter'. We observe, as expected, that the overall mutation rate for fathers is seven times higher than for mothers. Also as expected, mothers have a low and lifelong constant DNA mutation rate. Surprisingly, however, we discover that (i) teenage fathers already set out from a much higher mutation rate than teenage mothers (potentially equivalent to 77-196 male germline cell divisions by puberty); and (ii) ageing men maintain sperm DNA quality similar to that of teenagers, presumably by using fresh batches of stem cells known as 'A-dark spermatogonia'.

Furuhashi, H. and W. G. Kelly (2010). "The epigenetics of germ-line immortality: lessons from an elegant model system." Dev Growth Differ **52**(6): 527-532.

Epigenetic mechanisms are thought to help regulate the unique transcription program that is established in germ cell development. During the germline cycle of many organisms, the epigenome undergoes waves of extensive resetting events, while a part of epigenetic modification remains faithful to specific loci. Little is known about the mechanisms underlying these events, how loci are selected for, or avoid, reprogramming, or even why these events are required. In particular, although the significance of genomic imprinting phenomena involving DNA methylation in mammals is now well accepted, the role of histone modification as a transgenerational epigenetic mechanism has been the subject of debate. Such epigenetic mechanisms may help regulate transcription programs and/or the pluripotent status

conferred on germ cells, and contribute to germ line continuity across generations. Recent studies provide new evidence for heritability of histone modifications through germ line cells and its potential effects on transcription regulation both in the soma and germ line of subsequent generations. Unraveling transgenerational epigenetic mechanisms involving highly conserved histone modifications in elegant model systems will accelerate the generation of new paradigms and inspire research in a wide variety of fields, including basic developmental studies and clinical stem cell research.

Gilgenkrantz, H. and A. Collin de l'Hortet (2011). "New insights into liver regeneration." Clin Res Hepatol Gastroenterol **35**(10): 623-629.

Even if the Greeks probably anticipated rather than discovered the extraordinary regenerative capacity of the liver with the Prometheus myth, this phenomenon still fascinates scientists nowadays with the same enthusiasm. There are good reasons to decipher this process other than to find an answer to our fantasy of immortality: it could indeed help patients needing large liver resections or living-donor liver transplantation, it could increase our understanding of liver pathology and finally it could enable novel cell-therapy approaches. For decades, most of our knowledge about the mechanisms involved in liver regeneration came from the classic two-thirds partial hepatectomy (PH) model. In this scenario, hepatocytes play the leading role, which raises the question of the simple existence of a stem cell population. Recently however, hepatic progenitor cells come again under the limelight, seeming to play a role in liver physiology and in various liver diseases such as steatosis or cirrhosis. Excellent reviews have recently addressed liver regeneration. Our goal is therefore to focus on recent improvements in the field, highlighting data mostly published in the last two years in order to draw a putative picture of what the future research axes on liver regeneration might look like.

Goding, C. R. (2011). "Commentary. A picture of Mitf in melanoma immortality." Oncogene **30**(20): 2304-2306.

The Mitf gene has a key role in melanocytes and melanoma by regulating cell cycle progression, survival and differentiation. Two papers in this issue of Oncogene (Cheli et al., 2011; Strub et al., 2011) reveal that low-Mitf cells can initiate tumors with high efficiency, and that Mitf blocks senescence by regulating genes implicated in S-phase progression and mitosis.

Goding, C. R., et al. (2014). "Cancer: pathological nuclear reprogramming?" Nat Rev Cancer **14**(8): 568-573.

The ability of stem cells to self-renew and generate different lineages during development and organogenesis is a fundamental, tightly controlled, and generally unidirectional process, whereas the 'immortality' of cancer cells could be regarded as pathological self-renewal. The molecular mechanisms that underpin the generation of induced pluripotent stem cells are remarkably similar to those that are deregulated in cancer - so much so that aberrant reprogramming is tumorigenic. The similarities also suggest that mutations in genes implicated in DNA methylation dynamics might represent a hallmark of cancers with a stem cell origin, and they highlight an alternative view of cancer that may be of clinical benefit.

Gomez, D. L., et al. (2016). "Telomerase as a Cancer Target. Development of New Molecules." Curr Top Med Chem **16**(22): 2432-2440.

Telomeres are the terminal part of the chromosome containing a long repetitive and noncodifying sequence that has as function protecting the chromosomes. In normal cells, telomeres lost part of such repetitive sequence in each mitosis, until telomeres reach a critical point, triggering at that time senescence and cell death. However, in most of tumor cells in each cell division a part of the telomere is lost, however the appearance of an enzyme called telomerase synthetize the segment that just has been lost, therefore conferring to tumor cells the immortality hallmark. Telomerase is significantly overexpressed in 80-95% of all malignant tumors, being present at low levels in few normal cells, mostly stem cells. Due to these characteristics, telomerase has become an attractive target for new and more effective anticancer agents. The capability of inhibiting telomerase in tumor cells should lead to telomere shortening, senescence and apoptosis. In this work, we analyze the different strategies for telomerase inhibition, either in development, preclinical or clinical stages taking into account their strong points and their caveats. We covered strategies such as nucleosides analogs, oligonucleotides, small molecule inhibitors, G-quadruplex stabilizers, immunotherapy, gene therapy, molecules that affect the telomere/ telomerase associated proteins, agents from microbial sources, among others, providing a balanced evaluation of the status of the inhibitors of this powerful target together with an analysis of the challenges ahead.

Gupta, S., et al. (2018). "HPV: Molecular pathways and targets." Curr Probl Cancer **42**(2): 161-174.

Infection of high-risk human papillomaviruses (HPVs) is a prerequisite for the development of cervical carcinoma. HPV infections are also implicated in the development of other types of carcinomas. Chronic or persistent infection of HPV is essential but HPV alone is inadequate, additional endogenous or exogenous cues are needed along with HPV to induce cervical carcinogenesis. The strategies that high-risk HPVs have developed in differentiating epithelial cells to reach a DNA-synthesis competent state leading to tumorigenic transformation are basically due to overexpression of the E6 and E7 oncoproteins and the activation of diverse cellular regulatory or signaling pathways that are targeted by them. Moreover, the Wnt/beta-catenin/Notch and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathways are deregulated in various cancers, and have also been implicated in HPV-induced cancers. These are basically related to the "cancer hallmarks," and include sustaining proliferative signals, the evasion of growth suppression and immune destruction, replicative immortality, inflammation, invasion, metastasis and angiogenesis, as well as genome instability, resisting cell death, and deregulation of cellular energetics. These information could eventually aid in identifying or developing new diagnostic, prognostic biomarkers, and may contribute to design more effective targeted therapeutics and treatment strategies. Although surgery, chemotherapy and radiotherapy can cure more than 90% of women with early stage cervical cancer, the recurrent and metastatic disease remains a major cause of cancer mortality. Numerous efforts have been made to design new drugs and develop gene therapies to treat cervical cancer. In recent years, research on treatment strategies has proposed several options, including the role of HPV E5, E6, and E7 oncogenes, which are retained and overexpressed in most of the cervical cancers and whose respective oncoproteins are critical to the induction and maintenance of the malignant phenotype. Other efforts have been focused on antitumor immunotherapy strategies. It is known that during the development of cervical cancer, a cascade of abnormal events is induced, including disruption of cell cycle control, perturbation of antitumor immune response, alteration of gene expression, deregulation of microRNA and cancer stem cell and stemness related markers expression could serve as novel molecular targets for reliable diagnosis and treatment of HPV-positive cancers. However, the search for new proposals for disease control and prevention has brought new findings and approaches in the context of molecular biology indicating innovations and perspectives in the early detection and prevention of the disease. Thus, in this article, we discuss molecular signaling pathways activated by HPV and potential targets or biomarkers for early detection or prevention and the treatment of HPV-associated cancers.

Hafner, S. J., et al. (2017). "Long noncoding RNAs in normal and pathological pluripotency." Semin Cell Dev Biol **65**: 1-10.

