Stem Cell Biology Research Literatures

Ma Hongbao [1], Margaret Young [2], Yang Yan [1]

[1] Brookdale Hospital, Brooklyn, New York 11212, USA; [2] Cambridge, MA 02138, USA
ma8080@gmail.com

Abstract: 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 stem cell biology related studies.
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1. 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 (Ma, et al, 2007). Stem cells play the key functions.

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

Alfaro, M. P., S. Saraswati, et al. "Molecular mediators of mesenchymal stem cell biology." Vitam Horm. 2011;87:39-59. doi: 10.1016/B978-0-12-386015-6.00023-8.

Mesenchymal stem cells (MSCs) have the ability to self-renew and differentiate into multiple lineages making them an appropriate candidate for stem cell therapy. In spite of achieving considerable success in preclinical models, limited success has been achieved in clinical settings with MSCs. A major impediment that is faced is low survival of MSCs in injured tissues following implantation. In order to enhance the reparative properties of MSCs, it is vital to understand the molecular signals that regulate MSC survival and self-renewal. This review assimilates information that characterizes MSCs and mentions their utilization in myocardial infarction therapy. Additionally, our attempt herein is to gather pertinent published information regarding the role of canonical Wnt and BMP signaling in regulating the potential of MSCs to self-renew, proliferate, differentiate, and survive.

Antoniou, D., A. Stergiopoulos, et al. "Recent advances in the involvement of long non-coding RNAs in neural stem cell biology and brain pathophysiology." Front Physiol. 2014 Apr 22;5:155. doi: 10.3389/fphys.2014.00155. eCollection 2014.

Exploration of non-coding genome has recently uncovered a growing list of formerly unknown regulatory long non-coding RNAs (lncRNAs) with important functions in stem cell pluripotency, development and homeostasis of several tissues. Although thousands of lncRNAs are expressed in mammalian brain in a highly patterned manner, their roles in brain development have just begun to emerge. Recent data suggest key roles for these molecules in gene regulatory networks controlling neuronal and glial cell differentiation. Analysis of the genomic distribution of genes encoding for lncRNAs indicates a physical association of these regulatory RNAs with transcription factors (TFs) with well-established roles in neural differentiation, suggesting that lncRNAs and TFs may form coherent regulatory networks with important functions in neural stem cells (NSCs). Additionally, many studies show that lncRNAs are involved in the pathophysiology of brain-related diseases/disorders. Here we discuss these observations and investigate the links between lncRNAs, brain development and brain-related diseases. Understanding the functions of lncRNAs in NSCs and brain organogenesis could revolutionize the basic principles of developmental biology and neuroscience.

Balakrishnan, S. K., M. Witcher, et al. "Functional and molecular characterization of the role of CTCF in human embryonic stem cell biology." PLoS One. 2012;7(8):e42424. doi: 10.1371/journal.pone.0042424. Epub 2012 Aug 3.

The CCCTC-binding factor CTCF is the only known vertebrate insulator protein and has been shown to regulate important developmental processes such as imprinting, X-chromosome inactivation and genomic architecture. In this study, we examined the role of CTCF in human embryonic stem cell (hESC) biology. We demonstrate that CTCF associates with several important pluripotency genes, including NANOG, SOX2, cMYC and LIN28 and is critical for hESC proliferation. CTCF depletion impacts expression of pluripotency genes and accelerates loss of pluripotency upon BMP4 induced differentiation, but does not result in spontaneous differentiation. We find that CTCF associates with the distal ends and internal sites of the co-regulated 160 kb NANOG-DPPA3-GDF3 locus. Each of these sites can function as a CTCF-dependent enhancer-blocking insulator in heterologous assays. In hESCs, CTCF exists in multisubunit protein complexes and can be poly(ADP)ribosylated. Known CTCF cofactors, such as Cohesin, differentially co-localize in the vicinity of specific CTCF binding sites within the NANOG locus. Importantly, the association of some cofactors and protein PARlation selectively changes upon differentiation although CTCF binding remains constant. Understanding how unique cofactors may impart specialized functions to CTCF at specific genomic locations will further illuminate its role in stem cell biology.

Barker, N., S. Tan, et al. "Lgr proteins in epithelial stem cell biology." Development. 2013 Jun;140(12):2484-94. doi: 10.1242/dev.083113.

The ultimate success of global efforts to exploit adult stem cells for regenerative medicine will depend heavily on the availability of robust, highly selective stem cell surface markers that facilitate the isolation of stem cells from human tissues. Any subsequent expansion or manipulation of isolated stem cells will also require an intimate knowledge of the mechanisms that regulate these cells, to ensure maintenance of their regenerative capacities and to minimize the risk of introducing undesirable growth traits that could pose health risks for patients. A subclass of leucine-rich repeat-containing G-protein-coupled receptor (Lgr) proteins has recently gained prominence as adult stem cell markers with crucial roles in maintaining stem cell functions. Here, we discuss the major impact that their discovery has had on our understanding of adult stem cell biology in various self-renewing tissues and in accelerating progress towards the development of effective stem cell therapies.

Bednar, F. and D. M. Simeone "Pancreatic cancer stem cell biology and its therapeutic implications." J Gastroenterol. 2011 Dec;46(12):1345-52. doi: 10.1007/s00535-011-0494-7. Epub 2011 Nov 3.

Pancreatic cancer remains one of the most difficult malignancies to treat. Significant developments in our understanding of pancreatic cancer biology have occurred over the past decade. One of the key advances has been the formulation of the cancer stem cell model of tumor growth and subsequent experimental proof of pancreatic cancer stem cell existence. Cancer stem cells contribute to pancreatic tumor growth and progression and are at least partially responsible for the relative resistance of the tumor to systemic chemotherapy and radiation. Significant questions remain about how the mutational profile of the tumor, the tumor microenvironment, and normal pancreatic developmental pathways contribute to pancreatic cancer stem cell biology. Answers to these questions will likely yield new therapeutic approaches for this deadly disease.

Beyer, T. A., M. Narimatsu, et al. "The TGFbeta superfamily in stem cell biology and early mammalian embryonic development." Biochim Biophys Acta. 2013 Feb;1830(2):2268-79. doi: 10.1016/j.bbagen.2012.08.025. Epub 2012 Sep 5.

BACKGROUND: Members of the Transforming Growth Factor-beta (TGFbeta) superfamily of cytokines are essential for early embryonic development and play crucial roles in pluripotency and differentiation of embryonic stem cells in vitro. SCOPE OF REVIEW: In this review, we discuss how TGFbeta family signals are read by cells and how they are modulated by the cellular context. Furthermore, we review recent advances in our understanding of TGFbeta function in embryonic stem cells and point out hot topics at the intersection of TGFbeta signaling and stem cell biology fields. MAJOR CONCLUSION: TGFbeta family signals are essential for early mammalian development and the importance of this pathway is reflected in pluripotent stem cells derived from the mammalian embryo. GENERAL SIGNIFICANCE: Understanding signaling pathways underlying pluripotency and cell fate specification holds promises for the advent of personalized regenerative medicine. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

Bhatia, P., K. Tsumagari, et al. "Stem cell biology in thyroid cancer: Insights for novel therapies." World J Stem Cells. 2014 Nov 26;6(5):614-9. doi: 10.4252/wjsc.v6.i5.614.

Currently, thyroid cancer is one of the most common endocrine cancer in the United States. A recent involvement of sub-population of stem cells, cancer stem cells, has been proposed in different histological types of thyroid cancer. Because of their

ability of self-renewal and differentiation into various specialized cells in the body, these putative cells drive tumor genesis, metastatic activity and are responsible to provide chemo- and radioresistant nature to the cancer cells in the thyroid gland. Our Review was conducted from previously published literature to provide latest apprises to investigate the role of embryonic, somatic and cancer stem cells, and discusses the hypothesis of epithelial-mesenchymal transition. Different methods for their identification and isolation through stemness markers using various in vivo and in vitro methods such as flow cytometry, thyrosphere formation assay, aldehyde dehydrogenase activity and ATP-binding cassette sub-family G member 2 efflux-pump mediated Hoechst 33342 dye exclusion have been discussed. The review also outlines various setbacks that still remain to target these tumor initiating cells. Future perspectives of therapeutic strategies and their potential to treat advanced stages of thyroid cancer are also disclosed in this review.

Bonfanti, P., Y. Barrandon, et al. "'Hearts and bones': the ups and downs of 'plasticity' in stem cell biology." EMBO Mol Med. 2012 May;4(5):353-61. doi: 10.1002/emmm.201200220. Epub 2012 Mar 2.

More than a decade ago, 'plasticity' suddenly became a 'fashionable' topic with overemphasized implications for regenerative medicine. The concept of 'plasticity' is supported by old transplantation work, at least for embryonic cells, and metaplasia is a classic example of plasticity observed in patients. Nevertheless, the publication of a series of papers showing rare conversion of a given cell type into another unrelated cell raised the possibility of using any unaffected tissue to create at will new cells to replace a different failing tissue or organ. This resulted in disingenuous interpretations and a reason not to fund anymore research on embryonic stem cells (ESc). Moreover, many papers on plasticity were difficult to reproduce and thus questioned; raising issues about plasticity as a technical artefact or a consequence of rare spontaneous cells fusion. More recently, reprogramming adult differentiated cells to a pluripotent state (iPS) became possible, and later, one type of differentiated cell could be directly reprogrammed into another (e.g. fibroblasts into neurons) without reverting to pluripotency. Although the latter results from different and more robust experimental protocols, these phenomena also exemplify 'plasticity'. In this review, we want to place 'plasticity' in a historical perspective still taking into account ethical and political implications.

Bostrom, K. I., A. Garfinkel, et al. "Concise review: applying stem cell biology to vascular structures." Stem Cells. 2012 Mar;30(3):386-91. doi: 10.1002/stem.1027.

