Stem Cell Niche 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 stem cell niche related studies.

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Key words: stem cell; life; research; literature

Introduction

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

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

Adameyko, I. and K. Fried "The Nervous System Orchestrates and Integrates Craniofacial Development: A Review." Front Physiol. 2016 Feb 19;7:49. doi: 10.3389/fphys.2016.00049. eCollection 2016.

Development of a head is a dazzlingly complex process: a number of distinct cellular sources including cranial ecto- and endoderm, mesoderm and neural crest contribute to facial and other structures. In the head, an extremely fine-tuned developmental coordination of CNS, peripheral neural components, sensory organs and a musculo-skeletal apparatus occurs, which provides protection and functional integration. The face can to a large extent be considered as an assembly of sensory systems encased and functionally fused with appendages represented by jaws. Here we review how the developing brain, neurogenic placodes and peripheral nerves influence the morphogenesis of surrounding tissues as a part of various general integrative processes in the head. The mechanisms of this impact, as we understand it now, span from the targeted release of the morphogens necessary for shaping to providing a niche for cellular sources required in later development. In this review we also discuss the most recent findings and ideas related to how peripheral nerves and nerve-associated cells contribute to craniofacial development, including teeth, during the post- neural crest period and potentially in regeneration.

Adlaf, E. W., A. Mitchell-Dick, et al. "Discerning Neurogenic vs. Non-Neurogenic Postnatal Lateral Ventricular Astrocytes via Activity-Dependent Input." Front Neurosci. 2016 Mar 24;10:111. doi: 10.3389/fnins.2016.00111. eCollection 2016.

Throughout development, neural stem cells (NSCs) give rise to differentiated neurons, astrocytes, and oligodendrocytes which together modulate perception, memory, and behavior in the adult nervous system. To understand how NSCs contribute to postnatal/adult brain remodeling and repair after injury, the lateral ventricular (LV) neurogenic niche in the rodent postnatal brain serves as an excellent model system. It is a specialized area containing self-renewing GFAP(+) astrocytes functioning as NSCs generating new neurons throughout life. In addition to this now well-studied regenerative process, the LV niche also generates differentiated astrocytes, playing an important role for glial scar formation after cortical

injury. While LV NSCs can be clearly distinguished from their neuroblast and oligodendrocyte progeny via molecular markers, the astrocytic identity of NSCs has complicated their distinction from terminally-differentiated astrocytes in the niche. Our current models of postnatal/adult LV neurogenesis do not take into account local astrogenesis, or the possibility that cellular markers may be similar between non-dividing GFAP(+) NSCs and their differentiated astrocyte daughters. Postnatal LV neurogenesis is regulated by NSC-intrinsic mechanisms interacting with extracellular/niche-driven cues. It is generally believed that these local effects are responsible for sustaining neurogenesis, though behavioral paradigms and disease states have suggested possibilities for neural circuit-level modulation. With recent experimental findings that neuronal stimulation can directly evoke responses in LV NSCs, it is possible that this exciting property will add a new dimension to identifying postnatal/adult NSCs. Here, we put forth a notion that neural circuit-level input can be a distinct characteristic defining postnatal/adult NSCs from non-neurogenic astroglia.

Adlesic, M., C. Frei, et al. "Cdk4 functions in multiple cell types to control Drosophila intestinal stem cell proliferation and differentiation." Biol Open. 2016 Feb 15;5(3):237-51. doi: 10.1242/bio.016584.

The proliferation of intestinal stem cells (ISCs) and differentiation of enteroblasts to form mature enteroendocrine cells and enterocytes in the Drosophila intestinal epithelium must be tightly regulated to maintain homeostasis. We show that genetic modulation of CyclinD/Cdk4 activity or mTOR-dependent signalling cell-autonomously regulates enterocyte growth, which influences ISC proliferation and enteroblast differentiation. Increased enterocyte growth results in higher numbers of ISCs and defective enterocyte growth reduces ISC abundance and proliferation in the midgut. Adult midguts deficient for Cdk4 show severe disruption of intestinal homeostasis characterised by decreased ISC self-renewal, enteroblast differentiation defects and low enteroendocrine cell and enterocyte numbers. The ISC/enteroblast phenotypes result from a combination of cell autonomous and non-autonomous requirements for Cdk4 function. One non-autonomous consequence of Cdk4-dependent deficient enterocyte growth is high expression of Delta in ISCs and Delta retention in enteroblasts. We postulate that aberrant activation of the Delta-Notch pathway is a possible partial cause of lost ISC stemness. These results support the idea that enterocytes contribute to a putative stem cell niche that maintains intestinal homeostasis in the Drosophila anterior midgut.

Aibibu, D., M. Hild, et al. "Textile cell-free scaffolds for in situ tissue engineering applications." J Mater Sci Mater Med. 2016 Mar;27(3):63. doi: 10.1007/s10856-015-5656-3. Epub 2016 Jan 22.

In this article, the benefits offered by micro-fibrous scaffold architectures fabricated by textile manufacturing techniques are discussed: How can established and novel fiber-processing techniques be exploited in order to generate templates matching the demands of the target cell niche? The problems related to the development of biomaterial fibers (especially from nature-derived materials) ready for textile manufacturing are addressed. Attention is also paid on how biological cues may be incorporated into micro-fibrous scaffold architectures by hybrid manufacturing approaches (e.g. nanofiber or hydrogel functionalization). After a critical review of exemplary recent research works on cell-free fiber based scaffolds for in situ TE, including clinical studies, we conclude that in order to make use of the whole range of favors which may be provided by engineered fibrous scaffold systems, there are four main issues which need to be addressed: (1) Logical combination of manufacturing techniques and materials. (2) Biomaterial fiber development. (3) Adaption of textile manufacturing techniques to the demands of scaffolds for regenerative medicine. (4) Incorporation of biological cues (e.g. stem cell homing factors).

Alessandri, K., M. Feyeux, et al. "A 3D printed microfluidic device for production of functionalized hydrogel microcapsules for culture and differentiation of human Neuronal Stem Cells (hNSC)." Lab Chip. 2016 Mar 30.

We present here a microfluidic device that generates sub-millimetric hollow hydrogel spheres, encapsulating cells and coated internally with a layer of reconstituted extracellular matrix (ECM) of a few microns thick. The spherical capsules, composed of alginate hydrogel, originate from the spontaneous instability of a multi-layered jet formed by co-extrusion using a coaxial flow device. We provide a simple design to manufacture this device using a DLP (digital light processing) 3D printer. Then, we demonstrate how the inner wall of the capsules can be decorated with a continuous ECM layer that is anchored to the alginate gel and mimics the basal membrane of a cellular niche. Finally, we used this approach to encapsulate human Neural Stem Cells (hNSC) derived from human Induced Pluripotent Stem Cells (hIPSC), which were further differentiated into neurons within the capsules with negligible loss of viability. Altogether, we show that these capsules may serve as cell micro-containers compatible with complex cell culture conditions and applications.

These developments widen the field of research and biomedical applications of the cell encapsulation technology.

Birbrair, A. and P. S. Frenette "Niche heterogeneity in the bone marrow." Ann N Y Acad Sci. 2016 Mar 25. doi: 10.1111/nyas.13016.

In adult mammals, hematopoietic stem cells (HSCs) are defined by their abilities to self-renew and to differentiate to form all blood cell lineages. These rare multipotent cells occupy specific locations in the bone marrow (BM) microenvironment. The specific microenvironment regulating HSCs, commonly referred to as the niche, comprises multiple cell types whose exact contributions are under active investigation. Understanding cellular cross talk involving HSCs in the BM microenvironment is of fundamental importance for harnessing therapies against benign and malignant blood diseases. In this review, we summarize and evaluate recent advances in our understanding of niche heterogeneity and its influence on HSC function.

Capilla-Gonzalez, V., J. M. Bonsu, et al. "Implications of irradiating the subventricular zone stem cell niche." Stem Cell Res. 2016 Mar;16(2):387-96. doi: 10.1016/j.scr.2016.02.031. Epub 2016 Feb 17.

Radiation therapy is a standard treatment for brain tumor patients. However, it comes with side effects, such as neurological deficits. While likely multi-factorial, the effect may in part be associated with the impact of radiation on the neurogenic niches. In the adult mammalian brain, the neurogenic niches are localized in the subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus of the hippocampus, where the neural stem cells (NSCs) reside. Several reports showed that radiation produces a drastic decrease in the proliferative capacity of these regions, which is related to functional decline. In particular, radiation to the SVZ led to a reduced long-term olfactory memory and a reduced capacity to respond to brain damage in animal models, as well as compromised tumor outcomes in patients. By contrast, other studies in humans suggested that increased radiation dose to the SVZ may be associated with longer progression-free survival in patients with high-grade glioma. In this review, we summarize the cellular and functional effects of irradiating the SVZ niche. In particular, we review the pros and cons of using radiation during brain tumor treatment, discussing the complex relationship between radiation dose to the SVZ and both tumor control and toxicity.

Carpino, G., R. Puca, et al. "Peribiliary Glands as a Niche of Extra-Pancreatic Precursors Yielding Insulin-Producing Cells in Experimental and Human Diabetes." Stem Cells. 2016 Feb 6. doi: 10.1002/stem.2311.