The striking similarities between pluripotent and cancer cells, such as immortality and increased stress resistance, have long been acknowledged. Numerous studies searched for and successfully identified common molecular players and pathways, thus providing an entirely new challenge and potential therapeutic angle by targeting cancer cells or a specific stem population of the tumor via pluripotency associated processes. However, these strategies have until now mainly been restricted to proteins. Nonetheless, it has become clear over the past decade that the overwhelming majority of the genome produces noncoding transcripts, many of which have proven both functional and crucial for key cellular processes, including stemness maintenance. Moreover, numerous long noncoding RNAs are deregulated in cancer, but little is known concerning their functions and molecular mechanisms. Consequently, it seems essential to integrate the noncoding transcripts into the picture of the stemness-cancer connection. Whereas a number of studies have addressed the expression of lncRNAs in cancer stem cells, no systematic approach has yet been undertaken to identify lncRNAs implicated in the maintenance of the embryonic stemness state that is hijacked by cancer cells. The aim of this review is to highlight long noncoding RNAs with shared functions in stemness and cancer and to outline the current state of a field in its infancy, the search for long noncoding transcripts in cancer stem cells.

Hannen, R. and J. W. Bartsch (2018). "Essential roles of telomerase reverse transcriptase hTERT in cancer stemness and metastasis." FEBS Lett **592**(12): 2023-2031.

Maintenance of chromosomal telomere length is a hallmark of cancer cells and a prerequisite for stemness. In 85-90% of all human cancers, telomere length maintenance is achieved by reactivation of telomerase, whereas in the remaining 10-15% cancers, alternative lengthening of telomeres (ALT) is observed. Reactivation of telomerase occurs by various mechanisms, one of which is accumulation of point mutations in the promoter region of the gene encoding the protein subunit hTERT. There are numerous studies linking either hTERT overexpression or the presence of hTERT mutations to an aggressive phenotype of several human cancers. Recent findings demonstrate that hTERT expression is not only associated with replicative immortality, but also with cancer cell

motility and stem cell phenotype. However, the mechanisms by which hTERT affects cancer cell migration, invasion, and distant metastasis on the one hand, and stemness and resistance on the other hand, are still poorly understood. Within this review, we aim to provide an overview on the functional involvement of hTERT in these cellular processes, focusing on metastasis formation and maintenance of stemness in different human cancers.

Irons, R. D. and P. J. Kerzic (2014). "Cytogenetics in benzene-associated myelodysplastic syndromes and acute myeloid leukemia: new insights into a disease continuum." Ann N Y Acad Sci **1310**: 84-88.

Hematopoiesis in health and disease results from complex interactions between primitive hematopoietic stem cells (HSCs) and the extrinsic influences of other cells in the bone marrow (BM) niche. Advances in stem cell biology, molecular genetics, and computational biology reveal that the immortality, self-renewal, and maintenance of blood homeostasis generally attributed to individual HSCs are functions of the cells' behavior in the normal BM environment. Here we discuss how these advances, together with results of outcomes-based clinical epidemiology studies, provide new insight into the importance of epigenetic events in leukemogenesis. For the chemical benzene (Bz), development of myeloid neoplasms depends predominantly on alterations within the microenvironments in which they arise. The primary persistent disease in Bz myelotoxicity is myelodysplastic syndrome, which precedes cytogenetic injury. Evidence indicates that acute myeloid leukemia arises as a secondary event, subsequent to evolution of the leukemia-initiating cell phenotype within the altered BM microenvironment. Further explorations into the nature of chemical versus de novo disease should consider this mechanism, which is biologically distinct from previous models of clonal cytogenetic injury. Understanding alterations of homeostatic regulation in the BM niche is important for validation of models of leukemogenesis, monitoring at-risk populations, and development of novel treatment and prevention strategies.

Iskender, B., et al. (2015). "Myrtucommulone-A treatment decreases pluripotency- and multipotency-associated marker expression in bladder cancer cell line HTB-9." J Nat Med **69**(4): 543-554.

Cancer and stem cells exhibit similar features, including self-renewal, differentiation and immortality. The expression of stem-cell-related genes in cancer cells is demonstrated to be potentially correlated with cancer cell behaviour, affecting both drug response and tumor recurrence. There is an emerging body of evidence that subpopulations of tumors carry a distinct molecular sign and are selectively resistant to chemotherapy. Therefore, it is important to find novel therapeutic agents that could suppress the stem-like features of cancer cells while inhibiting their proliferation. Myrtucommulone-A (MC-A) is an active compound of a nonprenylated acylphloroglucinol isolated from the leaves of myrtle. Here we have investigated the potential of MC-A in inhibiting the expression of self-renewal regulatory factors and cancer stem cell markers in a bladder cancer cell line HTB-9. We used RT-PCR, immunocytochemistry, flow cytometry and western blotting to examine the expression of pluripotency- and multipotency-associated markers with or without treatment with MC-A. Treatment with MC-A not only decreased cancer cell viability and proliferation but also resulted in a decrease in the expression of pluripotency- and multipotency-associated markers such as NANOG, OCT-4, SOX-2, SSEA-4, TRA-1-60, CD90, CD73 and CD44. MC-A treatment was also observed to decrease the sphere-forming ability of HTB-9 cells. In summary, this study provides valuable information on the presence of stem-cell marker expression in HTB-9 cells and our results imply that MC-A could be utilized to target cancer cells with stem-like characteristics.

Ivancich, M., et al. (2017). "Treating Cancer by Targeting Telomeres and Telomerase." Antioxidants (Basel) **6**(1).

Telomerase is expressed in more than 85% of cancer cells. Tumor cells with metastatic potential may have a high telomerase activity, allowing cells to escape from the inhibition of cell proliferation due to shortened telomeres. Human telomerase primarily consists of two main components: hTERT, a catalytic subunit, and hTR, an RNA template whose sequence is complimentary to the telomeric 5'-dTTAGGG-3' repeat. In humans, telomerase activity is typically restricted to renewing tissues, such as germ cells and stem cells, and is generally absent in normal cells. While hTR is constitutively expressed in most tissue types, hTERT expression levels are low enough that telomere length cannot be maintained, which sets a proliferative lifespan on normal cells. However, in the majority of cancers, telomerase maintains stable telomere length, thereby conferring cell immortality. Levels of hTERT mRNA are directly related to telomerase activity, thereby making it a more suitable therapeutic target than hTR. Recent data suggests that stabilization of telomeric G-quadruplexes may act to indirectly inhibit telomerase action by blocking hTR binding. Telomeric DNA has the propensity to spontaneously form intramolecular G-quadruplexes, four-stranded DNA secondary structures that are stabilized by the stacking of guanine residues in a planar arrangement. The functional roles of telomeric G-quadruplexes are not

completely understood, but recent evidence suggests that they can stall the replication fork during DNA synthesis and inhibit telomere replication by preventing telomerase and related proteins from binding to the telomere. Long-term treatment with G-quadruplex stabilizers induces a gradual reduction in the length of the G-rich 3' end of the telomere without a reduction of the total telomere length, suggesting that telomerase activity is inhibited. However, inhibition of telomerase, either directly or indirectly, has shown only moderate success in cancer patients. Another promising approach of targeting the telomere is the use of guanine-rich oligonucleotides (GROs) homologous to the 3' telomere overhang sequence (T-oligos). T-oligos, particularly a specific 11-base oligonucleotide (5'-dGTTAGGGTTAG-3') called T11, have been shown to induce DNA damage responses (DDRs) such as senescence, apoptosis, and cell cycle arrest in numerous cancer cell types with minimal or no cytostatic effects in normal, non-transformed cells. As a result, T-oligos and other GROs are being investigated as prospective anticancer therapeutics. Interestingly, the DDRs induced by T-oligos in cancer cells are similar to the effects seen after progressive telomere degradation in normal cells. The loss of telomeres is an important tumor suppressor mechanism that is commonly absent in transformed malignant cells, and hence, T-oligos have garnered significant interest as a novel strategy to combat cancer. However, little is known about their mechanism of action. In this review, we discuss the current understanding of how T-oligos exert their antiproliferative effects in cancer cells and their role in inhibition of telomerase. We also discuss the current understanding of telomerase in cancer and various therapeutic targets related to the telomeres and telomerase.

Jager, K. and M. Walter (2016). "Therapeutic Targeting of Telomerase." Genes (Basel) **7**(7).