The vasculature, an organ that penetrates every other organ, is ideally poised to be the site where pools of stem cells are placed, to be deployed and committed in response to feedback regulation, and to respond to demands for new vascular structures. These pools of multipotent cells are often under the regulation of various members of the transforming growth factor-beta superfamily, including the bone morphogenetic proteins and their antagonists. Regulation of stem cell populations affects their recruitment, differentiation, spatial organization, and their coordination with host tissue. Loss and dysregulation of feedback control cause a variety of diseases that involve ectopic tissue formation, including atherosclerotic lesion formation and calcification, diabetic vasculopathies, and arteriovenous malformations.

Briest, F., A. Berndt, et al. "Tumor-stroma interactions in tumorigenesis: lessons from stem cell biology." Front Biosci (Elite Ed). 2012 Jan 1;4:1871-87.

Research in recent years has accumulated a wealth of novel insight into mechanisms by which tumor cells interact with activated fibroblasts, endothelial cells, inflammatory and immune cells and the extracellular matrix. Cancer and stromal cells co-evolve throughout tumorigenesis. As a result, the tumor stroma is now regarded as an essential contributor to tumor establishment, progression and dissemination. Moreover, the formation of suitable stroma niches has emerged as a prime determinant of metastasis. Notably, malignant tumors adopt numerous mechanisms that are also operative in embryonic and adult stem cell biology. Tumor sites show functional characteristics with striking similarities to stem cell niches. This review summarizes the current view of disease-relevant communication between tumor cells and the tumor stroma and relates it to interactions of stem cells and their respective niches. Progress in understanding the pivotal role of the microenvironment in both tumor and stem cell biology renders the tumor stroma an interesting potential future target for specific cancer therapies.

Campbell, J. J., N. Davidenko, et al. "A multifunctional 3D co-culture system for studies of mammary tissue morphogenesis and stem cell biology." PLoS One. 2011;6(9):e25661. doi: 10.1371/journal.pone.0025661. Epub 2011 Sep 30.

Studies on the stem cell niche and the efficacy of cancer therapeutics require complex multicellular structures and interactions between different cell types and extracellular matrix (ECM) in

three dimensional (3D) space. We have engineered a 3D in vitro model of mammary gland that encompasses a defined, porous collagen/hyaluronic acid (HA) scaffold forming a physiologically relevant foundation for epithelial and adipocyte co-culture. Polarized ductal and acinar structures form within this scaffold recapitulating normal tissue morphology in the absence of reconstituted basement membrane (rBM) hydrogel. Furthermore, organoid developmental outcome can be controlled by the ratio of collagen to HA, with a higher HA concentration favouring acinar morphological development. Importantly, this culture system recapitulates the stem cell niche as primary mammary stem cells form complex organoids, emphasising the utility of this approach for developmental and tumorigenic studies using genetically altered animals or human biopsy material, and for screening cancer therapeutics for personalised medicine.

Crews, L. A. and C. H. Jamieson "Chronic myeloid leukemia stem cell biology." Curr Hematol Malig Rep. 2012 Jun;7(2):125-32. doi: 10.1007/s11899-012-0121-6.

Leukemia progression and relapse is fueled by leukemia stem cells (LSC) that are resistant to current treatments. In the progression of chronic myeloid leukemia (CML), blast crisis progenitors are capable of adopting more primitive but deregulated stem cell features with acquired resistance to targeted therapies. This in turn promotes LSC behavior characterized by aberrant self-renewal, differentiation, and survival capacity. Multiple reports suggest that cell cycle alterations, activation of critical signaling pathways, aberrant microenvironmental cues from the hematopoietic niche, and aberrant epigenetic events and deregulation of RNA processing may facilitate the enhanced survival and malignant transformation of CML progenitors. Here we review the molecular evolution of CML LSC that promotes CML progression and relapse. Recent advances in these areas have identified novel targets that represent important avenues for future therapeutic approaches aimed at selectively eradicating the LSC population while sparing normal hematopoietic progenitors in patients suffering from chronic myeloid malignancies.

Crippa, S., M. Cassano, et al. "Role of miRNAs in muscle stem cell biology: proliferation, differentiation and death." Curr Pharm Des. 2012;18(13):1718-29.

miRNAs are small non-coding RNAs that regulate post-transcriptionally gene expression by degradation or translational repression of specific target mRNAs. In the 90s, lin-4 and let-7 were firstly identified as small regulatory RNAs able to control C. elegans larval development, by specifically targeting the 3'UTR of lin-14 and lin-28, respectively. These findings have introduced a novel and wide layer of complexity in the regulation of mRNA and protein expression. Lin-4 and let-7 are now considered the founding members of an abundant class of small fine-tuned RNAs, called microRNAs (miRNAs), in viruses, green algae, plants, flies, worms, and in mammals. In humans, the estimated number of genes encoding for miRNAs is as high as 1000 and around 30% of the protein-coding genes are post-transcriptionally controlled by miRNAs. This article reviews the role of miRNAs in regulating several biological responses in muscle cells, ranging from proliferation, differentiation and adaptation to stress cues. Cardiac and skeletal muscles are powerful examples to summarize the activity of miRNAs in cell fate specification, lineage differentiation and metabolic pathways. Indeed, specific miRNAs control the number of proliferating muscle progenitors to guarantee the proper formation of the heart and muscle fibers and to assure the self-renewal of muscle progenitors during adult tissue regeneration. On the other side, several other miRNAs promote the differentiation of muscle progenitors into skeletal myofibers or into cardiomyocytes, where metabolic activity, survival and remodeling process in response to stress, injury and chronic diseases are also fine-tuned by miRNAs.

Das, U. N. "Essential fatty acids and their metabolites as modulators of stem cell biology with reference to inflammation, cancer, and metastasis." Cancer Metastasis Rev. 2011 Dec;30(3-4):311-24. doi: 10.1007/s10555-011-9316-x.

Stem cells are pluripotent and expected to be of benefit in the management of coronary heart disease, stroke, diabetes mellitus, cancer, and Alzheimer's disease in which pro-inflammatory cytokines are increased. Identifying endogenous bioactive molecules that have a regulatory role in stem cell survival, proliferation, and differentiation may aid in the use of stem cells in various diseases including cancer. Essential fatty acids form precursors to both pro- and anti-inflammatory molecules have been shown to regulate gene expression, enzyme activity, modulate inflammation and immune response, gluconeogenesis via direct and indirect pathways, function directly as agonists of a number of G protein-coupled receptors, activate phosphatidylinositol 3-kinase/Akt and p44/42 mitogen-activated protein kinases, and stimulate cell proliferation via Ca(2+), phospholipase C/protein kinase, events that are also necessary for stem cell survival, proliferation, and differentiation. Hence, it is likely that bioactive lipids play a significant role in various diseases by modulating the proliferation and differentiation of

embryonic stem cells in addition to their capacity to suppress inflammation. Ephrin Bs and reelin, adhesion molecules, and microRNAs regulate neuronal migration and cancer cell metastasis. Polyunsaturated fatty acids and their products seem to modulate the expression of ephrin Bs and reelin and several adhesion molecules and microRNAs suggesting that bioactive lipids participate in neuronal regeneration and stem cell proliferation, migration, and cancer cell metastasis. Thus, there appears to be a close interaction among essential fatty acids, their bioactive products, and inflammation and cancer growth and its metastasis.

Devalle, S., R. C. Sartore, et al. "Implications of aneuploidy for stem cell biology and brain therapeutics." Front Cell Neurosci. 2012 Sep 5;6:36. doi: 10.3389/fncel.2012.00036. eCollection 2012.

Understanding the cellular basis of neurological disorders have advanced at a slow pace, especially due to the extreme invasiveness of brain biopsying and limitations of cell lines and animal models that have been used. Since the derivation of pluripotent stem cells (PSCs), a novel source of cells for regenerative medicine and disease modeling has become available, holding great potential for the neurology field. However, safety for therapy and accurateness for modeling have been a matter of intense debate, considering that genomic instability, including the gain and loss of chromosomes (aneuploidy), has been repeatedly observed in those cells. Despite the fact that recent reports have described some degree of aneuploidy as being normal during neuronal differentiation and present in healthy human brains, this phenomenon is particularly controversial since it has traditionally been associated with cancer and disabling syndromes. It is therefore necessary to appreciate, to which extent, aneuploid pluripotent stem cells are suitable for regenerative medicine and neurological modeling and also the limits that separate constitutive from disease-related aneuploidy. In this review, recent findings regarding chromosomal instability in PSCs and within the brain will be discussed.

Forsberg, K. and S. Di Giovanni Cross Talk between Cellular Redox Status, Metabolism, and p53 in Neural Stem Cell Biology, Neuroscientist. 2014 Jan 31;20(4):326-342.

In recent years, the importance of the cellular redox status for neural stem cell (NSC) homeostasis has become increasingly clear. Similarly, the transcription factor and tumor suppressor p53 has been implicated in the regulation of cell metabolism, in antioxidant response, and in stem cell quiescence and fate commitment. Here, we explore the known and putative functions of p53 in antioxidant response and metabolic control and examine how reactive oxygen species, p53, and related cellular signaling may regulate NSC homeostasis, quiescence, and differentiation. We also discuss the role that PI3K-Akt-mTOR signaling plays in NSC biology and oxidative signaling and how p53 contributes to the regulation of this signaling cascade. Finally, we invite reflection on the several unanswered questions of the role that p53 plays in NSC biology and metabolism, anticipating future directions.

Furusawa, C. and K. Kaneko "A dynamical-systems view of stem cell biology." Science. 2012 Oct 12;338(6104):215-7. doi: 10.1126/science.1224311.

During development, cells undergo a unidirectional course of differentiation that progressively decreases the number of cell types they can potentially become. Stem cells, however, keep their potential to both proliferate and differentiate. A very important issue then is to understand the characteristics that distinguish stem cells from other cell types and allow them to conduct stable proliferation and differentiation. Here, we review relevant dynamical-systems approaches to describe the state transition between stem and differentiated cells, with an emphasis on fluctuating and oscillatory gene expression levels, as these represent the specific properties of stem cells. Relevance between recent experimental results and dynamical-systems descriptions of stem cell differentiation is also discussed.

