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Current Opinion in Cell Biology

Interaction between epigenetic and metabolism in aging stem cells

Anne Brunet[1,3] and Thomas A Rando[2,3,4]

Aging is accompanied by a decline in tissue function, regeneration, and repair. A large part of this decline is caused by the deterioration of tissue stem cell function. Understanding the mechanisms that drive stem cell aging and how to counteract them is a critical step for enhancing tissue repair and maintenance during aging. Emerging evidence indicates that epigenetic modifiers and metabolism regulators interact to impact lifespan, suggesting that this mechanism may also affect stem cell function with age. This review focuses on the interaction between chromatin and metabolism in the regulation of tissue stem cells during aging. We also discuss how these mechanisms integrate environmental stimuli such as nutrient stress to regulate stem cell function. Finally, this review examines new perspectives for regeneration, rejuvenation, and treatment of age-related decline of stem cell function.

Addresses
[1] Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA
[2] Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA
[3] Glenn Center for the Biology of Aging, Stanford University, USA
[4] Center for Tissue Regeneration, Repair and Restoration, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Corresponding author: Brunet, Anne (anne.brunet@stanford.edu)

Current Opinion in Cell Biology 2017, **45**:1–7

This review comes from a themed issue on **Cell regulation**

Edited by **Davide Ruggero** and **Reuben Shaw**

For a complete overview see the Issue and the Editorial

Available online 24th January 2017

http://dx.doi.org/10.1016/j.ceb.2016.12.009

Tissue-specific stem cells are present in virtually every adult tissue in mammals and are essential for tissue homeostasis and repair after injury (Box 1). The striking decline in stem cell function during aging, coupled with a bias in the type of differentiated cells they generate, could drive the deterioration in tissue function and diminished capacity for tissue repair in older individuals [1]. Stem cell function is regulated in response to exposure of individuals to a variety of external stimuli, including nutrient stress (*e.g.*, starvation or caloric restriction, or high fat diets). Knowledge of the mechanisms by which stem cells integrate signals from the environment will be critical to identify strategies to preserve or reactivate their function in old age.

Understanding the interaction between cellular metabolism and chromatin features in stem cells is confounded by the complexity of stem cell fates compared to many other somatic cells. Stem cells, by their very nature, give rise to progeny that are vastly different in terms of virtually every biological parameter. For example, quiescent stem cells exhibit minimal metabolic activity, have few mitochondria and other organelles, and have a minuscule cytoplasmic volume. In contrast, proliferating progeny manifest dramatic energetic shifts, increases in biosynthetic activity, and cell growth. As these progeny differentiate into mature, tissue-specific cells, there are again dramatic structural and functional changes. The dynamic interaction between cellular metabolism and the epigenome is emerging as pivotal to the control of stem cell transitions and function (Figure 1). This review will discuss recent work connecting metabolism and chromatin regulators in mammalian tissue-specific stem cells, focusing primarily on mechanisms that are relevant to the process of aging and that could be used to restore function to old stem cells.

Interaction between epigenetic and metabolic pathways in organismal aging

The importance of epigenetic mechanisms in controlling aging has been extensively reviewed [2–5]. In this section, we will present recent studies that have uncovered intriguing connections between key chromatin regulators and metabolic pathways in the regulation of lifespan in yeast, worms, and flies. These studies help illustrate the importance of the interactions between chromatin and metabolism in the regulation of processes that may be important in cell and tissue aging. For example, deletion of the chromatin remodeler SWI/SNF (ISW2) extends replicative lifespan in yeast, in a manner that mimics caloric restriction [6]. Consistent with these findings, genome-wide analysis indicates that in ISW2-deficient yeast, changes in nucleosome positioning partially replicate those of calorie-restricted cells [6]. As nucleosome positioning is critical for gene expression regulation, these results suggest that a common mechanism, regulated by both chromatin remodelers and caloric restriction, impacts many target genes in a coordinated manner. Chromatin remodelers of the SWI/SNF family also play a key role in modulating lifespan in *Caenorhabditis elegans* [6,7], notably in partnership with FOXO/DAF-16

Box 1 Adult stem cells.

In many stem cell compartments, the lineage consists of a quiescent stem cell that can activate (proliferate) and generate more committed progenitors and differentiated progeny [66]. Adult stem cells can be unipotent (*i.e.*, generate one differentiated cell type) or multipotent (*i.e.*, generate several differentiated cell types). For example, muscle stem cells (MuSCs) are unipotent and give rise to one cell type—muscle fibers. In contrast, hematopoietic stem cells (HSCs) and neural stem cells (NSCs) are multipotent and can give rise to several types of differentiated cells (NCS, *e.g.*, give rise to neurons, astrocytes and oligodendrocytes). Some stem cells are very important for tissue homeostasis (HSCs, intestinal stem cells [ISCs]). Other stem cells are activated in response to injury (MuSCs and to a lesser extent NSCs), although they can also contribute to some aspect of homeostasis (NSCs).

