Stem Cell Aging 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 aging related studies.

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Key words: stem cell; life; aging; 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.

Ahuja, A. K., K. Jodkowska, et al. "A short G1 phase imposes constitutive replication stress and fork remodelling in mouse embryonic stem cells." Nat Commun. 2016 Feb 15;7:10660. doi: 10.1038/ncomms10660.

Embryonic stem cells (ESCs) represent a transient biological state, where pluripotency is coupled with fast proliferation. ESCs display a constitutively active DNA damage response (DDR), but its molecular determinants have remained elusive. Here we show in cultured ESCs and mouse embryos that H2AX phosphorylation is dependent on Ataxia telangiectasia and Rad3 related (ATR) and is associated with chromatin loading of the ssDNA-binding proteins RPA and RAD51. Single-molecule analysis of replication intermediates reveals massive ssDNA gap accumulation, reduced fork speed and frequent fork reversal. All these marks of replication stress do not impair the mitotic process and are rapidly lost at differentiation onset. Delaying the G1/S transition in ESCs allows formation of 53BP1 nuclear bodies and suppresses ssDNA accumulation, fork slowing and reversal in the following S-phase. Genetic inactivation of fork slowing and reversal leads to chromosomal breakage in unperturbed ESCs. We propose that rapid cell cycle progression makes ESCs dependent on effective replication-coupled mechanisms to protect genome integrity.

Baker, D. J., B. G. Childs, et al. "Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan." Nature. 2016 Feb 11;530(7589):184-9. doi: 10.1038/nature16932. Epub 2016 Feb 3.

Cellular senescence, a stress-induced irreversible growth arrest often characterized by expression of p16(Ink4a) (encoded by the Ink4a/Arf locus, also known as Cdkn2a) and a distinctive secretory phenotype, prevents the proliferation of preneoplastic cells and has beneficial roles in tissue remodelling during embryogenesis and wound healing. Senescent cells accumulate in various tissues and organs over time, and have been speculated to have a role in ageing. To explore the physiological relevance and consequences of naturally occurring senescent cells, here we use a previously established transgene, INK-ATTAC, to induce apoptosis in p16(Ink4a)-expressing cells of wild-type mice by injection of AP20187 twice a week starting at one

year of age. We show that compared to vehicle alone, AP20187 treatment extended median lifespan in both male and female mice of two distinct genetic backgrounds. The clearance of p16(Ink4a)-positive cells delayed tumorigenesis and attenuated age-related deterioration of several organs without apparent side effects, including kidney, heart and fat, where clearance preserved the functionality of glomeruli, cardio-protective KATP channels and adipocytes, respectively. Thus, p16(Ink4a)-positive cells that accumulate during adulthood negatively influence lifespan and promote age-dependent changes in several organs, and their therapeutic removal may be an attractive approach to extend healthy lifespan.

Bei, Y., Q. Zhou, et al. "Telocytes in cardiac regeneration and repair." Semin Cell Dev Biol. 2016 Jan 28. pii: S1084-9521(16)30037-4. doi: 10.1016/j.semcdb.2016.01.037.

Telocytes (TCs) are a novel type of stromal cells reported by Popescu's group in 2010. The unique feature that distinguishes TCs from other "classical" stromal cells is their extremely long and thin telopodes (Tps). As evidenced by electron microscopy, TCs are widely distributed in almost all tissues and organs. TCs contribute to form a three-dimensional interstitial network and play as active regulators in intercellular communication via homocellular/heterocellular junctions or shed vesicles. Interestingly, increasing evidence suggests the potential role of TCs in regenerative medicine. Although the heart retains some limited endogenous regenerative capacity, cardiac regenerative and repair response is however insufficient to make up the loss of cardiomyocytes upon injury. Developing novel strategies to increase cardiomyocyte renewal and repair is of great importance for the treatment of cardiac diseases. In this review, we focus on the role of TCs in cardiac regeneration and repair. We particularly describe the intercellular communication between TCs and cardiomyocytes, stem/progenitor cells, endothelial cells, and fibroblasts. Also, we discuss the current knowledge about TCs in cardiac repair after myocardial injury, as well as their potential roles in cardiac development and aging. TC-based therapy or TC-derived exosome delivery might be used as novel therapeutic strategies to promote cardiac regeneration and repair.

Bhattacharya, M., A. R. Sharma, et al. "The crucial role and regulations of miRNAs in zebrafish development." Protoplasma. 2016 Jan 28.

To comprehend the events during developmental biology, fundamental knowledge about the basic machinery of regulation is a prerequisite. MicroRNA (miRNAs) act as regulators in most of the biological processes and recently, it has been concluded that miRNAs can act as modulatory factors even during developmental process from lower to higher animal. Zebrafish, because of its favorable attributes like tiny size, transparent embryo, and rapid external embryonic development, has gained a preferable status among all other available experimental animal models. Currently, zebrafish is being utilized for experimental studies related to stem cells, regenerative molecular medicine as well drug discovery. Therefore, it is important to understand precisely about the various miRNAs that controls developmental biology of this vertebrate model. In here, we have discussed about the miRNA-controlled zebrafish developmental stages with a special emphasis on different miRNA families such as miR-430, miR-200, and miR-133. Moreover, we have also reviewed the role of various miRNAs during embryonic and vascular development stages of zebrafish. In addition, efforts have been made to summarize the involvement of miRNAs in the development of different body parts such as the brain, eye, heart, muscle, and fin, etc. In each section, we have tried to fulfill the gaps of zebrafish developmental biology with the help of available knowledge of miRNA research. We hope that precise knowledge about the miRNA-regulated developmental stages of zebrafish may further help the researchers to efficiently utilize this vertebrate model for experimental purpose.

Bhullar, A. S., C. T. Putman, et al. "Potential Role of Omega-3 Fatty Acids on the Myogenic Program of Satellite Cells." Nutr Metab Insights. 2016 Feb 3;9:1-10. doi: 10.4137/NMI.S27481. eCollection 2016.

Skeletal muscle loss is associated with aging as well as pathological conditions. Satellite cells (SCs) play an important role in muscle regeneration. Omega-3 fatty acids are widely studied in a variety of muscle wasting diseases; however, little is known about their impact on skeletal muscle regeneration. The aim of this review is to evaluate studies examining the effect of omega-3 fatty acids, alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid on the regulation of SC proliferation and differentiation. This review highlights mechanisms by which omega-3 fatty acids may modulate the myogenic program of the stem cell population within skeletal muscles and identifies considerations for future studies. It is proposed that minimally three myogenic transcriptional regulatory factors, paired box 7 (Pax7), myogenic differentiation 1 protein, and myogenin, should be measured to confirm the stage of SCs within the myogenic program affected by omega-3 fatty acids.

Blanc, R. S., G. Vogel, et al. "PRMT7 Preserves Satellite Cell Regenerative Capacity." Cell Rep. 2016 Feb 16;14(6):1528-39. doi: 10.1016/j.celrep.2016.01.022. Epub 2016 Feb 4.

Regeneration of skeletal muscle requires the continued presence of quiescent muscle stem cells (satellite cells), which become activated in response to injury. Here, we report that whole-body protein arginine methyltransferase PRMT7(-/-) adult mice and mice conditionally lacking PRMT7 in satellite cells using Pax7-CreERT2 both display a significant reduction in satellite cell function, leading to defects in regenerative capacity upon muscle injury. We show that PRMT7 is preferentially expressed in activated satellite cells and, interestingly, PRMT7-deficient satellite cells undergo cell-cycle arrest and premature cellular senescence. These defects underlie poor satellite cell stem cell capacity to regenerate muscle and self-renew after injury. PRMT7-deficient satellite cells express elevated levels of the CDK inhibitor p21CIP1 and low levels of its repressor, DNMT3b. Restoration of DNMT3b in PRMT7-deficient cells rescues PRMT7-mediated senescence. Our findings define PRMT7 as a regulator of the DNMT3b/p21 axis required to maintain muscle stem cell regenerative capacity.

Blondel, S., A. L. Egesipe, et al. "Drug screening on Hutchinson Gilford progeria pluripotent stem cells reveals aminopyrimidines as new modulators of farnesylation." Cell Death Dis. 2016 Feb 18;7:e2105. doi: 10.1038/cddis.2015.374.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic disorder characterized by a dramatic appearance of premature aging. HGPS is due to a single-base substitution in exon 11 of the LMNA gene (c.1824C>T) leading to the production of a toxic form of the prelamin A protein called progerin. Because farnesylation process had been shown to control progerin toxicity, in this study we have developed a screening method permitting to identify new pharmacological inhibitors of farnesylation. For this, we have used the unique potential of pluripotent stem cells to have access to an unlimited and relevant biological resource and test 21 608 small molecules. This study identified several compounds, called monoaminopyrimidines, which target two key enzymes of the farnesylation process, farnesyl pyrophosphate synthase and farnesyl transferase, and rescue in vitro phenotypes associated with HGPS. Our results opens up new therapeutic possibilities for the treatment of HGPS by identifying a new family of protein farnesylation inhibitors, and which may also be applicable to cancers and diseases associated with mutations that involve farnesylated proteins.

Carraro, U., S. Boncompagni, et al. "Persistent Muscle Fiber Regeneration in Long Term Denervation. Past, Present, Future." Eur J Transl Myol. 2015 Mar 11;25(2):4832. doi: 10.4081/ejtm.2015.4832. eCollection 2015 Mar 11.

Despite the ravages of long term denervation there is structural and ultrastructural evidence for survival of muscle fibers in mammals, with some fibers surviving at least ten months in rodents and 3-6 years in humans. Further, in rodents there is evidence that muscle fibers may regenerate even after repeated damage in the absence of the nerve, and that this potential is maintained for several months after denervation. While in animal models permanently denervated muscle sooner or later loses the ability to contract, the muscles may maintain their size and ability to function if electrically stimulated soon after denervation. Whether in mammals, humans included, this is a result of persistent de novo formation of muscle fibers is an open issue we would like to explore in this review. During the past decade, we have studied muscle biopsies from the quadriceps muscle of Spinal Cord Injury (SCI) patients suffering with Conus and Cauda Equina syndrome, a condition that fully and irreversibly disconnects skeletal muscle fibers from their damaged innervating motor neurons. We have demonstrated that human denervated muscle fibers survive years of denervation and can be rescued from severe atrophy by home-based Functional Electrical Stimulation (h-bFES). Using immunohistochemistry with both non-stimulated and the h-bFES stimulated human muscle biopsies, we have observed the persistent presence of muscle fibers which are positive to labeling by an antibody which specifically recognizes the embryonic myosin heavy chain (MHCemb). Relative to the total number of fibers present, only a small percentage of these MHCemb positive fibers are detected, suggesting that they are regenerating muscle fibers and not pre-existing myofibers re-expressing embryonic isoforms. Although embryonic isoforms of acetylcholine receptors are known to be re-expressed and to spread from the end-plate to the sarcolemma of muscle fibers in early phases of muscle denervation, we suggest that the MHCemb positive muscle fibers we observe result from the activation, proliferation and fusion of satellite cells, the myogenic precursors present under the basal lamina of the muscle fibers. Using morphological features and molecular biomarkers, we show that severely atrophic muscle fibers, with a peculiar cluster reorganization of myonuclei, are present in rodent muscle seven-months after neurectomy and in human muscles 30-months after complete Conus-Cauda Equina Syndrome and that these are structurally distinct from early myotubes. Beyond reviewing evidence from rodent and human

studies, we add some ultrastructural evidence of muscle fiber regeneration in long-term denervated human muscles and discuss the options to substantially increase the regenerative potential of severely denervated human muscles not having been treated with h-bFES. Some of the mandatory procedures, are ready to be translated from animal experiments to clinical studies to meet the needs of persons with long-term irreversible muscle denervation. An European Project, the trial Rise4EU (Rise for You, a personalized treatment for recovery of function of denervated muscle in long-term stable SCI) will hopefully follow.

Chaker, Z., C. George, et al. "Hypothalamic neurogenesis persists in the aging brain and is controlled by energy-sensing IGF-I pathway." Neurobiol Aging. 2016 May;41:64-72. doi: 10.1016/j.neurobiolaging.2016.02.008. Epub 2016 Feb 17.

Hypothalamic tanycytes are specialized glial cells lining the third ventricle. They are recently identified as adult stem and/or progenitor cells, able to self-renew and give rise to new neurons postnatally. However, the long-term neurogenic potential of tanycytes and the pathways regulating lifelong cell replacement in the adult hypothalamus are largely unexplored. Using inducible nestin-CreER(T2) for conditional mutagenesis, we performed lineage tracing of adult hypothalamic stem and/or progenitor cells (HySC) and demonstrated that new neurons continue to be born throughout adult life. This neurogenesis was targeted to numerous hypothalamic nuclei and produced different types of neurons in the dorsal periventricular regions. Some adult-born neurons integrated the median eminence and arcuate nucleus during aging and produced growth hormone releasing hormone. We showed that adult hypothalamic neurogenesis was tightly controlled by insulin-like growth factors (IGF). Knockout of IGF-1 receptor from hypothalamic stem and/or progenitor cells increased neuronal production and enhanced alpha-tanycyte self-renewal, preserving this stem cell-like population from age-related attrition. Our data indicate that adult hypothalamus retains the capacity of cell renewal, and thus, a substantial degree of structural plasticity throughout lifespan.

Dambroise, E., L. Monnier, et al. "Two phases of aging separated by the Smurf transition as a public path to death." Sci Rep. 2016 Mar 22;6:23523. doi: 10.1038/srep23523.

Aging's most obvious characteristic is the time dependent increase of an individual's probability to die. This lifelong process is accompanied by a large number of molecular and physiological changes. Although numerous genes involved in aging have been identified in the past decades its leading factors have yet to be determined. To identify the very processes driving aging we have developed in the past years an assay to identify physiologically old individuals in a synchronized population of Drosophila melanogaster. Those individuals show an age-dependent increase of intestinal permeability followed by a high risk of death. Here we show that this physiological marker of aging is conserved in 3 invertebrate species Drosophila mojavensis, Drosophila virilis, Caenorhabditis elegans as well as in 1 vertebrate species Danio rerio. Our findings suggest that intestinal barrier dysfunction may be an important event in the aging process conserved across a broad range of species, thus raising the possibility that it may also be the case in Homo sapiens.