Peribiliary glands (PBGs) are niches in the biliary tree and containing heterogeneous endodermal stem/progenitors cells that can differentiate, in vitro and in vivo, towards pancreatic islets. The aim of this study was to evaluate, in experimental and human diabetes, proliferation of cells in PBGs and differentiation of the biliary tree stem/progenitor cells (BTSCs) towards insulin-producing cells. Diabetes was generated in mice by intraperitoneal injection of a single dose of 200 mg/kg (N=12) or 120 mg/kg (N=12) of streptozotocin. Liver, pancreas and extrahepatic biliary trees were en bloc dissected and examined. Cells in PBGs proliferated in experimental diabetes, and their proliferation was greatest in the PBGs of the hepato-pancreatic ampulla, and inversely correlated with the pancreatic islet area. In rodents, the cell proliferation in PBGs was characterized by the expansion of Sox9-positive stem/progenitor cells that gave rise to insulin-producing cells. Insulin-producing cells were located mostly in PBGs in the portion of the biliary tree closest to the duodenum, and their appearance was associated with up-regulation of MafA and Gli1 gene expression. In patients with type 2 diabetes, PBGs at the level of the hepato-pancreatic ampulla contained cells showing signs of proliferation and pancreatic fate commitment. In vitro, high glucose concentrations induced the differentiation of human BTSCs cultures towards pancreatic beta cell fates. The cells in PBGs respond to diabetes with proliferation and differentiation towards insulin-producing cells indicating that PBG niches may rescue pancreatic islet impairment in diabetes. These findings offer important implications for the patho-physiology and complications of this disease.

Clausi, M. G., E. Kumari, et al. "Unmasking the responses of the stem cells and progenitors in the subventricular zone after neonatal and pediatric brain injuries." Neural Regen Res. 2016 Jan;11(1):45-8. doi: 10.4103/1673-5374.175041.

There is great interest in the regenerative potential of the neural stem cells and progenitors that populate the subventricular zone (SVZ). However, a comprehensive understanding of SVZ cell responses to brain injuries has been hindered by the lack of sensitive approaches to study the cellular composition of this niche. Here we review progress being made in deciphering the cells of the SVZ gleaned from the use of a recently designed flow cytometry panel that allows SVZ cells to be parsed into multiple subsets of progenitors as well as putative stem cells. We review how this approach has begun to unmask both the heterogeneity of SVZ cells as well as the dynamic

shifts in cell populations with neonatal and pediatric brain injuries. We also discuss how flow cytometric analyses also have begun to reveal how specific cytokines, such as Leukemia inhibitory factor are coordinating SVZ responses to injury.

Davies, J. M., R. Santaolalla, et al. "Use of Cancer Stem Cells to Investigate the Pathogenesis of Colitis-associated Cancer." Inflamm Bowel Dis. 2016 Apr;22(4):976-83. doi: 10.1097/MIB.0000000000000756.

Colitis-associated cancer (CAC) can develop in patients with inflammatory bowel disease with long-term uncontrolled inflammation. The mutational history and tumor microenvironment observed in CAC patients is distinct from that observed in sporadic colon cancer and suggests a different etiology. Recently, much attention has been focused on understanding the cellular origin of cancer and the cancer stem cells, which is key to growth and progression. Cancer stem cells are often chemo-resistant making them attractive targets for improving patient outcomes. New techniques have rapidly been evolving allowing for a better understanding of the normal intestinal stem cell function and behavior in the niche. Use of these new technologies will be crucial to understanding cancer stem cells in both sporadic and CAC. In this review, we will explore emerging methods related to the study of normal and cancer stem cells in the intestine, and examine potential avenues of investigation and application to understanding the pathogenesis of CAC.

De Luca, L., S. Trino, et al. "MiRNAs and piRNAs from bone marrow mesenchymal stem cell extracellular vesicles induce cell survival and inhibit cell differentiation of cord blood hematopoietic stem cells: a new insight in transplantation." Oncotarget. 2016 Feb 9;7(6):6676-92. doi: 10.18632/oncotarget.6791.

Hematopoietic stem cells (HSC), including umbilical cord blood CD34+ stem cells (UCB-CD34+), are used for the treatment of several diseases. Although different studies suggest that bone marrow mesenchymal stem cells (BM-MSC) support hematopoiesis, the exact mechanism remains unclear. Recently, extracellular vesicles (EVs) have been described as a novel avenue of cell communication, which may mediate BM-MSC effect on HSC. In this work, we studied the interaction between UCB-CD34+ cells and BM-MSC derived EVs. First, by sequencing EV derived miRNAs and piRNAs we found that EVs contain RNAs able to influence UCB-CD34+ cell fate. Accordingly, a gene expression profile of UCB-CD34+ cells treated with EVs, identified about 100 down-regulated genes among those targeted by EV-derived miRNAs and piRNAs (e.g. miR-27b/MPL, miR-21/ANXA1, miR-181/EGR2), indicating that EV content was able to modify gene expression profile of receiving cells. Moreover, we demonstrated that UCB-CD34+ cells, exposed to EVs, significantly changed different biological functions, becoming more viable and less differentiated. UCB-CD34+ gene expression profile also identified 103 up-regulated genes, most of them codifying for chemokines, cytokines and their receptors, involved in chemotaxis of different BM cells, an essential function of hematopoietic reconstitution. Finally, the exposure of UCB-CD34+ cells to EVs caused an increased expression CXCR4, paralleled by an in vivo augmented migration from peripheral blood to BM niche in NSG mice. This study demonstrates the existence of a powerful cross talk between BM-MSC and UCB-CD34+ cells, mediated by EVs, providing new insight in the biology of cord blood transplantation.

Demitrack, E. S. and L. C. Samuelson "Notch regulation of gastrointestinal stem cells." J Physiol. 2016 Feb 5. doi: 10.1113/JP271667.

The gastrointestinal (GI) tract epithelium is continuously replenished by actively cycling stem and progenitor cells. These cell compartments are regulated to balance proliferation and stem cell renewal with differentiation into the various mature cell types to maintain tissue homeostasis. In this topical review we focus on the role of the Notch signaling pathway to regulate GI stem cell function in adult small intestine and stomach. We first present the current view of stem and progenitor cell populations in these tissues and then summarize the studies that have established the Notch pathway as a key regulator of gastric and intestinal stem cell function. Notch signaling has been shown to be a niche factor required for maintenance of GI stem cells in both tissues. In addition, Notch has been described to regulate epithelial cell differentiation. Recent studies have revealed key similarities and differences in how Notch regulates stem cell function in the stomach compared to intestine. We summarize the literature regarding Notch regulation of GI stem cell proliferation and differentiation, highlighting tissue specific functions to compare and contrast Notch in the stomach and intestine. This article is protected by copyright. All rights reserved.

Franca, L. R., R. A. Hess, et al. "The Sertoli cell: one hundred fifty years of beauty and plasticity." Andrology. 2016 Mar;4(2):189-212. doi: 10.1111/andr.12165. Epub 2016 Feb 4.

It has been one and a half centuries since Enrico Sertoli published the seminal discovery of the

testicular 'nurse cell', not only a key cell in the testis, but indeed one of the most amazing cells in the vertebrate body. In this review, we begin by examining the three phases of morphological research that have occurred in the study of Sertoli cells, because microscopic anatomy was essentially the only scientific discipline available for about the first 75 years after the discovery. Biochemistry and molecular biology then changed all of biological sciences, including our understanding of the functions of Sertoli cells. Immunology and stem cell biology were not even topics of science in 1865, but they have now become major issues in our appreciation of Sertoli cell's role in spermatogenesis. We end with the universal importance and plasticity of function by comparing Sertoli cells in fish, amphibians, and mammals. In these various classes of vertebrates, Sertoli cells have quite different modes of proliferation and epithelial maintenance, cystic vs. tubular formation, yet accomplish essentially the same function but in strikingly different ways.

Gheisari, Y., M. Vasei, et al. "A Three-Dimensional Scaffold-Based System for Modeling the Bone Marrow Tissue." Stem Cells Dev. 2016 Mar 15;25(6):492-8. doi: 10.1089/scd.2015.0182.

Hematopoietic stem and progenitor cells (HPC) niche, consisting of HPC and their surrounding stromal components, is the fundamental unit for bone marrow (BM) tissue engineering. Previously, mouse BM-derived cell complexes with HPC niche unit properties called "niche-like units" were isolated and characterized. This study was aimed to evaluate the possibility of bioengineering marrow tissue in heterotypic sites using niche-like units in combination with three-dimensional scaffolds. BM niche-like units were isolated from GFP-transgenic C57BL/6 mice and seeded on electrospun poly (L-lactide) nanofiber scaffolds, which were then roll-folded and aseptically implanted into the peritoneal cavity of irradiated wild-type mice. One month after implantation, donor-derived cells were detected in peripheral blood of the recipients and contributed to restoration of all blood lineages. The transplanted bioengineered tissue histologically resembled native BM structure and was connected to the mouse systemic circulation. Long-term self-renewal was confirmed by serial transplantation into tertiary recipients. In conclusion, this study establishes a novel system for BM tissue engineering, which can be used to improve the HPC transplantation outcomes especially in cases where HPC niche is damaged and also as an in vivo model to test the effects of different factors on hematopoiesis.