Telomere length and cell function can be preserved by the human reverse transcriptase telomerase (hTERT), which synthesizes the new telomeric DNA from a RNA template, but is normally restricted to cells needing a high proliferative capacity, such as stem cells. Consequently, telomerase-based therapies to elongate short telomeres are developed, some of which have successfully reached the stage I in clinical trials. Telomerase is also permissive for tumorigenesis and 90% of all malignant tumors use telomerase to obtain immortality. Thus, reversal of telomerase upregulation in tumor cells is a potential strategy to treat cancer. Natural and small-molecule telomerase inhibitors, immunotherapeutic approaches, oligonucleotide inhibitors, and telomerase-directed gene therapy are useful treatment strategies. Telomerase is more widely expressed than any other tumor marker. The low expression in normal tissues, together with the longer telomeres in normal stem cells versus cancer cells, provides some degree of specificity with low risk of toxicity. However, long term telomerase inhibition may elicit negative effects in highly-proliferative cells which need telomerase for survival, and it may interfere with telomere-independent physiological functions. Moreover, only a few hTERT molecules are required to overcome senescence in cancer cells, and telomerase inhibition requires proliferating cells over a sufficient number of population doublings to induce tumor suppressive senescence. These limitations may explain the moderate success rates in many clinical studies. Despite extensive studies, only one vaccine and one telomerase antagonist are routinely used in clinical work. For complete eradication of all subpopulations of cancer cells a simultaneous targeting of several mechanisms will likely be needed. Possible technical improvements have been proposed including the development of more specific inhibitors, methods to increase the efficacy of vaccination methods, and personalized approaches. Telomerase activation and cell rejuvenation is successfully used in regenerative medicine for tissue engineering and reconstructive surgery. However, there are also a number of pitfalls in the treatment with telomerase activating procedures for the whole organism and for longer periods of time. Extended cell lifespan may accumulate rare genetic and epigenetic aberrations that can contribute to malignant transformation. Therefore, novel vector systems have been developed for a 'mild' integration of telomerase into the host genome and loss of the vector in rapidly-proliferating cells. It is currently unclear if this technique can also be used in human beings to treat chronic diseases, such as atherosclerosis.

Kornbluth, S. and R. Fissore (2015). "Vertebrate Reproduction." Cold Spring Harb Perspect Biol **7**(10): a006064.

Vertebrate reproduction requires a myriad of precisely orchestrated events-in particular, the maternal production of oocytes, the paternal production of sperm, successful fertilization, and initiation of early embryonic cell divisions. These processes are governed by a host of signaling pathways. Protein kinase and phosphatase signaling pathways involving Mos, CDK1, RSK, and PP2A regulate meiosis during maturation of the oocyte. Steroid signals-specifically testosterone-regulate spermatogenesis, as does signaling by G-protein-coupled hormone receptors. Finally, calcium signaling is essential for both sperm motility and fertilization. Altogether, this signaling symphony ensures the production of viable offspring, offering a chance of genetic immortality.

Kovalenko, O. A., et al. (2010). "Expression of (NES-)hTERT in cancer cells delays cell cycle progression and increases sensitivity to genotoxic stress." PLoS One **5**(5): e10812.

Telomerase is a reverse transcriptase associated with cellular immortality through telomere maintenance. This enzyme is activated in 90% of human cancers, and inhibitors of telomerase are currently in clinical trials to counteract tumor growth. Many aspects of telomerase biology have been investigated for therapy, particularly inhibition of the enzyme, but little was done regarding its subcellular shuttling. We have recently shown that mutations in the nuclear export signal of hTERT, the catalytic component of telomerase, led to a mutant ((NES-)hTERT) that failed to immortalize cells despite nuclear localization and catalytic activity. Expression of (NES-)hTERT in primary fibroblast resulted in telomere-based premature senescence and mitochondrial dysfunction. Here we show that expression of (NES-)hTERT in LNCaP, SQ20B and HeLa cells rapidly and significantly decreases their proliferation rate and ability to form colonies in soft agar while not interfering with endogenous telomerase activity. The cancer cells showed increased DNA damage at telomeric and extra-telomeric sites, and became sensitive to ionizing radiation and hydrogen peroxide exposures. Our data show that expression of (NES-)hTERT efficiently counteracts cancer cell growth in vitro in at least two different ways, and suggest manipulation with the NES of hTERT or its subcellular shuttling as a new strategy for cancer treatment.

Lackner, D. H., et al. (2012). "Organismal propagation in the absence of a functional telomerase pathway in Caenorhabditis elegans." EMBO J **31**(8): 2024-2033.

To counteract replication-dependent telomere shortening most eukaryotic cells rely on the telomerase pathway, which is crucial for the maintenance of proliferative potential of germ and stem cell populations of multicellular organisms. Likewise, cancer cells usually engage the telomerase pathway for telomere maintenance to gain immortality. However, in approximately 10% of human cancers telomeres are maintained through telomerase-independent alternative lengthening of telomeres (ALT) pathways. Here, we describe the generation and characterization of C. elegans survivors in a strain lacking the catalytic subunit of telomerase and the nematode telomere-binding protein CeOB2. These clonal strains, some of which have been propagated for >180 generations, represent the first example of a multicellular organism with canonical telomeres that can survive without a functional telomerase pathway. The animals display the heterogeneous telomere length characteristic for ALT cells, contain single-stranded C-circles, a transcription profile pointing towards an adaptation to chronic stress and are therefore a unique and valuable tool to decipher the ALT mechanism.

Lapinska, K., et al. (2018). "Cancer Progenitor Cells: The Result of an Epigenetic Event?" Anticancer Res **38**(1): 1-6.

The concept of cancer stem cells was proposed in the late 1990s. Although initially the idea seemed controversial, the existence of cancer stem cells is now well established. However, the process leading to the formation of cancer stem cells is still not clear and thus requires further research. This article discusses epigenetic events that possibly produce cancer progenitor cells from predisposed cells by the influence of their environment. Every somatic cell possesses an epigenetic signature in terms of histone modifications and DNA methylation, which are obtained during lineage-specific differentiation of pluripotent stem cells, which is specific to that particular tissue. We call this signature an epigenetic switch. The epigenetic switch is not fixed. Our epigenome alters with aging. However, depending on the predisposition of the cells of a particular tissue and their microenvironment, the balance of the switch (histone modifications and the DNA methylation) may be tilted to immortality in a few cells, which generates cancer progenitor cells.

Laursen, M. B., et al. (2014). "Human B-cell cancer cell lines as a preclinical model for studies of drug effect in diffuse large B-cell lymphoma and multiple myeloma." Exp Hematol **42**(11): 927-938.

Drug resistance in cancer refers to recurrent or primary refractory disease following drug therapy. At the cellular level, it is a consequence of molecular functions that ultimately enable the cell to resist cell death-one of the classical hallmarks of cancer. Thus, drug resistance is a fundamental aspect of the cancer cell phenotype, in parallel with sustained proliferation, immortality, angiogenesis, invasion, and metastasis. Here we present a preclinical model of human B-cell cancer cell lines used to identify genes involved in specific drug resistance. This process includes a standardized technical setup for specific drug screening, analysis of global gene expression, and the statistical considerations required to develop resistance gene signatures. The state of the art is illustrated by the first-step classical drug screen (including the CD20 antibody rituximab, the DNA intercalating topoisomerase II inhibitor doxorubicin, the mitotic inhibitor vincristine, and the alkylating agents cyclophosphamide and melphalan) along with the generation of gene lists predicting the chemotherapeutic outcome as validated retrospectively

in clinical trial datasets. This B-cell lineage-specific preclinical model will allow us to initiate a range of laboratory studies, with focus on specific gene functions involved in molecular resistance mechanisms.

Lee, M., et al. (2018). "Telomere sequence content can be used to determine ALT activity in tumours." Nucleic Acids Res **46**(10): 4903-4918.

The replicative immortality of human cancer cells is achieved by activation of a telomere maintenance mechanism (TMM). To achieve this, cancer cells utilise either the enzyme telomerase, or the Alternative Lengthening of Telomeres (ALT) pathway. These distinct molecular pathways are incompletely understood with respect to activation and propagation, as well as their associations with clinical outcomes. We have identified significant differences in the telomere repeat composition of tumours that use ALT compared to tumours that do not. We then employed a machine learning approach to stratify tumours according to telomere repeat content with an accuracy of 91.6%. Importantly, this classification approach is applicable across all tumour types. Analysis of pathway mutations that were under-represented in ALT tumours, across 1,075 tumour samples, revealed that the autophagy, cell cycle control of chromosomal replication, and transcriptional regulatory network in embryonic stem cells pathways are involved in the survival of ALT tumours. Overall, our approach demonstrates that telomere sequence content can be used to stratify ALT activity in cancers, and begin to define the molecular pathways involved in ALT activation.