Daynac, M., L. Morizur, et al. "Age-related neurogenesis decline in the subventricular zone is associated with specific cell cycle regulation changes in activated neural stem cells." Sci Rep. 2016 Feb 19;6:21505. doi: 10.1038/srep21505.

Although neural stem cells (NSCs) sustain continuous neurogenesis throughout the adult lifespan of mammals, they progressively exhibit proliferation defects that contribute to a sharp reduction in subventricular neurogenesis during aging. However, little is known regarding the early age-related events in neurogenic niches. Using a fluorescence-activated cell sorting technique that allows for the prospective purification of the main neurogenic populations from the subventricular zone (SVZ), we demonstrated an early decline in adult neurogenesis with a dramatic loss of progenitor cells in 4 month-old young adult mice. Whereas the activated and quiescent NSC pools remained stable up to 12 months, the proliferative status of activated NSCs was already altered by 6 months, with an overall extension of the cell cycle resulting from a specific lengthening of G1. Whole genome analysis of activated NSCs from 2- and 6-month-old mice further revealed distinct transcriptomic and molecular signatures, as well as a modulation of the TGFbeta signalling pathway. Our microarray study constitutes a cogent identification of new molecular players and signalling pathways regulating adult neurogenesis and its early modifications.

Di Filippo, E. S., R. Mancinelli, et al. "Myomir dysregulation and reactive oxygen species in aged human satellite cells." Biochem Biophys Res Commun. 2016 Apr 29;473(2):462-70. doi: 10.1016/j.bbrc.2016.03.030. Epub 2016 Mar 11.

Satellite cells that reside on the myofibre surface are crucial for the muscle homeostasis and

regeneration. Aging goes along with a less effective regeneration of skeletal muscle tissue mainly due to the decreased myogenic capability of satellite cells. This phenomenon impedes proper maintenance and contributes to the age-associated decline in muscle mass, known as sarcopenia. The myogenic potential impairment does not depend on a reduced myogenic cell number, but mainly on their difficulty to complete a differentiation program. The unbalanced production of reactive oxygen species in elderly people could be responsible for skeletal muscle impairments. microRNAs are conserved post-transcriptional regulators implicated in numerous biological processes including adult myogenesis. Here, we measure the ROS level and analyze myomiR (miR-1, miR-133b and miR-206) expression in human myogenic precursors obtained from Vastus lateralis of elderly and young subjects to provide the molecular signature responsible for the differentiation impairment of elderly activated satellite cells.

Dos Santos, M., A. Michopoulou, et al. "Perlecan expression influences the keratin 15-positive cell population fate in the epidermis of aging skin." Aging (Albany NY). 2016 Mar 17.

The epidermis is continuously renewed by stem cell proliferation and differentiation. Basal keratinocytes append the dermal-epidermal junction, a cell surface-associated, extracellular matrix that provides structural support and influences their behaviour. It consists of laminins, type IV collagen, nidogens, and perlecan, which are necessary for tissue organization and structural integrity. Perlecan is a heparan sulfate proteoglycan known to be involved in keratinocyte survival and differentiation. Aging affects the dermal epidermal junction resulting in decreased contact with keratinocytes, thus impacting epidermal renewal and homeostasis. We found that perlecan expression decreased during chronological skin aging. Our in vitro studies revealed reduced perlecan transcript levels in aged keratinocytes. The production of in vitro skin models revealed that aged keratinocytes formed a thin and poorly organized epidermis. Supplementing these models with purified perlecan reversed the phenomenon allowing restoration of a well-differentiated multi-layered epithelium. Perlecan down-regulation in cultured keratinocytes caused depletion of the cell population that expressed keratin 15. This phenomenon depended on the perlecan heparan sulphate moieties, which suggested the involvement of a growth factor. Finally, we found defects in keratin 15 expression in the epidermis of aging skin. This study highlighted a new role for perlecan in maintaining the self-renewal capacity of basal keratinocytes.

Dulphy, N., A. S. Chretien, et al. "Underground Adaptation to a Hostile Environment: Acute Myeloid Leukemia vs. Natural Killer Cells." Front Immunol. 2016 Mar 9;7:94. doi: 10.3389/fimmu.2016.00094. eCollection 2016.

Acute myeloid leukemia (AML) is a heterogeneous group of malignancies which incidence increases with age. The disease affects the differentiation of hematopoietic stem or precursor cells in the bone marrow and can be related to abnormal cytogenetic and/or specific mutational patterns. AML blasts can be sensitive to natural killer (NK) cell antitumor response. However, NK cells are frequently defective in AML patients leading to tumor escape. NK cell defects affect not only the expression of the activating NK receptors, including the natural cytotoxicity receptors, the NK group 2, member D, and the DNAX accessory molecule-1, but also cytotoxicity and IFN-gamma release. Such perturbations in NK cell physiology could be related to the adaptation of the AML to the immune pressure and more generally to patient's clinical features. Various mechanisms are potentially involved in the inhibition of NK-cell functions in AML, including defects in the normal lymphopoiesis, reduced expression of activating receptors through cell-to-cell contacts, and production of immunosuppressive soluble agents by leukemic blasts. Therefore, the continuous cross-talk between AML and NK cells participates to the leukemia immune escape and eventually to patient's relapse. Methods to restore or stimulate NK cells seem to be attractive strategies to treat patients once the complete remission is achieved. Moreover, our capacity in stimulating the NK cell functions could lead to the development of preemptive strategies to eliminate leukemia-initiating cells before the emergence of the disease in elderly individuals presenting preleukemic mutations in hematopoietic stem cells.

Emamalizadeh, B., J. Jamshidi, et al. "RIT2 Polymorphisms: Is There a Differential Association?" Mol Neurobiol. 2016 Mar 3.

Neurological disorders include a wide variety of mostly multifactorial diseases related to the development, survival, and function of the neuron cells. Single-nucleotide polymorphisms (SNPs) have been extensively studied in neurological disorders, and in a number of instances have been reproducibly linked to disease as risk factors. The RIT2 gene has been recently shown to be associated with a number of neurological disorders, such as Parkinson's disease (PD) and autism. In the study reported here, we investigated the association of the rs12456492 and rs16976358 SNPs of the RIT2 gene with PD, essential tremor (ET), autism, schizophrenia (SCZ), and bipolar

disorder (BPD; total of 2290 patients), and 1000 controls, by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Significant association was observed between rs12456492 and two disorders, PD and ET, whereas rs16976358 was found to be associated with autism, SCZ, and BPD. Our findings are indicative of differential association between the RIT2 SNPs and different neurological disorders.

Ferri, A. L., A. Bersano, et al. "Mesenchymal stem cells for ischemic stroke: progresses and possibilities." Curr Med Chem. 2016 Feb 21.

Stroke is the most common reason of death and quality of life impairments due to neurological deficits in industrialized countries, currently afflicting 15 million people every year, and the numbers are expected to increase, mostly due to population aging. Although some acute phase therapies such as intravenous recombinant tissue plasminogen activator (rt-PA) and more recently endovascular treatment have been identified to improve stroke outcome, these therapies are available only for a small proportion of patients. The social and economic impact of stroke is immense because one of five stroke patient's dies and one of three are left with disabilities that limit their self-sufficient. The use of stem cells to replace brain cells lost during stroke is a very long-term goal and not easy to achieve given the fact that most types of brain cells are destroyed, and the transplanted cells must integrate and restore neural pathways to restore the function of damaged parts of the brain. Over the past decade the use of mesenchymal stromal cells in cell therapy (MSCs) has emerged as a particular attractive option MSCs are a class of multipotent, self-renewing cells that give rise to differentiated progeny when implanted into appropriate tissues. Herein, we present an updated review on the application of MSCs in stroke focusing on several key parameters including the source and route of delivery of MSCs into the brain, the post-stroke administration times to which the cells are transplanted, and the types of endpoints used to measure whether the therapies are working. Experimental data of transplantation of MSCs in animal stroke models reported an improved functional recovery. However, although the transplantation of MSCs is considered to influence very diverse events by modulating the inflammatory environment, stimulating endogenous neurogenesis and angiogenesis and reducing the formation of glial scar, the underlying precise mechanism of this phenomenon remains still unknown. Lastly, the results from early clinical trials highlight the need of optimization of many variables including cell selection, route of administration in order to translate the benefits from preclinical studies into safe and successful clinical applications.

Focosi, D. and M. Pistello "Effect of Induced Pluripotent Stem Cell Technology in Blood Banking." Stem Cells Transl Med. 2016 Mar;5(3):269-74. doi: 10.5966/sctm.2015-0257. Epub 2016 Jan 27.

Population aging has imposed cost-effective alternatives to blood donations. Artificial blood is still at the preliminary stages of development, and the need for viable cells seems unsurmountable. Because large numbers of viable cells must be promptly available for clinical use, stem cell technologies, expansion, and banking represent ideal tools to ensure a regular supply. Provided key donors can be identified, induced pluripotent stem cell (iPSC) technology could pave the way to a new era in transfusion medicine, just as it is already doing in many other fields of medicine. The present review summarizes the current state of research on iPSC technology in the field of blood banking, highlighting hurdles, and promises.

Fontan-Lozano, A., V. Capilla-Gonzalez, et al. "Impact of transient down-regulation of DREAM in human embryonic stem cell pluripotency: The role of DREAM in the maintenance of hESCs." Stem Cell Res. 2016 Mar 4;16(3):568-578. doi: 10.1016/j.scr.2016.03.001.

Little is known about the functions of downstream regulatory element antagonist modulator (DREAM) in embryonic stem cells (ESCs). However, DREAM interacts with cAMP response element-binding protein (CREB) in a Ca2+-dependent manner, preventing CREB binding protein (CBP) recruitment. Furthermore, CREB and CBP are involved in maintaining ESC self-renewal and pluripotency. However, a previous knockout study revealed the protective function of DREAM depletion in brain aging degeneration and that aging is accompanied by a progressive decline in stem cells (SCs) function. Interestingly, we found that DREAM is expressed in different cell types, including human ESCs (hESCs), human adipose-derived stromal cells (hASCs), human bone marrow-derived stromal cells (hBMSCs), and human newborn foreskin fibroblasts (hFFs), and that transitory inhibition of DREAM in hESCs reduces their pluripotency, increasing differentiation. We stipulate that these changes are partly mediated by increased CREB transcriptional activity. Overall, our data indicates that DREAM acts in the regulation of hESC pluripotency and could be a target to promote or prevent differentiation in embryonic cells.

Garcia-Prat, L., P. Munoz-Canoves, et al. "Dysfunctional autophagy is a driver of muscle stem cell functional decline with aging." Autophagy. 2016

Mar 3;12(3):612-3. doi: 10.1080/15548627.2016.1143211.

Regeneration of skeletal muscle relies on its resident stem cells, also known as satellite cells, which are normally quiescent. With aging, satellite cell quiescence is lost concomitant with a muscle regenerative decline. Here we demonstrate that autophagy sustains quiescence over time and that its failure with age drives senescence, which accounts for stem cell loss of function. Pharmacological and genetic reestablishment of autophagy restores homeostasis and regenerative functions in geriatric satellite cells, which has relevance for the elderly population.

Gibon, E., L. Lu, et al. "Aging, inflammation, stem cells, and bone healing." Stem Cell Res Ther. 2016 Mar 22;7(1):44. doi: 10.1186/s13287-016-0300-9.

Complex interactions among cells of the monocyte-macrophage-osteoclast lineage and the mesenchymal stem cell-osteoblast lineage play a major role in the pathophysiology of bone healing. Whereas the former lineage directs inflammatory events and bone resorption, the latter represents a source of cells for bone regeneration and immune modulation. Both of these lineages are affected by increasing age, which is associated with higher baseline levels of inflammatory mediators, and a significant reduction in osteogenic capabilities. Given the above, fracture healing, osteoporosis, and other related events in the elderly present numerous challenges, which potentially could be aided by new therapeutic approaches to modulate both inflammation and bone regeneration.

Gocmez, S. S., N. Gacar, et al. "Protective effects of resveratrol on aging-induced cognitive impairment in rats." Neurobiol Learn Mem. 2016 Mar 31;131:131-136. doi: 10.1016/j.nlm.2016.03.022.

Resveratrol, a polyphenol phytoalexine, has been shown to play a neuroprotective role in the neurodegenerative process in Alzheimer's disease (AD) and improve memory function in dementia. However, the in vivo effect of resveratrol in normal aging models of learning and memory has not yet been evaluated. Therefore, the present neurobehavioral study was undertaken to evaluate the effect of resveratrol on cognitive impairment induced by aging in passive avoidance and Morris water maze (MWM) tests. Male Wistar albino rats were divided into four groups: young control (4month), young resveratrol (4month+RESV), old control (24month) and old resveratrol (24month+RESV). Resveratrol (50mg/kg/day) was given to the 4month+RESV and 24month+RESV groups orally for 12weeks. There was no significant difference between the groups for the first day of latency, while in aged rats, the second day of latency was significantly shortened compared to the young group in the passive avoidance test ($p<0.05$). Additionally, in the MWM test, the results showed a decrease in the time spent in the escape platform's quadrant in the probe test in aged rats ($p<0.05$). The administration of resveratrol at 50mg/kg/day increased the retention scores in the passive avoidance test and the time spent in the escape platform's quadrant in the MWM task ($p<0.05$). Furthermore resveratrol attenuated the protein levels of TNFalpha and IL1beta in the 24-month group. These findings indicate that aging impairs emotional and spatial learning-memory and resveratrol reverses the effect of age-related learning and memory impairment. The results of this study suggest that resveratrol is effective in preventing cognitive deficit in aged rats by inhibiting the production of inflammatory cytokines.

Golpanian, S., D. L. DiFede, et al. "Rationale and design of the allogeneiC human mesenchymal stem cells (hMSC) in patients with aging fRAilTy via intravenoUS delivery (CRATUS) study: A phase I/II, randomized, blinded and placebo controlled trial to evaluate the safety and potential efficacy of allogeneic human mesenchymal stem cell infusion in patients with aging frailty." Oncotarget. 2016 Feb 25. doi: 10.18632/oncotarget.7727.

