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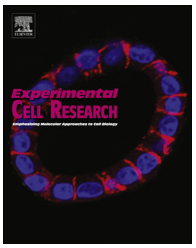

Review Article

Epigenetic regulation of hematopoietic stem cell aging

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ABSTRACT

Aging is invariably associated with alterations of the hematopoietic stem cell (HSC) compartment, including loss of functional capacity, altered clonal composition, and changes in lineage contribution. Although accumulation of DNA damage occurs during HSC aging, it is unlikely such consistent aging phenotypes could be solely attributed to changes in DNA integrity. Another mechanism by which heritable traits could contribute to the changes in the functional potential of aged HSCs is through alterations in the epigenetic landscape of adult stem cells. Indeed, recent studies on hematopoietic stem cells have suggested that altered epigenetic profiles are associated with HSC aging and play a key role in modulating the functional potential of HSCs at different stages during ontogeny. Even small changes of the epigenetic landscape can lead to robustly altered expression patterns, either directly by loss of regulatory control or through indirect, additive effects, ultimately leading to transcriptional changes of the stem cells. Potential drivers of such changes in the epigenetic landscape of aged HSCs include proliferative history, DNA damage, and deregulation of key epigenetic enzymes and complexes. This review will focus largely on the two most characterized epigenetic marks – DNA methylation and histone modifications – but will also discuss the potential role of non-coding RNAs in regulating HSC function during aging.

Contents

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Introduction

In the hematopoietic system, aging is associated with diminished lymphoid potential, increased auto-immunity, and elevated prevalence of hematological malignancies. Many studies have provided insight into functional changes in the hematopoietic stem cell (HSC) compartment that contribute to age-associated decline. Differences include alterations of lineage-biased clonal composition [1–5], cell polarity changes [6], increased inflammatory response [7], elevated levels of ROS [8], and accrual of DNA damage [9–13]. Robust and reproducible differences in the expression of many genes have been observed in aged compared to young HSCs [7,14–16], suggesting that age-associated differences in transcriptional regulation, potentially via alterations in the epigenetic landscape, may underlie the functional changes associated with HSC aging.

The definition of epigenetic regulation has evolved since it was coined by Waddington [17] and while it is still used to describe how a phenotype is achieved from a genotype, it now broadly encompasses all heritable changes in gene expression that are not due to changes in DNA sequence [18,19]. Epigenetic modifications allow for every cell in the body to share the same genetic code, yet generate the vast cellular diversity found throughout the body and during development from the embryonic state through adulthood. The two most commonly discussed epigenetic marks are DNA methylation and histone modifications, as these are modifications that affect the structure and accessibility of the DNA, directly impacting the transcriptional state of genetic loci. Non-coding RNA and their effects on gene expression are increasingly being considered to fall within the spectrum of epigenetic regulators given their interactions with both histone modifiers and DNA methyl-transferases. This review will focus largely on the two most characterized epigenetic marks – DNA methylation and histone modifications – but will also discuss the potential role of non-coding RNAs in regulating HSC function during aging.

DNA methylation

DNA methylation patterns, typically methylated CpGs, are established during early development and DNA methyltransferase enzymes (Dnmt's) are responsible for both the establishment and maintenance of these modifications throughout life. *Dnmt1* is largely responsible for DNA methylation maintenance, while *Dnmt3a* and *Dnmt3b* are *de novo* methyltransferases. These methylases are critical for development, and mice with targeted deficiencies of any of these genes are non-viable [20,21]. To evaluate their role in hematopoiesis, mice with conditional knockouts of these genes have been generated and demonstrate the importance of DNA methylation in the HSC compartment. Specifically, loss of *Dnmt1* in HSCs leads to dysregulation of lineage output, with a skewing towards myelopoiesis, and defects in self-renewal [22,23] while a conditional knockout of *Dnmt3a* alone drives a loss in differentiation potential after serial transplant [24], and loss of both *Dnmt3a* and *Dnmt3b* in HSCs leads to an even more severe arrest of HSC differentiation [25]. The genes regulating active DNA demethylation, the ten-eleven translocation (Tet) family enzymes, are also important for HSC function. Loss of expression of *Tet2* in HSCs leads to an increased primitive compartment, encompassing both stem and progenitor cells, suggesting that HSCs deficient in *Tet2* have a competitive advantage [26–28]. Interestingly, Dnmt family members and *Tet2* have been shown to be differentially expressed in aged compared to young HSCs [15,16] and mice with null alleles of several of these genes share some of the phenotypes associated with aged HSCs including myeloid skewing [27] and predisposition to cancer [27,28].

To address if aged HSCs have altered methylation patterns that contribute to changes in their functional potential, recent publications have looked at DNA methylation profiles in fetal, young and old murine HSCs [15,16,29] and in human progenitor cells [30]. These studies have shown locus specific differences in DNA methylation profiles associated with aging of the HSC compartment, with some regions gaining methylation whereas other regions become more hypomethylated [15,16]. Interestingly, hypermethylated regions are enriched for targets of the Polycomb Repressive Complex 2 (PRC2), which establish the repressive H3K27me3 histone modification [15,16,29], suggesting an interplay between these two epigenetic marks. The relationship between H3K27me3 and DNA methylation is complex, with several studies showing that increased DNA methylation prevents PRC2 interaction with chromatin in CpG-rich regions, implicating an antagonistic relationship between H3K27me3 and DNA methylation [31–34]; however, in CpG sparce regions this antagonism is not seen as both H3K27me3 and DNA methylation are found at CpG poor regions of the genome [34]. Furthermore, global loss of DNA methylation leads to deficiencies of H3K27me3 at certain regions [34,35] suggesting the importance of DNA methylation in ensuring proper localization of histone modifications. Examination of how histone modifications (explicitly H3K27me3) influences DNA methylation patterns is less characterized, but again there appears to be a complex interaction in which PRC2 components are necessary to ensure appropriate DNA methylation during development [31,36] since loss of H3K27me3 leads to both increases and decreases in DNA methylation at different genomic regions [31]. In HSCs, the age-associated diminution of expression of PRC2 core components *Ezh2*, *Eed* and *Suz12* correspond with increased DNA methylation at targets of the complex. Though speculative, this observation suggests that loss of repression by PRC2 binding at selected targets allows these regions to become accessible to de-novo DNA methylation associated with HSC aging [15,16].

Interestingly, whereas increased DNA methylation is generally regarded as a repressive mark associated with diminished gene expression, this correlation is generally not observed during HSC aging. While there are some exceptions, most regions that either gain or lose DNA methylation during HSC aging are not associated with altered gene expression [15,16]. This raises the possibility that differential DNA methylation may not directly impact expression of genes in stem cell compartments, but instead may have heritable and possibly detrimental effects on the progeny of the stem cells. Indeed, within the blood and skin, it has been demonstrated that DNA methylation is tightly coordinated during differentiation from stem cells to the effector cells [37], and thus

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