Liggett, L. A. and J. DeGregori (2017). "Changing mutational and adaptive landscapes and the genesis of cancer." Biochim Biophys Acta Rev Cancer **1867**(2): 84-94.

By the time the process of oncogenesis has produced an advanced cancer, tumor cells have undergone extensive evolution. The cellular phenotypes resulting from this evolution have been well studied, and include accelerated growth rates, apoptosis resistance, immortality, invasiveness, and immune evasion. Yet with all of our current knowledge of tumor biology, the details of early oncogenesis have been difficult to observe and understand. Where different oncogenic mutations may work together to enhance the survival of a tumor cell, in isolation they are often pro-apoptotic, pro-differentiative or pro-senescent, and therefore often, somewhat paradoxically, disadvantageous to a cell. It is also becoming clear that somatic mutations, including those in known oncogenic drivers, are common in tissues starting at a young age. These observations raise the question: how do we largely avoid cancer for most of our lives? Here we propose that evolutionary forces can help explain this paradox. As humans and other organisms age or experience external insults such as radiation or smoking, the structure and function of tissues progressively degrade, resulting in altered stem cell niche microenvironments. As tissue integrity declines, it becomes less capable of supporting and maintaining resident stem cells. These stem cells then find themselves in a microenvironment to which they are poorly adapted, providing a competitive advantage to those cells that can restore their functionality and fitness through mutations or epigenetic changes. The resulting oncogenic clonal expansions then increase the odds of further cancer progression. Understanding how the causes of cancer, such as aging or smoking, affect tissue microenvironments to control the impact of mutations on somatic cell fitness can help reconcile the discrepancy between marked mutation accumulation starting early in life and the somatic evolution that leads to cancer at advanced ages or following carcinogenic insults. This article is part of a Special Issue entitled: Evolutionary principles - heterogeneity in cancer?, edited by Dr. Robert A. Gatenby.

Liu, J. P. and R. Chen (2015). "Stressed SIRT7: facing a crossroad of senescence and immortality." Clin Exp Pharmacol Physiol **42**(6): 567-569.

SIRT7 with coenzyme NAD catalyzes protein de-acetylation. In stress response, SIRT7 regulates protein folding in mitochondria with unknown mechanisms. Decreases in SIRT7 entrain hematopoietic stem cell senescence, but increasing SIRT7 causes elevation of hematopoietic stem cell regenerative function. We discuss the recent findings on SIRT7 and its binding proteins, NRF1 and GABPbeta1, in decision making between the choices of inducing cell aging and immortality.

Menendez, J. A., et al. (2012). "Metformin is synthetically lethal with glucose withdrawal in cancer cells." Cell Cycle **11**(15): 2782-2792.

Glucose deprivation is a distinctive feature of the tumor microecosystem caused by the imbalance between poor supply and an extraordinarily high consumption rate. The metabolic reprogramming from mitochondrial respiration to aerobic glycolysis in cancer cells (the "Warburg effect") is linked to oncogenic transformation in a manner that frequently implies the inactivation of metabolic checkpoints such as the energy rheostat AMP-activated protein kinase (AMPK). Because the concept of synthetic lethality in oncology can be applied not only to genetic and epigenetic intrinsic differences between normal and cancer cells but also to extrinsic ones such as altered microenvironment, we recently hypothesized that stress-energy mimickers such as the AMPK agonist metformin should produce metabolic synthetic lethality

in a glucose-starved cell culture milieu imitating the adverse tumor growth conditions in vivo. Under standard high-glucose conditions, metformin supplementation mostly caused cell cycle arrest without signs of apoptotic cell death. Under glucose withdrawal stress, metformin supplementation circumvented the ability of oncogenes (e.g., HER2) to protect breast cancer cells from glucose-deprivation apoptosis. Significantly, representative cell models of breast cancer heterogeneity underwent massive apoptosis (by >90% in some cases) when glucose-starved cell cultures were supplemented with metformin. Our current findings may uncover crucial issues regarding the cell-autonomous metformin's anti-cancer actions: (1) The offently claimed clinically irrelevant, non-physiological concentrations needed to observe the metformin's anti-cancer effects in vitro merely underlie the artifactual interference of erroneous glucose-rich experimental conditions that poorly reflect glucose-starved in vivo conditions; (2) the preferential killing of cancer stem cells (CSC) by metformin may simply expose the best-case scenario for its synthetically lethal activity because an increased dependency on Warburg-like aerobic glycolysis (hyperglycolytic phenotype) is critical to sustain CSC stemness and immortality; (3) the microenvironment-mediated contextual synthetic lethality of metformin should be expected to enormously potentiate the anti-cancer effect of anti-angiogenesis agents that promote severe oxygen and glucose deprivation in certain areas of the tumor tissues.

Morris, B. J., et al. (2015). "FOXO3: A Major Gene for Human Longevity--A Mini-Review." Gerontology **61**(6): 515-525.

BACKGROUND: The gene FOXO3, encoding the transcription factor forkhead box O-3 (FoxO3), is one of only two for which genetic polymorphisms have exhibited consistent associations with longevity in diverse human populations. OBJECTIVE: Here, we review the multitude of actions of FoxO3 that are relevant to health, and thus healthy ageing and longevity. METHODS: The study involved a literature search for articles retrieved from PubMed using FoxO3 as keyword. RESULTS: We review the molecular genetics of FOXO3 in longevity, then current knowledge of FoxO3 function relevant to ageing and lifespan. We describe how FoxOs are involved in energy metabolism, oxidative stress, proteostasis, apoptosis, cell cycle regulation, metabolic processes, immunity, inflammation and stem cell maintenance. The single FoxO in Hydra confers immortality to this fresh water polyp, but as more complex organisms evolved, this role has been usurped by the need for FoxO to control a broader range of specialized pathways across a wide spectrum of tissues assisted by the advent of as many as 4 FoxO subtypes in mammals. The major themes of FoxO3 are similar, but not identical, to other FoxOs and include regulation of cellular homeostasis, particularly of stem cells, and of inflammation, which is a common theme of age-related diseases. Other functions concern metabolism, cell cycle arrest, apoptosis, destruction of potentially damaging reactive oxygen species and proteostasis. CONCLUSIONS: The mechanism by which longevity-associated alleles of FOXO3 reduce age-related mortality is currently of great clinical interest. The prospect of optimizing FoxO3 activity in humans to increase lifespan and reduce age-related diseases represents an exciting avenue of clinical investigation. Research strategies directed at developing therapeutic agents that target FoxO3, its gene and proteins in the pathway(s) FoxO3 regulates should be encouraged and supported.

Nakamura, H., et al. (2019). "Pulmonary carcinosarcoma characterized by small round cells with neuroendocrine, myogenic, and chondrogenic differentiation: An extremely rare case." Pathol Int **69**(5): 282-287.

Carcinosarcoma is a clonal tumor developed through sarcomatoid changes in a carcinoma via the epithelial-mesenchymal transition (EMT). Here, we present an extremely rare case of pulmonary carcinosarcoma characterized by components suggesting pluripotency, namely neuroendocrine, myogenic, and chondrogenic differentiation, based on immunohistochemical analysis. A 42-year-old Japanese man was admitted to our hospital. Analysis of tumor tissue after right upper lobe lobectomy revealed a transition between carcinomatous and sarcomatous components. Immunohistochemical analysis suggested immortality owing to complete loss of p53 and diffuse expression of p16 in both the carcinomatous and sarcomatous components. There were also scattered cell groups expressing aldehyde dehydrogenase 1 family member A1, SOX2, CD133, and c-kit, suggesting the possible presence of cancer stem cells. Our findings in this case suggested that the EMT may play a key role in mediating the immortality of tumor cells in carcinosarcoma and facilitating the pluripotency of cancer stem cells.

Noormohammadi, A., et al. (2016). "Somatic increase of CCT8 mimics proteostasis of human pluripotent stem cells and extends C. elegans lifespan." Nat Commun **7**: 13649.