Frailty is a syndrome associated with reduced physiological reserves that increases an individual's vulnerability for developing increased morbidity and/or mortality. While most clinical trials have focused on exercise, nutrition, pharmacologic agents, or a multifactorial approach for the prevention and attenuation of frailty, none have studied the use of cell-based therapies. We hypothesize that the application of allogeneic human mesenchymal stem cells (allo-hMSCs) as a therapeutic agent for individuals with frailty is safe and efficacious. The CRATUS trial comprises an initial non-blinded phase I study, followed by a blinded, randomized phase I/II study (with an optional follow-up phase) that will address the safety and pre-specified beneficial effects in patients with the aging frailty syndrome. In the initial phase I protocol, allo-hMSCs will be administered in escalating doses via peripheral intravenous infusion (n=15) to patients allocated to three treatment groups: Group 1 (n=5, 20 million allo-hMSCs), Group 2 (n=5, 100 million allo-hMSCs), and Group 3 (n=5, 200 million allo-hMSCs). Subsequently, in the randomized phase, allo-hMSCs or matched placebo will be administered to patients (n=30) randomly allocated in a 1:1:1 ratio to one of two doses of MSCs versus placebo: Group A (n=10, 100 million allo-hMSCs), Group B (n=10, 200 million

allo-hMSCs), and Group C (n=10, placebo). Primary and secondary objectives are, respectively, to demonstrate the safety and efficacy of allo-hMSCs administered in frail older individuals. This study will determine the safety of intravenous infusion of stem cells and compare phenotypic outcomes in patients with aging frailty.

Greenman, C. D. and T. Chou "Kinetic theory of age-structured stochastic birth-death processes." Phys Rev E. 2016 Jan;93(1):012112. doi: 10.1103/PhysRevE.93.012112. Epub 2016 Jan 11.

Classical age-structured mass-action models such as the McKendrick-von Foerster equation have been extensively studied but are unable to describe stochastic fluctuations or population-size-dependent birth and death rates. Stochastic theories that treat semi-Markov age-dependent processes using, e.g., the Bellman-Harris equation do not resolve a population's age structure and are unable to quantify population-size dependencies. Conversely, current theories that include size-dependent population dynamics (e.g., mathematical models that include carrying capacity such as the logistic equation) cannot be easily extended to take into account age-dependent birth and death rates. In this paper, we present a systematic derivation of a new, fully stochastic kinetic theory for interacting age-structured populations. By defining multiparticle probability density functions, we derive a hierarchy of kinetic equations for the stochastic evolution of an aging population undergoing birth and death. We show that the fully stochastic age-dependent birth-death process precludes factorization of the corresponding probability densities, which then must be solved by using a Bogoliubov--Born--Green--Kirkwood--Yvon-like hierarchy. Explicit solutions are derived in three limits: no birth, no death, and steady state. These are then compared with their corresponding mean-field results. Our results generalize both deterministic models and existing master equation approaches by providing an intuitive and efficient way to simultaneously model age- and population-dependent stochastic dynamics applicable to the study of demography, stem cell dynamics, and disease evolution.

Hamanoue, M., K. Morioka, et al. "Cell-permeable p38 MAP kinase promotes migration of adult neural stem/progenitor cells." Sci Rep. 2016 Apr 12;6:24279. doi: 10.1038/srep24279.

Endogenous neural stem/progenitor cells (NPCs) can migrate toward sites of injury, but the migration activity of NPCs is insufficient to regenerate damaged brain tissue. In this study, we showed that p38 MAP kinase (p38) is expressed in doublecortin-positive adult NPCs. Experiments using the p38 inhibitor SB203580 revealed that endogenous p38 participates in NPC migration. To enhance NPC migration, we generated a cell-permeable wild-type p38 protein (PTD-p38WT) in which the HIV protein transduction domain (PTD) was fused to the N-terminus of p38. Treatment with PTD-p38WT significantly promoted the random migration of adult NPCs without affecting cell survival or differentiation; this effect depended on the cell permeability and kinase activity of the fusion protein. These findings indicate that PTD-p38WT is a novel and useful tool for unraveling the roles of p38, and that this protein provides a reasonable approach for regenerating the injured brain by enhancing NPC migration.

Kapiloff, M. S. and C. A. Emter "The cardiac enigma: current conundrums in heart failure research." F1000Res. 2016 Jan 18;5. pii: F1000 Faculty Rev-72. doi: 10.12688/f1000research.7278.1. eCollection 2016.

The prevalence of heart failure is expected to increase almost 50% in the next 15 years because of aging of the general population, an increased frequency of comorbidities, and an improved survival following cardiac events. Conventional treatments for heart failure have remained largely static over the past 20 years, illustrating the pressing need for the discovery of novel therapeutic agents for this patient population. Given the heterogeneous nature of heart failure, it is important to specifically define the cellular mechanisms in the heart that drive the patient's symptoms, particularly when considering new treatment strategies. This report highlights the latest research efforts, as well as the possible pitfalls, in cardiac disease translational research and discusses future questions and considerations needed to advance the development of new heart failure therapies. In particular, we discuss cardiac remodeling and the translation of animal work to humans and how advancements in our understanding of these concepts relative to disease are central to new discoveries that can improve cardiovascular health.

Kawakami, M., H. Ishikawa, et al. "Induction and differentiation of adipose-derived stem cells from human buccal fat pads into salivary gland cells." Hum Cell. 2016 Feb 3.

Atrophy or hypofunction of the salivary gland because of aging or disease leads to hyposalivation that affects patient quality of life by causing dry mouth, deterioration of mastication/deglutition, and poor oral hygiene status. Current therapy for atrophy or hypofunction of the salivary gland in clinical practice focuses on symptom relief using drugs and artificial saliva; therefore, there is still a need to develop new therapies. To investigate

potential novel therapeutic targets, we induced the differentiation of salivary gland cells by co-culturing human adipose-derived stem cells isolated from buccal fat pads (hBFP-ASCs) with human salivary-gland-derived fibroblasts (hSG-fibros). We examined their potential for transplantation and tissue neogenesis. Following the culture of hBFP-ASCs and hSG-fibros, differentiated cells were transplanted into the submandibular glands of SCID mice, and their degree of differentiation in tissues was determined. We also examined their potential for functional tissue reconstitution using a three-dimensional (3D) culture system. Co-cultured cells expressed salivary-glandrelated markers and generated new tissues following transplantation in vivo. Moreover, cell reconstituted glandular structures in the 3D culture system. In conclusion, coculture of hSG-fibros with hBFP-ASCs led to successful differentiation into salivary gland cells that could be transplanted to generate new tissues.

Madonna, R., C. Cadeddu, et al. "Modelling chemotherapy-induced cardiotoxicity by human pluripotent stem cells." Curr Drug Targets. 2016 Apr 1.

Novel antineoplastic therapies have greatly improved cancer survival; nevertheless they are bringing to new forms of cardiomyopathy, that can often limit proper cancer treatments. Novel cardioprotective therapies are therefore needed, for improving clinical outcomes in cancer patients. In order to test novel therapeutic strategies, there is an increasing need for appropriate experimental models of chemotherapy-induced cardiomyopathy. Induced pluripotent stem (iPS) cell- and human embryonic stem cell (hESC)-derived cardiomyocytes may be used as alternative in vitro models for studying mechanisms that underly chemotherapy-induced cardiomyopathy . In this review we discuss the use of iPS- and hESC-derived cardiomyocytes for evaluating additional pharmacological targets and for predicting chemotherapy-induced cardiotoxicity.

Maneix, L. and A. Catic "Touch and go: nuclear proteolysis in the regulation of metabolic genes and cancer." FEBS Lett. 2016 Apr;590(7):908-23. doi: 10.1002/1873-3468.12087. Epub 2016 Feb 18.

The recruitment of transcription factors to promoters and enhancers is a critical step in gene regulation. Many of these proteins are quickly removed from DNA after they completed their function. Metabolic genes in particular are dynamically regulated and continuously adjusted to cellular requirements. Transcription factors controlling metabolism are therefore under constant surveillance by the ubiquitin-proteasome system, which can degrade DNA-bound proteins in a site-specific manner. Several of these metabolic transcription factors are critical to cancer cells, as they promote uncontrolled growth and proliferation. This review highlights recent findings in the emerging field of nuclear proteolysis and outlines novel paradigms for cancer treatment, with an emphasis on multiple myeloma.

Maredziak, M., K. Marycz, et al. "The Influence of Aging on the Regenerative Potential of Human Adipose Derived Mesenchymal Stem Cells." Stem Cells Int. 2016;2016:2152435. doi: 10.1155/2016/2152435. Epub 2016 Jan 28.

Tissue regeneration using human adipose derived mesenchymal stem cells (hASCs) has significant potential as a novel treatment for many degenerative bone and joint diseases. Previous studies have established that age negatively affects the proliferation status and the osteogenic and chondrogenic differentiation potential of mesenchymal stem cells. The aim of this study was to assess the age-related maintenance of physiological function and differentiation potential of hASCs in vitro. hASCs were isolated from patients of four different age groups: (1) >20 years (n = 7), (2) >50 years (n = 7), (3) >60 years (n = 7), and (4) >70 years (n = 7). The hASCs were characterized according to the number of fibroblasts colony forming unit (CFU-F), proliferation rate, population doubling time (PDT), and quantified parameters of adipogenic, chondrogenic, and osteogenic differentiation. Compared to younger cells, aged hASCs had decreased proliferation rates, decreased chondrogenic and osteogenic potential, and increased senescent features. A shift in favor of adipogenic differentiation with increased age was also observed. As many bone and joint diseases increase in prevalence with age, it is important to consider the negative influence of age on hASCs viability, proliferation status, and multilineage differentiation potential when considering the potential therapeutic applications of hASCs.

Matsumura, H., Y. Mohri, et al. "Hair follicle aging is driven by transepidermal elimination of stem cells via COL17A1 proteolysis." Science. 2016 Feb 5;351(6273):aad4395. doi: 10.1126/science.aad4395. Epub 2016 Feb 4.

Hair thinning and loss are prominent aging phenotypes but have an unknown mechanism. We show that hair follicle stem cell (HFSC) aging causes the stepwise miniaturization of hair follicles and eventual hair loss in wild-type mice and in humans. In vivo fate analysis of HFSCs revealed that the DNA damage response in HFSCs causes proteolysis of type XVII collagen (COL17A1/BP180), a critical molecule

for HFSC maintenance, to trigger HFSC aging, characterized by the loss of stemness signatures and by epidermal commitment. Aged HFSCs are cyclically eliminated from the skin through terminal epidermal differentiation, thereby causing hair follicle miniaturization. The aging process can be recapitulated by Col17a1 deficiency and prevented by the forced maintenance of COL17A1 in HFSCs, demonstrating that COL17A1 in HFSCs orchestrates the stem cell-centric aging program of the epithelial mini-organ.

Mazzulli, J. R., L. F. Burbulla, et al. "Detection of Free and Protein-Bound ortho-Quinones by Near-Infrared Fluorescence." Anal Chem. 2016 Feb 16;88(4):2399-405. doi: 10.1021/acs.analchem.5b04420. Epub 2016 Feb 3.

Aging and oxidative stress are two prominent pathological mechanisms for Parkinson's disease (PD) that are strongly associated with the degeneration of dopamine (DA) neurons in the midbrain. DA and other catechols readily oxidize into highly reactive o-quinone species that are precursors of neuromelanin (NM) pigment and under pathological conditions can modify and damage macromolecules. The role of DA oxidation in PD pathogenesis remains unclear in part due to the lack of appropriate disease models and the absence of a simple method for the quantification of DA-derived oxidants. Here, we describe a rapid, simple, and reproducible method for the quantification of o-quinones in cells and tissues that relies on the near-infrared fluorescent properties of these species. Importantly, we demonstrate that catechol-derived oxidants can be quantified in human neuroblastoma cells and midbrain dopamine neurons derived from induced pluripotent stem cells, providing a novel model to study the downstream actions of o-quinones. This method should facilitate further study of oxidative stress and DA oxidation in PD and related diseases that affect the dopaminergic system.

Mendelsohn, A. R. and J. W. Larrick "Rejuvenating Muscle Stem Cell Function: Restoring Quiescence and Overcoming Senescence." Rejuvenation Res. 2016 Apr;19(2):182-6. doi: 10.1089/rej.2016.1829.

Elderly humans gradually lose strength and the capacity to repair skeletal muscle. Skeletal muscle repair requires functional skeletal muscle satellite (or stem) cells (SMSCs) and progenitor cells. Diminished stem cell numbers and increased dysfunction correlate with the observed gradual loss of strength during aging. Recent reports attribute the loss of stem cell numbers and function to either increased entry into a presenescent state or the loss of self-renewal capacity due to an inability to maintain quiescence resulting in stem cell exhaustion. Earlier work has shown that exposure to factors from blood of young animals and other treatments could restore SMSC function. However, cells in the presenescent state are refractory to the beneficial effects of being transplanted into a young environment. Entry into the presenescent state results from loss of autophagy, leading to increased ROS and epigenetic modification at the CDKN2A locus due to decreased H2Aub, upregulating cell senescence biomarker p16ink4a. However, the presenescent SMSCs can be rejuvenated by agents that stimulate autophagy, such as the mTOR inhibitor rapamycin. Autophagy plays a critical role in SMSC homeostasis. These results have implications for the development of senolytic therapies that attempt to destroy p16ink4a expressing cells, since such therapies would also destroy a reservoir of potentially rescuable regenerative stem cells. Other work suggests that in humans, loss of SMSC self-renewal capacity is primarily due to decreased expression of sprouty1. DNA hypomethylation at the SPRY1 gene locus downregulates sprouty1, causing inability to maintain quiescence and eventual exhaustion of the stem cell population. A unifying hypothesis posits that in aging humans, first loss of quiescence occurs, depleting the stem cell population, but that remaining SMSCs are increasingly subject to presenescence in the very old.