Grant, C., D. A. Chudakova, et al. "Expression of embryonic stem cell markers in keloid-associated lymphoid tissue." J Clin Pathol. 2016 Mar 30. pii: jclinpath-2015-203483. doi: 10.1136/jclinpath-2015-203483.

AIMS: To identify, characterise and localise the population of primitive cells in keloid scars (KS). METHODS: 5-microm-thick formalin-fixed paraffin-embedded sections of KS samples from 10 patients underwent immunohistochemical (IHC) staining for the embryonic stem cell (ESC) markers OCT4, SOX2, pSTAT3 and NANOG, and keloid-associated lymphoid tissue (KALT) markers CD4 and CD20. NanoString gene expression analysis and in situ hybridisation (ISH) were used to determine the abundance and localisation of the mRNA for these ESC markers. RESULTS: IHC staining revealed the expression of the ESC markers OCT4, SOX2, pSTAT3 and NANOG by a population of cells within KS tissue. These are localised to the endothelium of the microvessels within the KALTs. NanoString gene expression analysis confirmed the abundance of the transcriptional expression of the same ESC markers. ISH localised the expression of the ESC transcripts to the primitive endothelium in KS tissue. CONCLUSIONS: This report demonstrates the expression of ESC markers OCT4, SOX2, pSTAT3 and NANOG by the endothelium of the microvessels within the KALTs. These findings show a unique niche of primitive cells within KS, expressing ESC markers, revealing a potential therapeutic target in the treatment of KS.

Guerra, M. M., C. Gonzalez, et al. "Understanding How the Subcommissural Organ and Other Periventricular Secretory Structures Contribute via the Cerebrospinal Fluid to Neurogenesis." Front Cell Neurosci. 2015 Dec 23;9:480. doi: 10.3389/fncel.2015.00480. eCollection 2015.

The dynamic and molecular composition of the cerebrospinal fluid (CSF) and, consequently, the CSF physiology is much more complex and fascinating than the simplistic view held for decades. Signal molecules either transported from blood to CSF or secreted into the CSF by circumventricular organs and CSF-contacting neurons, use the CSF to reach their targets in the brain, including the pre- and postnatal neurogenic niche. The subcommissural organ (SCO), a highly conserved brain gland present throughout the vertebrate phylum, is one of the sources for signals, as well as the choroid plexus, tanycytes and CSF-contacting neurons. The SCO secretes into the fetal and adult CSF SCO-spondin, transthyretin, and basic fibroblast growth factor. These proteins participate in certain aspects of neurogenesis, such as cell cycle of neural stem cells, neuronal differentiation, and axon pathfinding. Through the CSF, the SCO-secretory proteins may reach virtually

any target in the embryonic and adult central nervous system. Since the SCO continues to secrete throughout life span, it seems likely that the neurogenetic property of the SCO compounds would be targeted to the niches where neurogenesis continues in adulthood. This review is aimed to bring into discussion early and new evidence concerning the role(s) of the SCO, and the probable mechanisms by which SCO compounds can readily reach the neurogenic niche of the subventricular zone flowing with the CSF to participate in the regulation of the neurogenic niche. As we unfold the multiples trans-fluid talks between discrete brain domains we will have more tools to influence such talks.

Happe, C. L. and A. J. Engler "Mechanical Forces Reshape Differentiation Cues That Guide Cardiomyogenesis." Circ Res. 2016 Jan 22;118(2):296-310. doi: 10.1161/CIRCRESAHA.115.305139.

Soluble morphogen gradients have long been studied in the context of heart specification and patterning. However, recent data have begun to challenge the notion that long-standing in vivo observations are driven solely by these gradients alone. Evidence from multiple biological models, from stem cells to ex vivo biophysical assays, now supports a role for mechanical forces in not only modulating cell behavior but also inducing it de novo in a process termed mechanotransduction. Structural proteins that connect the cell to its niche, for example, integrins and cadherins, and that couple to other growth factor receptors, either directly or indirectly, seem to mediate these changes, although specific mechanistic details are still being elucidated. In this review, we summarize how the wingless (Wnt), transforming growth factor-beta, and bone morphogenetic protein signaling pathways affect cardiomyogenesis and then highlight the interplay between each pathway and mechanical forces. In addition, we will outline the role of integrins and cadherins during cardiac development. For each, we will describe how the interplay could change multiple processes during cardiomyogenesis, including the specification of undifferentiated cells, the establishment of heart patterns to accomplish tube and chamber formation, or the maturation of myocytes in the fully formed heart.

Holmfeldt, P., M. Ganuza, et al. "Functional screen identifies regulators of murine hematopoietic stem cell repopulation." J Exp Med. 2016 Mar 7;213(3):433-49. doi: 10.1084/jem.20150806. Epub 2016 Feb 15.

Understanding the molecular regulation of hematopoietic stem and progenitor cell (HSPC) engraftment is paramount to improving transplant outcomes. To discover novel regulators of HSPC repopulation, we transplanted >1,300 mice with shRNA-transduced HSPCs within 24 h of isolation and transduction to focus on detecting genes regulating repopulation. We identified 17 regulators of HSPC repopulation: Arhgef5, Armcx1, Cadps2, Crispld1, Emcn, Foxa3, Fstl1, Glis2, Gprasp2, Gpr56, Myct1, Nbea, P2ry14, Smarca2, Sox4, Stat4, and Zfp251. Knockdown of each of these genes yielded a loss of function, except in the cases of Armcx1 and Gprasp2, whose loss enhanced hematopoietic stem cell (HSC) repopulation. The discovery of multiple genes regulating vesicular trafficking, cell surface receptor turnover, and secretion of extracellular matrix components suggests active cross talk between HSCs and the niche and that HSCs may actively condition the niche to promote engraftment. We validated that Foxa3 is required for HSC repopulating activity, as Foxa3(-/-) HSC fails to repopulate ablated hosts efficiently, implicating for the first time Foxa genes as regulators of HSPCs. We further show that Foxa3 likely regulates the HSC response to hematologic stress. Each gene discovered here offers a window into the novel processes that regulate stable HSPC engraftment into an ablated host.

Horgusluoglu, E., K. Nudelman, et al. "Adult neurogenesis and neurodegenerative diseases: A systems biology perspective." Am J Med Genet B Neuropsychiatr Genet. 2016 Feb 16. doi: 10.1002/ajmg.b.32429.

New neurons are generated throughout adulthood in two regions of the brain, the olfactory bulb and dentate gyrus of the hippocampus, and are incorporated into the hippocampal network circuitry; disruption of this process has been postulated to contribute to neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. Known modulators of adult neurogenesis include signal transduction pathways, the vascular and immune systems, metabolic factors, and epigenetic regulation. Multiple intrinsic and extrinsic factors such as neurotrophic factors, transcription factors, and cell cycle regulators control neural stem cell proliferation, maintenance in the adult neurogenic niche, and differentiation into mature neurons; these factors act in networks of signaling molecules that influence each other during construction and maintenance of neural circuits, and in turn contribute to learning and memory. The immune system and vascular system are necessary for neuronal formation and neural stem cell fate determination. Inflammatory cytokines regulate adult neurogenesis in response to immune system activation, whereas the vasculature regulates the neural stem cell niche. Vasculature, immune/support

cell populations (microglia/astrocytes), adhesion molecules, growth factors, and the extracellular matrix also provide a homing environment for neural stem cells. Epigenetic changes during hippocampal neurogenesis also impact memory and learning. Some genetic variations in neurogenesis related genes may play important roles in the alteration of neural stem cells differentiation into new born neurons during adult neurogenesis, with important therapeutic implications. In this review, we discuss mechanisms of and interactions between these modulators of adult neurogenesis, as well as implications for neurodegenerative disease and current therapeutic research. (c) 2016 Wiley Periodicals, Inc.

Horiguchi, H., M. Kobune, et al. "Extracellular vesicle miR-7977 is involved in hematopoietic dysfunction of mesenchymal stromal cells via poly(rC) binding protein 1 reduction in myeloid neoplasms." Haematologica. 2016 Apr;101(4):437-47. doi: 10.3324/haematol.2015.134932. Epub 2016 Jan 22.