Human embryonic stem cells can replicate indefinitely while maintaining their undifferentiated state and, therefore, are immortal in culture. This capacity may demand avoidance of any imbalance in protein homeostasis (proteostasis) that would otherwise

compromise stem cell identity. Here we show that human pluripotent stem cells exhibit enhanced assembly of the TRiC/CCT complex, a chaperonin that facilitates the folding of 10% of the proteome. We find that ectopic expression of a single subunit (CCT8) is sufficient to increase TRiC/CCT assembly. Moreover, increased TRiC/CCT complex is required to avoid aggregation of mutant Huntingtin protein. We further show that increased expression of CCT8 in somatic tissues extends Caenorhabditis elegans lifespan in a TRiC/CCT-dependent manner. Ectopic expression of CCT8 also ameliorates the age-associated demise of proteostasis and corrects proteostatic deficiencies in worm models of Huntington's disease. Our results suggest proteostasis is a common principle that links organismal longevity with hESC immortality.

Ohgushi, M., et al. (2015). "Rho-Signaling-Directed YAP/TAZ Activity Underlies the Long-Term Survival and Expansion of Human Embryonic Stem Cells." Cell Stem Cell **17**(4): 448-461.

Human embryonic stem cells (hESCs) can survive and proliferate for an extended period of time in culture, but unlike that of tumor-derived cells, this form of cellular immortality does not depend on genomic aberrations. In this study, we sought to elucidate the molecular basis of this long-term growth property of hESCs. We found that the survival of hESCs depends on the small GTPase Rho and its activator AKAP-Lbc. We show that AKAP-Lbc/Rho signaling sustains the nuclear function of the transcriptional cofactors YAP and TAZ by modulating actin microfilament organization. By inducing reprogramming and differentiation, we found that dependency on this Rho signaling pathway is associated with the pluripotent state. Thus, our findings show that the capacity of hESCs to undergo long-term expansion in vitro is intrinsically coupled to their cellular identity through interconnected molecular circuits that link cell survival to pluripotency.

Pech, M. F., et al. (2015). "High telomerase is a hallmark of undifferentiated spermatogonia and is required for maintenance of male germline stem cells." Genes Dev **29**(23): 2420-2434.

Telomerase inactivation causes loss of the male germline in worms, fish, and mice, indicating a conserved dependence on telomere maintenance in this cell lineage. Here, using telomerase reverse transcriptase (Tert) reporter mice, we found that very high telomerase expression is a hallmark of undifferentiated spermatogonia, the mitotic population where germline stem cells reside. We exploited these high telomerase levels as a basis for purifying undifferentiated spermatogonia using fluorescence-activated cell sorting. Telomerase levels in undifferentiated spermatogonia and embryonic stem cells are comparable and much greater than in somatic progenitor compartments. Within the germline, we uncovered an unanticipated gradient of telomerase activity that also enables isolation of more mature populations. Transcriptomic comparisons of Tert(High) undifferentiated spermatogonia and Tert(Low) differentiated spermatogonia by RNA sequencing reveals marked differences in cell cycle and key molecular features of each compartment. Transplantation studies show that germline stem cell activity is confined to the Tert(High) cKit(-) population. Telomere shortening in telomerase knockout strains causes depletion of undifferentiated spermatogonia and eventual loss of all germ cells after undifferentiated spermatogonia drop below a critical threshold. These data reveal that high telomerase expression is a fundamental characteristic of germline stem cells, thus explaining the broad dependence on telomerase for germline immortality in metazoans.

Petralia, R. S., et al. (2014). "Aging and longevity in the simplest animals and the quest for immortality." Ageing Res Rev **16**: 66-82.

Here we review the examples of great longevity and potential immortality in the earliest animal types and contrast and compare these to humans and other higher animals. We start by discussing aging in single-celled organisms such as yeast and ciliates, and the idea of the immortal cell clone. Then we describe how these cell clones could become organized into colonies of different cell types that lead to multicellular animal life. We survey aging and longevity in all of the basal metazoan groups including ctenophores (comb jellies), sponges, placozoans, cnidarians (hydras, jellyfish, corals and sea anemones) and myxozoans. Then we move to the simplest bilaterian animals (with a head, three body cell layers, and bilateral symmetry), the two phyla of flatworms. A key determinant of longevity and immortality in most of these simple animals is the large numbers of pluripotent stem cells that underlie the remarkable abilities of these animals to regenerate and rejuvenate themselves. Finally, we discuss briefly the evolution of the higher bilaterians and how longevity was reduced and immortality lost due to attainment of greater body complexity and cell cycle strategies that protect these complex organisms from developing tumors. We also briefly consider how the evolution of multiple aging-related mechanisms/pathways hinders our ability to understand and modify the aging process in higher organisms.

Pilsworth, J. A., et al. (2018). "TERT promoter mutation in adult granulosa cell tumor of the ovary." Mod Pathol **31**(7): 1107-1115.

The telomerase reverse transcriptase (TERT) gene is highly expressed in stem cells and silenced upon differentiation. Cancer cells can attain immortality by activating TERT to maintain telomere length and telomerase activity, which is a crucial step of tumorigenesis. Two somatic mutations in the TERT promoter (C228T; C250T) have been identified as gain-of-function mutations that promote transcriptional activation of TERT in multiple cancers, such as melanoma and glioblastoma. A recent study investigating TERT promoter mutations in ovarian carcinomas found C228T and C250T mutations in 15.9% of clear cell carcinomas. However, it is unknown whether these mutations are frequent in other ovarian cancer subtypes, in particular, sex cord-stromal tumors including adult granulosa cell tumors. We performed whole-genome sequencing on ten adult granulosa cell tumors with matched normal blood and identified a TERT C228T promoter mutation in 50% of tumors. We found that adult granulosa cell tumors with mutated TERT promoter have increased expression of TERT mRNA and exhibited significantly longer telomeres compared to those with wild-type TERT promoter. Extension cohort analysis using allelic discrimination revealed the TERT C228T mutation in 51 of 229 primary adult granulosa cell tumors (22%), 24 of 58 recurrent adult granulosa cell tumors (41%), and 1 of 22 other sex cord-stromal tumors (5%). There was a significant difference in overall survival between patients with TERT C228T promoter mutation in the primary tumors and those without it ($p = 0.00253$, log-rank test). In seven adult granulosa cell tumors, we found the TERT C228T mutation present in recurrent tumors and absent in the corresponding primary tumor. Our data suggest that TERT C228T promoter mutations may have an important role in progression of adult granulosa cell tumors.

Piper, S. L., et al. (2012). "Inducible immortality in hTERT-human mesenchymal stem cells." J Orthop Res **30**(12): 1879-1885.

Human mesenchymal stem cells (hMSCs) are attractive candidates for tissue engineering and cell-based therapy because of their multipotentiality and availability in adult donors. However, in vitro expansion and differentiation of these cells is limited by replicative senescence. The proliferative capacity of hMSCs can be enhanced by ectopic expression of telomerase, allowing for long-term culture. However, hMSCs with constitutive telomerase expression demonstrate unregulated growth and even tumor formation. To address this problem, we used an inducible Tet-On gene expression system to create hMSCs in which ectopic telomerase expression can be induced selectively by the addition of doxycycline (i-hTERT hMSCs). i-hTERT hMSCs have inducible hTERT expression and telomerase activity, and are able to proliferate significantly longer than wild type hMSCs when hTERT expression is induced. They stop proliferating when hTERT expression is turned off and can be rescued when expression is re-induced. They retain multipotentiality in vitro even at an advanced age. We also used a selective inhibitor of telomere elongation to show that the mechanism driving immortalization of hMSCs by hTERT is dependent upon maintenance of telomere length. Thanks to their extended lifespan, preserved multipotentiality and controlled growth, i-hTERT hMSCs may prove to be a useful tool for the development and testing of novel stem cell therapies.

Proenca, A. M., et al. (2019). "Cell aging preserves cellular immortality in the presence of lethal levels of damage." PLoS Biol **17**(5): e3000266.

Cellular aging, a progressive functional decline driven by damage accumulation, often culminates in the mortality of a cell lineage. Certain lineages, however, are able to sustain long-lasting immortality, as prominently exemplified by stem cells. Here, we show that Escherichia coli cell lineages exhibit comparable patterns of mortality and immortality. Through single-cell microscopy and microfluidic techniques, we find that these patterns are explained by the dynamics of damage accumulation and asymmetric partitioning between daughter cells. At low damage accumulation rates, both aging and rejuvenating lineages retain immortality by reaching their respective states of physiological equilibrium. We show that both asymmetry and equilibrium are present in repair mutants lacking certain repair chaperones, suggesting that intact repair capacity is not essential for immortal proliferation. We show that this growth equilibrium, however, is displaced by extrinsic damage in a dosage-dependent response. Moreover, we demonstrate that aging lineages become mortal when damage accumulation rates surpass a threshold, whereas rejuvenating lineages within the same population remain immortal. Thus, the processes of damage accumulation and partitioning through asymmetric cell division are essential in the determination of proliferative mortality and immortality in bacterial populations. This study provides further evidence for the characterization of cellular aging as a general process, affecting prokaryotes and eukaryotes alike and according to similar evolutionary constraints.