Mohrin, M. and D. Chen "The mitochondrial metabolic checkpoint and aging of hematopoietic stem cells." Curr Opin Hematol. 2016 Mar 4.

PURPOSE OF REVIEW: Cell-cycle checkpoints are surveillance mechanisms in eukaryotic cells that monitor the condition of the cell, repair cellular damages, and allow the cell to progress through the various phases of the cell cycle when conditions become favorable. We review recent advances in hematopoietic stem cell (HSC) biology, highlighting a mitochondrial metabolic checkpoint that is essential for HSCs to return to the quiescent state. RECENT FINDINGS: As quiescent HSCs enter the cell cycle, mitochondrial biogenesis is induced, which is associated with increased mitochondrial protein folding stress and mitochondrial oxidative stress. Mitochondrial unfolded protein response and mitochondrial oxidative stress response are activated to alleviate stresses and allow HSCs to exit the cell cycle and return to quiescence. Other mitochondrial maintenance mechanisms include mitophagy and asymmetric segregation of aged mitochondria. SUMMARY: Because loss of HSC quiescence results in the depletion of the HSC pool and compromised tissue regeneration, deciphering the molecular mechanisms that regulate the mitochondrial metabolic checkpoint in HSCs will increase our understanding of hematopoiesis and how it becomes dysregulated under pathological conditions and during aging. More

broadly, this knowledge is instrumental for understanding the maintenance of cells that convert between quiescence and proliferation to support their physiological functions.

Morales, M. G., J. Abrigo, et al. "Angiotensin-(1-7) attenuates disuse skeletal muscle atrophy in mice via its receptor, Mas." Dis Model Mech. 2016 Apr 1;9(4):441-9. doi: 10.1242/dmm.023390. Epub 2016 Feb 5.

Immobilization is a form of disuse characterized by a loss of strength and muscle mass. Among the main features are decreased IGF-1/Akt signalling and increased ubiquitin-proteasome pathway signalling, which induce greater myosin heavy chain degradation. Activation of the classical renin-angiotensin system (RAS) causes deleterious effects in skeletal muscle, including muscle wasting. In contrast, angiotensin-(1-7) [Ang-(1-7)], a peptide of the non-classical RAS, produces beneficial effects in skeletal muscle. However, the role of Ang-(1-7) in skeletal muscle disuse atrophy and independent of classical RAS activation has not been evaluated. Therefore, we assessed the functions of Ang-(1-7) and the Mas receptor in disuse muscle atrophyin vivousing unilateral cast immobilization of the hind limb in male, 12-week-old wild-type (WT) and Mas-knockout (Mas KO) mice for 1 and 14 days. Additionally, we evaluated the participation of IGF-1/IGFR-1/Akt signalling and ubiquitin-proteasome pathway expression on the effects of Ang-(1-7) immobilization-induced muscle atrophy. Our results found that Ang-(1-7) prevented decreased muscle strength and reduced myofiber diameter, myosin heavy chain levels, and the induction of atrogin-1 and MuRF-1 expressions, all of which normally occur during immobilization. Analyses indicated that Ang-(1-7) increases IGF-1/IGFR-1/Akt pathway signalling through IGFR-1 and Akt phosphorylation, and the concomitant activation of two downstream targets of Akt, p70S6K and FoxO3. These anti-atrophic effects of Ang-(1-7) were not observed in Mas KO mice, indicating crucial participation of the Mas receptor. This report is the first to propose anti-atrophic effects of Ang-(1-7) via the Mas receptor and the participation of the IGF-1/IGFR-1/Akt/p70S6K/FoxO3 mechanism in disuse skeletal muscle atrophy.

Nekrasov, E. D., V. A. Vigont, et al. "Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons." Mol Neurodegener. 2016 Apr 14;11(1):27. doi: 10.1186/s13024-016-0092-5.

BACKGROUND: Huntington's disease (HD) is an incurable hereditary neurodegenerative disorder, which manifests itself as a loss of GABAergic medium spiny (GABA MS) neurons in the striatum and caused by an expansion of the CAG repeat in exon 1 of the huntingtin gene. There is no cure for HD, existing pharmaceutical can only relieve its symptoms. RESULTS: Here, induced pluripotent stem cells were established from patients with low CAG repeat expansion in the huntingtin gene, and were then efficiently differentiated into GABA MS-like neurons (GMSLNs) under defined culture conditions. The generated HD GMSLNs recapitulated disease pathology in vitro, as evidenced by mutant huntingtin protein aggregation, increased number of lysosomes/autophagosomes, nuclear indentations, and enhanced neuronal death during cell aging. Moreover, store-operated channel (SOC) currents were detected in the differentiated neurons, and enhanced calcium entry was reproducibly demonstrated in all HD GMSLNs genotypes. Additionally, the quinazoline derivative, EVP4593, reduced the number of lysosomes/autophagosomes and SOC currents in HD GMSLNs and exerted neuroprotective effects during cell aging. CONCLUSIONS: Our data is the first to demonstrate the direct link of nuclear morphology and SOC calcium deregulation to mutant huntingtin protein expression in iPSCs-derived neurons with disease-mimetic hallmarks, providing a valuable tool for identification of candidate anti-HD drugs. Our experiments demonstrated that EVP4593 may be a promising anti-HD drug.

Nishida, M., Y. Kumagai, et al. "Redox signaling regulated by electrophiles and reactive sulfur species." J Clin Biochem Nutr. 2016 Mar;58(2):91-8. doi: 10.3164/jcbn.15-111. Epub 2016 Feb 17.

Redox signaling is a key modulator of oxidative stress induced by nonspecific insults of biological molecules generated by reactive oxygen species. Current redox biology is revisiting the traditional concept of oxidative stress, such that toxic effects of reactive oxygen species are protected by diverse antioxidant systems upregulated by oxidative stress responses that are physiologically mediated by redox-dependent cell signaling pathways. Redox signaling is thus precisely regulated by endogenous electrophilic substances that are generated from reactive oxygen species and nitric oxide and its derivative reactive species during stress responses. Among electrophiles formed endogenously, 8-nitroguanosine 3',5'-cyclic monophosphate (8-nitro-cGMP) has unique cell signaling functions, and pathways for its biosynthesis, signaling mechanism, and metabolism in cells have been clarified. Reactive sulfur species such as cysteine hydropersulfides that are abundant in cells are likely involved in 8-nitro-cGMP metabolism. These new aspects of redox

biology may stimulate innovative and multidisciplinary research in cell and stem cell biology; infectious diseases, cancer, metabolic syndrome, ageing, and neurodegenerative diseases; and other oxidative stress-related disorders. This review focuses on the most recent progress in the biosynthesis, cell signaling, and metabolism of 8-nitro-cGMP, which is a likely target for drug development and lead to discovery of novel therapeutics for many diseases.

Noren Hooten, N., A. Martin-Montalvo, et al. "Metformin-mediated increase in DICER1 regulates microRNA expression and cellular senescence." Aging Cell. 2016 Mar 17. doi: 10.1111/acel.12469.

Metformin, an oral hypoglycemic agent, has been used for decades to treat type 2 diabetes mellitus. Recent studies indicate that mice treated with metformin live longer and have fewer manifestations of age-related chronic disease. However, the molecular mechanisms underlying this phenotype are unknown. Here, we show that metformin treatment increases the levels of the microRNA-processing protein DICER1 in mice and in humans with diabetes mellitus. Our results indicate that metformin upregulates DICER1 through a post-transcriptional mechanism involving the RNA-binding protein AUF1. Treatment with metformin altered the subcellular localization of AUF1, disrupting its interaction with DICER1 mRNA and rendering DICER1 mRNA stable, allowing DICER1 to accumulate. Consistent with the role of DICER1 in the biogenesis of microRNAs, we found differential patterns of microRNA expression in mice treated with metformin or caloric restriction, two proven life-extending interventions. Interestingly, several microRNAs previously associated with senescence and aging, including miR-20a, miR-34a, miR-130a, miR-106b, miR-125, and let-7c, were found elevated. In agreement with these findings, treatment with metformin decreased cellular senescence in several senescence models in a DICER1-dependent manner. Metformin lowered p16 and p21 protein levels and the abundance of inflammatory cytokines and oncogenes that are hallmarks of the senescence-associated secretory phenotype (SASP). These data lead us to hypothesize that changes in DICER1 levels may be important for organismal aging and to propose that interventions that upregulate DICER1 expression (e.g., metformin) may offer new pharmacotherapeutic approaches for age-related disease.

Ogawa, T., Y. Kodera, et al. "Natural thioallyl compounds increase oxidative stress resistance and lifespan in Caenorhabditis elegans by modulating SKN-1/Nrf." Sci Rep. 2016 Feb 22;6:21611. doi: 10.1038/srep21611.

Identification of biologically active natural compounds that promote health and longevity, and understanding how they act, will provide insights into aging and metabolism, and strategies for developing agents that prevent chronic disease. The garlic-derived thioallyl compounds S-allylcysteine (SAC) and S-allylmercaptocysteine (SAMC) have been shown to have multiple biological activities. Here we show that SAC and SAMC increase lifespan and stress resistance in Caenorhabditis elegans and reduce accumulation of reactive oxygen species (ROS). These compounds do not appear to activate DAF-16 (FOXO orthologue) or mimic dietary restriction (DR) effects, but selectively induce SKN-1 (Nrf1/2/3 orthologue) targets involved in oxidative stress defense. Interestingly, their treatments do not facilitate SKN-1 nuclear accumulation, but slightly increased intracellular SKN-1 levels. Our data also indicate that thioallyl structure and the number of sulfur atoms are important for SKN-1 target induction. Our results indicate that SAC and SAMC may serve as potential agents that slow aging.

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.

Otero-Vinas, M. and V. Falanga "Mesenchymal Stem Cells in Chronic Wounds: The Spectrum from Basic

to Advanced Therapy." Adv Wound Care (New Rochelle). 2016 Apr 1;5(4):149-163.

Significance: Almost 7 million Americans have chronic cutaneous wounds and billions of dollars are spent on their treatment. The number of patients with nonhealing wounds keeps increasing worldwide due to an ever-aging population, increasing number of obese and diabetic patients, and cardiovascular disease. Recent Advances: Advanced treatments for difficult wounds are needed. Therapy with mesenchymal stem cells (MSCs) is attractive due to their differentiating potential, their immunomodulating properties, and their paracrine effects. Critical Issues: New technologies (including growth factors and skin substitutes) are now widely used for stimulating wound healing. However, in spite of these advances, the percentage of complete wound closure in most clinical situations is around 50-60%. Moreover, there is a high rate of wound recurrence. Future Directions: Recently, it has been demonstrated that MSCs speed up wound healing by decreasing inflammation, by promoting angiogenesis, and by decreasing scarring. However, there are some potential limitations to successful MSC therapy. These limitations include the need to improve cell delivery methods, cell viability, heterogeneity in MSC preparations, and suboptimal wound bed preparation. Further large, controlled clinical trials are needed to establish the safety of MSCs before widespread clinical application.

Palmer, A. K. and J. L. Kirkland "Aging and adipose tissue: potential interventions for diabetes and regenerative medicine." Exp Gerontol. 2016 Feb 26. pii: S0531-5565(16)30054-7. doi: 10.1016/j.exger.2016.02.013.

Adipose tissue dysfunction occurs with aging and has systemic effects, including peripheral insulin resistance, ectopic lipid deposition, and inflammation. Fundamental aging mechanisms, including cellular senescence and progenitor cell dysfunction, occur in adipose tissue with aging and may serve as potential therapeutic targets in age-related disease. In this review, we examine the role of adipose tissue in healthy individuals and explore how aging leads to adipose tissue dysfunction, redistribution, and changes in gene regulation. Adipose tissue plays a central role in longevity, and interventions restricted to adipose tissue may impact lifespan. Conversely, obesity may represent a state of accelerated aging. We discuss the potential therapeutic potential of targeting basic aging mechanisms, including cellular senescence, in adipose tissue, using type II diabetes and regenerative medicine as examples. We make the case that aging should not be neglected in the study of adipose-derived stem cells for regenerative medicine strategies, as elderly patients make up a large portion of individuals in need of such therapies.

Paoletti, C., S. Quintin, et al. "Kinetics of Formation and Asymmetrical Distribution of Hsp104-Bound Protein Aggregates in Yeast." Biophys J. 2016 Apr 12;110(7):1605-14. doi: 10.1016/j.bpj.2016.02.034.

Budding yeast cells have a finite replicative life span; that is, a mother cell produces only a limited number of daughter cells before it slows division and dies. Despite the gradual aging of the mother cell, all daughters are born rejuvenated and enjoy a full replicative lifespan. It has been proposed that entry of mother cells into senescence is driven by the progressive accumulation and retention of damaged material, including protein aggregates. This additionally allows the daughter cells to be born damage free. However, the mechanism underlying such asymmetrical segregation of protein aggregates by mother and daughter cells remains controversial, in part because of the difficulties inherent in tracking the dynamics and fate of protein aggregates in vivo. To overcome such limitations, we have developed single-cell real-time imaging methodology to track the formation of heat-induced protein aggregates in otherwise unperturbed dividing cells. By combining the imaging data with a simple computational model of protein aggregation, we show that the establishment of asymmetrical partitioning of protein aggregates upon division is driven by the large bud-specific dilution rate associated with polarized growth and the absence of significant mother/bud exchange of protein aggregates during the budded phase of the cell cycle. To our knowledge, this study sheds new light on the mechanism of establishment of a segregation bias, which can be accounted for by simple physical arguments.

Perez, L. M., J. Suarez, et al. "Obesity-driven alterations in adipose-derived stem cells are partially restored by weight loss." Obesity (Silver Spring). 2016 Mar;24(3):661-9. doi: 10.1002/oby.21405. Epub 2016 Feb 1.