The failure of normal hematopoiesis is observed in myeloid neoplasms. However, the precise mechanisms governing the replacement of normal hematopoietic stem cells in their niche by myeloid neoplasm stem cells have not yet been clarified. Primary acute myeloid leukemia and myelodysplastic syndrome cells induced aberrant expression of multiple hematopoietic factors including Jagged-1, stem cell factor and angiopoietin-1 in mesenchymal stem cells even in non-contact conditions, and this abnormality was reverted by extracellular vesicle inhibition. Importantly, the transfer of myeloid neoplasm-derived extracellular vesicles reduced the hematopoietic supportive capacity of mesenchymal stem cells. Analysis of extracellular vesicle microRNA indicated that several species, including miR-7977 from acute myeloid leukemia cells, were higher than those from normal CD34(+)cells. Remarkably, the copy number of miR-7977 in bone marrow interstitial fluid was elevated not only in acute myeloid leukemia, but also in myelodysplastic syndrome, as compared with lymphoma without bone marrow localization. The transfection of the miR-7977 mimic reduced the expression of the posttranscriptional regulator, poly(rC) binding protein 1, in mesenchymal stem cells. Moreover, the miR-7977 mimic induced aberrant reduction of hematopoietic growth factors in mesenchymal stem cells, resulting in decreased hematopoietic-supporting capacity of bone marrow CD34(+)cells. Furthermore, the reduction of hematopoietic growth factors including Jagged-1, stem cell factor and angiopoietin-1 were reverted by target protection of poly(rC) binding protein 1, suggesting that poly(rC) binding protein 1 could be involved in the stabilization of several growth factors. Thus, miR-7977 in extracellular vesicles may be a critical factor that induces failure of normal hematopoiesis via poly(rC) binding protein 1 suppression.

Kitajima, Y., S. Ogawa, et al. "Visualizing the Functional Heterogeneity of Muscle Stem Cells." Methods Mol Biol. 2016 Apr 7.

Skeletal muscle stem cells are satellite cells that play crucial roles in tissue repair and regeneration after muscle injury. Accumulating evidence indicates that satellite cells are genetically and functionally heterogeneous, even within the same muscle. A small population of satellite cells possesses "stemness" and exhibits the remarkable ability to regenerate through robust self-renewal when transplanted into a regenerating muscle niche. In contrast, not all satellite cells self-renew. For example, some cells are committed myogenic progenitors that immediately undergo myogenic differentiation with minimal cell division after activation. Recent studies illuminate the cellular and molecular characteristics of the functional heterogeneity among satellite cells. To evaluate heterogeneity and stem cell dynamics, here we describe methods to conduct a clonal analysis of satellite cells and to visualize a slowly dividing cell population.

Klein, D. "Vascular Wall-Resident Multipotent Stem Cells of Mesenchymal Nature within the Process of Vascular Remodeling: Cellular Basis, Clinical Relevance, and Implications for Stem Cell Therapy." Stem Cells Int. 2016;2016:1905846. doi: 10.1155/2016/1905846. Epub 2016 Jan 10.

Until some years ago, the bone marrow and the endothelial cell compartment lining the vessel lumen (subendothelial space) were thought to be the only sources providing vascular progenitor cells. Now, the vessel wall, in particular, the vascular adventitia, has been established as a niche for different types of stem and progenitor cells with the capacity to differentiate into both vascular and nonvascular cells. Herein, vascular wall-resident multipotent stem cells of mesenchymal nature (VW-MPSCs) have gained importance because of their large range of differentiation in combination with their distribution throughout the postnatal organism which is related to their existence in the adventitial niche, respectively. In general, mesenchymal stem cells, also designated as mesenchymal stromal cells (MSCs), contribute to the maintenance of organ integrity by their ability to replace defunct cells or secrete cytokines locally and thus support repair and healing processes of the affected tissues. This review will focus on the central role of VW-MPSCs within vascular reconstructing processes (vascular remodeling) which are absolute

prerequisite to preserve the sensitive relationship between resilience and stability of the vessel wall. Further, a particular advantage for the therapeutic application of VW-MPSCs for improving vascular function or preventing vascular damage will be discussed.

Kusuma, G. D., M. H. Abumaree, et al. "Mesenchymal Stem/Stromal Cells Derived From a Reproductive Tissue Niche Under Oxidative Stress Have High Aldehyde Dehydrogenase Activity." Stem Cell Rev. 2016 Feb 15.

The use of mesenchymal stem/stromal cells (MSC) in regenerative medicine often requires MSC to function in environments of high oxidative stress. Human pregnancy is a condition where the mother's tissues, and in particular her circulatory system, are exposed to increased levels of oxidative stress. MSC in the maternal decidua basalis (DMSC) are in a vascular niche, and thus would be exposed to oxidative stress products in the maternal circulation. Aldehyde dehydrogenases (ALDH) are a large family of enzymes which detoxify aldehydes and thereby protect stem cells against oxidative damage. A subpopulation of MSC express high levels of ALDH (ALDHbr) and these are more potent in repairing and regenerating tissues. DMSC was compared with chorionic villous MSC (CMSC) derived from the human placenta. CMSC reside in vascular niche and are exposed to the fetal circulation, which is in lower oxidative state. We screened an ALDH isozyme cDNA array and determined that relative to CMSC, DMSC expressed high levels of ALDH1 family members, predominantly ALDH1A1. Immunocytochemistry gave qualitative confirmation at the protein level. Immunofluorescence detected ALDH1 immunoreactivity in the DMSC and CMSC vascular niche. The percentage of ALDHbr cells was calculated by Aldefluor assay and DMSC showed a significantly higher percentage of ALDHbr cells than CMSC. Finally, flow sorted ALDHbr cells were functionally potent in colony forming unit assays. DMSC, which are derived from pregnancy tissues that are naturally exposed to high levels of oxidative stress, may be better candidates for regenerative therapies where MSC must function in high oxidative stress environments.

Kusumbe, A. P., S. K. Ramasamy, et al. "Age-dependent modulation of vascular niches for haematopoietic stem cells." Nature. 2016 Apr 21;532(7599):380-384. doi: 10.1038/nature17638. Epub 2016 Apr 13.

Blood vessels define local microenvironments in the skeletal system, play crucial roles in osteogenesis and provide niches for haematopoietic stem cells. The properties of niche-forming vessels and their changes in the ageing organism remain incompletely understood. Here we show that Notch signalling in endothelial cells leads to the expansion of haematopoietic stem cell niches in bone, which involves increases in CD31-positive capillaries and platelet-derived growth factor receptor-beta (PDGFRbeta)-positive perivascular cells, arteriole formation and elevated levels of cellular stem cell factor. Although endothelial hypoxia-inducible factor signalling promotes some of these changes, it fails to enhance vascular niche function because of a lack of arterialization and expansion of PDGFRbeta-positive cells. In ageing mice, niche-forming vessels in the skeletal system are strongly reduced but can be restored by activation of endothelial Notch signalling. These findings indicate that vascular niches for haematopoietic stem cells are part of complex, age-dependent microenvironments involving multiple cell populations and vessel subtypes.

Ladd, M. R., D. F. Nino, et al. "Generation of an artificial intestine for the management of short bowel syndrome." Curr Opin Organ Transplant. 2016 Apr;21(2):178-85. doi: 10.1097/MOT.0000000000000284.

PURPOSE OF REVIEW: This article discusses the current state of the art in artificial intestine generation in the treatment of short bowel syndrome. RECENT FINDINGS: Short bowel syndrome defines the condition in which patients lack sufficient intestinal length to allow for adequate absorption of nutrition and fluids, and thus need parenteral support. Advances toward the development of an artificial intestine have improved dramatically since the first attempts in the 1980s, and the last decade has seen significant advances in understanding the intestinal stem cell niche, the growth of complex primary intestinal stem cells in culture, and fabrication of the biomaterials that can support the growth and differentiation of these stem cells. There has also been recent progress in understanding the role of the microbiota and the immune cells on the growth of intestinal cultures on scaffolds in animal models. Despite recent progress, there is much work to be done before the development of a functional artificial intestine for short bowel syndrome is successfully achieved. SUMMARY: Continued concerted efforts by cell biologists, bioengineers, and clinician-scientists will be required for the development of an artificial intestine as a clinical treatment modality for short bowel syndrome.

Lassiter, C. M., J. S. Gal, et al. "Embryonic stem cell-derived neural progenitors transplanted to the hippocampus migrate on host vasculature." Stem Cell

Res. 2016 Mar 9;16(3):579-588. doi: 10.1016/j.scr.2016.02.043.

This study describes the migration of transplanted ESNPs either injected directly into the hippocampus of a mouse, seeded onto hippocampal slices, or under in vitro culture conditions. We show that transplanted mouse ESNPs associate with, and appear to migrate on the surface of the vasculature, and that human ESNPs also associate with blood vessels when seeded on hippocampal slices, and migrate towards BECs in vitro using a Boyden chamber assay. This initial adhesion to vessels is mediated, at least in part, via the integrin alpha6beta1, as observed for SVZ neural progenitor cells. Our data are consistent with CXCL12, expressed by the astroglial-vasculature niche, playing an important role in the migration of transplanted neural progenitors within and outside of the hippocampus.

Marichal, N., G. Fabbiani, et al. "Purinergic signalling in a latent stem cell niche of the rat spinal cord." Purinergic Signal. 2016 Mar 17.