Qiu, B., et al. (2012). "Expression and correlation of Bcl-2 with pathological grades in human glioma stem cells." Oncol Rep **28**(1): 155-160.

The anti-apoptotic gene, B-cell lymphoma-2 (Bcl-2), has been reported to be overexpressed in

gliomas and is related to tumor prognosis, suggesting a potential therapeutic target. Additionally, recent studies have demonstrated the existence of brain glioma stem cells (BGSCs) which are tumorigenic, self-renewable and dominate the biological behavior of gliomas. Currently BGSCs are committed as a new target of glioma therapies. However, few studies have focused on the expression of Bcl-2 in BGSCs. We performed a series of experiments to culture BGSCs from eight clinical specimens, followed by real-time RT-PCR and immunoassays to compare the expression levels of Bcl-2 in BGSCs and their corresponding primary glioma cells (PGCs). The results showed that Bcl-2 mRNA and protein expression levels are higher in BGSCs compared to their counterparts, and the expression levels are related to glioma malignancies. As an anti-apoptotic gene, Bcl-2 assigns immortality characteristics to cells, which coincide with the pivotal biological feature of BGSCs. The experimental results indicated that BGSCs would evade apoptosis for higher Bcl-2 expression, and may interpret the drug resistance of glioma to cytotoxic drugs and other pro-apoptotic agents. New therapies targeting Bcl-2 must induce apoptosis in BGSCs, thus, resulting in treatment or even eradication of glioma.

Rao, F., et al. (2011). "Medaka tert produces multiple variants with differential expression during differentiation in vitro and in vivo." Int J Biol Sci **7**(4): 426-439.

Embryonic stem (ES) cells have immortality for self-renewal and pluripotency. Differentiated human cells undergo replicative senescence. In human, the telomerase reverse transcriptase (Tert), namely the catalytic subunit of telomerase, exhibits differential expression to regulate telomerase activity governing cellular immortality or senescence, and telomerase activity or tert expression is a routine marker of pluripotent ES cells. Here we have identified the medaka tert gene and determined its expression and telomerase activity in vivo and in vitro. We found that the medaka tert locus produces five variants called terta to terte encoding isoforms TertA to TertE. The longest TertA consists of 1090 amino acid residues and displays a maximum of 34% identity to the human TERT and all the signature motifs of the Tert family. TertB to TertE are novel isoforms and have considerable truncation due to alternative splicing. The terta RNA is ubiquitous in embryos, adult tissues and cell lines, and accompanies ubiquitous telomerase activity in vivo and in vitro as revealed by TRAP assays. The tertb RNA was restricted to the testis, absent in embryos before gastrulation and barely detectable in various cell lines The tertc transcript was absent in undifferentiated ES cells but became evident upon ES cell differentiation, in vivo it was barely detectable in early embryos and became evident when embryogenesis proceeds. Therefore, ubiquitous terta expression correlates with ubiquitous telomerase activity in medaka, and expression of other tert variants appears to delineate cell differentiation in vitro and in vivo.

Rinkevich, B. (2011). "Cell cultures from marine invertebrates: new insights for capturing endless stemness." Mar Biotechnol (NY) **13**(3): 345-354.

Despite several decades of extensive research efforts, there is yet no single permanent cell line available from marine invertebrates as these cells stop dividing in vitro within 24-72 h after their isolation, starting cellular quiescence. This ubiquitous quiescent state should be modified in a way that at least some of the quiescent cells will become pluripotent, so they will have the ability to divide and become immortal. Following the above need, this essay introduces the rationale that the discipline of marine invertebrates' cell culture should gain from applying of two research routes, relevant to mammalian systems but less explored in the marine arena. The first is the use of adult stem cells (ASC) from marine organisms. Many marine invertebrate taxa maintain large pools of ASC in adulthood. Ample evidence attests that these cells from sponges, cnidarians, flatworms, crustaceans, mollusks, echinoderms, and ascidians play important roles in maintenance, regeneration, and asexual cloning, actively proliferating in vivo, resembling the vertebrates' cancer stem cells features. The second route is to target resting somatic cell constituents, manipulating them in the same way as has recently been performed on mammalian induced pluripotent stem (iPS) cells. While "iPS cells" are the outcome of an experimental manipulation, ASC are natural and rather frequent in a number of marine invertebrates. Above two cell categories reveal that there are more than a few types of seeds (cells) waiting to be sowed in the right soil (in vitro environmental conditions) for acquiring stemness and immortality. This rationale carries the potential to revolutionize the discipline of marine invertebrate cell cultures. When cultured "correctly," ASC and "iPS cells" from marine invertebrates may stay in their primitive stage and proliferate without differentiating into cells lineages, harnessing the stem cell's inherent abilities of self-replication versus differentiated progenies, toward the development of immortal cell lines.

Saini, A., et al. (2013). "'From death, lead me to immortality' - mantra of ageing skeletal muscle." Curr Genomics **14**(4): 256-267.

Skeletal muscle is a post-mitotic tissue maintained by repair and regeneration through a population of stem cell-like satellite cells. Following

muscle injury, satellite cell proliferation is mediated by local signals ensuring sufficient progeny for tissue repair. Age-related changes in satellite cells as well as to the local and systemic environment potentially impact on the capacity of satellite cells to generate sufficient progeny in an ageing organism resulting in diminished regeneration. 'Rejuvenation' of satellite cell progeny and regenerative capacity by environmental stimuli effectors suggest that a subset of age-dependent satellite cell changes may be reversible. Epigenetic regulation of satellite stem cells that include DNA methylation and histone modifications which regulate gene expression are potential mechanisms for such reversible changes and have been shown to control organismal longevity. The area of health and ageing that is likely to benefit soonest from advances in the biology of adult stem cells is the emerging field of regenerative medicine. Further studies are needed to elucidate the mechanisms by which epigenetic modifications regulate satellite stem cell function and will require an increased understanding of stem-cell biology, the environment of the aged tissue and the interaction between the two.

Singh, M. (2016). "Pediatrics in 21(st) Century and Beyond." Indian J Pediatr **83**(12-13): 1420-1425.

Pediatrics is a dynamic discipline and there is awareness and hope for actualizing outstanding achievements in the field of child health in 21(st) century and beyond. Improved lifestyle and quality of children's health is likely to reduce the burden of adult diseases and enhance longevity because seeds of most adult diseases are sown in childhood. Identification and decoding of human genome is expected to revolutionize the practice of pediatrics. The day is not far off when a patient will walk into doctor's chamber with an electronic or digital health history on a CD or palmtop and a decoded genomic constitution. There will be reduced burden of genetic diseases because of selective abortions of "defective" fetuses and replacement of "bad" genes with "good" ones by genetic engineering. Availability of totipotent stem cells and developments in transplant technology are likely to revolutionize the management of a variety of hematologic cancers and life-threatening genetic disorders. The possibility of producing flawless designer babies by advances in assisted reproductive technologies (ARTs) is likely to be mired by several ethical and legal issues.The availability of newer vaccines by recombinant technology for emerging infective and for non-infective lifestyle diseases is likely to improve survival and quality of life. There is going to be a greater focus on the "patient" having the disease rather than "disease" per se by practicing holistic pediatrics by effective utilization of alternative or complementary strategies for health care. Due to advances in technology, pediatrics may get further dehumanized. A true healer cannot simply rely on technology; there must be a spiritual bond between the patient and the physician by exploiting the concept of psycho-neuro-immunology and body-mind interactions. In the years to come, physicians are likely to play "god" but medicine can't achieve immortality because anything born must die in accordance with nature's recycling blueprint. The medical science is likely to improve longevity but our goal should be to improve the quality of life.

So, A. Y., et al. (2014). "Dual mechanisms by which miR-125b represses IRF4 to induce myeloid and B-cell leukemias." Blood **124**(9): 1502-1512.