Geiselhart, A., A. Lier, et al. "Disrupted Signaling through the Fanconi Anemia Pathway Leads to Dysfunctional Hematopoietic Stem Cell Biology: Underlying Mechanisms and Potential Therapeutic Strategies." Anemia. 2012;2012:265790. doi: 10.1155/2012/265790. Epub 2012 May 23.

Fanconi anemia (FA) is the most common inherited bone marrow failure syndrome. FA patients suffer to varying degrees from a heterogeneous range of developmental defects and, in addition, have an increased likelihood of developing cancer. Almost all FA patients develop a severe, progressive bone marrow failure syndrome, which impacts upon the production of all hematopoietic lineages and, hence, is thought to be driven by a defect at the level of the hematopoietic stem cell (HSC). This hypothesis would also correlate with the very high incidence of MDS and AML that is observed in FA patients. In this paper, we discuss the evidence that supports the role of dysfunctional HSC biology in driving the etiology of the disease. Furthermore, we consider the different model systems currently available to study the biology of cells defective in the FA signaling pathway and

how they are informative in terms of identifying the physiologic mediators of HSC depletion and dissecting their putative mechanism of action. Finally, we ask whether the insights gained using such disease models can be translated into potential novel therapeutic strategies for the treatment of the hematologic disorders in FA patients.

Gundry, R. L., P. W. Burridge, et al. "Pluripotent stem cell heterogeneity and the evolving role of proteomic technologies in stem cell biology." Proteomics. 2011 Oct;11(20):3947-61. doi: 10.1002/pmic.201100100. Epub 2011 Sep 8.

Stem cells represent obvious choices for regenerative medicine and are invaluable for studies of human development and drug testing. The proteomic landscape of pluripotent stem cells (PSCs), in particular, is not yet clearly defined; consequently, this field of research would greatly benefit from concerted efforts designed to better characterize these cells. In this concise review, we provide an overview of stem cell potency, highlight the types and practical implications of heterogeneity in PSCs and provide a detailed analysis of the current view of the pluripotent proteome in a unique resource for this rapidly evolving field. Our goal in this review is to provide specific insights into the current status of the known proteome of both mouse and human PSCs. This has been accomplished by integrating published data into a unified PSC proteome to facilitate the identification of proteins, which may be informative for the stem cell state as well as to reveal areas where our current view is limited. These analyses provide insight into the challenges faced in the proteomic analysis of PSCs and reveal one area--the cell surface subproteome--that would especially benefit from enhanced research efforts.

Hodgkinson, C. P., V. Naidoo, et al. "Abi3bp is a multifunctional autocrine/paracrine factor that regulates mesenchymal stem cell biology." Stem Cells. 2013 Aug;31(8):1669-82. doi: 10.1002/stem.1416.

Mesenchymal stem cells (MSCs) transplanted into injured myocardium promote repair through paracrine mechanisms. We have previously shown that MSCs over-expressing AKT1 (Akt-MSCs) exhibit enhanced properties for cardiac repair. In this study, we investigated the relevance of Abi3bp toward MSC biology. Abi3bp formed extracellular deposits with expression controlled by Akt1 and ubiquitin-mediated degradation. Abi3bp knockdown/knockout stabilized focal adhesions and promoted stress-fiber formation. Furthermore, MSCs from Abi3bp knockout mice displayed severe deficiencies in osteogenic and adipogenic differentiation. Knockout or stable knockdown of Abi3bp increased MSC and Akt-MSC proliferation, promoting S-phase entry via cyclin-d1, ERK1/2, and Src. Upon Abi3bp binding to integrin-beta1 Src associated with paxillin which inhibited proliferation. In vivo, Abi3bp knockout increased MSC number and proliferation in bone marrow, lung, and liver. In summary, we have identified a novel extracellular matrix protein necessary for the switch from proliferation to differentiation in MSCs.

Homem, C. C. and J. A. Knoblich "Drosophila neuroblasts: a model for stem cell biology." Development. 2012 Dec 1;139(23):4297-310. doi: 10.1242/dev.080515.

Drosophila neuroblasts, the stem cells of the developing fly brain, have emerged as a key model system for neural stem cell biology and have provided key insights into the mechanisms underlying asymmetric cell division and tumor formation. More recently, they have also been used to understand how neural progenitors can generate different neuronal subtypes over time, how their cell cycle entry and exit are coordinated with development, and how proliferation in the brain is spared from the growth restrictions that occur in other organs upon starvation. In this Primer, we describe the biology of Drosophila neuroblasts and highlight the most recent advances made using neuroblasts as a model system.

Honore, B. and H. Vorum "Proteomic analysis as a means to approach limbal stem cell biology in a search for stem cell markers." Proteomics Clin Appl. 2014 Apr;8(3-4):178-84. doi: 10.1002/prca.201300049. Epub 2014 Mar 7.

The cornea consists of three main layers: an outer surface epithelium, the stroma, and the endothelium. A clear cornea is necessary for optimal vision and is maintained and repaired from limbal epithelial stem cells located in the limbus between the cornea and the sclera. Diseases and injury may result in deficiency of the stem cells impairing their ability to renew the corneal epithelium. Patients with limbal stem cell deficiency experience chronic pain and ultimately blindness. Attempts to treat the disease are based on replacement of the stem cells by transplantation or by culturing the stem cells. We here review the proteomic techniques that so far have been used to approach characterization of limbal stem cells and markers to identify them. It is apparent that the field is in a rather inchoate state due to the scarcity and relative inaccessibility of the stem cells. However, the importance of revealing limbal stem cell biology and identifying stem cell biomarkers calls for greater use of emerging methodology. Strategies for future studies are discussed.

Horton, S. J. and B. J. Huntly "Recent advances in acute myeloid leukemia stem cell biology." Haematologica. 2012 Jul;97(7):966-74. doi: 10.3324/haematol.2011.054734. Epub 2012 Apr 17.

The existence of cancer stem cells has long been postulated, but was proven less than 20 years ago following the demonstration that only a small sub-fraction of leukemic cells from acute myeloid leukemia patients were able to propagate the disease in xenografts. These cells were termed leukemic stem cells since they exist at the apex of a loose hierarchy, possess extensive self-renewal and the ability to undergo limited differentiation into leukemic blasts. Acute myeloid leukemia is a heterogeneous condition at both the phenotypic and molecular level with a variety of distinct genetic alterations giving rise to the disease. Recent studies have highlighted that this heterogeneity extends to the leukemic stem cell, with this dynamic compartment evolving to overcome various selection pressures imposed upon it during disease progression. The result is a complex situation in which multiple pools of leukemic stem cells may exist within individual patients which differ both phenotypically and molecularly. Since leukemic stem cells are thought to be resistant to current chemotherapeutic regimens and mediate disease relapse, their study also has potentially profound clinical implications. Numerous studies have generated important recent advances in the field, including the identification of novel leukemic stem cell-specific cell surface antigens and gene expression signatures. These tools will no doubt prove invaluable for the rational design of targeted therapies in the future.

Ito, K. and K. Ito "Newly Identified Roles of PML in Stem Cell Biology." Front Oncol. 2013 Mar 14;3:50. doi: 10.3389/fonc.2013.00050. eCollection 2013.

It has long been believed that the tumor suppressor promyelocytic leukemia (PML), the core component of the nuclear substructures known as the PML-nuclear bodies, plays a key part in acute PML (APL), as it is first cloned at the breakpoint of the t(15;17) translocation typical of that disease. Research over the past decade, however, has radically changed our view of how this tumor suppressor is regulated, how it can be therapeutically targeted, and how it functions in a number of tissue systems. One noteworthy recent study, for instance, revealed that PML regulates the activation of fatty acid metabolism, and that this metabolic reprograming plays an essential role in cancer biology and stem cell biology through the control it exerts over stem cell fate decisions. These findings sparked exciting new investigations of PML as a critical "rheostat" responsible for fine-tuning tissue homeostasis, and thus created at the intersection of cancer and stem cell biology a new field of study with important therapeutic implications.

Jones, S. P., G. J. Guillemin, et al. "The kynurenine pathway in stem cell biology." Int J Tryptophan Res. 2013 Sep 15;6:57-66. doi: 10.4137/IJTR.S12626.

The kynurenine pathway (KP) is the main catabolic pathway of the essential amino acid tryptophan. The KP has been identified to play a critical role in regulating immune responses in a variety of experimental settings. It is also known to be involved in several neuroinflammatory diseases including Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. This review considers the current understanding of the role of the KP in stem cell biology. Both of these fundamental areas of cell biology have independently been the focus of a burgeoning research interest in recent years. A systematic review of how the two interact has not yet been conducted. Several inflammatory and infectious diseases in which the KP has been implicated include those for which stem cell therapies are being actively explored at a clinical level. Therefore, it is highly relevant to consider the evidence showing that the KP influences stem cell biology and impacts the functional behavior of progenitor cells.

Kaur, S. and B. Singhal "When nano meets stem: the impact of nanotechnology in stem cell biology." J Biosci Bioeng. 2012 Jan;113(1):1-4. doi: 10.1016/j.jbiosc.2011.08.024. Epub 2011 Sep 28.

Nanotechnology and biomedical treatments using stem cells are among the latest conduits of biotechnological research. Even more recently, scientists have begun finding ways to mate these two specialties of science. The advent of nanotechnology has paved the way for an explicit understanding of stem cell therapy in vivo and by recapitulation of such in vivo environments in the culture, this technology seems to accommodate a great potential in providing new vistas to stem cell research. Nanotechnology carries in its wake, the development of highly stable, efficient and specific gene delivery systems for both in vitro and in vivo genetic engineering of stem cells, use of nanoscale systems (such as microarrays) for investigation of gene expression in stem cells, creation of dynamic three-dimensional nano-environments for in vitro and in vivo maintenance and differentiation of stem cells and development of extremely sensitive in vivo detection systems to gain insights into the mechanisms of stem cell differentiation and apoptosis in different disease models. The present review presents an overview of the current applications and

future prospects for the use of nanotechnology in stem cell biology.

