Evolutionary Significance of Epigenetic Mechanisms in Red Blood Cells and Implications in Carcinogenesis

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Abstract

Mechanisms that control the epigenome of organisms, such as DNA methylation and non-coding RNAs, consequently modulate the expression of certain genes. Evolutionary development in red blood cells stems from these modifications in the epigenetics of the cell that are integral in the functional adaptation and specialization of the cells. The incorporation of histone modifications and noncoding RNAs, in addition to the utilization of DNA methylation and acetylation, allocates adaptation in gene expression in response to environmental conditions without changes to genetic code. Particularly in hematologic malignancies, oncogenesis results from the dysregulation of epigenetic alterations. Therefore, potential new therapeutic targets, including DNA methyltransferase inhibitors, histone deacetylase inhibitors, and BET inhibitors, offer potential strategies to treat hematological malignancies with greater efficacy.

Introduction

Epigenetics is a more recently emerging field that encompasses a range of alterations to gene expression without modifications to the DNA sequence that result in heritable changes. This regulation of gene expression is facilitated by mechanisms that include DNA methylation and the usage of macromolecules like noncoding RNAs. The specialization of RBCs in vertebrates is shaped by epigenetic modifications, which lead to the differentiation and functional adaptation of the RBCs. However, because histone modifications and aberrant methylation patterns can result in tumor initiation and progression, dysregulation of the epigenome can become a pathway for cancer, notably in hematological malignancies (Geissler et al.).
Epigenetic mechanisms govern the speciation of cells across species: epigenetic modification simultaneously activates erythropoietic pathways and silences genes that are not essential in vertebrates. As over time in the evolution of vertebrates, the oxygen-transporting function of red blood cells (RBCs) became increasingly vital, epigenetic modifiers modulated the expression of genes specific to the RBCs (Michel). However, oncogenes could be activated or tumor suppressor genes could be silenced if these pathways were to be dysregulated. A driver of this malignant transformation is epigenetic alterations. Therefore, understanding the specific mechanisms that resulted from RBC evolution can open new avenues for therapeutic intervention (Key et al.).

Epigenetic Mechanisms in Red Blood Cell Evolution

A conserved epigenetic modification among vertebrate species, DNA methylation aids in the regulation of gene expression; this includes the function and development of red blood cells (RBCs). By governing the process by which progenitor cells differentiate into mature red blood cells through erythropoiesis, DNA methylation modulates the growth of RBCs (H. Li). The association of reduced ABO gene expression with the hypermethylation of the ABO gene promoted in malignant cells was underscored by recent studies to show the implications DNA methylation has on surface proteins in red blood cells: the prior suppression of ABO genes reduces the concentration of A and B antigens on the RBC surface and affects the blood compatibility in transfusion medicine and transplantation practices (K. Ogasawara et al.).

Known for their role in regulating the methylation status of their promoter regions, GATA-1 and RUNX1—erythroid-specific transcription factors—can be altered for methylation as well. Promoting and inhibiting the binding of such transcription patterns through altered methylation patterns can disrupt gene expression downstream which is essential for red blood cell development (K. Ogasawara et al.). Moreover, the loss of regulators that control oxidative stress responses, like NRF2, was seen in a study that employed transgenic mouse models to demonstrate DNA hydroxymethylation and disrupted gene expression of erythropoietic genes

(X. Zhu et al.). This highlights the role DNA methylation plays during erythropoiesis in the maintenance of the patterns of gene activation and gene silencing.

While DNA methylation is indeed a conserved trait, comparative studies have demonstrated that the patterns associated with the process differ among vertebrate species. However, methylation marks that correlate with the development of RBCs remain conserved. This adds further evidence to suggest that across diverse vertebrate lineages, methylation holds a fundamental role. Similarly, in vitro models from studies showed that manipulation of DNA methylation via histone deacetylase inhibitors (HDACIs) was observed to alter the expression of genes, including ABO, in cell lines to support the notion that modulation of RBC gene expression can stem from epigenetic modifications (Szczepanek et al.). The ABO locus has also been associated with broader health outcomes, such as venous thrombosis and coronary artery disease, via genome-wide association studies (GWAS) (K. Ogasawara et al.). Therefore, the influence methylation has on erythropoiesis has an effect on the pathogenesis of disease.

Evolutionary Significance of Methylation in Gene Silencing and Erythropoiesis Activation

The ability for DNA methylation to simultaneously activate gene expression pathways and silence non-essential genes exemplifies its evolutionary significance: the resulting epigenetic flexibility allocates vertebrates to modulate gene expression without necessitating inherent alterations in genetic code in order to adequately adapt to variances in environmental conditions (DaSilva et al.). For instance, in hypoxic environments, hypoxia-inducible factors (HIF) can activate erythropoietic pathways when essential for survival (R. Bhattacharyaa et al.). The pathway itself is governed by a combination of DNA methylation and histone modifications to enhance oxygen-carrying capacity when organisms are living in environments with low oxygen concentrations.