The oncomir microRNA-125b (miR-125b) is upregulated in a variety of human neoplastic blood disorders and constitutive upregulation of miR-125b in mice can promote myeloid and B-cell leukemia. We found that miR-125b promotes myeloid and B-cell neoplasm by inducing tumorigenesis in hematopoietic progenitor cells. Our study demonstrates that miR-125b induces myeloid leukemia by enhancing myeloid progenitor output from stem cells as well as inducing immortality, self-renewal, and tumorigenesis in myeloid progenitors. Through functional and genetic analyses, we demonstrated that miR-125b induces myeloid and B-cell leukemia by inhibiting interferon regulatory factor 4 (IRF4) but through distinct mechanisms; it induces myeloid leukemia through repressing IRF4 at the messenger RNA (mRNA) level without altering the genomic DNA and induces B-cell leukemia via genetic deletion of the gene encoding IRF4.

Surani, M. A. (2012). "Cellular reprogramming in pursuit of immortality." Cell Stem Cell **11**(6): 748-750.

The discovery that phenotypic diversity among differentiated cells results from epigenetic and not genetic differences, and can be reset to restore pluripotency, promises revolutionary advances in medicine. I discuss how this and related seminal discoveries have brought us to an exciting future.

Tam, C., et al. (2019). "LncRNAs with miRNAs in regulation of gastric, liver, and colorectal cancers: updates in recent years." Appl Microbiol Biotechnol **103**(12): 4649-4677.

Long noncoding RNA (lncRNA) is a kind of RNAi molecule composed of hundreds to thousands of nucleotides. There are several major types of functional lncRNAs which participate in some important cellular pathways. LncRNA-RNA interaction controls mRNA translation and degradation or serves as a microRNA (miRNA) sponge for silencing. LncRNA-protein interaction regulates protein activity in transcriptional

activation and silencing. LncRNA guide, decoy, and scaffold regulate transcription regulators of enhancer or repressor region of the coding genes for alteration of expression. LncRNA plays a role in cellular responses including the following activities: regulation of chromatin structural modification and gene expression for epigenetic and cell function control, promotion of hematopoiesis and maturation of immunity, cell programming in stem cell and somatic cell development, modulation of pathogen infection, switching glycolysis and lipid metabolism, and initiation of autoimmune diseases. LncRNA, together with miRNA, are considered the critical elements in cancer development. It has been demonstrated that tumorigenesis could be driven by homeostatic imbalance of lncRNA/miRNA/cancer regulatory factors resulting in biochemical and physiological alterations inside the cells. Cancer-driven lncRNAs with other cellular RNAs, epigenetic modulators, or protein effectors may change gene expression level and affect the viability, immortality, and motility of the cells that facilitate cancer cell cycle rearrangement, angiogenesis, proliferation, and metastasis. Molecular medicine will be the future trend for development. LncRNA/miRNA could be one of the potential candidates in this category. Continuous studies in lncRNA functional discrepancy between cancer cells and normal cells and regional and rational genetic differences of lncRNA profiles are critical for clinical research which is beneficial for clinical practice.

Tanabe, K., et al. (2014). "Induction of pluripotency by defined factors." Proc Jpn Acad Ser B Phys Biol Sci **90**(3): 83-96.

The "reversion of cell fate from differentiated states back into totipotent or pluripotent states" has been an interest of many scientists for a long time. With the help of knowledge accumulated by those scientists, we succeeded in converting somatic cells to a pluripotent cell lineage by the forced expression of defined factors. These established induced pluripotent stem (iPS) cells have similar features to embryonic stem (ES) cells, including pluripotency and immortality. The iPS cell technology provides unprecedented opportunities for regenerative medicine and drug discovery.

Tomlinson, P. B. and B. A. Huggett (2012). "Cell longevity and sustained primary growth in palm stems." Am J Bot **99**(12): 1891-1902.

Longevity, or organismal life span, is determined largely by the period over which constituent cells can function metabolically. Plants, with modular organization (the ability continually to develop new organs and tissues) differ from animals, with unitary organization (a fixed body plan), and this difference is reflected in their respective life spans, potentially much longer in plants than animals. We draw attention to the observation that palm trees, as a group of monocotyledons without secondary growth comparable to that of lignophytes (plants with secondary growth from a bifacial cambium), retain by means of sustained primary growth living cells in their trunks throughout their organismal life span. Does this make palms the longest-lived trees because they can grow as individuals for several centuries? No conventional lignophyte retains living metabolically active differentiated cell types in its trunk for this length of time, even though the tree as a whole can exist for millennia. Does this contrast also imply that the long-lived cells in a palm trunk have exceptional properties, which allows this seeming immortality? We document the long-life of many tall palm species and their inherent long-lived stem cell properties, comparing such plants to conventional trees. We provide a summary of aspects of cell age and life span in animals and plants. Cell replacement is a feature of animal function, whereas conventional trees rely on active growth centers (meristems) to sustain organismal development. However, the long persistence of living cells in palm trunks is seen not as evidence for unique metabolic processes that sustain longevity, but is a consequence of unique constructional features. This conclusion suggests that the life span of plant cells is not necessarily genetically determined.

Torres-Padilla, M. E. and R. Ciosk (2013). "A germline-centric view of cell fate commitment, reprogramming and immortality." Development **140**(3): 487-491.

To ensure species continuity, the tantalising developmental plasticity of early embryonic cells, also called totipotency, must be transmitted to the offspring. This responsibility rests within the reproductive cell lineage: the germ line. At the recent EMBO/EMBL symposium 'Germline - Immortality through Totipotency', researchers discussed the mechanisms that establish and control totipotency, with an eye towards the mechanisms that may endow germ cells with the ability to propagate totipotency across generations.

Umezawa, A., et al. (2019). "Amnion-derived cells as a reliable resource for next-generation regenerative medicine." Placenta **84**: 50-56.

The placenta is composed of the amnion, chorionic plate, villous and smooth chorion, decidua basalis, and umbilical cord. The amnion is a readily obtainable source of a large number of cells and cell types, including epithelium, mesenchyme, and endothelium, and is thus an allogeneic resource for regenerative medicine. Endothelial cells are obtained

from large arteries and veins in the amniotic membrane as well as the umbilical cord. The amnion-derived cells exhibit transdifferentiation capabilities, including chondrogenesis and cardiomyogenesis, by introduction of transcription factors, in addition to their original and potential phenotypes. The amnion is also a source for production of induced pluripotent stem cells (AM-iPSCs). The AM-iPSCs exhibit stable phenotypes, such as multipotency and immortality, and a unique gene expression pattern. Through the use of amnion-derived cells, as well as other placenta-derived cells, preclinical proof of concept has been achieved in a mouse model of muscular dystrophy.

Vilchez, D., et al. (2013). "FOXO4 is necessary for neural differentiation of human embryonic stem cells." Aging Cell **12**(3): 518-522.

Proteostasis is critical for maintaining cell function and proteome stability may play an important role in human embryonic stem cell (hESC) immortality. Notably, hESC populations exhibit a high assembly of active proteasomes, a key node of the proteostasis network. FOXO4, an insulin/IGF-1 responsive transcription factor, regulates proteasome activity in hESCs. We find that loss of FOXO4 reduces the potential of hESCs to differentiate into neural lineages. Therefore, FOXO4 crosses evolutionary boundaries and links hESC function to invertebrate longevity modulation.

Vinnitsky, V. (2014). "The development of a malignant tumor is due to a desperate asexual self-cloning process in which cancer stem cells develop the ability to mimic the genetic program of germline cells." Intrinsically Disord Proteins **2**(1): e29997.