Koh, C. P., C. E. Ng, et al. Hematopoietic stem cell enhancer: a powerful tool in stem cell biology, Histol Histopathol. 2015 Jun;30(6):661-672. Epub 2015 Jan 9.

There has been considerable interest in identifying a cis-regulatory element that targets gene expression to stem cells. Such an element, termed stem cell enhancer, holds the promise of providing important insights into the transcriptional programs responsible for inherent stem cell-specific properties such as self-renewal capacity. The element also serves as a molecular handle for stem cell-specific marking, transgenesis and gene targeting, thereby becoming invaluable to stem cell research. A series of candidate enhancers have been identified for hematopoietic stem cells (HSCs). This review summarizes currently known HSC enhancers with emphasis on an intronic enhancer in the Runx1 gene which is essential for the generation and maintenance of HSCs. The element, named eR1 (+24m), is active specifically in HSCs, but not in progenitors, and is hence the most definitive HSC enhancer.

Kranenburg, O., B. L. Emmink, et al. "Proteomics in studying cancer stem cell biology." Expert Rev Proteomics. 2012 Jun;9(3):325-36. doi: 10.1586/epr.12.24.

Normal multipotent tissue stem cells (SCs) are the driving force behind tissue turnover and repair. The cancer stem cell theory holds that tumors also contain stem-like cells that drive tumor growth and metastasis formation. However, very little is known about the regulation of SC maintenance pathways in cancer and how these are affected by cancer-specific genetic alterations and by treatment. Proteomics is emerging as a powerful tool to identify the signaling complexes and pathways that control multi- and pluri-potency and SC differentiation. Here, the authors review the novel insights that these studies have provided and present a comprehensive strategy for the use of proteomics in studying cancer SC biology.

Lammens, T., I. D'Hont, et al. "Long non-coding RNAs in pluripotent stem cell biology." Vet Q. 2013 Dec;33(4):202-6. doi: 10.1080/01652176.2013.866297. Epub 2013 Dec 16.

Pluripotent stem cells are defined by their unlimited self-renewal capacities and potential to differentiate into any cell lineage. Many crucial determinants for the induction and maintenance of this pluripotent state have been identified. Long non-coding RNAs have recently emerged as key regulators of pluripotent stem cells and have enhanced our understanding of their potential functions in tissue regeneration. This review provides an overview of recent important insights into the roles of long non-coding RNAs as regulators and markers of pluripotency.

Lehner, B., B. Sandner, et al. "The dark side of BrdU in neural stem cell biology: detrimental effects on cell cycle, differentiation and survival." Cell Tissue Res. 2011 Sep;345(3):313-28. doi: 10.1007/s00441-011-1213-7. Epub 2011 Aug 12.

5-Bromo-2'-deoxyuridin (BrdU) is frequently used in anaylsis of neural stem cell biology, in particular to label and to fate-map dividing cells. However, up to now, only a few studies have addressed the question as to whether BrdU labeling per se affects the cells to be investigated. Here, we focused on the potential impact of BrdU on neurosphere cultures derived from the adult rat brain and on proliferation of progenitors in vivo. In vitro, neurospheres were pulsed for 48 h with BrdU, and cell proliferation, cell cycle, differentiation, survival and adhesion properties were subsequently analyzed. BrdU inhibited the expansion of neural progenitors as assessed by MTS assay and increased the fraction of cells in the G0/G1-phase of the cell cycle. Moreover, BrdU increased cell death and dose-dependently induced adherence of NPCs. Cell adherence was accompanied by a reduced amount of active matrix-metalloproteinase-2 (MMP-2). Furthermore, BrdU repressed neuronal and oligodendroglial differentiation, whereas astroglial fate was not affected. In contrast to the in vitro situation, BrdU apparently did not influence endogenous proliferation of NPCs or neurogenesis in concentrations that are typically used for labeling of neural progenitors in vivo. Our results reveal so far uncharacterized effects of BrdU on adult NPCs. We conclude that, because of its ubiquitous use in stem cell biology, any potential effect of BrdU of NPCs has to be scrutinized prior to interpretation of data.

Mangel, M. and M. B. Bonsall "Stem cell biology is population biology: differentiation of hematopoietic multipotent progenitors to common lymphoid and myeloid progenitors." Theor Biol Med Model. 2013 Jan 17;10:5. doi: 10.1186/1742-4682-10-5.

The hematopoietic stem cell (HSC) system is a demand control system, with the demand coming from the organism, since the products of the common myeloid and lymphoid progenitor (CMP, CLP respectively) cells are essential for activity and defense against disease. We show how ideas from population biology (combining population dynamics and evolutionary considerations) can illuminate the feedback control of the HSC system by the fully

differentiated products, which has recently been verified experimentally. We develop models for the penultimate differentiation of HSC Multipotent Progenitors (MPPs) into CLP and CMP and introduce two concepts from population biology into stem cell biology. The first concept is the Multipotent Progenitor Commitment Response (MPCR) which is the probability that a multipotent progenitor cell follows a CLP route rather than a CMP route. The second concept is the link between the MPCR and a measure of Darwinian fitness associated with organismal performance and the levels of differentiated lymphoid and myeloid cells. We show that many MPCRs are consistent with homeostasis, but that they will lead to different dynamics of cells and signals following a wound or injury and thus have different consequences for Darwinian fitness. We show how coupling considerations of life history to dynamics of the HSC system and its products allows one to compute the selective pressures on cellular processes. We discuss ways that this framework can be used and extended.

Matunis, E. L., R. R. Stine, et al. "Recent advances in Drosophila male germline stem cell biology." Spermatogenesis. 2012 Jul 1;2(3):137-144.

The ability of stem cells to divide asymmetrically to produce both self-renewing and differentiating daughter cells sustains many adult tissues, but germline stem cells (GSCs) are unique among stem cells as they perpetuate the genome of the species. The cellular and molecular mechanisms regulating most mammalian stem cells in their endogenous local microenvironments, or niches, are quite challenging to study. However, studies of stem cell niches such as those found in the Drosophila gonads have proven very useful. In these tissues, GSCs are housed in a readily identifiable niche, and the ability to genetically manipulate these cells and their neighbors has uncovered several fundamental mechanisms that are relevant to stem cells more generally. Here, we summarize recent work on the regulation of GSCs in the Drosophila testis niche by intercellular signals, and on the intracellular mechanisms that cooperate with these signals to ensure the survival of the germline. This review focuses on GSCs within the adult Drosophila testis; somatic stem cells in this tissue are reviewed by Zoller and Schulz in this issue.(1) For a review of the testis niche as a whole, see de Cuevas and Matunis,(2) and for more comprehensive reviews of the Drosophila testis, refer to Fuller(3) and Davies and Fuller.(4).

Mertins, S. D., D. A. Scudiero, et al. "A small molecule (pluripotin) as a tool for studying cancer stem cell biology: proof of concept." PLoS One. 2013;8(2):e57099. doi: 10.1371/journal.pone.0057099. Epub 2013 Feb 21.

BACKGROUND: Cancer stem cells (CSC) are thought to be responsible for tumor maintenance and heterogeneity. Bona fide CSC purified from tumor biopsies are limited in supply and this hampers study of CSC biology. Furthermore, purified stem-like CSC subpopulations from existing tumor lines are unstable in culture. Finding a means to overcome these technical challenges would be a useful goal. In a first effort towards this, we examined whether a chemical probe that promotes survival of murine embryonic stem cells without added exogenous factors can alter functional characteristics in extant tumor lines in a fashion consistent with a CSC phenotype. METHODOLOGY/PRINCIPAL FINDINGS: The seven tumor lines of the NCI60 colon subpanel were exposed to SC-1 (pluripotin), a dual kinase and GTPase inhibitor that promotes self-renewal, and then examined for tumorigenicity under limiting dilution conditions and clonogenic activity in soft agar. A statistically significant increase in tumor formation following SC-1 treatment was observed ($p<0.04$). Cloning efficiencies and expression of putative CSC surface antigens (CD133 and CD44) were also increased. SC-1 treatment led to sphere formation in some colon tumor lines. Finally, SC-1 inhibited in vitro kinase activity of RSK2, and another RSK2 inhibitor increased colony formation implicating a role for this kinase in eliciting a CSC phenotype. CONCLUSIONS/SIGNIFICANCE: These findings validate a proof of concept study exposure of extant tumor lines to a small molecule may provide a tractable in vitro model for understanding CSC biology.

Osei-Bempong, C., F. C. Figueiredo, et al. "The limbal epithelium of the eye--a review of limbal stem cell biology, disease and treatment." Bioessays. 2013 Mar;35(3):211-9. doi: 10.1002/bies.201200086. Epub 2012 Nov 5.

The limbus is a narrow band of tissue that encircles the cornea, the transparent 'window' into the eye. The outermost layer of the cornea is the epithelium, which is necessary for clear vision. The limbus acts as a 'reservoir' for limbal stem cells which maintain and regenerate the corneal epithelium. It also functions as a barrier to the conjunctiva and its blood vessels. Limbal stem cell deficiency is a general term for diseases which are characterised by the impairment of the limbus, limbal stem cells and their ability to replenish the corneal epithelium through proliferation and differentiation. Consequently, sufferers experience chronic pain and progressive blindness. This paper will highlight the salient

milestones of limbal stem cell biology and potential future treatments for limbal stem cell deficiency.

Oshimori, N. and E. Fuchs "The harmonies played by TGF-beta in stem cell biology." Cell Stem Cell. 2012 Dec 7;11(6):751-64. doi: 10.1016/j.stem.2012.11.001.

To rejuvenate tissues and/or repair wounds, stem cells must receive extrinsic signals from their surrounding environment and integrate them with their intrinsic abilities to self-renew and differentiate to make tissues. Increasing evidence suggests that the superfamily of transforming growth factor-betas (TGF-betas) constitute integral components in the intercellular crosstalk between stem cells and their microenvironment. In this review, we summarize recent advances in our understanding of TGF-beta superfamily functions in embryonic and adult stem cells. We discuss how these pathways help to define the physiological environment where stem cells reside, and how perturbations in the signaling circuitry contribute to cancers.