The ependyma of the spinal cord harbours stem cells which are activated by traumatic spinal cord injury. Progenitor-like cells in the central canal (CC) are organized in spatial domains. The cells lining the lateral aspects combine characteristics of ependymocytes and radial glia (RG) whereas in the dorsal and ventral poles, CC-contacting cells have the morphological phenotype of RG and display complex electrophysiological phenotypes. The signals that may affect these progenitors are little understood. Because ATP is massively released after spinal cord injury, we hypothesized that purinergic signalling plays a part in this spinal stem cell niche. We combined immunohistochemistry, in vitro patch-clamp whole-cell recordings and Ca2+ imaging to explore the effects of purinergic agonists on ependymal progenitor-like cells in the neonatal (P1-P6) rat spinal cord. Prolonged focal application of a high concentration of ATP (1 mM) induced a slow inward current. Equimolar concentrations of BzATP generated larger currents that reversed close to 0 mV, had a linear current-voltage relationship and were blocked by Brilliant Blue G, suggesting the presence of functional P2X7 receptors. Immunohistochemistry showed that P2X7 receptors were expressed around the CC and the processes of RG. BzATP also generated Ca2+ waves in RG that were triggered by Ca2+ influx and propagated via Ca2+ release from internal stores through activation of ryanodine receptors. We speculate that the intracellular Ca2+ signalling triggered by P2X7 receptor activation may be an epigenetic mechanism to modulate the behaviour of progenitors in response to ATP released after injury.

Mies, A., E. Bulycheva, et al. "Alterations within the Osteo-Hematopoietic Niche in MDS and their Therapeutic Implications." Curr Pharm Des. 2016 Feb 26.

Hematopoietic and mesenchymal stem and progenitor cells are organized in the osteo hematopoietic niche, a complex microenvironment ensuring self renewal and differentiation. Perturbations of the niche architecture, the mutual cellular interactions and signaling pathways disrupt tissue homeostasis resulting in cytopenia and malignant diseases such as myelodysplastic syndromes (MDS), supporting the concept of niche induced oncogenesis. Analyzing the available treatment options for patients harboring MDS, it becomes evident that many of them specifically modify components of the stem cell niche. Hereby especially compounds inhibiting the TGF beta superfamily seem to represent a promising novel approach for patients with anemia as a result of ineffective erythropoiesis. Moreover, apart from affecting tumorigenesis, these drugs appear to influence bone structure and function as well as hematopoiesis in elderly MDS patients with a disturbed microarchitecture of the bone marrow. In the present review we will dissect the contribution of components of the stem cell niche for the pathogenesis of MDS and discuss current therapeutic strategies targeting components of the niche, focusing on the modulation of TGF beta signaling.

Minuth, W. W. and L. Denk "Special Morphological Features at the Interface of the Renal Stem/Progenitor Cell Niche Force to Reinvestigate Transport of Morphogens During Nephron Induction." Biores Open Access. 2016 Jan 1;5(1):49-60. doi: 10.1089/biores.2015.0039. eCollection 2016.

Formation of a nephron depends on reciprocal signaling of different morphogens between epithelial and mesenchymal cells within the renal stem/progenitor cell niche. Previously, it has been surmised that a close proximity exists between both involved cell types and that morphogens are transported between them by diffusion. However, actual morphological data illustrate that mesenchymal and epithelial stem/progenitor cell bodies are separated by a striking interface. Special fixation of specimens by glutaraldehyde (GA) solution including cupromeronic blue, ruthenium red, or tannic acid for electron microscopy depicts that the interface is not void but filled in extended areas by textured extracellular matrix. Surprisingly, projections of mesenchymal cells cross the interface to contact epithelial cells. At those sites the plasma membranes of a mesenchymal and an epithelial cell are connected

via tunneling nanotubes. Regarding detected morphological features in combination with involved morphogens, their transport cannot longer be explained solely by diffusion. Instead, it has to be sorted according to biophysical properties of morphogens and to detected environment. Thus, the new working hypothesis is that morphogens with good solubility such as glial cell line-derived neurotrophic factor (GDNF) or fibroblast growth factors (FGFs) are transported by diffusion. Morphogens with minor solubility such as bone morphogenetic proteins (BMPs) are secreted and stored for delivery on demand in illustrated extracellular matrix. In contrast, morphogens with poor solubility such as Wnts are transported in mesenchymal cell projections along the plasma membrane or via illustrated tunneling nanotubes. However, the presence of an intercellular route between mesenchymal and epithelial stem/progenitor cells by tunneling nanotubes also makes it possible that all morphogens are transported this way.

Notara, M., N. Refaian, et al. "Short-Term Ultraviolet A Irradiation Leads to Dysfunction of the Limbal Niche Cells and an Antilymphangiogenic and Anti-inflammatory Micromilieu." Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):928-39. doi: 10.1167/iovs.15-18343.

PURPOSE: We analyzed the effects of short-term ultraviolet A (UVA) irradiation on the putative limbal stem cell phenotype, limbal fibroblasts, corneal inflammation, and corneal (lymph)angiogenic privilege. METHODS: Primary human limbal epithelial cells and fibroblasts were irradiated with 5.2 J/cm2 of UVA. The limbal epithelial cell phenotype was assessed using P63a, cytokeratin 15, integrin b1 (marking stem and transient amplifying cells), and cytokeratin 3 (a differentiation marker) as well as by a colony-forming efficiency (CFE) assay. An epithelial-fibroblast coculture model was used to compare the ability of irradiated and nonirradiated fibroblasts to support the putative limbal stem cell phenotype. The effects of the conditioned media of irradiated and nonirradiated cells on proliferation and tube formation of human lymphatic and blood endothelial cells also were tested. The levels of factors related to angiogenesis and inflammation were assessed in a protein array and using ELISA. RESULTS: Ultraviolet A induced phenotypical changes of limbal epithelial cells, as their CFE and putative stem cell/transient amplifying marker expression decreased. Limbal epithelial cells cocultured with UVA-irradiated limbal fibroblasts also exhibited differentiation and CFE decrease. Conditioned media from irradiated limbal epithelial cells and fibroblasts inhibited lymphatic endothelial cell proliferation and tube network complexity. Levels of monocyte chemoattractant protein 1 (MCP1) were reduced following UVA irradiation of both cell populations, while levels of IFN-gamma increased in irradiated limbal epithelial cells. CONCLUSIONS: These data imply a key role of cellular components of the limbal niche following short-term UVA irradiation. Overall, UVA irradiation leads to dysfunction of these cells and a anti(lymph)angiogenic and anti-inflammatory micromilieu.

Oburoglu, L., M. Romano, et al. "Metabolic regulation of hematopoietic stem cell commitment and erythroid differentiation." Curr Opin Hematol. 2016 May;23(3):198-205. doi: 10.1097/MOH.0000000000000234.

PURPOSE OF REVIEW: Hematopoietic stem cell (HSC) renewal and lineage differentiation are finely tuned processes, regulated by cytokines, transcription factors and cell-cell contacts. However, recent studies have shown that fuel utilization also conditions HSC fate. This review focuses on our current understanding of the metabolic pathways that govern HSC self-renewal, commitment and specification to the erythroid lineage. RECENT FINDINGS: HSCs reside in a hypoxic bone marrow niche that favors anaerobic glycolysis. Although this metabolic pathway is required for stem cell maintenance, other pathways also play critical roles. Fatty acid oxidation preserves HSC self-renewal by promoting asymmetric division, whereas oxidative phosphorylation induces lineage commitment. Committed erythroid progenitors support the production of 2.4 million erythrocytes per second in human adults via a synchronized regulation of iron, amino acid and glucose metabolism. Iron is indispensable for heme biosynthesis in erythroblasts; a process finely coordinated by at least two hormones, hepcidin and erythroferrone, together with multiple cell surface iron transporters. Furthermore, hemoglobin production is promoted by amino acid-induced mTOR signaling. Erythropoiesis is also strictly dependent on glutamine metabolism; under conditions where glutaminolysis is inhibited, erythropoietin-signaled progenitors are diverted to a myelomonocytic fate. Indeed, the utilization of both glutamine and glucose in de-novo nucleotide biosynthesis is a sine qua non for erythroid differentiation. SUMMARY: Diverse metabolic networks function in concert with transcriptional, translational and epigenetic programs to regulate HSC potential and orient physiological as well as pathological erythroid differentiation.

Ogino, T., M. Sawada, et al. "Characterization of multiciliated ependymal cells that emerge in the

neurogenic niche of the aged zebrafish brain." J Comp Neurol. 2016 Mar 16. doi: 10.1002/cne.24001.

In mammals, ventricular walls of the developing brain maintain a neurogenic niche, where radial glial cells act as neural stem cells (NSCs) and generate new neurons in the embryo. In the adult brain, the neurogenic niche is maintained in the ventricular-subventricular zone (V-SVZ) of the lateral wall of lateral ventricles and the hippocampal dentate gyrus. In the neonatal V-SVZ, radial glial cells transform into astrocytic postnatal NSCs and multiciliated ependymal cells. On the other hand, in zebrafish, radial glial cells continue to cover the surface of the adult telencephalic ventricle, and maintain a higher neurogenic potential in the adult brain. However, the cell composition of the neurogenic niche of the aged zebrafish brain has not been investigated. Here we show that multiciliated ependymal cells emerge in the neurogenic niche of the aged zebrafish telencephalon. These multiciliated cells appear predominantly in the dorsal part of the ventral telencephalic ventricular zone, which also contains clusters of migrating new neurons. Scanning electron microscopy and live imaging analyses indicated that these multiple cilia beat coordinately and generate constant fluid flow within the ventral telencephalic ventricle. Analysis of the cell composition by transmission electron microscopy revealed that the neurogenic niche in the aged zebrafish contains different types of cells, with ultrastructures similar to those of ependymal cells, transit-amplifying cells, and migrating new neurons in postnatal mice. These data suggest that the transformation capacity of radial glial cells is conserved but its timing is different between fish and mice. This article is protected by copyright. All rights reserved.