To date there is no explanation why the development of almost all types of solid tumors occurs sharing a similar scenario: (1) creation of a cancer stem cell (CSC), (2) CSC multiplication and formation of a multicellular tumor spheroid (TS), (3) vascularization of the TS and its transformation into a vascularized primary tumor, (4) metastatic spreading of CSCs, (5) formation of a metastatic TSs and its transformation into metastatic tumors, and (6) potentially endless repetition of this cycle of events. The above gaps in our knowledge are related to the biology of cancer and specifically to tumorigenesis, which covers the process from the creation of a CSC to the formation of a malignant tumor and the development of metastases. My Oncogerminative Theory of Tumorigenesis considers tumor formation as a dynamic self-organizing process that mimics a self-organizing process of early embryo development. In the initial step in that process, gene mutations combined with epigenetic dysregulation cause somatic cells to be reprogrammed into CSCs, which are immortal pseudo-germline cells. Mimicking the behavior of fertilized germline cells, the CSC achieves immortality by passing through the stages of its life-cycle and developing into a pseudo-blastula-stage embryo, which manifests in the body as a malignant tumor. In this view, the development of a malignant tumor from a CSC is a phenomenon of developmental biology, which we named a desperate asexual self-cloning event. The theory explains seven core characteristics of malignant tumors: (1) CSC immortality, (2) multistep development of a malignant tumor from a single CSC, (3) heterogeneity of malignant tumor cell populations, (4) metastatic spread of CSCs, (5) invasive growth, (6) malignant progression, and (7) selective immune tolerance toward cancer cells. The Oncogerminative Theory of Tumorigenesis suggests new avenues for discovery of revolutionary therapies to treat, prevent, and eradicate cancer.

Wang, H. and J. J. Unternaehrer (2019). "Epithelial-mesenchymal Transition and Cancer Stem Cells: At the Crossroads of Differentiation and Dedifferentiation." Dev Dyn **248**(1): 10-20.

In this review, we explore the connections between epithelial-mesenchymal transition (EMT) and differentiation status. EMTs in development have been described as differentiation events, while in most cases EMTs in cancer have been depicted as dedifferentiation events. We will briefly summarize both embryo development and cancer progression with regard to the involvement of EMT and cell differentiation status. We further present the studies that provide evidence that EMT results in both differentiation and dedifferentiation. Finally, we present our resolution to this dilemma by suggesting that EMT brings about dedifferentiation that enables subsequent differentiation. In normal development, EMT events may cause a partial reversal of differentiation to overcome differentiation barriers. When EMT is aberrantly activated in cancer, cells gain attributes of stem cells that contribute to self-renewal capabilities and are able to differentiate to all cell types represented in the tumor. The resulting cancer stem cells attain hallmarks of cancer, including replicative immortality, resistance to cell death, and invasiveness. Developmental Dynamics 248:10-20, 2019. (c) 2018 Wiley Periodicals, Inc.

Williams, D. (2015). "Thyroid Growth and Cancer." Eur Thyroid J **4**(3): 164-173.

It is proposed that most papillary thyroid cancers originate in infancy and childhood, based on the early rise in sporadic thyroid carcinoma incidence, the pattern of radiation-induced risk (highest in those exposed as infants), and the high prevalence of sporadic papillary thyroid cancers in children and adolescents (ultrasound screening after the Fukushima

accident). The early origin can be linked to the growth pattern of follicular cells, with a high mitotic rate in infancy falling to very low replacement levels in adult life. The cell of origin of thyroid cancers, the differentiated follicular cell, has a limited growth potential. Unlike cancers originating in stem cells, loss of the usually tight link between differentiation and replicative senescence is required for immortalisation. It is suggested that this loss distinguishes larger clinically significant papillary thyroid cancers from micro-papillary thyroid cancers of little clinical significance. Papillary carcinogenesis can then be divided into 3 stages: (1) initiation, the first mutation in the carcinogenic cascade, for radiation-induced papillary thyroid cancers usually a RET rearrangement, (2) progression, acquisition of the additional mutations needed for low-grade malignancy, and (3) escape, further mutations giving immortality and a higher net growth rate. Most papillary thyroid cancers will not have achieved full immortality by adulthood, and remain as so-called micro-carcinomas with a very low growth rate. The use of the term 'cancer' to describe micro-papillary thyroid cancers in older patients encourages overtreatment and alarms patients. Invasive papillary thyroid tumours show a spectrum of malignancy, which at its lowest poses no threat to life. The treatment protocols and nomenclature for small papillary carcinomas need to be reconsidered in the light of the new evidence available, the continuing discovery of smaller lesions, and the model of thyroid carcinogenesis proposed.

Yang, T. and K. Rycaj (2015). "Targeted therapy against cancer stem cells." Oncol Lett **10**(1): 27-33.

Research into cancer stem cells (CSCs), which have the ability to self-renew and give rise to more mature (differentiated) cancer cells, and which may be the cells responsible for the overall organization of a tumor, has progressed rapidly and concomitantly with recent advances in studies of normal tissue stem cells. CSCs have been reported in a wide spectrum of human tumors. Like normal tissue stem cells, CSCs similarly exhibit significant phenotypic and functional heterogeneity. The ability of CSCs to self-renew results in the immortality of malignant cells at the population level, whereas the ability of CSCs to differentiate, either fully or partially, generates the cellular hierarchy and heterogeneity commonly observed in solid tumors. CSCs also appear to have maximized their pro-survival mechanisms leading to their relative resistance to anti-cancer therapies and subsequent relapse. Studies in animal models of human cancers have also provided insight into the heterogeneity and characteristics of CSCs, helping to establish a platform for the development of novel targeted therapies against specific CSCs. In the present study, we briefly review the most recent progress in dissecting CSC heterogeneity and targeting CSCs in various human tumor systems. We also highlight a few examples of CSC-targeted drug development and clinical trials, with the ultimate aim of developing more effective therapeutic regimens that are capable of preventing tumor recurrence and metastasis.

Yoshioka, K., et al. (2015). "Development of cancer-initiating cells and immortalized cells with genomic instability." World J Stem Cells **7**(2): 483-489.

Cancers that develop after middle age usually exhibit genomic instability and multiple mutations. This is in direct contrast to pediatric tumors that usually develop as a result of specific chromosomal translocations and epigenetic aberrations. The development of genomic instability is associated with mutations that contribute to cellular immortalization and transformation. Cancer occurs when cancer-initiating cells (CICs), also called cancer stem cells, develop as a result of these mutations. In this paper, we explore how CICs develop as a result of genomic instability, including looking at which cancer suppression mechanisms are abrogated. A recent in vitro study revealed the existence of a CIC induction pathway in differentiating stem cells. Under aberrant differentiation conditions, cells become senescent and develop genomic instabilities that lead to the development of CICs. The resulting CICs contain a mutation in the alternative reading frame of CDKN2A (ARF)/p53 module, i.e., in either ARF or p53. We summarize recently established knowledge of CIC development and cellular immortality, explore the role of the ARF/p53 module in protecting cells from transformation, and describe a risk factor for genomic destabilization that increases during the process of normal cell growth and differentiation and is associated with the downregulation of histone H2AX to levels representative of growth arrest in normal cells.

Zheng, L., et al. (2018). "Regulation of c-MYC transcriptional activity by transforming growth factor-beta 1-stimulated clone 22." Cancer Sci **109**(2): 395-402.

c-MYC stimulates cell proliferation through the suppression of cyclin-dependent kinase (CDK) inhibitors including P15 (CDKN2B) and P21 (CDKN1A). It also activates E-box-mediated transcription of various target genes including telomerase reverse transcriptase (TERT) that is involved in cellular immortality and tumorigenesis. Transforming growth factor-beta 1 (TGF-beta1)-stimulated clone 22 (TSC-22/TSC22D1) encodes a highly conserved leucine zipper protein that is induced by various stimuli, including TGF-beta. TSC-22 inhibits cell growth in mammalian cells and in

Xenopus embryos. However, underlying mechanisms of growth inhibition by TSC-22 remain unclear. Here, we show that TSC-22 physically interacts with c-MYC to inhibit the recruitment of c-MYC on the P15 (CDKN2B) and P21 (CDKN1A) promoters, effectively inhibiting c-MYC-mediated suppression of P15 (CDKN2B) and also P21 (CDKN1A) promoter activities. In contrast, TSC-22 enhances c-MYC-mediated activation of the TERT promoter. Additionally, the expression of TSC-22 in embryonic stem cells inhibits cell growth without affecting its pluripotency-related gene expression. These results indicate that TSC-22 differentially regulates c-MYC-mediated transcriptional activity to regulate cell proliferation.

Zhou, Y., et al. (2013). "Stem cells' exodus: a journey to immortality." Dev Cell **24**(2): 113-114.

Stem cell niches provide a regulatory microenvironment that retains stem cells and promotes self-renewal. Recently in Developmental Cell, Rinkevich et al. (2013) showed that cell islands (CIs) of Botryllus schlosseri, a colonial chordate, provide niches for maintaining cycling stem cells that migrate from degenerated CIs to newly formed buds.

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