Pearl, R. A., S. J. Leedham, et al. "The safety of autologous fat transfer in breast cancer: lessons from stem cell biology." J Plast Reconstr Aesthet Surg. 2012 Mar;65(3):283-8. doi: 10.1016/j.bjps.2011.07.017. Epub 2011 Aug 4.

Autologous fat grafting is versatile tool in plastic surgery and is increasing used for reconstruction following breast conserving surgery for breast cancer. Part of the reconstructive qualities of the transferred fat may be due to the presence of adipose derived mesenchymal stem cells (ADMSC) playing an angiogenic and an adipogenic role. In this context it must be considered if autologously engrafted fat tissue could contribute to carcinogenesis following breast conserving surgery. In this article we review the current stem cell biology evidence on engraftment, transdifferentiation and potential carcinogenic contribution in the breast and other solid organ stem cell niches in an attempt to highlight possible areas of concern.

Pieters, T. and F. van Roy "Role of cell-cell adhesion complexes in embryonic stem cell biology." J Cell Sci. 2014 Jun 15;127(Pt 12):2603-13. doi: 10.1242/jcs.146720.

Pluripotent embryonic stem cells (ESCs) can self-renew or differentiate into any cell type within an organism. Here, we focus on the roles of cadherins and catenins - their cytoplasmic scaffold proteins - in the fate, maintenance and differentiation of mammalian ESCs. E-cadherin is a master stem cell regulator that is required for both mouse ESC (mESC) maintenance and differentiation. E-cadherin interacts with key components of the naive stemness pathway and ablating it prevents stem cells from forming well-differentiated teratomas or contributing to chimeric animals. In addition, depleting E-cadherin converts naive mouse ESCs into primed epiblast-like stem cells (EpiSCs). In line with this, a mesenchymal-to-epithelial transition (MET) occurs during reprogramming of somatic cells towards induced pluripotent stem cells (iPSCs), leading to downregulation of N-cadherin and acquisition of high E-cadherin levels. beta-catenin exerts a dual function; it acts in cadherin-based adhesion and in WNT signaling and, although WNT signaling is important for stemness, the adhesive function of beta-catenin might be crucial for maintaining the naive state of stem cells. In addition, evidence is rising that other junctional proteins are also important in ESC biology. Thus, precisely regulated levels and activities of several junctional proteins, in particular E-cadherin, safeguard naive pluripotency and are a prerequisite for complete somatic cell reprogramming.

Pinto, J. P., R. K. Reddy Kalathur, et al. "StemCellNet: an interactive platform for network-oriented investigations in stem cell biology." Nucleic Acids Res. 2014 Jul;42(Web Server issue):W154-60. doi: 10.1093/nar/gku455. Epub 2014 May 22.

Stem cells are characterized by their potential for self-renewal and their capacity to differentiate into mature cells. These two key features emerge through the interplay of various factors within complex molecular networks. To provide researchers with a dedicated tool to investigate these networks, we have developed StemCellNet, a versatile web server for interactive network analysis and visualization. It rapidly generates focused networks based on a large collection of physical and regulatory interactions identified in human and murine stem cells. The StemCellNet web-interface has various easy-to-use tools for selection and prioritization of network components, as well as for integration of expression data provided by the user. As a unique feature, the networks generated can be screened against a compendium of stemness-associated genes. StemCellNet can also indicate novel candidate genes by evaluating their connectivity patterns. Finally, an optional dataset of generic interactions, which provides large coverage of the human and mouse proteome, extends the versatility of StemCellNet to other biomedical research areas in which stem cells play important roles, such as in degenerative diseases or cancer. The StemCellNet web server is freely accessible at http://stemcellnet.sysbiolab.eu.

Plickert, G., U. Frank, et al. "Hydractinia, a pioneering model for stem cell biology and reprogramming

somatic cells to pluripotency." Int J Dev Biol. 2012;56(6-8):519-34.

Hydractinia, a representative marine colonial hydroid, was the first organism in the history of biology in which migratory precursors of germ cells were described and termed "stem cells" (Weismann, 1883). These stem cells, now known as interstitial cells (i-cells), are thought to remain pluripotent throughout their life. Using animals depleted of their own stem cells and repopulated with allogeneic mutant donor stem cells, it was shown that Hydractinia i-cells differentiate into any cell type including epithelial cells and germ cells that express germ line markers such as Vasa, Piwi and Nanos. In Hydra, i-cells also provide germ cells and somatic cells with the exception of epithelial cells. The latter derive from two subpopulations of differentiated epithelial cells with self-renewal capacity. In Hydractinia, forced expression of the Oct4-like transcription factor, Polynem (Pln), in epithelial cells transforms them into stem cells that develop neoplasms. I-cells express the Wnt-receptor Frizzled and are Wnt responsive. Activation of Wnt signaling induces the production of numerous nematocytes (stinging cells) and nerve cells. In parallel, supernumerary tentacles develop. I-cells also express Myc and Nanos. Their misexpression causes severe developmental defects. Hydractinia polyp buds arise from aggregating stem cells, in contrast to Hydra buds, which derive from evaginating epithelial cells. Wnt activation increases budding frequency and the emergence of ectopic head structures. The potential of stem cells to invade neighbors may have provided selection pressure for the evolution of allorecognition and histo-incompatibility. Hence, Hydractinia have now attained the position of a powerful model in stem cell research, axis formation and allorecognition.

Quesenberry, P. J., M. S. Dooner, et al. "A new stem cell biology: the continuum and microvesicles." Trans Am Clin Climatol Assoc. 2012;123:152-66; discussion 166.

The hierarchical models of stem cell biology have been based on work first demonstrating pluripotental spleen-colony-forming units, then showing progenitors with many differentiation fates assayed in in vitro culture; there followed the definition and separation of "stem cells" using monoclonal antibodies to surface epitopes and fluorescent-activated cell characterization and sorting (FACS). These studies led to an elegant model of stem cell biology in which primitive dormant G0 stem cells with tremendous proliferative and differentiative potential gave rise to progressively more restricted and differentiated classes of stem/progenitor cells, and finally differentiated marrow hematopoietic cells. The holy grail of hematopoietic stem cell biology became the purification of the stem cell and the clonal definition of this cell. Most recently, the long-term repopulating hematopoietic stem cell (LT-HSC) has been believed to be a lineage negative sca-1+C-kit+ Flk3- and CD150+ cell. However, a series of studies over the past 10 years has indicated that murine marrow stem cells continuously change phenotype with cell cycle passage. We present here studies using tritiated thymidine suicide and pyronin-Hoechst FACS separations indicating that the murine hematopoietic stem cell is a cycling cell. This would indicate that the hematopoietic stem cell must be continuously changing in phenotype and, thus, could not be purified. The extant data indicate that murine marrow stem cells are continually transiting cell cycle and that the purification has discarded these cycling cells. Further in vivo BrdU studies indicate that the "quiescent" LT-HSC in G0 rapidly transits cycle. Further complexity of the marrow stem cell system is indicated by studies on cell-derived microvesicles showing that they enter marrow cells and transcriptionally alter their cell fate and phenotype. Thus, the stem cell model is a model of continuing changing potential tied to cell cycle and microvesicle exposure. The challenge of the future is to define the stem cell population, not purify the stem cell. We are at the beginning of elucidation of quantum stemomics.

Ramos, A. and F. D. Camargo "The Hippo signaling pathway and stem cell biology." Trends Cell Biol. 2012 Jul;22(7):339-46. doi: 10.1016/j.tcb.2012.04.006. Epub 2012 May 31.

Stem cell (SC) activity fluctuates throughout an organism's lifetime to maintain homeostatic conditions in all tissues. As animals develop and age, their organs must remodel and regenerate themselves in response to environmental and physiological demands. Recently, the highly conserved Hippo signaling pathway, discovered in Drosophila melanogaster, has been implicated as a key regulator of organ size control across species. Deregulation is associated with substantial overgrowth phenotypes and eventual onset of cancer in various tissues. Importantly, emerging evidence suggests that the Hippo pathway can modulate its effects on tissue size by the direct regulation of SC proliferation and maintenance. These findings provide an attractive model for how this pathway might communicate physiological needs for growth to tissue-specific SC pools. In this review, we summarize the current and emerging data linking Hippo signaling to SC function.

Ratajczak, M. Z., E. Zuba-Surma, et al. "Very small embryonic-like stem cells (VSELs) represent a real challenge in stem cell biology: recent pros and cons in

the midst of a lively debate." Leukemia. 2014 Mar;28(3):473-84. doi: 10.1038/leu.2013.255. Epub 2013 Sep 10.

The concept that adult tissue, including bone marrow (BM), contains early-development cells with broader differentiation potential has again been recently challenged. In response, we would like to review the accumulated evidence from several independent laboratories that adult tissues, including BM, harbor a population of very rare stem cells that may cross germ layers in their differentiation potential. Thus, the BM stem cell compartment hierarchy needs to be revisited. These dormant, early-development cells that our group described as very small embryonic-like stem cells (VSELs) most likely overlap with similar populations of stem cells that have been identified in adult tissues by other investigators as the result of various experimental strategies and have been given various names. As reported, murine VSELs have some pluripotent stem cell characteristics. Moreover, they display several epiblast/germline markers that suggest their embryonic origin and developmental deposition in adult BM. Moreover, at the molecular level, changes in expression of parentally imprinted genes (for example, Igf2-H19) and resistance to insulin/insulin-like growth factor signaling (IIS) regulates their quiescent state in adult tissues. In several emergency situations related to organ damage, VSELs can be activated and mobilized into peripheral blood, and in appropriate animal models they contribute to tissue organ/regeneration. Interestingly, their number correlates with lifespan in mice, and they may also be involved in some malignancies. VSELs have been successfully isolated in several laboratories; however, some investigators experience problems with their isolation.

Rennie, K., A. Gruslin, et al. "Applications of amniotic membrane and fluid in stem cell biology and regenerative medicine." Stem Cells Int. 2012;2012:721538. doi: 10.1155/2012/721538. Epub 2012 Oct 10.