OBJECTIVE: The therapeutic potential of adipose-derived stem cells (ASCs) is reduced by various stress-inducing conditions that affect tissue homeostasis such as diabetes, aging, and obesity. Previous works have provided evidence of negative effects of obesity on ASC populations, but it is unclear whether this persists after a weight loss. This study evaluated whether weight loss can restore the attenuated properties found in ASCs derived from populations with obesity (oASCs). METHODS: In vitro functional analyses were performed to investigate the possible recovery properties in mouse oASCs. Using ASCs isolated from subcutaneous

tissue from formerly obese mice (dASCs) and control mice (cASCs), cell proliferation, viability, and some regenerative properties in these cells were analyzed compared with oASCs to evaluate the functional cell state. RESULTS: Cell proliferation, viability, and some regenerative properties are strengthened in dASCs and cASCs compared with oASCs. Nevertheless, metabolic analysis reveals a mitochondrial load misbalance and function leading to impaired respiration in dASCs. CONCLUSIONS: This study demonstrates that an initial obese environment triggers a detrimental state in ASCs that is not completely recovered after weight loss.

Perrigue, P. M., J. Najbauer, et al. "Histone demethylase JMJD3 at the intersection of cellular senescence and cancer." Biochim Biophys Acta. 2016 Mar 5;1865(2):237-244. doi: 10.1016/j.bbcan.2016.03.002.

Cellular senescence is defined by an irreversible growth arrest and is an important biological mechanism for suppression of tumor formation. Although deletion/mutation to DNA sequences is one mechanism by which cancer cells can escape senescence, little is known about the epigenetic factors contributing to this process. Histone modifications and chromatin remodeling related to the function of a histone demethylase, jumonji domain-containing protein 3 (JMJD3; also known as KDM6B), play an important role in development, tissue regeneration, stem cells, inflammation, and cellular senescence and aging. The role of JMJD3 in cancer is poorly understood and its function may be at the intersection of many pathways promoted in a dysfunctional manner such as activation of the senescence-associated secretory phenotype (SASP) observed in aging.

Pitzler, L., M. Auler, et al. "miR-126-3p promotes matrix-dependent perivascular cell attachment, migration and intercellular interaction." Stem Cells. 2016 Mar 2. doi: 10.1002/stem.2308.

microRNAs (miRNAs) can regulate the interplay between perivascular cells (PVC) and endothelial cells (EC) during angiogenesis, but the relevant PVC-specific miRNAs are not yet defined. Here, we identified miR-126-3p and miR-146a to be exclusively upregulated in PVC upon interaction with EC, determined their influence on the PVC phenotype and elucidate their mole cular mechanisms of action. Specifically the increase of miR-126-3p strongly promoted the motility of PVC on the basement membrane-like composite and stabilized networks of endothelial cells. Subsequent miRNA target analysis showed that miR-126-3p inhibits SPRED1 and PLK2 expression, induces ERK1/2 phosphorylation and stimulates TLR3 expression to modulate cell-cell and cell-matrix contacts of PVC. Gain of expression experiments in vivo demonstrated that miR-126-3p stimulates PVC coverage of newly formed vessels and transform immature into mature, less permeable vessels. In conclusion we showed that miR-126-3p regulates matrix-dependent PVC migration and intercellular interaction to modulate vascular integrity.

Pizarro, J. G. and G. Cristofari "Post-Transcriptional Control of LINE-1 Retrotransposition by Cellular Host Factors in Somatic Cells." Front Cell Dev Biol. 2016 Mar 7;4:14. doi: 10.3389/fcell.2016.00014. eCollection 2016.

Long INterspersed Element-1 (LINE-1 or L1) retrotransposons form the only autonomously active family of transposable elements in humans. They are expressed and mobile in the germline, in embryonic stem cells and in the early embryo, but are silenced in most somatic tissues. Consistently, they play an important role in individual genome variations through insertional mutagenesis and sequence transduction, which occasionally lead to novel genetic diseases. In addition, they are reactivated in nearly half of the human epithelial cancers, contributing to tumor genome dynamics. The L1 element codes for two proteins, ORF1p and ORF2p, which are essential for its mobility. ORF1p is an RNA-binding protein with nucleic acid chaperone activity and ORF2p possesses endonuclease and reverse transcriptase activities. These proteins and the L1 RNA assemble into a ribonucleoprotein particle (L1 RNP), considered as the core of the retrotransposition machinery. The L1 RNP mediates the synthesis of new L1 copies upon cleavage of the target DNA and reverse transcription of the L1 RNA at the target site. The L1 element takes benefit of cellular host factors to complete its life cycle, however several cellular pathways also limit the cellular accumulation of L1 RNPs and their deleterious activities. Here, we review the known cellular host factors and pathways that regulate positively or negatively L1 retrotransposition at post-transcriptional level, in particular by interacting with the L1 machinery or L1 replication intermediates; and how they contribute to control L1 activity in somatic cells.

Prudent, M., F. Stauber, et al. "Small-Scale Perfusion Bioreactor of Red Blood Cells for Dynamic Studies of Cellular Pathways: Proof-of-Concept." Front Mol Biosci. 2016 Mar 30;3:11. doi: 10.3389/fmolb.2016.00011. eCollection 2016.

To date, the development of bioreactors for the study of red blood cells (RBCs, daily transfused in

the case of disease or hemorrhage) has focused on hematopoietic stem cells. Despite the fact that mature RBCs are enucleated and do not expand, they possess complex cellular and metabolic pathways, as well as post-translation modification signaling and gas-exchange regulation. In order to dynamically study the behavior of RBCs and their signaling pathways under various conditions, a small-scale perfusion bioreactor has been developed. The most advanced design developed here consists of a fluidized bed of 7.6 mL containing 3.10(9) cells and perfused at 8.5 muL/min. Mimicking RBC storage conditions in transfusion medicine, as a proof-of-concept, we investigated the ex vivo aging of RBCs under both aerobic and anaerobic conditions. Hence, RBCs stored in saline-adenine-glucose-mannitol (SAGM) were injected in parallel into two bioreactors and perfused with a modified SAGM solution over 14 days at room temperature under air or argon. The formation of a fluidized bed enabled easy sampling of the extracellular medium over the storage period used for the quantitation of glucose consumption and lactate production. Hemolysis and microvesiculation increased during aging and were reduced under anaerobic (argon) conditions, which is consistent with previously reported findings. Glucose and lactate levels showed expected trends, i.e., decreased and increased during the 2-week period, respectively; whereas extracellular glucose consumption was higher under aerobic conditions. Metabolomics showed depletion of glycolsis and pentose phosphate pathway metabolites, and an accumulation of purine metabolite end-products. This novel approach, which takes advantage of a fluidized bed of cells in comparison to traditional closed bags or tubes, does not require agitation and limit shear stress, and constantly segragates extracellular medium from RBCs. It thus gives access to several difficult-to-obtain on- and off-line parameters in the extracellular medium. This dynamic bioreactor system does not only allow us to probe the behavior of RBCs under different storage conditions, but it also could be a powerful tool to study physiological or pathological RBCs exposed to various conditions and stimuli.

Pusic, K. M., A. D. Pusic, et al. "Environmental Enrichment Stimulates Immune Cell Secretion of Exosomes that Promote CNS Myelination and May Regulate Inflammation." Cell Mol Neurobiol. 2016 Mar 18.

Environmental enrichment (EE) consists of increased physical, intellectual, and social activity, and has wide-ranging effects, including enhancing cognition, learning and memory, and motor coordination. Animal studies have demonstrated that EE improves outcome of brain trauma and neurodegenerative disorders, including demyelinating diseases like multiple sclerosis, making it a promising therapeutic option. However, the complexity of applying a robust EE paradigm makes clinical use difficult. A better understanding of the signaling involved in EE-based neuroprotection may allow for development of effective mimetics as an alternative. In prior work, we found that exosomes isolated from the serum of rats exposed to EE impact CNS myelination. Exosomes are naturally occurring nanovesicles containing mRNA, miRNA, and protein, which play important roles in cell function, disease, and immunomodulation. When applied to hippocampal slice cultures or nasally administered to naive rats, EE-serum exosomes significantly increase myelin content, oligodendrocyte precursor (OPC) and neural stem cell levels, and reduce oxidative stress (OS). We found that rat EE exosomes were enriched in miR-219, which is necessary and sufficient for OPC differentiation into myelinating cells. Thus, peripherally produced exosomes may be a useful therapy for remyelination. Here, we aim to better characterize the impact of EE on CNS health and to determine the cellular source of nutritive exosomes found in serum. We found that exosomes isolated from various circulating immune cell types all increased slice culture myelin content, contained miR-219, and reduced OS, suggesting that EE globally alters immune function in a way that supports brain health.

Rajagopalan, S., A. Rane, et al. "Regulation of ATP13A2 via PHD2-HIF1alpha Signaling Is Critical for Cellular Iron Homeostasis: Implications for Parkinson's Disease." J Neurosci. 2016 Jan 27;36(4):1086-95. doi: 10.1523/JNEUROSCI.3117-15.2016.

We previously reported that pharmacological inhibition of a class of enzymes known as prolyl hydroxylase domain proteins (PHDs) has neuroprotective effects in various in vitro and in vivo models of Parkinson's disease (PD). We hypothesized that this was due to inhibition of the PHD2 isoform, preventing it from hydroxylating the transcription factor hypoxia inducible factor 1 alpha (HIF1alpha), targeting it for eventual proteasomal degradation. HIF1alpha itself induces the transcription of various cellular stress genes, including several involved in iron metabolism. Although all three isoforms of PHD are expressed within vulnerable dopaminergic (DAergic) substantia nigra pars compacta neurons, only select downregulation of the PHD2 isoform was found to protect against in vivo neurodegenerative effects associated with the mitochondrial neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. These findings were corroborated in induced pluripotent

stem cell-derived neurons, providing validation in a pertinent human cell model. PHD2 inhibition was found to result in increased expression of ATP13A2, mutation of which is responsible for a rare juvenile form of PD known as Kufor-Rakeb syndrome. Knockdown of ATP13A2 expression within human DAergic cells was found to abrogate restoration of cellular iron homeostasis and neuronal cell viability elicited by inhibition of PHD2 under conditions of mitochondrial stress, likely via effects on lysosomal iron storage. These data suggest that regulation of ATP13A2 by the PHD2-HIF1alpha signaling pathway affects cellular iron homeostasis and DAergic neuronal survival. This constitutes a heretofore unrecognized process associated with loss of ATP13A2 function that could have wide-ranging implications for it as a therapeutic target for PD and other related conditions. SIGNIFICANCE STATEMENT: Reductions in PHD2 activity within dopaminergic neurons in vivo and in cultured human induced pluripotent stem cell-derived neurons protects against mitochondrial stress-induced neurotoxicity. Protective effects are dependent on downstream HIF-1alpha expression. Knockdown of ATP13A2, a gene linked to a rare juvenile form of Parkinson's disease and recently identified as a novel HIF1alpha target, was found to abrogate maintenance of cellular iron homeostasis and neuronal viability elicited by PHD2 inhibition in vivo and in cultured dopaminergic cells under conditions of mitochondrial stress. Mechanistically, this was due to ATP13A2's role in maintaining lysosomal iron stores. This constitutes a novel mechanism by which alterations in ATP13A2 activity may be driving PD-related neuropathology.

Ratnappan, R., J. D. Ward, et al. "Nuclear hormone receptors as mediators of metabolic adaptability following reproductive perturbations." Worm. 2016 Feb 18;5(1):e1151609. doi: 10.1080/21624054.2016.1151609. eCollection 2016 Jan-Mar.

Previously, we identified a group of nuclear hormone receptors (NHRs) that promote longevity in the nematode Caenorhabditis elegans following germline-stem cell (GSC) loss. This group included NHR-49, the worm protein that performs functions similar to vertebrate PPARalpha, a key regulator of lipid metabolism. We showed that NHR-49/PPARalpha enhances mitochondrial beta-oxidation and fatty acid desaturation upon germline removal, and through the coordinated enhancement of these processes allows the animal to retain lipid homeostasis and undergo lifespan extension. NHR-49/PPARalpha expression is elevated in GSC-ablated animals, in part, by DAF-16/FOXO3A and TCER-1/TCERG1, two other conserved, pro-longevity transcriptional regulators that are essential for germline-less longevity. In exploring the roles of the other pro-longevity NHRs, we discovered that one of them, NHR-71/HNF4, physically interacted with NHR-49/PPARalpha. NHR-71/HNF4 did not have a broad impact on the expression of beta-oxidation and desaturation targets of NHR-49/PPARalpha. But, both NHR-49/PPARalpha and NHR-71/HNF4 were essential for the increased expression of DAF-16/FOXO3A- and TCER-1/TCERG1-downstream target genes. In addition, nhr-49 inactivation caused a striking membrane localization of KRI-1, the only known common upstream regulator of DAF-16/FOXO3A and TCER-1/TCERG1, suggesting that it may operate in a positive feedback loop to potentiate the activity of this pathway. These data underscore how selective interactions between NHRs that function as nodes in metabolic networks, confer functional specificity in response to different physiological stimuli.

Regan, J. C., M. Khericha, et al. "Sex difference in pathology of the ageing gut mediates the greater response of female lifespan to dietary restriction." Elife. 2016 Feb 16;5. pii: e10956. doi: 10.7554/eLife.10956.

Women live on average longer than men but have greater levels of late-life morbidity. We have uncovered a substantial sex difference in the pathology of the aging gut in Drosophila. The intestinal epithelium of the aging female undergoes major deterioration, driven by intestinal stem cell (ISC) division, while lower ISC activity in males associates with delay or absence of pathology, and better barrier function, even at old ages. Males succumb to intestinal challenges to which females are resistant, associated with fewer proliferating ISCs, suggesting a trade-off between highly active repair mechanisms and late-life pathology in females. Dietary restriction reduces gut pathology in aging females, and extends female lifespan more than male. By genetic sex reversal of a specific gut region, we induced female-like aging pathologies in males, associated with decreased lifespan, but also with a greater increase in longevity in response to dietary restriction.

Rios, C., G. D'Ippolito, et al. "Low Oxygen Modulates Multiple Signaling Pathways Increasing Self-Renewal while Decreasing Differentiation, Senescence and Apoptosis in Stromal MIAMI Cells." Stem Cells Dev. 2016 Apr 8.