O'Hagan-Wong, K., S. Nadeau, et al. "Increased IL-6 secretion by aged human mesenchymal stromal cells disrupts hematopoietic stem and progenitor cells' homeostasis." Oncotarget. 2016 Feb 24. doi: 10.18632/oncotarget.7690.

Hematopoietic stem and progenitor cell (HSPC) homeostasis declines with age, leading to impaired hematopoiesis. Mesenchymal stromal cells (MSC) are critical components of the bone marrow niche and key regulators of the balance between HSPC proliferation and quiescence. Accrual of DNA damage, a hallmark of cellular aging, occurs in aged MSC. Whether MSC aging alters the bone marrow niche triggering HSPC dysfunction is unknown. Using a human MSC-HSPC co-culture system, we demonstrated that DNA damaged MSC have impaired capacity to maintain CD34+CD38- HSPC quiescence. Furthermore, human MSC from adult donors display some hallmarks of cellular senescence and have a decreased capacity to maintain HSPC quiescence and the most primitive CD34+CD38- subset compared to MSC from pediatric donors. IL-6 neutralization restores the MSC-HPSC crosstalk in senescent and adult MSC-HSPC co-cultures highlighting the relevance of the local microenvironment in maintaining HSPC homeostasis. These results provide new evidence implicating components of the MSC secretome in HSPC aging.

Oikawa, T. "Cancer Stem Cells and Their Cellular Origins in Primary Liver and Biliary Tract Cancers." Hepatology. 2016 Feb 5. doi: 10.1002/hep.28485.

Liver and biliary tract cancers are highly aggressive, heterogeneous in their phenotypic traits, and result in clinical outcomes that are difficult to manage. Cancers have subpopulations of cells termed cancer stem cells (CSCs) that share common intrinsic signaling pathways for self-renewal and differentiation with normal stem cells. These CSCs likely have the potential to evolve over time and to give rise to new genetically and functionally diverse subclones by accumulating genetic mutations. Extrinsic signaling from the tumor microenvironment, including the CSC niche, has been implicated in tumor initiation/progression and heterogeneity through dynamic cross talk. CSCs have become recognized as pivotal sources of tumor initiation/progression, relapse/metastasis and chemo-resistance. The origins of CSCs are hypothesized to derive from the transformation of normal stem/progenitors and/or from the reprogramming of adult cells that converts them to stem/progenitor traits. However, the precise mechanisms have not yet been fully elucidated. This review focuses on the candidate normal cells of origin of liver and biliary tract cancers and the future directions of therapies targeting CSCs. This article is protected by copyright. All rights reserved.

O'Leary, D. P., E. O'Leary, et al. "Effects of surgery on the cancer stem cell niche." Eur J Surg Oncol. 2016 Mar;42(3):319-25. doi: 10.1016/j.ejso.2015.12.008. Epub 2016 Jan 13.

Recent identification of a cancer stem cell (CSC) phenotype in solid tumors has greatly enhanced the understanding of the mechanisms responsible for cancer cell metastasis. In keeping with Pagets 'seed and soil' theory, CSCs display dependence upon stromal derived factors found within the niche in which they reside. Inflammatory mediators act as a 'fertilizer' within this niche when interacting with CSCs at the tumor-stromal interface and can potentiate the metastatic ability of CSCs. Interestingly, the same components of the pro-inflammatory milieu experienced by cancer patients perioperatively are known to promote the metastagenic potential of CSCs.

On the basis of this observation we discuss how surgery-induced inflammation potentiates colon CSC involvement in the metastatic process. We hypothesize that the high rates of recurrence and metastasis associated with tumor resection are potentiated by the effects of surgery-induced inflammation on CSCs. Finally we discuss potential therapeutic strategies for use in the perioperative window to protect cancer patients from the oncological effects of the pro-inflammatory milieu.

Ouspenskaia, T., I. Matos, et al. "WNT-SHH Antagonism Specifies and Expands Stem Cells prior to Niche Formation." Cell. 2016 Jan 14;164(1-2):156-69. doi: 10.1016/j.cell.2015.11.058.

Adult stem cell (SC) maintenance and differentiation are known to depend on signals received from the niche. Here, however, we demonstrate a mechanism for SC specification and regulation that is niche independent. Using immunofluorescence, live imaging, genetics, cell-cycle analyses, in utero lentiviral transduction, and lineage-tracing, we show that in developing hair buds, SCs are born from asymmetric divisions that differentially display WNT and SHH signaling. Displaced WNT(lo) suprabasal daughters become SCs that respond to paracrine SHH and symmetrically expand. By contrast, basal daughters remain WNT(hi). They express but do not respond to SHH and hence maintain slow-cycling, asymmetric divisions. Over time, they become short-lived progenitors, generating differentiating daughters rather than SCs. Thus, in contrast to an established niche that harbors a fixed SC pool whose expelled progeny differentiate, asymmetric divisions first specify and displace early SCs into an environment conducive to expansion and later restrict their numbers by switching asymmetric fates.

Pacini, S., S. Barachini, et al. "Mesangiogenic Progenitor Cells Derived from One Novel CD64(bright)CD31(bright)CD14(neg) Population in Human Adult Bone Marrow." Stem Cells Dev. 2016 May 1;25(9):661-73. doi: 10.1089/scd.2015.0344. Epub 2016 Apr 11.

Mesenchymal stromal cells (MSCs) have been the object of extensive research for decades, due to their intrinsic clinical value. Nonetheless, the unambiguous identification of a unique in vivo MSC progenitor is still lacking, and the hypothesis that these multipotent cells could possibly arise from different in vivo precursors has been gaining consensus in the last years. We identified a novel multipotent cell population in human adult bone marrow that we first named Mesodermal Progenitor Cells (MPCs) for the ability to differentiate toward the mesenchymal lineage, while still retaining angiogenic potential. Despite extensive characterization, MPCs positioning within the differentiation pathway and whether they can be ascribed as possible distinctive progenitor of the MSC lineage is still unclear. In this study, we describe the ex vivo isolation of one novel bone marrow subpopulation (Pop#8) with the ability to generate MPCs. Multicolor flow cytometry in combination with either fluorescence-activated cell sorting or magnetic-activated cell sorting were applied to characterize Pop#8 as CD64(bright)CD31(bright)CD14(neg). We defined Pop#8 properties in culture, including the potential of Pop#8-derived MPCs to differentiate into MSCs. Gene expression data were suggestive of Pop#8 in vivo involvement in hematopoietic stem cell niche constitution/maintenance. Pop#8 resulted over three logs more frequent than other putative MSC progenitors, corroborating the idea that most of the controversies regarding culture-expanded MSCs could be the consequence of different culture conditions that select or promote particular subpopulations of precursors.

Petanidis, S., E. Kioseoglou, et al. "In vitro and ex vivo vanadium antitumor activity in (TGF-beta)-induced EMT. Synergistic activity with carboplatin and correlation with tumor metastasis in cancer patients." Int J Biochem Cell Biol. 2016 May;74:121-34. doi: 10.1016/j.biocel.2016.02.015. Epub 2016 Feb 23.

Epithelial to mesenchymal transition (EMT) plays a key role in tumor progression and metastasis as a crucial event for cancer cells to trigger the metastatic niche. Transforming growth factor-beta (TGF-beta) has been shown to play an important role as an EMT inducer in various stages of carcinogenesis. Previous reports had shown that antitumor vanadium inhibits the metastatic potential of tumor cells by reducing MMP-2 expression and inducing ROS-dependent apoptosis. However, the role of vanadium in (TGF-beta)-induced EMT remains unclear. In the present study, we report for the first time on the inhibitory effects of vanadium on (TGF-beta)-mediated EMT followed by down-regulation of ex vivo cancer stem cell markers. The results demonstrate blockage of (TGF-beta)-mediated EMT by vanadium and reduction in the mitochondrial potential of tumor cells linked to EMT and cancer metabolism. Furthermore, combination of vanadium and carboplatin (a) resulted in synergistic antitumor activity in ex vivo cell cultures, and (b) prompted G0/G1 cell cycle arrest and sensitization of tumor cells to carboplatin-induced apoptosis. Overall, the findings highlight the multifaceted antitumor action of vanadium and its synergistic antitumor efficacy with

current chemotherapy drugs, knowledge that could be valuable for targeting cancer cell metabolism and cancer stem cell-mediated metastasis in aggressive chemoresistant tumors.

Pierantozzi, E., B. Vezzani, et al. "Tissue-Specific Cultured Human Pericytes: Perivascular Cells from Smooth Muscle Tissue Have Restricted Mesodermal Differentiation Ability." Stem Cells Dev. 2016 May 1;25(9):674-86. doi: 10.1089/scd.2015.0336. Epub 2016 Apr 8.