The amniotic membrane (AM) and amniotic fluid (AF) have a long history of use in surgical and prenatal diagnostic applications, respectively. In addition, the discovery of cell populations in AM and AF which are widely accessible, nontumorigenic and capable of differentiating into a variety of cell types has stimulated a flurry of research aimed at characterizing the cells and evaluating their potential utility in regenerative medicine. While a major focus of research has been the use of amniotic membrane and fluid in tissue engineering and cell replacement, AM- and AF-derived cells may also have capabilities in protecting and stimulating the repair of injured tissues via paracrine actions, and acting as vectors for biodelivery of exogenous factors to treat injury and diseases. Much progress has been made since the discovery of AM and AF cells with stem cell characteristics nearly a decade ago, but there remain a number of problematic issues stemming from the inherent heterogeneity of these cells as well as inconsistencies in isolation and culturing methods which must be addressed to advance the field towards the development of cell-based therapies. Here, we provide an overview of the recent progress and future perspectives in the use of AM- and AF-derived cells for therapeutic applications.

Rosewell, I. R. and A. Giangreco "Murine aggregation chimeras and wholemount imaging in airway stem cell biology." Methods Mol Biol. 2012;916:263-74. doi: 10.1007/978-1-61779-980-8_20.

Local tissue stem cells are known to exist in mammalian lungs but their role in epithelial maintenance remains unclear. We therefore developed murine aggregation chimera and wholemount imaging techniques to assess the contribution of these cells to lung homeostasis and repair. In this chapter we provide further details regarding the generation of murine aggregation chimera mice and their subsequent use in wholemount lung imaging. We also describe methods related to the interpretation of this data that allows for quantitative assessment of airway stem cell activation versus quiescence. Using these techniques, it is possible to compare the growth and differentiation capacity of various lung epithelial cells in normal, repairing, and diseased states.

Rousseaux, S. "Two decades of reproductive biomedicine and stem cell biology in Iran: the Royan Institute." Int J Dev Biol. 2014;58(9):643-7. doi: 10.1387/ijdb.140245sr.

The Royan Institute in Tehran, Iran, has developed over the last 23 years and is today a leading institute in the Middle East dedicated to research and technological development programs coupled with clinical activities in the area of reproductive and stem cell biology. Here an insight into its history and future plans is given through a dialogue with one of its pioneer members and current Director, Prof. Hamid Gourabi. The Royan Institute is a remarkable example of a successful achievement in organizing basic and translational research under challenging environmental conditions.

Sage, J. "The retinoblastoma tumor suppressor and stem cell biology." Genes Dev. 2012 Jul 1;26(13):1409-20. doi: 10.1101/gad.193730.112.

Stem cells play a critical role during embryonic development and in the maintenance of

homeostasis in adult individuals. A better understanding of stem cell biology, including embryonic and adult stem cells, will allow the scientific community to better comprehend a number of pathologies and possibly design novel approaches to treat patients with a variety of diseases. The retinoblastoma tumor suppressor RB controls the proliferation, differentiation, and survival of cells, and accumulating evidence points to a central role for RB activity in the biology of stem and progenitor cells. In some contexts, loss of RB function in stem or progenitor cells is a key event in the initiation of cancer and determines the subtype of cancer arising from these pluripotent cells by altering their fate. In other cases, RB inactivation is often not sufficient to initiate cancer but may still lead to some stem cell expansion, raising the possibility that strategies aimed at transiently inactivating RB might provide a novel way to expand functional stem cell populations. Future experiments dedicated to better understanding how RB and the RB pathway control a stem cell's decisions to divide, self-renew, or give rise to differentiated progeny may eventually increase our capacity to control these decisions to enhance regeneration or help prevent cancer development.

Salvetti, A., L. Rossi, et al. "In vivo biocompatibility of boron nitride nanotubes: Effects on stem cell biology and tissue regeneration in planarians." Nanomedicine (Lond). 2015 Apr 2:1-12.

AIM: Boron nitride nanotubes (BNNTs) represent an extremely interesting class of nanomaterials, and recent findings have suggested a number of applications in the biomedical field. Anyhow, extensive biocompatibility investigations are mandatory before any further advancement toward preclinical testing. MATERIALS & METHODS: Here, we report on the effects of multiwalled BNNTs in freshwater planarians, one of the best-characterized in vivo models for developmental biology and regeneration research. RESULTS & DISCUSSION: Obtained results indicate that BNNTs are biocompatible in the investigated model, since they do not induce oxidative DNA damage and apoptosis, and do not show adverse effects on planarian stem cell biology and on de novo tissue regeneration. In summary, collected findings represent another important step toward BNNT realistic applications in nanomedicine.

Samardzija, C., M. Quinn, et al. "Attributes of Oct4 in stem cell biology: perspectives on cancer stem cells of the ovary." J Ovarian Res. 2012 Nov 21;5(1):37. doi: 10.1186/1757-2215-5-37.

Epithelial ovarian cancer (EOC) remains the most lethal of all the gynaecological malignancies with drug resistance and recurrence remaining the major therapeutic barrier in the management of the disease. Although several studies have been undertaken to understand the mechanisms responsible for chemoresistance and subsequent recurrence in EOC, the exact mechanisms associated with chemoresistance/recurrence continue to remain elusive. Recent studies have shown that the parallel characteristics commonly seen between embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSC) are also shared by a relatively rare population of cells within tumors that display stem cell-like features. These cells, termed 'cancer initiating cells' or 'cancer stem cells (CSCs)' have been shown not only to display increased self renewal and pluripotent abilities as seen in ESCs and iPSCs, but are also highly tumorigenic in in vivo mouse models. Additionally, these CSCs have been implicated in tumor recurrence and chemoresistance, and when isolated have consistently shown to express the master pluripotency and embryonic stem cell regulating gene Oct4. This article reviews the involvement of Oct4 in cancer progression and chemoresistance, with emphasis on ovarian cancer. Overall, we highlight why ovarian cancer patients, who initially respond to conventional chemotherapy subsequently relapse with recurrent chemoresistant disease that is essentially incurable.

Scheitz, C. J. and T. Tumbar "New insights into the role of Runx1 in epithelial stem cell biology and pathology." J Cell Biochem. 2013 May;114(5):985-93. doi: 10.1002/jcb.24453.

The transcription factor Runx1 has been studied in leukemia and blood for decades, but recently it has been also implicated in epithelial biology and pathology. Particularly in mouse skin Runx1 modulates Wnt signaling levels thereby regulating timely induction of hair follicle specification, proper maturation of the emerging adult hair follicle stem cells in embryogenesis, and timely stem cell (SC) activation during adult homeostasis. Moreover, Runx1 acts as a tumor promoter in mouse skin squamous tumor formation and maintenance, likely by repressing p21 and promoting Stat3 activation. Similarly, Runx1 is essential for oral epithelium tumorigenesis mediated in mice by Ras, and for growth of three kinds of human epithelial cancer cells. In contrast, Runx1 has a tumor suppressor function in the mouse intestine and shows tumor subtype specific behavior in human breast cancer. Multiple studies revealed Runx1 SNPs to be associated with human cancers and autoimmune disease. With this information as background, the field is poised for functional and mechanistic studies to

elucidate the role of Runx1 in formation and/or progression of epithelial-based human disease.

Shiota, G. and T. Yasui "Progress in stem cell biology in regenerative medicine for liver disease." Hepatol Res. 2012 Jan;42(1):15-21. doi: 10.1111/j.1872-034X.2011.00874.x. Epub 2011 Sep 22.

Regenerative medicine using stem cells has attracted much attention, since stem cells are responsible for highly proliferative activity and multipotential ability of differentiation. Induced pluripotent stem cells and embryonic stem cells or the adult stem cells such as bone marrow-derived stem cells and adipose tissue-derived stem cells have been expected as a cell source of regenerative medicine. Since differentiating methods of human stem cells into the defined lineage of cells remains to be developed, we focus on the differentiating strategies of pluripotent stem cells and mesenchymal stem cells into liver lineage, especially on cytokine function and gene expression during hepatic differentiation. The survey of previously published papers discloses that the protocols that mimic the liver developmental process seem to be effective in obtaining functional hepatocytes. However, in order to develop hepatic regenerative medicine that is useful in a clinical setting, more effective and potent strategies that obtain mature hepatocytes are required.

Sirakov, M., E. Kress, et al. "Thyroid hormones and their nuclear receptors: new players in intestinal epithelium stem cell biology?" Cell Mol Life Sci. 2014 Aug;71(15):2897-907. doi: 10.1007/s00018-014-1586-3. Epub 2014 Mar 7.

Thyroid hormones participate in the development and homeostasis of several organs and tissues. It is well documented that they act via nuclear receptors, the TRs, which are transcription factors whose function is modulated by the hormone T3. Importantly, T3-induced physiological response within a cell depends on the specific TR expression and on the T3 bioavailability. However, in addition to this T3-dependent control of TR functionality, increasing data show that the action of TRs is coordinated and integrated with other signaling pathways, specifically at the level of stem/progenitor cell populations. By focusing on the intestinal epithelium of both amphibians and mammals we summarize here new data in support of a role for thyroid hormones and the TR nuclear receptors in stem cell biology. This new concept may be extended to other organs and have biological relevance in therapeutic approaches aimed to target stem cells such as tissue engineering and cancer.

Sykes, S. M. and D. T. Scadden "Modeling human hematopoietic stem cell biology in the mouse." Semin Hematol. 2013 Apr;50(2):92-100. doi: 10.1053/j.seminhematol.2013.03.029. Epub 2013 Jun 11.

Hematopoietic stem cells (HSCs) have the immense task of supplying an organism with enough blood to sustain a lifespan. Much of what is known about how this scant population of cells can meet the varying demand of producing more than 10(11) cells per day comes from studies conducted in an animal that is a fraction of our size and lives roughly 1/30th of our lifespan. The differences in longevity can be expected to impose different demands on a cell essential for existence. It is therefore unsurprising that while the mouse has proven invaluable in defining the organizing principals of how hematopoiesis is governed, mediators of cell localization as well as a range of experimental methods, the differences in cell cycling, DNA repair and specific molecular features of HSCs in humans are evident and important. Here, the utility and drawbacks of the mouse as an experimental model for human HSC biology are discussed.