Human bone marrow multipotent mesenchymal stromal cells (hMSCs) number decreases with aging. Sub-populations of hMSCs can differentiate into cells found in bone, vasculature,

cartilage, gut, and other tissues, and participate in their repair. Maintaining throughout adult life, such cell sub-populations should help prevent or delay the onset of age-related degenerative conditions. Low oxygen tension, the physiological environment in progenitor cell-rich regions of the bone marrow microarchitecture, stimulates the self-renewal of marrow-isolated adult multilineage inducible (MIAMI) cells and expression of Sox 2, Nanog, Oct4a nuclear accumulation, Notch intracellular domain (NICD), notch target genes, neuronal transcriptional repressor element 1 (RE1) silencing transcription factor (REST), and hypoxia-inducible factor-1 alpha (HIF-1). Additionally, by decreasing the expression of (i) the pro-apoptotic proteins apoptosis-inducing factor (AIF) and Bak, and (ii) senescence-associated p53 expression and beta-galactosidase activity. Furthermore, low oxygen increases canonical Wnt pathway signaling, co-receptor Lrp5 expression, and PI3K/Akt pathway activation. Lrp5 inhibition decreases self-renewal marker Sox2 mRNA, Oct4a nuclear accumulation and cell numbers. Wortmannin-mediated PI3K/Akt pathway inhibition leads to increased osteoblastic differentiation at both, low and high, oxygen tensions. We demonstrate that low oxygen stimulates a complex signaling network involving PI3K/Akt, Notch, and canonical Wnt pathways, which mediate the observed increase in nuclear Oct4a and REST, with simultaneous decrease in p53, AIF and Bak. Collectively, these pathway activations contribute to increased self-renewal with concomitant decreased differentiation, cell cycle arrest, apoptosis and/or senescence in MIAMI cells. Importantly, the PI3K/Akt pathway plays a central mechanistic role in the oxygen tension-regulated self-renewal vs. osteoblastic differentiation of progenitor cells.

Sala, D. and A. Sacco "Signal transducer and activator of transcription 3 signaling as a potential target to treat muscle wasting diseases." Curr Opin Clin Nutr Metab Care. 2016 May;19(3):171-6. doi: 10.1097/MCO.0000000000000273.

PURPOSE OF REVIEW: The review summarizes our current knowledge of the role of signal transducer and activator of transcription 3 (STAT3) signaling in skeletal muscle regeneration and the maintenance of muscle mass. RECENT FINDINGS: STAT3 signaling plays a pivotal role in regulating the function of multiple cell types in skeletal muscle. This includes muscle stem cells, myofibers, and macrophages. It regulates muscle stem cell function by antagonizing self-renewal. STAT3 also functions in myofibers to regulate skeletal muscle mass. This is highly relevant under pathological conditions where STAT3 activation promotes protein degradation and muscle atrophy. Transient pharmacological inhibition of STAT3 partially prevents muscle wasting. However, the mechanisms responsible for the improvement of muscle condition are not currently well understood. This is because of the complexity of the system, as STAT3 has a critical role in regulating the function of several cell types residing in skeletal muscle. SUMMARY: Muscle wasting is associated with several human diseases such as muscle dystrophies or cancer cachexia. However, currently there are no effective treatments for this condition, and there is a critical need to identify new potential targets for the development of efficient therapeutic approaches.

Segales, J., A. B. Islam, et al. "Chromatin-wide and transcriptome profiling integration uncovers p38alpha MAPK as a global regulator of skeletal muscle differentiation." Skelet Muscle. 2016 Mar 15;6:9. doi: 10.1186/s13395-016-0074-x. eCollection 2016.

BACKGROUND: Extracellular stimuli induce gene expression responses through intracellular signaling mediators. The p38 signaling pathway is a paradigm of the mitogen-activated protein kinase (MAPK) family that, although originally identified as stress-response mediator, contributes to establishing stem cell differentiation fates. p38alpha is central for induction of the differentiation fate of the skeletal muscle stem cells (satellite cells) through not fully characterized mechanisms. METHODS: To investigate the global gene transcription program regulated by p38alpha during satellite cell differentiation (myogenesis), and to specifically address whether this regulation occurs through direct action of p38alpha on gene promoters, we performed a combination of microarray gene expression and genome-wide binding analyses. For experimental robustness, two myogenic cellular systems with genetic and chemical loss of p38alpha function were used: (1) satellite cells derived from mice with muscle-specific deletion of p38alpha, and (2) the C2C12 murine myoblast cell line cultured in the absence or presence of the p38alpha/beta inhibitor SB203580. Analyses were performed at cell proliferation and early differentiation stages. RESULTS: We show that p38alpha binds to a large set of active promoters during the transition of myoblasts from proliferation to differentiation stages. p38alpha-bound promoters are enriched with binding motifs for several transcription factors, with Sp1, Tcf3/E47, Lef1, FoxO4, MyoD, and NFATc standing out in all experimental conditions. p38alpha association with chromatin correlates very well with high levels of transcription, in agreement with its classical function as an activator of myogenic differentiation. Interestingly, p38alpha also associates

with genes repressed at the onset of differentiation, thus highlighting the relevance of p38-dependent chromatin regulation for transcriptional activation and repression during myogenesis. CONCLUSIONS: These results uncover p38alpha association and function on chromatin at novel classes of target genes during skeletal muscle cell differentiation. This is consistent with this MAPK isoform being a transcriptional regulator.

Selich, A., J. Daudert, et al. "Massive Clonal Selection and Transiently Contributing Clones During Expansion of Mesenchymal Stem Cell Cultures Revealed by Lentiviral RGB-Barcode Technology." Stem Cells Transl Med. 2016 May;5(5):591-601. doi: 10.5966/sctm.2015-0176. Epub 2016 Mar 31.

: Mesenchymal stem (or stromal) cells (MSCs) have been used in more than 400 clinical trials for the treatment of various diseases. The clinical benefit and reproducibility of results, however, remain extremely variable. During the in vitro expansion phase, which is necessary to achieve clinically relevant cell numbers, MSCs show signs of aging accompanied by different contributions of single clones to the mass culture. Here we used multicolor lentiviral barcode labeling to follow the clonal dynamics during in vitro MSC expansion from whole umbilical cord pieces (UCPs). The clonal composition was analyzed by a combination of flow cytometry, fluorescence microscopy, and deep sequencing. Starting with highly complex cell populations, we observed a massive reduction in diversity, transiently dominating populations, and a selection of single clones over time. Importantly, the first wave of clonal constriction already occurred in the early passages during MSC expansion. Consecutive MSC cultures from the same UCP implied the existence of more primitive, MSC culture-initiating cells. Our results show that microscopically homogenous MSC mass cultures consist of many subpopulations, which undergo clonal selection and have different capabilities. Among other factors, the clonal composition of the graft might have an impact on the functional properties of MSCs in experimental and clinical settings. SIGNIFICANCE: Mesenchymal stem cells (MSCs) can easily be obtained from various adult or embryonal tissues and are frequently used in clinical trials. For their clinical application, MSCs have to be expanded in vitro. This unavoidable step influences the features of MSCs, so that clinical benefit and experimental results are often highly variable. Despite a homogenous appearance under the microscope, MSC cultures undergo massive clonal selection over time. Multicolor fluorescence labeling and deep sequencing were used to demonstrate the dynamic clonal composition of MSC cultures, which might ultimately explain the variable clinical performance of the cells.

Selman, C., A. Sinclair, et al. "Evidence that hematopoietic stem cell function is preserved during aging in long-lived S6K1 mutant mice." Oncotarget. 2016 Apr 13. doi: 10.18632/oncotarget.8729.

The mechanistic target of rapamycin (mTOR) signalling pathway plays a highly conserved role in aging; mice lacking ribosomal protein S6 kinase 1 (S6K1-/-) have extended lifespan and healthspan relative to wild type (WT) controls. Exactly how reduced mTOR signalling induces such effects is unclear, although preservation of stem cell function may be important. We show, using gene expression analyses, that there was a reduction in expression of cell cycle genes in young (12 week) and aged (80 week) S6K1-/- BM-derived c-Kit+ cells when compared to age-matched WT mice, suggesting that these cells are more quiescent in S6K1-/- mice. In addition, we investigated hematopoietic stem cell (HSC) frequency and function in young and aged S6K1-/-and WT mice. Young, but not aged, S6K1-/- mice had more LSK (lineage-, c-Kit+, Sca-1+) cells (% of bone marrow (BM)), including the most primitive long-term repopulating HSCs (LT-HSC) relative to WT controls. Donor-derived engraftment of LT-HSCs in recipient mice was unaffected by genotype in young mice, but was enhanced in transplants using LT-HSCs derived from aged S6K1-/- mice. Our results are the first to provide evidence that age-associated HSC functional decline is ameliorated in a long-lived mTOR mutant mouse.

Shelar, S. B., M. Narasimhan, et al. "Disruption of nuclear factor (erythroid-derived-2)-like 2 antioxidant signaling: a mechanism for impaired activation of stem cells and delayed regeneration of skeletal muscle." FASEB J. 2016 Feb 2. pii: fj.201500153.

Recently we have reported that age-dependent decline in antioxidant levels accelerated apoptosis and skeletal muscle degeneration. Here, we demonstrate genetic ablation of the master cytoprotective transcription factor, nuclear factor (erythroid-derived-2)-like 2 (Nrf2), aggravates cardiotoxin (CTX)-induced tibialis anterior (TA) muscle damage. Disruption of Nrf2 signaling sustained the CTX-induced burden of reactive oxygen species together with compromised expression of antioxidant genes and proteins. Transcript/protein expression of phenotypic markers of muscle differentiation, namely paired box 7 (satellite cell) and early myogenic differentiation and terminal differentiation (myogenin and myosin heavy chain 2) were increased on d 2 and 4 postinjury but later returned to baseline levels on d 8 and 15 in wild-type

(WT) mice. In contrast, these responses were persistently augmented in Nrf2-null mice suggesting that regulation of the regeneration-related signaling mechanisms require Nrf2 for normal functioning. Furthermore, Nrf2-null mice displayed slower regeneration marked by dysregulation of embryonic myosin heavy chain temporal expression. Histologic observations illustrated that Nrf2-null mice displayed smaller, immature TA muscle fibers compared with WT counterparts on d 15 after CTX injury. Improvement in TA muscle morphology and gain in muscle mass evident in the WT mice was not noticeable in the Nrf2-null animals. Taken together these data show that the satellite cell activation, proliferation, and differentiation requires a functional Nrf2 system for effective healing following injury.- Shelar, S. B., Narasimhan, M., Shanmugam, G., Litovsky, S. H., Gounder, S. S., Karan, G., Arulvasu, C., Kensler, T. W., Hoidal, J. R., Darley-Usmar, V. M., Rajasekaran, N. S. Disruption of nuclear factor (erythroid-derived-2)-like 2 antioxidant signaling: a mechanism for impaired activation of stem cells and delayed regeneration of skeletal muscle.

Sheshadri, P. and A. Kumar "Managing odds in stem cells: insights into the role of mitochondrial antioxidant enzyme MnSOD." Free Radic Res. 2016 May;50(5):570-84. doi: 10.3109/10715762.2016.1155708.

Reactive oxygen species (ROS) have been poised at a straddled state of being beneficiary as well detrimental depending on its threshold levels. Maintaining the homeostasis of ROS is imperative for normal cellular physiology, wherein physiological concentrations of ROS are involved in cell signaling and elevated ROS contribute to the development of various diseases. Superoxide dismutases (SODs), enzymes involved in dismutation of superoxide anion to hydrogen peroxide, arrive as a first line of defense when there is perturbation in the homeostasis of ROS. As mitochondria are the main site of superoxide production, among SODs, mitochondrial manganese SOD (MnSOD) is the primary antioxidant enzyme that protects cells from ROS. Most importantly, knockout of MnSOD leads to postnatal lethality and tissue-specific conditional knockout in brain resulted in death of mice, conclusively portraying the essential role of MnSOD in development. Although MnSOD has been extensively discussed with the purview of tumor biology and aging, understanding the crucial role of MnSOD in stem cell physiology is still at its infant stage. Ever increasing progress in stem cell research has recently unveiled the essential role of MnSOD in self-renewal and differentiation of stem cells. In this review, we will conglomerate the current aspects by which MnSOD can contribute to embryonic stem cells' and adult stem cells' functions and interpret the necessity of understanding MnSOD for further stem cell mediated applications.

Solano Fonseca, R., S. Mahesula, et al. "Neurogenic Niche Microglia Undergo Positional Remodeling and Progressive Activation Contributing to Age-Associated Reductions in Neurogenesis." Stem Cells Dev. 2016 Apr 1;25(7):542-55. doi: 10.1089/scd.2015.0319. Epub 2016 Mar 16.

Neural stem cells (NSCs) exist throughout life in the ventricular-subventricular zone (V-SVZ) of the mammalian forebrain. During aging NSC function is diminished through an unclear mechanism. In this study, we establish microglia, the immune cells of the brain, as integral niche cells within the V-SVZ that undergo age-associated repositioning in the V-SVZ. Microglia become activated early before NSC deficits during aging resulting in an antineurogenic microenvironment due to increased inflammatory cytokine secretion. These age-associated changes were not observed in non-neurogenic brain regions, suggesting V-SVZ microglia are specialized. Using a sustained inflammatory model in young adult mice, we induced microglia activation and inflammation that was accompanied by reduced NSC proliferation in the V-SVZ. Furthermore, in vitro studies revealed secreted factors from activated microglia reduced proliferation and neuron production compared to secreted factors from resting microglia. Our results suggest that age-associated chronic inflammation contributes to declines in NSC function within the aging neurogenic niche.

Sousa-Victor, P. and P. Munoz-Canoves "Regenerative decline of stem cells in sarcopenia." Mol Aspects Med. 2016 Feb 24. pii: S0098-2997(16)30006-1. doi: 10.1016/j.mam.2016.02.002.