Microvascular pericytes (PCs) are considered the adult counterpart of the embryonic mesoangioblasts, which represent a multipotent cell population that resides in the dorsal aorta of the developing embryo. Although PCs have been isolated from several adult organs and tissues, it is still controversial whether PCs from different tissues exhibit distinct differentiation potentials. To address this point, we investigated the differentiation potentials of isogenic human cultured PCs isolated from skeletal (sk-hPCs) and smooth muscle tissues (sm-hPCs). We found that both sk-hPCs and sm-hPCs expressed known pericytic markers and did not express endothelial, hematopoietic, and myogenic markers. Both sk-hPCs and sm-hPCs were able to differentiate into smooth muscle cells. In contrast, sk-hPCs, but not sm-hPCs, differentiated in skeletal muscle cells and osteocytes. Given the reported ability of the Notch pathway to regulate skeletal muscle and osteogenic differentiation, sk-hPCs and sm-hPCs were treated with N-[N-(3,5- difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAPT), a known inhibitor of Notch signaling. DAPT treatment, as assessed by histological and molecular analysis, enhanced myogenic differentiation and abolished osteogenic potential of sk-hPCs. In contrast, DAPT treatment did not affect either myogenic or osteogenic differentiation of sm-hPCs. In summary, these results indicate that, despite being isolated from the same anatomical niche, cultured PCs from skeletal muscle and smooth muscle tissues display distinct differentiation abilities.

Pineda, G., K. M. Lennon, et al. "Tracking of Normal and Malignant Progenitor Cell Cycle Transit in a Defined Niche." Sci Rep. 2016 Apr 4;6:23885. doi: 10.1038/srep23885.

While implicated in therapeutic resistance, malignant progenitor cell cycle kinetics have been difficult to quantify in real-time. We developed an efficient lentiviral bicistronic fluorescent, ubiquitination-based cell cycle indicator reporter (Fucci2BL) to image live single progenitors on a defined niche coupled with cell cycle gene expression analysis. We have identified key differences in cell cycle regulatory gene expression and transit times between normal and chronic myeloid leukemia progenitors that may inform cancer stem cell eradication strategies.

Ponder, K. L., A. Barcena, et al. "Preeclampsia and Inflammatory Preterm Labor Alter the Human Placental Hematopoietic Niche." Reprod Sci. 2016 Mar 3. pii: 1933719116632926.

BACKGROUND: The human placenta is a source of hematopoietic stem and progenitor cells (HSPCs). The RUNX1 transcription factor is required for the formation of functional HSPCs. The impact of preeclampsia (PE) and preterm labor (PTL, spontaneous preterm labor [sPTL] and inflammatory preterm labor [iPTL]) on HSPC localization and RUNX1 expression in the human placenta is unknown. METHODS: We compared the frequency and density of HSPC in control samples from sPTL (n = 6) versus PE (n = 6) and iPTL (n = 6). We examined RUNX1 protein and RNA expression in placentas from normal pregnancies (5-22 weeks, n = 8 total) and in placentas from the aforementioned pregnancy complications (n = 5/group). RESULTS: Hematopoietic stem and progenitor cells were rare cell types, associated predominantly with the vasculature of placental villi. The HSPC density was greater in the chorionic plate (CP) compared to the villi ($P < .001$) and greater in PE and iPTL samples as compared to controls within the CP (not significant) and overall ($P < .05$). During the fetal period, RUNX1 was expressed in the mesenchyme of the CP and villi. Inflammatory PTL samples were more likely to exhibit intraluminal RUNX1+ cell populations ($P < .001$) and RUNX1+ cell clusters attached to arterial endothelial cells. CONCLUSION: Placental HSPCs likely arise from hematopoietic niches comprised RUNX1+ mesenchyme and vascular endothelium. Pregnancy complications that result in preterm birth differentially affect placental HSPC localization and RUNX1 expression. Our results support previous findings that inflammation positively regulates hematopoiesis. We present new evidence that hemogenic endothelium may be active at later stages of human fetal development in the context of inflammation.

Regalado-Santiago, C., E. Juarez-Aguilar, et al. "Mimicking Neural Stem Cell Niche by Biocompatible Substrates." Stem Cells Int. 2016;2016:1513285. doi: 10.1155/2016/1513285. Epub 2016 Jan 6.

Neural stem cells (NSCs) participate in the maintenance, repair, and regeneration of the central nervous system. During development, the primary NSCs are distributed along the ventricular zone of the neural tube, while, in adults, NSCs are mainly

restricted to the subependymal layer of the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus in the hippocampus. The circumscribed areas where the NSCs are located contain the secreted proteins and extracellular matrix components that conform their niche. The interplay among the niche elements and NSCs determines the balance between stemness and differentiation, quiescence, and proliferation. The understanding of niche characteristics and how they regulate NSCs activity is critical to building in vitro models that include the relevant components of the in vivo niche and to developing neuroregenerative approaches that consider the extracellular environment of NSCs. This review aims to examine both the current knowledge on neurogenic niche and how it is being used to develop biocompatible substrates for the in vitro and in vivo mimicking of extracellular NSCs conditions.

Rezza, A., Z. Wang, et al. "Signaling Networks among Stem Cell Precursors, Transit-Amplifying Progenitors, and their Niche in Developing Hair Follicles." Cell Rep. 2016 Mar 29;14(12):3001-18. doi: 10.1016/j.celrep.2016.02.078. Epub 2016 Mar 19.

The hair follicle (HF) is a complex miniorgan that serves as an ideal model system to study stem cell (SC) interactions with the niche during growth and regeneration. Dermal papilla (DP) cells are required for SC activation during the adult hair cycle, but signal exchange between niche and SC precursors/transit-amplifying cell (TAC) progenitors that regulates HF morphogenetic growth is largely unknown. Here we use six transgenic reporters to isolate 14 major skin and HF cell populations. With next-generation RNA sequencing, we characterize their transcriptomes and define unique molecular signatures. SC precursors, TACs, and the DP niche express a plethora of ligands and receptors. Signaling interaction network analysis reveals a bird's-eye view of pathways implicated in epithelial-mesenchymal interactions. Using a systematic tissue-wide approach, this work provides a comprehensive platform, linked to an interactive online database, to identify and further explore the SC/TAC/niche crosstalk regulating HF growth.

Sainz, B., Jr., E. Carron, et al. "Cancer Stem Cells and Macrophages: Implications in Tumor Biology and Therapeutic Strategies." Mediators Inflamm. 2016;2016:9012369. doi: 10.1155/2016/9012369. Epub 2016 Feb 14.

Cancer stem cells (CSCs) are a unique subset of cells within tumors with stemlike properties that have been proposed to be key drivers of tumor initiation and progression. CSCs are functionally defined by their unlimited self-renewal capacity and their ability to initiate tumor formation in vivo. Like normal stem cells, CSCs exist in a cellular niche comprised of numerous cell types including tumor-associated macrophages (TAMs) which provides a unique microenvironment to protect and promote CSC functions. TAMs provide pivotal signals to promote CSC survival, self-renewal, maintenance, and migratory ability, and in turn, CSCs deliver tumor-promoting cues to TAMs that further enhance tumorigenesis. Studies in the last decade have aimed to understand the molecular mediators of CSCs and TAMs, and recent advances have begun to elucidate the complex cross talk that occurs between these two cell types. In this review, we discuss the molecular interactions that define CSC-TAM cross talk at each stage of tumor progression and examine the clinical implications of targeting these interactions.

Santos, C. A., L. R. Andrade, et al. "Gastrospheres of human gastric mucosa cells: an in vitro model of stromal and epithelial stem cell niche reconstruction." Histol Histopathol. 2016 Feb 2:11726.

The molecular characterization of mechanisms involved in the gastrointestinal tract disorders needs an in vitro 3D culture model able to mimic the in vivo gastric microenvironment. Herein, we propose a 3D coculture system where gastric epithelial and stromal cells are grown together building spherical and solid structures using the NASA bioreactor - cell culture system (RCCS), a bioreactor. Epithelial and stromal cells from human antral gastric mucosa were isolated from endoscopic gastric biopsies. Thereafter, these cells were mechanically and enzymatically dispersed by treatment with dispase and collagenase, respectively. Using specific culture procedures, these cells formed 3D structures by using a RCCS, named "gastrospheres". Briefly, gastrospheres were obtained by initial seeding of 2.5x104 cells/well in 96 well culture plates. At 24 h after their formation, they were transferred into RCCS, and maintained for 7, 14, 21, and 28 days. The gastrospheres were morphologically characterized by immunocytochemisty to evaluate extracellular matrix (ECM), and by electron microscopy. These analysis of gastrospheres revealed that the epithelial cells were cytokeratin (CK) and lectin reactive and were arranged in the outer layer; stromal cells presented long cytoplasmic processes and were localized inside the gastrosphere. They were vimentin (VIM) and alpha-smooth muscle actin (alpha-SMA) positive and expressed ECM components such as laminin (LN), fibronectin (FN), and type IV collagen (CIV). Electron microscopy revealed groups of cohesive gastric cells surrounded by complex stromal structures, with multiple

microvilli, and tight cellular junctions interspersed with extracellular matrix fibrils and fibers. The presence of some nestin-positive cells was observed in the inner region of the gastrospheres, suggesting an intermediary localization between epithelial and stromal cells. Altogether, our data suggest that in vitro gastrospheres recapitulate the in vivo gastric niche microenvironment.