During aging, two key aspects of stem cell function are primarily affected in multiple stem cell lineages: the transition from quiescent stem cells to activated stem cells and the bias in generated differentiated cell types. For example, HSCs exhibit a myeloid bias during aging whereas NSCs exhibit an astrocytic bias. Single cells studies have recently revealed additional cellular transitions in stem cell lineages, and such transitions could also be affected during aging [67–69].

Stem cells are present within complex 'niches' that are often in tight connection with blood vessels, thereby providing an interface with the systemic environment and factors in the blood (metabolites, hormones, growth factors, *etc.*) [70,71]. In the brain, neural stem cells are also in contact with the cerebral spinal fluid [72], providing an additional source for external stimuli, such as metabolites.

transcription factor downstream of the insulin-signaling pathway [7]. Furthermore, changes in global chromatin structure were observed in conditions (mitochondrial deficiency) that extend lifespan in *C. elegans* [8]. These studies in yeast and worms, coupled with the observed changes in nucleosome positioning during aging in mouse tissues [9], highlight the importance of chromatin structure and nucleosome positioning in integrating metabolic changes to regulate lifespan [10].

In addition to chromatin remodelers, several histone modifiers, including Sirtuin deacetylases, have been shown to link metabolic state to organismal lifespan regulation [11]. Recently, in *Drosophila*, key metabolites including acetylCoA were found to be increased during aging. This increase is accompanied by an increase in global histone acetylation, notably acetylated lysine 12 on histone H4 (H4K12ac). Consistent with these observations, mutation in the H4K12 acetyltransferase *Chameau* extends the lifespan of male flies [12•]. Histone methylation regulators, including H3K4me3, H3K36me3, and H3K27me3 regulators, have also been found to regulate lifespan in *C. elegans* [13–17]. Interestingly, the conserved H3K27me3 demethylase Jmjd-3.1/JMJD3 and the H3K27me2 demethylase Jmjd-1.2/PHF8 were recently found to specifically mediate longevity caused by mitochondrial deficiency in *C. elegans* [18••]. Mitochondrial deficiency triggers the specific upregulation of nuclear-encoded genes involved in the response to mitochondrial unfolded protein response [18••]; this could mediate long-lasting transcriptional responses in response to deficit in mitochondrial function. In mammals, PHF8 and JMJD3 expression is correlated with the longevity of outbred mice [18••]. Thus, histone modifiers that are responsive to cellular metabolic state are key determinants of organismal longevity.

These recent examples highlight the interaction between chromatin state and cellular metabolism in influencing longevity, at least in model organisms. The interrelated processes of chromatin regulation and metabolism are increasingly being studied in the areas of stem cell aging and general stem cell biology in mammals. In the following sections, we discuss recent findings that reveal key epigenetic changes that are associated with stem cell aging and that, in some cases, reflect the potential impact of cellular metabolism on the epigenetic state.

Epigenetics and stem cell aging

Epigenetic changes associated with somatic stem cell aging have been reported for multiple stem cell populations, notably hematopoietic stem cells (HSCs) and muscle stem cells (MuSCs)/satellite cells [19,20]. In both HSCs and MuSCs, there is an age-dependent increase in the repressive histone modification H3K27me3, whereas H3K4me3, a mark associated with active genes, shows increase in breadth in HSCs but decreases slightly in intensity in quiescent MuSCs with age. In each case, the increase in H3K27me3 is associated with a down-regulation of a limited number of genes associated with stem cell function. These results are interesting in light of the recent finding that the H3K27me3 demethylase UTX is important for MuSC-mediated muscle regeneration [21]. However, the specific effects of these chromatin changes on stem cell function remain to be tested, particularly given that different regulators of the same H3K27me3 mark (*e.g.*, the H3K27me3 demethylases UTX and JMJD3) can either extend or shorten lifespan in model organisms [14,18••,22].

Changes in a number of other chromatin features, most of which are also altered with age, have been shown to regulate stem cell function [23]. For example, changes in DNA methylation affect the differentiation potential of HSCs [24,25]. Furthermore, H3K9 methylation, a mediator of heterochromatin formation, is important for HSC differentiation [26]. H4K20 methylation controls MuSC quiescence by promoting the formation of facultative heterochromatin [27•]. Finally, exceptionally broad H3K4me3 domains form a signature for cell function/identity, and these extended domains mark genes that are critical for the ability of neural stem cells (NSCs) to self-renew and to differentiate into neurons [28]. How these different epigenetic marks are affected in aging stem cells is not yet known. It will be important to develop methods to modify the epigenetic state of specific genetic loci to