Tamm, C., L. Kjellen, et al. "Heparan sulfate biosynthesis enzymes in embryonic stem cell biology." J Histochem Cytochem. 2012 Dec;60(12):943-9. doi: 10.1369/0022155412465090. Epub 2012 Oct 4.

Embryonic stem (ES) cells are derived from the inner cell mass of the blastocyst and can give rise to all cell types in the body. The fate of ES cells depends on the signals they receive from their surrounding environment, which either promote self-renewal or initiate differentiation. Heparan sulfate proteoglycans are macromolecules found on the cell surface and in the extracellular matrix. Acting as low-affinity receptors on the cell surface, heparan sulfate (HS) side chains modulate the functions of numerous growth factors and morphogens, having wide impact on the extracellular information received by cells. ES cells lacking HS fail to differentiate but can be induced to do so by adding heparin. ES cells defective in various components of the HS biosynthesis machinery, thus expressing differently flawed HS, exhibit lineage-specific effects. Here we discuss recent studies on the biological functions of HS in ES cell developmental processes. Since ES cells have significant potential applications in tissue/cell engineering for cell replacement therapies, understanding the functional mechanisms of HS in manipulating ES cell growth in vitro is of utmost importance, if the stem cell regenerative medicine from scientific fiction ever will be made real.

Tomellini, E., C. Lagadec, et al. "Role of p75 neurotrophin receptor in stem cell biology: more than just a marker." Cell Mol Life Sci. 2014 Jul;71(13):2467-81. doi: 10.1007/s00018-014-1564-9. Epub 2014 Jan 31.

p75(NTR), the common receptor for both neurotrophins and proneurotrophins, has been widely studied because of its role in many tissues, including the nervous system. More recently, a close relationship between p75(NTR) expression and pluripotency has been described. p75(NTR) was shown to be expressed in various types of stem cells and has been used to prospectively isolate stem cells with different degrees of potency. Here, we give an overview of the current knowledge on p75(NTR) in stem cells, ranging from embryonic to adult stem cells, and cancer stem cells. In an attempt to address its potential role in the control of stem cell biology, the molecular mechanisms underlying p75(NTR) signaling in different models are also highlighted. p75(NTR)-mediated functions include survival, apoptosis, migration, and differentiation, and depend on cell type, (pro)neurotrophin binding, interacting transmembrane co-receptors expression, intracellular adaptor molecule availability, and post-translational modifications, such as regulated proteolytic processing. It is therefore conceivable that p75(NTR) can modulate cell-fate decisions through its highly ramified signaling pathways. Thus, elucidating the potential implications of p75(NTR) activity as well as the underlying molecular mechanisms of p75(NTR) will shed new light on the biology of both normal and cancer stem cells.

Trounson, A. "A rapidly evolving revolution in stem cell biology and medicine." Reprod Biomed Online. 2013 Dec;27(6):756-64. doi: 10.1016/j.rbmo.2013.07.005. Epub 2013 Jul 18.

The developments arising from human IVF are remarkable. Embryos were studied for developmental patterns that have consequences for viability and fertility. Growing human blastocysts in vitro allowed further exploration of the differentiation of primitive embryonic cells, leading to the discovery of human embryonic stem cells (ESC). The availability of perhaps unlimited numbers of human ESC could inform the study of differentiation and also provide cells for therapies in human regenerative medicine. The developments in cell biology have been impressive, including the discovery of induced pluripotent stem cells - adult cells transduced by specific transcription factors to behave like human ESC. Key regulators of development such as activators or inhibitors of lineage progression have also been explored, particularly the fibroblast growth factor, Wnt and transforming growth factor beta signalling pathways and miRNA. Such regulators can be utilized in algorithms to predict how cells differentiate in vitro. Using multistep differentiation protocols, many different cell types can be formed and matured into functionally effective cells, some of which are already in translational research for clinical applications. Possible future developments include destruction of cancer stem cells, reversal of type I diabetes, restoration of vision, repair of motor function, cure for HIV/AIDS and heart muscle regeneration.

Van der Jeught, M., T. O'Leary, et al. The post-inner cell mass intermediate: implications for stem cell biology and assisted reproductive technology, Hum Reprod Update. 2015 Jun 18. pii: dmv028.

BACKGROUND: Until recently, the temporal events that precede the generation of pluripotent embryonic stem cells (ESCs) and their equivalence with specific developmental stages in vivo was poorly understood. Our group has discovered the existence of a transient epiblast-like structure, coined the post-inner cell mass (ICM) intermediate or PICMI, that emerges before human ESC (hESCs) are established, which supports their primed nature (i.e. already showing some predispositions towards certain cell types) of pluripotency. METHODS: The PICMI results from the progressive epithelialization of the ICM and it expresses a mixture of early and late epiblast markers, as well as some primordial germ cell markers. The PICMI is a closer progenitor of hESCs than the ICM and it can be seen as the first proof of why all existing hESCs, until recently, display a primed state of pluripotency. RESULTS: Even though the pluripotent characteristics of ESCs differ from mouse (naive) to human (primed), it has recently been shown in mice that a similar process of self-organization at the transition from ICM to (naive) mouse ESCs (mESCs) transforms the amorphous ICM into a rosette of polarized epiblast cells, a mouse PICMI. The transient PICMI stage is therefore at the origin of both mESCs and hESCs. In addition, several groups have now reported the conversion from primed to the naive (mESCs-like) hESCs, broadening the pluripotency spectrum and opening new opportunities for the use of pluripotent stem cells. CONCLUSIONS: In this review, we discuss the recent discoveries of mouse and human transient states from ICM to ESCs and their relation towards the state of pluripotency in the eventual stem cells, being naive or primed. We will now further investigate how these intermediate and/or different pluripotent stages may impact the use of human stem cells in regenerative medicine and assisted reproductive technology.

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References

1. Alfaro, M. P., S. Saraswati, et al. "Molecular mediators of mesenchymal stem cell biology." Vitam Horm. 2011;87:39-59. doi: 10.1016/B978-0-12-386015-6.00023-8.
2. Antoniou, D., A. Stergiopoulos, et al. "Recent advances in the involvement of long non-coding RNAs in neural stem cell biology and brain pathophysiology." Front Physiol. 2014 Apr 22;5:155. doi: 10.3389/fphys.2014.00155. eCollection 2014.
3. Balakrishnan, S. K., M. Witcher, et al. "Functional and molecular characterization of the role of CTCF in human embryonic stem cell biology." PLoS One. 2012;7(8):e42424. doi: 10.1371/journal.pone.0042424. Epub 2012 Aug 3.
4. Barker, N., S. Tan, et al. "Lgr proteins in epithelial stem cell biology." Development. 2013 Jun;140(12):2484-94. doi: 10.1242/dev.083113.
5. Bednar, F. and D. M. Simeone "Pancreatic cancer stem cell biology and its therapeutic implications." J Gastroenterol. 2011 Dec;46(12):1345-52. doi: 10.1007/s00535-011-0494-7. Epub 2011 Nov 3.
6. Beyer, T. A., M. Narimatsu, et al. "The TGFbeta superfamily in stem cell biology and early mammalian embryonic development." Biochim Biophys Acta. 2013 Feb;1830(2):2268-79. doi: 10.1016/j.bbagen.2012.08.025. Epub 2012 Sep 5.
7. Bhatia, P., K. Tsumagari, et al. "Stem cell biology in thyroid cancer: Insights for novel therapies." World J Stem Cells. 2014 Nov 26;6(5):614-9. doi: 10.4252/wjsc.v6.i5.614.
8. Bonfanti, P., Y. Barrandon, et al. "'Hearts and bones': the ups and downs of 'plasticity' in stem cell biology." EMBO Mol Med. 2012 May;4(5):353-61. doi: 10.1002/emmm.201200220. Epub 2012 Mar 2.
9. Bostrom, K. I., A. Garfinkel, et al. "Concise review: applying stem cell biology to vascular structures." Stem Cells. 2012 Mar;30(3):386-91. doi: 10.1002/stem.1027.
10. Briest, F., A. Berndt, et al. "Tumor-stroma interactions in tumorigenesis: lessons from stem cell biology." Front Biosci (Elite Ed). 2012 Jan 1;4:1871-87.
11. Campbell, J. J., N. Davidenko, et al. "A multifunctional 3D co-culture system for studies of mammary tissue morphogenesis and stem cell biology." PLoS One. 2011;6(9):e25661. doi: 10.1371/journal.pone.0025661. Epub 2011 Sep 30.
12. Crews, L. A. and C. H. Jamieson "Chronic myeloid leukemia stem cell biology." Curr Hematol Malig Rep. 2012 Jun;7(2):125-32. doi: 10.1007/s11899-012-0121-6.
13. Crippa, S., M. Cassano, et al. "Role of miRNAs in muscle stem cell biology: proliferation, differentiation and death." Curr Pharm Des. 2012;18(13):1718-29.
14. Das, U. N. "Essential fatty acids and their metabolites as modulators of stem cell biology with reference to inflammation, cancer, and metastasis." Cancer Metastasis Rev. 2011 Dec;30(3-4):311-24. doi: 10.1007/s10555-011-9316-x.
15. Devalle, S., R. C. Sartore, et al. "Implications of aneuploidy for stem cell biology and brain therapeutics." Front Cell Neurosci. 2012 Sep 5;6:36. doi: 10.3389/fncel.2012.00036. eCollection 2012.
16. Forsberg, K. and S. Di Giovanni Cross Talk between Cellular Redox Status, Metabolism, and p53 in Neural Stem Cell Biology, Neuroscientist. 2014 Jan 31;20(4):326-342.
17. Furusawa, C. and K. Kaneko "A dynamical-systems view of stem cell biology." Science. 2012 Oct 12;338(6104):215-7. doi: 10.1126/science.1224311.
18. Geiselhart, A., A. Lier, et al. "Disrupted Signaling through the Fanconi Anemia Pathway Leads to Dysfunctional Hematopoietic Stem Cell Biology: Underlying Mechanisms and Potential Therapeutic Strategies." Anemia. 2012;2012:265790. doi: 10.1155/2012/265790. Epub 2012 May 23.
19. Gundry, R. L., P. W. Burridge, et al. "Pluripotent stem cell heterogeneity and the evolving role of proteomic technologies in stem cell biology." Proteomics. 2011 Oct;11(20):3947-61. doi: 10.1002/pmic.201100100. Epub 2011 Sep 8.
20. Hodgkinson, C. P., V. Naidoo, et al. "Abi3bp is a multifunctional autocrine/paracrine factor that regulates mesenchymal stem cell biology." Stem Cells. 2013 Aug;31(8):1669-82. doi: 10.1002/stem.1416.
21. Homem, C. C. and J. A. Knoblich "Drosophila neuroblasts: a model for stem cell biology." Development. 2012 Dec 1;139(23):4297-310. doi: 10.1242/dev.080515.
22. Honore, B. and H. Vorum "Proteomic analysis as a means to approach limbal stem cell biology in a search for stem cell markers." Proteomics Clin Appl. 2014 Apr;8(3-4):178-84. doi: 10.1002/prca.201300049. Epub 2014 Mar 7.
23. Horton, S. J. and B. J. Huntly "Recent advances in acute myeloid leukemia stem cell biology." Haematologica. 2012 Jul;97(7):966-74. doi: 10.3324/haematol.2011.054734. Epub 2012 Apr 17.
24. Ito, K. and K. Ito "Newly Identified Roles of PML in Stem Cell Biology." Front Oncol. 2013 Mar 14;3:50. doi: 10.3389/fonc.2013.00050. eCollection 2013.
25. Jones, S. P., G. J. Guillemin, et al. "The kynurenine pathway in stem cell biology." Int J Tryptophan Res. 2013 Sep 15;6:57-66. doi: 10.4137/IJTR.S12626.
26. Kaur, S. and B. Singhal "When nano meets stem: the impact of nanotechnology in stem cell biology." J Biosci Bioeng. 2012 Jan;113(1):1-4. doi: 10.1016/j.jbiosc.2011.08.024. Epub 2011 Sep 28.
27. Koh, C. P., C. E. Ng, et al. Hematopoietic stem cell enhancer: a powerful tool in stem cell biology, Histol Histopathol. 2015 Jun;30(6):661-672. Epub 2015 Jan 9.
28. Kranenburg, O., B. L. Emmink, et al. "Proteomics in studying cancer stem cell biology." Expert Rev Proteomics. 2012 Jun;9(3):325-36. doi: 10.1586/epr.12.24.
29. Lammens, T., I. D'Hont, et al. "Long non-coding RNAs in pluripotent stem cell biology." Vet Q. 2013 Dec;33(4):202-6. doi: 10.1080/01652176.2013.866297. Epub 2013 Dec 16.
30. Lehner, B., B. Sandner, et al. "The dark side of BrdU in neural stem cell biology: detrimental effects on cell cycle, differentiation and survival." Cell Tissue Res. 2011 Sep;345(3):313-28. doi: 10.1007/s00441-011-1213-7. Epub 2011 Aug 12.
31. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
32. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
33. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.

34. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
35. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
36. Mangel, M. and M. B. Bonsall "Stem cell biology is population biology: differentiation of hematopoietic multipotent progenitors to common lymphoid and myeloid progenitors." Theor Biol Med Model. 2013 Jan 17;10:5. doi: 10.1186/1742-4682-10-5.
37. Matunis, E. L., R. R. Stine, et al. "Recent advances in Drosophila male germline stem cell biology." Spermatogenesis. 2012 Jul 1;2(3):137-144.
38. Mertins, S. D., D. A. Scudiero, et al. "A small molecule (pluripotin) as a tool for studying cancer stem cell biology: proof of concept." PLoS One. 2013;8(2):e57099. doi: 10.1371/journal.pone.0057099. Epub 2013 Feb 21.
39. National Center for Biotechnology Information, U.S. National Library of Medicine**.** http://www.ncbi.nlm.nih.gov/pubmed. 2015.
40. Osei-Bempong, C., F. C. Figueiredo, et al. "The limbal epithelium of the eye--a review of limbal stem cell biology, disease and treatment." Bioessays. 2013 Mar;35(3):211-9. doi: 10.1002/bies.201200086. Epub 2012 Nov 5.
41. Oshimori, N. and E. Fuchs "The harmonies played by TGF-beta in stem cell biology." Cell Stem Cell. 2012 Dec 7;11(6):751-64. doi: 10.1016/j.stem.2012.11.001.
42. Pearl, R. A., S. J. Leedham, et al. "The safety of autologous fat transfer in breast cancer: lessons from stem cell biology." J Plast Reconstr Aesthet Surg. 2012 Mar;65(3):283-8. doi: 10.1016/j.bjps.2011.07.017. Epub 2011 Aug 4.
43. Pieters, T. and F. van Roy "Role of cell-cell adhesion complexes in embryonic stem cell biology." J Cell Sci. 2014 Jun 15;127(Pt 12):2603-13. doi: 10.1242/jcs.146720.
44. Pinto, J. P., R. K. Reddy Kalathur, et al. "StemCellNet: an interactive platform for network-oriented investigations in stem cell biology." Nucleic Acids Res. 2014 Jul;42(Web Server issue):W154-60. doi: 10.1093/nar/gku455. Epub 2014 May 22.
45. Plickert, G., U. Frank, et al. "Hydractinia, a pioneering model for stem cell biology and reprogramming somatic cells to pluripotency." Int J Dev Biol. 2012;56(6-8):519-34.
46. Quesenberry, P. J., M. S. Dooner, et al. "A new stem cell biology: the continuum and microvesicles." Trans Am Clin Climatol Assoc. 2012;123:152-66; discussion 166.
47. Ramos, A. and F. D. Camargo "The Hippo signaling pathway and stem cell biology." Trends Cell Biol. 2012 Jul;22(7):339-46. doi: 10.1016/j.tcb.2012.04.006. Epub 2012 May 31.
48. Ratajczak, M. Z., E. Zuba-Surma, et al. "Very small embryonic-like stem cells (VSELs) represent a real challenge in stem cell biology: recent pros and cons in the midst of a lively debate." Leukemia. 2014 Mar;28(3):473-84. doi: 10.1038/leu.2013.255. Epub 2013 Sep 10.
49. Rennie, K., A. Gruslin, et al. "Applications of amniotic membrane and fluid in stem cell biology and regenerative medicine." Stem Cells Int. 2012;2012:721538. doi: 10.1155/2012/721538. Epub 2012 Oct 10.
50. Rosewell, I. R. and A. Giangreco "Murine aggregation chimeras and wholemount imaging in airway stem cell biology." Methods Mol Biol. 2012;916:263-74. doi: 10.1007/978-1-61779-980-8_20.
51. Rousseaux, S. "Two decades of reproductive biomedicine and stem cell biology in Iran: the Royan Institute." Int J Dev Biol. 2014;58(9):643-7. doi: 10.1387/ijdb.140245sr.
52. Sage, J. "The retinoblastoma tumor suppressor and stem cell biology." Genes Dev. 2012 Jul 1;26(13):1409-20. doi: 10.1101/gad.193730.112.
53. Salvetti, A., L. Rossi, et al. "In vivo biocompatibility of boron nitride nanotubes: Effects on stem cell biology and tissue regeneration in planarians." Nanomedicine (Lond). 2015 Apr 2:1-12.
54. Samardzija, C., M. Quinn, et al. "Attributes of Oct4 in stem cell biology: perspectives on cancer stem cells of the ovary." J Ovarian Res. 2012 Nov 21;5(1):37. doi: 10.1186/1757-2215-5-37.
55. Scheitz, C. J. and T. Tumbar "New insights into the role of Runx1 in epithelial stem cell biology and pathology." J Cell Biochem. 2013 May;114(5):985-93. doi: 10.1002/jcb.24453.
56. Shiota, G. and T. Yasui "Progress in stem cell biology in regenerative medicine for liver disease." Hepatol Res. 2012 Jan;42(1):15-21. doi: 10.1111/j.1872-034X.2011.00874.x. Epub 2011 Sep 22.
57. Sirakov, M., E. Kress, et al. "Thyroid hormones and their nuclear receptors: new players in intestinal epithelium stem cell biology?" Cell Mol Life Sci. 2014 Aug;71(15):2897-907. doi: 10.1007/s00018-014-1586-3. Epub 2014 Mar 7.
58. Sykes, S. M. and D. T. Scadden "Modeling human hematopoietic stem cell biology in the mouse." Semin Hematol. 2013 Apr;50(2):92-100. doi: 10.1053/j.seminhematol.2013.03.029. Epub 2013 Jun 11.
59. Tamm, C., L. Kjellen, et al. "Heparan sulfate biosynthesis enzymes in embryonic stem cell biology." J Histochem Cytochem. 2012 Dec;60(12):943-9. doi: 10.1369/0022155412465090. Epub 2012 Oct 4.
60. Tomellini, E., C. Lagadec, et al. "Role of p75 neurotrophin receptor in stem cell biology: more than just a marker." Cell Mol Life Sci. 2014 Jul;71(13):2467-81. doi: 10.1007/s00018-014-1564-9. Epub 2014 Jan 31.
61. Trounson, A. "A rapidly evolving revolution in stem cell biology and medicine." Reprod Biomed Online. 2013 Dec;27(6):756-64. doi: 10.1016/j.rbmo.2013.07.005. Epub 2013 Jul 18.
62. Van der Jeught, M., T. O'Leary, et al. The post-inner cell mass intermediate: implications for stem cell biology and assisted reproductive technology, Hum Reprod Update. 2015 Jun 18. pii: dmv028.
63. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.