Skeletal muscle mass and function decline with aging, a process known as sarcopenia, which restrains posture maintenance, mobility and quality of life in the elderly. Sarcopenia is also linked to a progressive reduction in the regenerative capacity of the skeletal muscle stem cells (satellite cells), which are critical for myofiber formation in early life stages and for sustaining repair in response to muscle damage or trauma. Here we will review the most recent findings on the causes underlying satellite cell functional decline with aging, and will discuss the prevalent view whereby age-associated extrinsic factor alterations impact negatively on satellite cell-intrinsic mechanisms, resulting in deficient muscle regeneration with aging. Further understanding of the interplay between satellite cell extrinsic and intrinsic factors in sarcopenia will facilitate therapies aimed at

improving muscle repair in the increasing aging population.

Tierney, M., C. Garcia, et al. "Innervation of dystrophic muscle following muscle stem cell therapy." Muscle Nerve. 2016 Mar 21. doi: 10.1002/mus.25115.

INTRODUCTION: Duchenne muscular dystrophy (DMD) is caused by the loss of the structural protein, dystrophin, resulting in muscle fragility. Muscle stem cell (MuSC) transplantation is a potential therapy for DMD. Whether donor-derived muscle fibers are structurally innervated is unknown. METHODS: Green Fluorescent Protein (GFP) expressing MuSCs were transplanted into the tibials anterior of adult dystrophic mdx/mTR mice. Three weeks later, the neuromuscular junction was labelled by immunohistochemistry. RESULTS: The percent overlap between pre- and post-synaptic immunolabeling was greater in donor-derived GFP+ myofibers, and fewer GFP+ myofibers were identified as denervated compared to control GFP- fibers (P = 0.001 and 0.03, student t-test). GFP+ fibers also demonstrated acetylcholine receptor fragmentation and expanded end-plate area, indicators of muscle reinnervation (P = 0.008 and 0.033, student t-test). CONCLUSION: Whether GFP+ fibers are a result of de novo synthesis or fusion with damaged endogenous fibers is unclear. Regardless, donor-derived fibers demonstrate clear histological innervation. This article is protected by copyright. All rights reserved.

Tierney, M. T. and A. Sacco "Satellite Cell Heterogeneity in Skeletal Muscle Homeostasis." Trends Cell Biol. 2016 Mar 3. pii: S0962-8924(16)00027-1. doi: 10.1016/j.tcb.2016.02.004.

The cellular turnover required for skeletal muscle maintenance and repair is mediated by resident stem cells, also termed satellite cells. Satellite cells normally reside in a quiescent state, intermittently entering the cell cycle to fuse with neighboring myofibers and replenish the stem cell pool. However, the mechanisms by which satellite cells maintain the precise balance between self-renewal and differentiation necessary for long-term homeostasis remain unclear. Recent work has supported a previously unappreciated heterogeneity in the satellite cell compartment that may underlie the observed variability in cell fate and function. In this review, we examine the work supporting this notion as well as the potential governing principles, developmental origins, and principal determinants of satellite cell heterogeneity.

Tobin, D. J. "Introduction to skin aging." J Tissue Viability. 2016 Mar 14. pii: S0965-206X(16)00028-0. doi: 10.1016/j.jtv.2016.03.002.

Cutaneous science has seen considerable development in the last 25 years, in part due to the Omics revolution, and the appreciation that this organ is hardwired into the body's key neuro-immuno-endocrine axes. Moreover, there is greater appreciation of how stratification of skin disorders will permit more targeted and more effective treatments. Against this has been how the remarkable extension in the average human life-span, though in the West at least, this parallels worrying increases in lifestyle-associated conditions like diabetes, skin cancer etc. These demographic trends bring greater urgency to finding clinical solutions for numerous age-related deficits in skin function caused by extrinsic and intrinsic factors. Mechanisms for aging skin include the actions of reactive oxygen species (ROS), mtDNA mutations, and telomere shortening, as well as hormonal changes. We have also significantly improved our understanding of how to harness the skin's considerable regenerative capacity e.g., via its remarkable investment of stem cell subpopulations. In this way we hope to develop new strategies to selectively target the skin's capacity to undergo optimal wound repair and regeneration. Here, the unsung hero of the skin regenerative power may be the humble hair follicle, replete with its compliment of epithelial, mesenchymal, neural and other stem cells. This review introduces the topic of human skin aging, with a focus on how maintenance of function in this complex multi-cell type organ is key for retaining quality of life into old age.

Tsai, H. Z., R. K. Lin, et al. "Drosophila mitochondrial topoisomerase III alpha affects the aging process via maintenance of mitochondrial function and genome integrity." J Biomed Sci. 2016 Apr 12;23(1):38. doi: 10.1186/s12929-016-0255-2.

BACKGROUND: Mitochondria play important roles in providing metabolic energy and key metabolites for synthesis of cellular building blocks. Mitochondria have additional functions in other cellular processes, including programmed cell death and aging. A previous study revealed Drosophila mitochondrial topoisomerase III alpha (Top3alpha) contributes to the maintenance of the mitochondrial genome and male germ-line stem cells. However, the involvement of mitochondrial Top3alpha in the mitochondrion-mediated aging process remains unclear. In this study, the M1L flies, in which Top3alpha protein lacks the mitochondrial import sequence and is thus present in cell nuclei but not in mitochondria, is used as a model system to examine the role of mitochondrial Top3alpha in the aging of

fruit flies. RESULTS: Here, we reported that M1L flies exhibit mitochondrial defects which affect the aging process. First, we observed that M1L flies have a shorter life span, which was correlated with a significant reduction in the mitochondrial DNA copy number, the mitochondrial membrane potential, and ATP content compared with those of both wildtype and transgene-rescued flies of the same age. Second, we performed a mobility assay and electron microscopic analysis to demonstrate that the locomotion defect and mitophagy of M1L flies were enhanced with age, as compared with the controls. Finally, we showed that the correlation between the mtDNA deletion level and aging in M1L flies resembles what was reported in mammalian systems. CONCLUSIONS: The results reported here demonstrate that mitochondrial Top3alpha ablation results in mitochondrial genome instability and its dysfunction, thereby accelerating the aging process.

Tsai, R. Y. "Balancing self-renewal against genome preservation in stem cells: How do they manage to have the cake and eat it too?" Cell Mol Life Sci. 2016 May;73(9):1803-23. doi: 10.1007/s00018-016-2152-y. Epub 2016 Feb 17.

Stem cells are endowed with the awesome power of self-renewal and multi-lineage differentiation that allows them to be major contributors to tissue homeostasis. Owing to their longevity and self-renewal capacity, they are also faced with a higher risk of genomic damage compared to differentiated cells. Damage on the genome, if not prevented or repaired properly, will threaten the survival of stem cells and culminate in organ failure, premature aging, or cancer formation. It is therefore of paramount importance that stem cells remain genomically stable throughout life. Given their unique biological and functional requirement, stem cells are thought to manage genotoxic stress somewhat differently from non-stem cells. The focus of this article is to review the current knowledge on how stem cells escape the barrage of oxidative and replicative DNA damage to stay in self-renewal. A clear statement on this subject should help us better understand tissue regeneration, aging, and cancer.

Uzer, G., R. K. Fuchs, et al. "Plasma and Nuclear Membranes Convey Mechanical Information to Regulate Mesenchymal Stem Cell Lineage." Stem Cells. 2016 Feb 17. doi: 10.1002/stem.2342.

Numerous factors including chemical, hormonal, spatial and physical cues determine stem cell fate. While the regulation of stem cell differentiation by soluble factors is well characterized, the role of mechanical force in the determination of lineage fate is just beginning to be understood. Investigation of the role of force on cell function has largely focused on "outside-in" signaling, initiated at the plasma membrane. When interfaced with the extracellular matrix, the cell utilizes integral membrane proteins, such as those found in focal adhesion complexes to translate force into biochemical signals. Akin to these "outside-in" connections, the internal cytoskeleton is physically linked to the nucleus, via proteins that span the nuclear membrane. Although structurally and biochemically distinct, these two forms of mechanical coupling influence stem cell lineage fate and, when disrupted, often lead to disease. Here we provide an overview of how mechanical coupling occurs at the plasma and nuclear membranes. We also discuss the role of force on stem cell differentiation, with focus on the biochemical signals generated at the cell membrane and the nucleus and how those signals influence various diseases. While the interaction of stem cells with their physical environment and how they respond to force is complex, an understanding of the mechanical regulation of these cells is critical in the design of novel therapeutics to combat diseases associated with aging, cancer, and osteoporosis.

Valero, J., I. Paris, et al. "Lifestyle Shapes the Dialogue between Environment, Microglia, and Adult Neurogenesis." ACS Chem Neurosci. 2016 Apr 20;7(4):442-53. doi: 10.1021/acschemneuro.6b00009. Epub 2016 Mar 22.

Lifestyle modulates brain function. Diet, stress levels, and physical exercise among other factors influence the "brain cognitive reserve", that is, the capacity of the brain to maintain a normal function when confronting neurodegenerative diseases, injury, and/or aging. This cognitive reserve relays on several cellular and molecular elements that contribute to brain plasticity allowing adaptive responses to cognitive demands, and one of its key components is the hippocampal neurogenic reserve. Hippocampal neural stem cells give rise to new neurons that integrate into the local circuitry and contribute to hippocampal functions such as memory and learning. Importantly, adult hippocampal neurogenesis is well-known to be modulated by the demands of the environment and lifestyle factors. Diet, stress, and physical exercise directly act on neural stem cells and/or their progeny, but, in addition, they may also indirectly affect neurogenesis by acting on microglia. Microglia, the guardians of the brain, rapidly sense changes in the brain milieu, and it has been recently shown that their function is affected by lifestyle factors. However, few studies have analyzed the modulatory effect of microglia on adult neurogenesis in these conditions. Here, we review the current

knowledge about the dialogue maintained between microglia and the hippocampal neurogenic cascade. Understanding how the communication between microglia and hippocampal neurogenesis is affected by lifestyle choices is crucial to maintain the brain cognitive reserve and prevent the maladaptive responses that emerge during disease or injury through adulthood and aging.

Vartak-Sharma, N., S. Nooka, et al. "Astrocyte Elevated Gene-1 (AEG-1) and the A(E)Ging HIV/AIDS-HAND." Prog Neurobiol. 2016 Apr 14. pii: S0301-0082(15)30091-5. doi: 10.1016/j.pneurobio.2016.03.006.

Recent attempts to analyze human immunodeficiency virus (HIV)-1-induced gene expression changes in astrocytes uncovered a multifunctional oncogene, astrocyte elevated gene-1 (AEG-1). Our previous studies revealed that AEG-1 regulates reactive astrocytes proliferation, migration and inflammation, all hallmarks of aging and CNS injury. Moreover, the involvement of AEG-1 in neurodegenerative disorders, such as Huntington's disease and migraine, and its induction in the aged brain suggest a plausible role in regulating overall CNS homeostasis and aging. Therefore, it is important to investigate AEG-1 specifically in aging-associated cognitive decline. In this study, we decipher the common mechanistic links in cancer, aging and HIV-1-associated neurocognitive disorders that likely contribute to AEG-1-based regulation of astrocyte responses and function. Despite AEG-1 incorporation into HIV-1 virions and its induction by HIV-1, tumor necrosis factor-alpha and interleukin-1beta, the specific role(s) of AEG-1 in astrocyte-driven HIV-1 neuropathogenesis are incompletely defined. We propose that AEG-1 plays a central role in a multitude of cellular stress responses involving mitochondria, endoplasmic reticulum and the nucleolus. It is thus important to further investigate AEG-1-based cellular and molecular regulation in order to successfully develop better therapeutic approaches that target AEG-1 to combat cancer, HIV-1 and aging.

Vida, A., O. Abdul-Rahman, et al. "Poly(ADP-ribose) polymerases in aging - friend or foe?" Curr Protein Pept Sci. 2016 Apr 19.

Poly(ADP-ribose) polymerases were originally described as DNA repair enzymes. PARP-1, PARP-2 and PARP-3 can be activated by DNA damage and the resulting activation of these enzymes that facilitate DNA repair, is a prerequisite of successful aging. PARP activation helps to maintain genomic integrity through supporting DNA repair systems; however, in parallel these enzymes limit metabolic fitness and make the organism more prone for metabolic diseases. In addition, several other pathways (e.g., proteostasis, nutrient sensing, stem cell proliferation or cellular communication) all contributing to aging, were shown to be PARP mediated. In this review we aim to summarize our current knowledge on the role of PARPs in aging.

Vidak, S. and R. Foisner "Molecular insights into the premature aging disease progeria." Histochem Cell Biol. 2016 Apr;145(4):401-17. doi: 10.1007/s00418-016-1411-1. Epub 2016 Feb 4.

Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare premature aging disease presenting many features resembling the normal aging process. HGPS patients die before the age of 20 years due to cardiovascular problems and heart failure. HGPS is linked to mutations in the LMNA gene encoding the intermediate filament protein lamin A. Lamin A is a major component of the nuclear lamina, a scaffold structure at the nuclear envelope that defines mechanochemical properties of the nucleus and is involved in chromatin organization and epigenetic regulation. Lamin A is also present in the nuclear interior where it fulfills lamina-independent functions in cell signaling and gene regulation. The most common LMNA mutation linked to HGPS leads to mis-splicing of the LMNA mRNA and produces a mutant lamin A protein called progerin that tightly associates with the inner nuclear membrane and affects the dynamic properties of lamins. Progerin expression impairs many important cellular processes providing insight into potential disease mechanisms. These include changes in mechanosignaling, altered chromatin organization and impaired genome stability, and changes in signaling pathways, leading to impaired regulation of adult stem cells, defective extracellular matrix production and premature cell senescence. In this review, we discuss these pathways and their potential contribution to the disease pathologies as well as therapeutic approaches used in preclinical and clinical tests.

Vincent-Fabert, C., N. Platet, et al. "PLZF mutation alters mouse hematopoietic stem cell function and cell cycle progression." Blood. 2016 Apr 14;127(15):1881-5. doi: 10.1182/blood-2015-09-666974. Epub 2016 Mar 3.