In order to allow adaptive traits to be propagated down lineages with alterations in DNA sequences, methylation provides a mechanism for transgenerational inheritance (Fallet et al.). Species such as chickens display such interest through their transmission of methylation patterns to resist diseases like Marek's disease (Y. He et al.). Therefore, the epigenetic consequences of DNA methylation can also play a role in the shaping of population genetics and, over time, evolutionary trajectories.

Histone Modifications in Red Blood Cell Differentiation

Found at the promoters of genes that are actively suppressed, H3K4me3 correlates with active transcription. Notable erythroid-specific gene loci experience greater levels of H3K4me3 during erythropoiesis in order to signal the activation of these genes. For example, the increase of H3K4me3 at γ-globin gene promoters in a study that involved the β-YAC transgenic mouse

model demonstrated heightened gene expression during erythroid differentiation (X. Zhu et al.). The inclusion of NRF2 and other transcription factors further enhances the transcriptional activity necessary for optimal red blood cell development (X. Zhu et al.).
Often catalyzed by polycomb group proteins, H3K27me3 is significant in transcriptional repression. This histone modification ensures that while red blood cells are being differentiated, only vital genes are being expressed. To support this notion, any loss of H3K27me3 at erythroid gene loci led to their activation (H. Bui et al.). As a result, any genes that stem from alternative lineages are repressed. Such epigenetic changes—usually mapped by ChIP-seq—showcase the role histone modifications play in red blood cell differentiation.

The specialization of red blood cells in vertebrates—specifically, mammals and birds—is upheld by the evolution in histone modification patterns; this adaptation is associated with endothermic organisms that require metabolic support and essential gas exchange. In these species, anucleate red blood cells with a decrease in size—which are more efficient at traversing capillary networks—were linked in evolutionary changes to histone modification patterns. The observation from the transition from larger, nucleated RBCs in ectothermic ancestors to smaller RBCs in modern vertebrates showed raised levels of H3K4me3 at erythroid gene promoters that modulate hemoglobin synthesis (G. Soslau et al.). Thus, the production of hemoglobin and other specialized red blood cell components was fostered by these active histone marks promoting transcriptional activity. Furthermore, histone modifications influence chromatin structure as well; open chromatin structures that are conducive to gene depression allocate the formation of long-range enhancer-promoter interactions to express globin genes (X. Zhu et al.).

Noncoding RNAs in the Regulation of Red Blood Cell Genes

miR-144 and miR-451 are notable examples of miRNAs that regulate erythroid differentiation, as the miRNAs modulate hemoglobin synthesis and erythrocyte maturation through the patterns of expression of the mechanisms' respective genes. During erythroid differentiation, the miRNAs are upregulated, which shows their influence on red blood cell development (Joshi et al.). To further underscore the importance of miRNAs in RBC function, research showed that oxidative stress and anemia result from dysregulation of miR-144 (Y. He et al.). The downregulation can cause impaired erythropoiesis as the miR-451 targets genes that oversee the regulation of erythroid progenitor proliferation and maturation directly. Thus, miRNAs can modify protein expression through mRNA degradation or translational repression in order to further modulate red blood cell gene expression.

By interacting with complexes that alter chromatin, lncRNAs can regulate genes specific to erythroids by influencing the epigenetic landscape surrounding target genes. Changes in the activity of chromatin modifiers have been shown to stem from lncRNA HOTAIR and its involvement in erythropoiesis (M. Rossmann and L. Zon). lncRNAs act as scaffolds on the

molecular level to facilitate the transcriptional program necessary for the differentiation of RBCs by recruiting transcription factors and chromatin remodelers to specific loci (Sharma et al.); (M. Rossmann and L. Zon). This mechanism aids in the regulation after transcription for erythroid genes.

Noncoding RNAs, while achieving a similar end response, can utilize entirely different mechanisms. By binding to the 3' untranslated regions (UTRs) of target mRNAs, miRNAs undergo a pathway that leads to either mRNA degradation or the inhibition of translation (Y. He et al.). This variation of regulation emphasizes the strict control of protein synthesis in RBC development to prevent overproduction or underproduction of the erythroid proteins. Contrarily, lncRNAs employ histone-modifying enzymes to modulate gene expression at the chromatin level by targeting the erythroid gene loci to promote or repress transcription. This interaction allows them to shape the epigenetic environment so that RBC development occurs in the correct epigenetic environment (M. Rossmann and L. Zon).

DNA Methylation and Hematological Cancers

Particularly hypermethylation and hypomethylation of genes, abnormal patterns of DNA methylation can result in the pathogenesis of hematological cancers such as leukemia. Hypermethylation suppresses the transcription of tumor suppressor genes to allocate unregulated cell growth (Cai et al.): for the RUNX3 gene, its hypermethylation results in disruption in optimal blood cell movement—as RUNX3 is a regulator of hematopoiesis—and results in leukemogenesis. Therefore, the silencing of RUNX3 is important in the context of leukemia, as RUNX3 will then contribute to the progression of acute myeloid leukemia (AML) due to the prevention of differentiation of blood cells (Pasha et al., 2019).