Savukinas, U. B., S. R. Enes, et al. "The Bystander Effect: MSC-Mediated Lung Repair." Stem Cells. 2016 Mar 17. doi: 10.1002/stem.2357.

Mesenchymal stem or stromal cells (MSCs), a heterogeneous subset of adult stem/progenitor cells, have surfaced as potential therapeutic units with significant clinical benefit for a wide spectrum of disease conditions, including those affecting the lung. Although MSCs carry both self-renewal and multi-lineage differentiation abilities, current dogma holds that MSCs mainly contribute to tissue regeneration and repair by modulating the host tissue via secreted cues. Thus, the therapeutic benefit of MSCs is thought to derive from so called bystander effects. The regenerative mechanisms employed by MSCs in the lung include modulation of the immune system as well as promotion of epithelial and endothelial repair. Apart from secreted factors, a number of recent findings suggest that MSCs engage in mitochondrial transfer and shedding of membrane vesicles as a means to enhance tissue repair following injury. Furthermore, it is becoming increasingly clear that MSCs are an integral component of epithelial lung stem cell niches. As such, MSCs play an important role in coupling information from the environment to stem and progenitor populations, such that homeostasis can be ensured even in the face of injury. It is the aim of this review to outline the major mechanisms by which MSCs contribute to lung regeneration, synthesizing recent pre-clinical findings with data from clinical trials and potential for future therapy.

Schmal, O., J. Seifert, et al. "Hematopoietic Stem and Progenitor Cell Expansion in Contact with Mesenchymal Stromal Cells in a Hanging Drop Model Uncovers Disadvantages of 3D Culture." Stem Cells Int. 2016;2016:4148093. doi: 10.1155/2016/4148093. Epub 2015 Dec 29.

Efficient ex vivo expansion of hematopoietic stem cells with a concomitant preservation of stemness and self-renewal potential is still an unresolved ambition. Increased numbers of methods approaching this issue using three-dimensional (3D) cultures were reported. Here, we describe a simplified 3D hanging drop model for the coculture of cord blood-derived CD34(+) hematopoietic stem and progenitor cells (HSPCs) with bone marrow-derived mesenchymal stromal cells (MSCs). When seeded as a mixed cell suspension, MSCs segregated into tight spheroids. Despite the high expression of niche-specific extracellular matrix components by spheroid-forming MSCs, HSPCs did not migrate into the spheroids in the initial phase of coculture, indicating strong homotypic interactions of MSCs. After one week, however, HSPC attachment increased considerably, leading to spheroid collapse as demonstrated by electron microscopy and immunofluorescence staining. In terms of HSPC proliferation, the conventional 2D coculture system was superior to the hanging drop model. Furthermore, expansion of primitive hematopoietic progenitors was more favored in 2D than in 3D, as analyzed in colony-forming assays. Conclusively, our data demonstrate that MSCs, when arranged with a spread (monolayer) shape, exhibit better HSPC supportive qualities than spheroid-forming MSCs. Therefore, 3D systems are not necessarily superior to traditional 2D culture in this regard.

Sciancalepore, A. G., A. Portone, et al. "Micropatterning control of tubular commitment in human adult renal stem cells." Biomaterials. 2016 Mar 31;94:57-69. doi: 10.1016/j.biomaterials.2016.03.042.

The treatment of renal injury by autologous, patient-specific adult stem cells is still an unmet need. Unsolved issues remain the spatial integration of stem cells into damaged areas of the organ, the commitment in the required cell type and the development of improved bioengineered devices. In this respect, biomaterials and architectures have to be specialized to control stem cell differentiation. Here, we perform an extensive study on micropatterned extracellular matrix proteins, which constitute a simple and non-invasive approach to drive the differentiation of adult renal progenitor/stem cells (ARPCs) from human donors. ARPCs are interfaced with fibronectin (FN) micropatterns, in the absence of exogenous chemicals or cellular reprogramming. We obtain the differentiation towards tubular cells of ARPCs cultured in basal medium conditions, the tubular commitment thus being specifically induced by micropatterned substrates. We characterize the stability of the tubular differentiation as well as the induction of a polarized phenotype in micropatterned ARPCs. Thus, the developed cues, driving the functional commitment of ARPCs, offer a route to recreate the microenvironment of the stem cell niche in vitro, that may serve, in perspective, for the development of ARPC-based bioengineered devices.

Szyska, M. and I. K. Na "Bone Marrow GvHD after Allogeneic Hematopoietic Stem Cell Transplantation." Front Immunol. 2016 Mar 30;7:118. doi: 10.3389/fimmu.2016.00118. eCollection 2016.

The bone marrow is the origin of all hematopoietic lineages and an important homing site for memory cells of the adaptive immune system. It has recently emerged as a graft-versus-host disease (GvHD) target organ after allogeneic stem cell transplantation (alloHSCT), marked by depletion of both hematopoietic progenitors and niche-forming cells. Serious effects on the restoration of hematopoietic function and immunological memory are common, especially in patients after myeloablative conditioning therapy. Cytopenia and durable immunodeficiency caused by the depletion of hematopoietic progenitors and destruction of bone marrow niches negatively influence the outcome of alloHSCT. The complex balance between immunosuppressive and cell-depleting treatments, GvHD and immune reconstitution, as well as the desirable graft-versus-tumor (GvT) effect remains a great challenge for clinicians.

Tabu, K., N. Muramatsu, et al. "A Synthetic Polymer Scaffold Reveals the Self-Maintenance Strategies of Rat Glioma Stem Cells by Organization of the Advantageous Niche." Stem Cells. 2016 Jan 29. doi: 10.1002/stem.2299.

Cancer stem cells (CSCs) are believed to be maintained within a micro-environmental niche. Here we used polymer microarrays for the rapid and efficient identification of glioma CSC (GSC) niche mimicries and identified a urethane-based synthetic polymer, upon which two groups of niche components, namely extracellular matrices (ECMs) and iron are revealed. In cultures, side population (SP) cells, defined as GSCs in the rat C6 glioma cell line, are more efficiently sustained in the presence of their differentiated progenies expressing higher levels of ECMs and transferrin, while in xenografts, ECMs are supplied by the vascular endothelial cells (VECs), including SP cell-derived ones with distinctively greater ability to retain xenobiotics than host VECs. Iron is stored in tumor infiltrating host macrophages (Mphis), whose protumoral activity is potently enhanced by SP cell-secreted soluble factor(s). Finally, co-expression of ECM-, iron-, and Mphi-related genes is found to be predictive of glioma patients' outcome. Our polymer-based approach reveals the intrinsic capacities of GSCs, to adapt the environment to organize a self-advantageous microenvironment niche, for their maintenance and expansion, which redefines the current concept of anti-CSC niche therapy and has the potential to accelerate cancer therapy development. (190 words)

Takase, H. M. and R. Nusse "Paracrine Wnt/beta-catenin signaling mediates proliferation of undifferentiated spermatogonia in the adult mouse testis." Proc Natl Acad Sci U S A. 2016 Feb 29. pii: 201601461.

Spermatogonial stem cells (SSCs) fuel the production of male germ cells but the mechanisms behind SSC self-renewal, proliferation, and differentiation are still poorly understood. Using the Wnt target gene Axin2 and genetic lineage-tracing experiments, we found that undifferentiated spermatogonia, comprising SSCs and transit amplifying progenitor cells, respond to Wnt/beta-catenin signals. Genetic elimination of beta-catenin indicates that Wnt/beta-catenin signaling promotes the proliferation of these cells. Signaling is likely initiated by Wnt6, which is uniquely expressed by neighboring Sertoli cells, the only somatic cells in the seminiferous tubule that support germ cells and act as a niche for SSCs. Therefore, unlike other stem cell systems where Wnt/beta-catenin signaling is implicated in self-renewal, the Wnt pathway in the testis specifically contributes to the proliferation of SSCs and progenitor cells.

Upadhyay, M., Y. Martino Cortez, et al. "Transposon Dysregulation Modulates dWnt4 Signaling to Control Germline Stem Cell Differentiation in Drosophila." PLoS Genet. 2016 Mar 28;12(3):e1005918. doi: 10.1371/journal.pgen.1005918. eCollection 2016 Mar.

Germline stem cell (GSC) self-renewal and differentiation are required for the sustained production of gametes. GSC differentiation in Drosophila oogenesis requires expression of the histone methyltransferase dSETDB1 by the somatic niche, however its function in this process is unknown. Here, we show that dSETDB1 is required for the expression of a Wnt ligand, Drosophila Wingless type mouse mammary virus integration site number 4 (dWnt4) in the somatic niche. dWnt4 signaling acts on the somatic niche cells to facilitate their encapsulation of the GSC daughter, which serves as a differentiation cue. dSETDB1 is known to repress transposable elements (TEs) to maintain genome integrity. Unexpectedly, we found that independent upregulation of TEs also downregulated dWnt4, leading to GSC differentiation defects. This suggests that dWnt4 expression is sensitive to the presence of TEs. Together our results reveal a chromatin-transposon-Wnt signaling axis that regulates stem cell fate.

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