Hematopoietic stem cells (HSCs) give rise to all blood populations due to their long-term self-renewal and multipotent differentiation capacities. Because they have to persist throughout an organism's life span, HSCs tightly regulate the balance between proliferation and quiescence. Here, we investigated the role of the transcription factor promyelocytic leukemia zinc finger (plzf) in HSC fate using the Zbtb16(lu/lu)mouse model, which harbors a natural

spontaneous mutation that inactivates plzf. Regenerative stress revealed that Zbtb16(lu/lu)HSCs had a lineage-skewing potential from lymphopoiesis toward myelopoiesis, an increase in the long-term-HSC pool, and a decreased repopulation potential. Furthermore, oldplzf-mutant HSCs present an amplified aging phenotype, suggesting that plzf controls age-related pathway. We found that Zbtb16(lu/lu)HSCs harbor a transcriptional signature associated with a loss of stemness and cell cycle deregulation. Lastly, cell cycle analyses revealed an important role for plzf in the regulation of the G1-S transition of HSCs. Our study reveals a new role for plzf in regulating HSC function that is linked to cell cycle regulation, and positions plzf as a key player in controlling HSC homeostasis.

Vo, N. V., R. A. Hartman, et al. "Molecular mechanisms of biological aging in intervertebral discs." J Orthop Res. 2016 Feb 17. doi: 10.1002/jor.23195.

Advanced age is the greatest risk factor for the majority of human ailments, including spine-related chronic disability and back pain, which stem from age-associated intervertebral disc degeneration (IDD). Given the rapid global rise in the aging population, understanding the biology of intervertebral disc aging in order to develop effective therapeutic interventions to combat the adverse effects of aging on disc health is now imperative. Fortunately, recent advances in aging research have begun to shed light on the basic biological process of aging. Here we review some of these insights and organize the complex process of disc aging into three different phases to guide research efforts to understand the biology of disc aging. The objective of this review is to provide an overview of the current knowledge and the recent progress made to elucidate specific molecular mechanisms underlying disc aging. In particular, studies over the last few years have uncovered cellular senescence and genomic instability as important drivers of disc aging. Supporting evidence comes from DNA repair-deficient animal models that show increased disc cellular senescence and accelerated disc aging. Additionally, stress-induced senescent cells have now been well documented to secrete catabolic factors, which can negatively impact the physiology of neighboring cells and ECM. These along with other molecular drivers of aging are reviewed in depth to shed crucial insights into the underlying mechanisms of age-related disc degeneration. We also highlight molecular targets for novel therapies and emerging candidate therapeutics that may mitigate age-associated IDD. This article is protected by copyright. All rights reserved.

Walker, R. G., T. Poggioli, et al. "Biochemistry and Biology of GDF11 and Myostatin: Similarities, Differences, and Questions for Future Investigation." Circ Res. 2016 Apr 1;118(7):1125-42. doi: 10.1161/CIRCRESAHA.116.308391.

Growth differentiation factor 11 (GDF11) and myostatin (or GDF8) are closely related members of the transforming growth factor beta superfamily and are often perceived to serve similar or overlapping roles. Yet, despite commonalities in protein sequence, receptor utilization and signaling, accumulating evidence suggests that these 2 ligands can have distinct functions in many situations. GDF11 is essential for mammalian development and has been suggested to regulate aging of multiple tissues, whereas myostatin is a well-described negative regulator of postnatal skeletal and cardiac muscle mass and modulates metabolic processes. In this review, we discuss the biochemical regulation of GDF11 and myostatin and their functions in the heart, skeletal muscle, and brain. We also highlight recent clinical findings with respect to a potential role for GDF11 and/or myostatin in humans with heart disease. Finally, we address key outstanding questions related to GDF11 and myostatin dynamics and signaling during development, growth, and aging.

Weidner, C. I., Q. Lin, et al. "DNA methylation in PRDM8 is indicative for dyskeratosis congenita." Oncotarget. 2016 Feb 17. doi: 10.18632/oncotarget.7458.

Dyskeratosis congenita (DKC) is associated with impaired telomere maintenance and with clinical features of premature aging. In this study, we analysed global DNA methylation (DNAm) profiles of DKC patients. Age-associated DNAm changes were not generally accelerated in DKC, but there were significant differences to DNAm patterns of healthy controls, particularly in CpG sites related to an internal promoter region of PR domain containing 8 (PRDM8). Notably, the same genomic region was also hypermethylated in aplastic anemia (AA) - another bone marrow failure syndrome. Site-specific analysis of DNAm level in PRDM8 with pyrosequencing and MassARRAY validated aberrant hypermethylation in 11 DKC patients and 27 AA patients. Telomere length, measured by flow-FISH, did not directly correlate with DNAm in PRDM8. Therefore the two methods may be complementary to also identify patients with still normal telomere length. In conclusion, blood of DKC patients reveals aberrant DNAm patterns, albeit age-associated DNAm patterns are not generally accelerated. Aberrant hypermethylation is particularly observed in PRDM8 and this may support identification and classification of bone marrow failure syndromes.

Wenderski, W. and I. Maze "Histone turnover and chromatin accessibility: Critical mediators of neurological development, plasticity, and disease." Bioessays. 2016 May;38(5):410-9. doi: 10.1002/bies.201500171. Epub 2016 Mar 15.

In postmitotic neurons, nucleosomal turnover was long considered to be a static process that is inconsequential to transcription. However, our recent studies in human and rodent brain indicate that replication-independent (RI) nucleosomal turnover, which requires the histone variant H3.3, is dynamic throughout life and is necessary for activity-dependent gene expression, synaptic connectivity, and cognition. H3.3 turnover also facilitates cellular lineage specification and plays a role in suppressing the expression of heterochromatic repetitive elements, including mutagenic transposable sequences, in mouse embryonic stem cells. In this essay, we review mechanisms and functions for RI nucleosomal turnover in brain and present the hypothesis that defects in histone dynamics may represent a common mechanism underlying neurological aging and disease.

West, M. D., F. Binette, et al. "The germline/soma dichotomy: implications for aging and degenerative disease." Regen Med. 2016 Apr;11(3):331-4. doi: 10.2217/rme-2015-0033. Epub 2016 Mar 24.

Human somatic cells are mortal due in large part to telomere shortening associated with cell division. Limited proliferative capacity may, in turn, limit response to injury and may play an important role in the etiology of age-related pathology. Pluripotent stem cells cultured in vitro appear to maintain long telomere length through relatively high levels of telomerase activity. We propose that the induced reversal of cell aging by transcriptional reprogramming, or alternatively, human embryonic stem cells engineered to escape immune surveillance, are effective platforms for the industrial-scale manufacture of young cells for the treatment of age-related pathologies. Such cell-based regenerative therapies will require newer manufacturing and delivery technologies to insure highly pure, identified and potent pluripotency-based therapeutic formulations.

Westenskow, P. D., F. Bucher, et al. "iPSC-Derived Retinal Pigment Epithelium Allografts Do Not Elicit Detrimental Effects in Rats: A Follow-Up Study." Stem Cells Int. 2016;2016:8470263. doi: 10.1155/2016/8470263. Epub 2016 Jan 5.

Phototransduction is accomplished in the retina by photoreceptor neurons and retinal pigment epithelium (RPE) cells. Photoreceptors rely heavily on the RPE, and death or dysfunction of RPE is characteristic of age-related macular degeneration (AMD), a very common neurodegenerative disease for which no cure exists. RPE replacement is a promising therapeutic intervention for AMD, and large numbers of RPE cells can be generated from pluripotent stem cells. However, questions persist regarding iPSC-derived RPE (iPS-RPE) viability, immunogenicity, and tumorigenesis potential. We showed previously that iPS-RPE prevent photoreceptor atrophy in dystrophic rats up until 24 weeks after implantation. In this follow-up study, we longitudinally monitored the same implanted iPS-RPE, in the same animals. We observed no gross abnormalities in the eyes, livers, spleens, brains, and blood in aging rats with iPSC-RPE grafts. iPS-RPE cells that integrated into the subretinal space outlived the photoreceptors and survived for as long as 2 1/2 years while nonintegrating RPE cells were ingested by host macrophages. Both populations could be distinguished using immunohistochemistry and electron microscopy. iPSC-RPE could be isolated from the grafts and maintained in culture; these cells also phagocytosed isolated photoreceptor outer segments. We conclude that iPS-RPE grafts remain viable and do not induce any obvious associated pathological changes.

Whittam, A. J., Z. N. Maan, et al. "Challenges and Opportunities in Drug Delivery for Wound Healing." Adv Wound Care (New Rochelle). 2016 Feb 1;5(2):79-88.

Significance: Chronic wounds remain a significant public health problem. Alterations in normal physiological processes caused by aging or diabetes lead to impaired tissue repair and the development of chronic and nonhealing wounds. Understanding the unique features of the wound environment will be required to develop new therapeutics that impact these disabling conditions. New drug-delivery systems (DDSs) may enhance current and future therapies for this challenging clinical problem. Recent Advances: Historically, physical barriers and biological degradation limited the efficacy of DDSs in wound healing. In aiming at improving and optimizing drug delivery, recent data suggest that combinations of delivery mechanisms, such as hydrogels, small molecules, RNA interference (RNAi), as well as growth factor and stem cell-based therapies (biologics), could offer exciting new opportunities for improving tissue repair. Critical Issues: The lack of effective therapeutic approaches to combat the significant disability associated with chronic wounds has become an area of increasing clinical concern. However, the unique challenges of the wound environment have limited the development of effective therapeutic options for clinical use. Future

Directions: New platforms presented in this review may provide clinicians and scientists with an improved understanding of the alternatives for drug delivery in wound care, which may facilitate the development of new therapeutic approaches for patients.

Wong, T. Y., Y. H. Chen, et al. "Differential Proteomic Analysis of Human Placenta-Derived Mesenchymal Stem Cells Cultured on Normal Tissue Culture Surface and Hyaluronan-Coated Surface." Stem Cells Int. 2016;2016:2809192. doi: 10.1155/2016/2809192. Epub 2015 Dec 29.

Our previous results showed that hyaluronan (HA) preserved human placenta-derived mesenchymal stem cells (PDMSC) in a slow cell cycling mode similar to quiescence, the pristine state of stem cells in vivo, and HA was found to prevent murine adipose-derived mesenchymal stem cells from senescence. Here, stable isotope labeling by amino acid in cell culture (SILAC) proteomic profiling was used to evaluate the effects of HA on aging phenomenon in stem cells, comparing (1) old and young passage PDMSC cultured on normal tissue culture surface (TCS); (2) old passage on HA-coated surface (CHA) compared to TCS; (3) old and young passage on CHA. The results indicated that senescence-associated protein transgelin (TAGLN) was upregulated in old TCS. Protein CYR61, reportedly senescence-related, was downregulated in old CHA compared to old TCS. The SIRT1-interacting Nicotinamide phosphoribosyltransferase (NAMPT) increased by 2.23-fold in old CHA compared to old TCS, and is 0.48-fold lower in old TCS compared to young TCS. Results also indicated that components of endoplasmic reticulum associated degradation (ERAD) pathway were upregulated in old CHA compared to old TCS cells, potentially for overcoming stress to maintain cell function and suppress senescence. Our data points to pathways that may be targeted by HA to maintain stem cells youth.

Wruck, W., F. Schroter, et al. "Meta-Analysis of Transcriptome Data Related to Hippocampus Biopsies and iPSC-Derived Neuronal Cells from Alzheimer's Disease Patients Reveals an Association with FOXA1 and FOXA2 Gene Regulatory Networks." J Alzheimers Dis. 2016 Feb 5;50(4):1065-82. doi: 10.3233/JAD-150733.

Although the incidence of Alzheimer's disease (AD) is continuously increasing in the aging population worldwide, effective therapies are not available. The interplay between causative genetic and environmental factors is partially understood. Meta-analyses have been performed on aspects such as polymorphisms, cytokines, and cognitive training. Here, we propose a meta-analysis approach based on hierarchical clustering analysis of a reliable training set of hippocampus biopsies, which is condensed to a gene expression signature. This gene expression signature was applied to various test sets of brain biopsies and iPSC-derived neuronal cell models to demonstrate its ability to distinguish AD samples from control. Thus, our identified AD-gene signature may form the basis for determination of biomarkers that are urgently needed to overcome current diagnostic shortfalls. Intriguingly, the well-described AD-related genes APP and APOE are not within the signature because their gene expression profiles show a lower correlation to the disease phenotype than genes from the signature. This is in line with the differing characteristics of the disease as early-/late-onset or with/without genetic predisposition. To investigate the gene signature's systemic role(s), signaling pathways, gene ontologies, and transcription factors were analyzed which revealed over-representation of response to stress, regulation of cellular metabolic processes, and reactive oxygen species. Additionally, our results clearly point to an important role of FOXA1 and FOXA2 gene regulatory networks in the etiology of AD. This finding is in corroboration with the recently reported major role of the dopaminergic system in the development of AD and its regulation by FOXA1 and FOXA2.

Yagihashi, S., W. Inaba, et al. "Dynamic pathology of islet endocrine cells in type 2 diabetes: beta-Cell growth, death, regeneration and their clinical implications." J Diabetes Investig. 2016 Mar;7(2):155-65. doi: 10.1111/jdi.12424. Epub 2015 Oct 15.

Diabetes is defined as a disease of hyperglycemic metabolic disorder caused by impaired insulin action or low insulin secretion, resulting in the occurrence of vascular complications. Based on this definition, diabetes therapy has long been oriented to correct hyperglycemia against the specific complications of diabetes. This definition has posed some difficulties, however, in understanding of the pathophysiology of this complicated disease and as such in the establishment of an effective treatment. With continuing efforts to explore the structural basis for diabetes onset and methodological development of immunohistochemistry, progressive decline of beta-cells is now established as a salient feature of type 2 diabetes. Accordingly, diabetes therapy has now turned out to protect beta-cells concurrently with the correction of hyperglycemia. Together with this effort, exploration of the means to regenerate beta-cells or to supply new beta-cells by, for example, induced pluripotential stem cells, are vigorously made with the search for the mechanism of beta-cell decline in diabetes. In the present review, we describe the

advances in the islet pathology in type 2 diabetes with special reference to the dynamic alterations of islet endocrine cells in the milieu of maturation, obesity, aging and ethnic differences. The effect of amyloid deposition is also discussed. We hope it will help with understanding the pathophysiology of diabetes, and suggest the future direction of diabetes treatment.

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

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