Another notable example of cancer progression stems from the hypermethylation of the MLH1 gene—a sequence that is responsible for the repair of DNA mismatches. The resulting genomic instability from the suppression of MLH1 results in an increased risk of mutations and chromosomal aberrations (Deycmar et al.); it is also a common epigenetic occurrence in hematological cancers, with hypermethylation of MLH1 a driver for malignancy. Similarly, another gene frequently silenced by hypermethylation in blood cancers, CDKN2A, is a gene that is regulated in the cell cycle by p16^INK4a; unchecked cell proliferation can result from the loss of p16^INK4a and further promote malignancy in cells (Wang et al., 2012).

By allocating the overexpression of genes that correlate with cell survival and proliferation, hypomethylation of oncogenes can also become a significant contributor to cancer progression. Malignant transformations of hematopoietic cells in leukemia can result from the hypomethylation of oncogenes such as MYC as the oncogenes increase in concentration. Zhang et al. (2010). Likewise, the aberrant hypomethylation of other factors like ANXA2 and TET2

follow similar patterns in the progression of cancer. TET2—a gene that is tasked with DNA demethylation—in particular can be problematic as mutations in its genomic sequence can disrupt epigenetic regulation in myeloid malignancies and promote the pathogenesis of leukemogenesis (Ko et al., 2010). With the alterations of DNA methylation patterns by either silencing regulatory genes or activating tumor growth through appropriate pathways, factors that control methylation patterns can result in the malignant phenotype. Therefore, epigenetic dysregulation offers for understanding of the mechanisms of disease, as the patterns are central to the pathology of hematological malignancies (Allegra et al.).

Histone Modifications in Cancer

The dysregulation of histone modifications, including acetylation and methylation, is a notable factor in the development of malignancies in hematolytic structures. Being regulators of chromatin structure and gene expression, histone modifications are tasked with the maintenance of gene activation and repression. However, blood cancers experience the activation of oncogenes and the silencing of tumor suppressor genes (Dakal et al.); for instance, Polycomb Repressive Complex 2 (PRC2) mediates the trimethylation of histone H3 at lysine 27 (H3K27me3), which silences genes such as CDKN2A (Ito et al.). This subsequently leads to the uncontrolled proliferation of cells and the progression of conditions like leukemia.

Histone marks at oncogene promoters can be hypomethylated to activate each respective activation. This can lead to transcriptional activation and overexpression of oncogenes, as seen with hypomethylation at the MYC promoter. (Guo et al., 2019). The promotion of oncogenesis is also supported by the consequent recruitment of transcription factors and alterations in chromatin structure from changes in histone modification patterns. When these pathways are coupled via global hypomethylation, tumorigenesis is exacerbated and leads to, at times, multiple variations of hematological cancers (Kamdje et al.). If potential targeted therapies were to be developed, research into histone deacetylase inhibitors to restore normal epigenetic patterns in cancer cells would be insightful.

Noncoding RNAs and Cancer

The appearance of dysregulated noncoding RNAs (ncRNAs) is integral to the pathogenesis of hematological cancers, as these macromolecules modulate gene expression post-transcription. MicroRNAs (miRNAs) can act as oncogenes or tumor suppressors, which makes them a strong factor in the regulation of gene expression and hematological malignancies. The promotion of malignancy through the targeting of apoptosis and immune regulation pathways is promoted by the upregulation of miR-155 in conditions such as diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL). Studies show that in patients with DLBCL, raised levels

of miR-155 have a strong association with poor prognosis. This correlation underscores the role miRNAs play in the progression of cancer.

Another variation of ncRNAs, lncRNAs like HOTAIR and MALAT1, emphasize cell proliferation and invasion through their recruiting of complexes that modify chromatin in order to silence tumor suppressor genes: HOTAIR specifically facilitates the proliferative cells of leukemia and increases the probability of relapse through its signaling to PRC2 (Amicone et al.). Similarity: circular RNAs (circRNAs) are another class of noncoding RNAs that prevent miRNAs from binding to their appropriate mRNAs by acting as a molecular sponge for the miRNAs. As a result, oncogene expression is promoted; for example, the MYC oncogene is a target of miR-145, and the presence of circRNA_100290 promotes cell proliferation by sponging miR-145 in AML (Zhou et al., 2021).

Beyond the promotion of oncogenesis, cRNAs can influence the methylation patterns of DNA and modify histones. DNA methyltransferases will be upregulated by the presence of lncRNA H19 in order to subsequently lead to the hypermethylation of tumor suppressor genes. Moreover, NEAT1 will silence tumor suppressors in multiple myeloma by recruiting complexes that alter chromatins. Thus, the interaction between ncRNAs and epigenetic regulators creates a feedback loop in order to promote malignancy (Alsayed et al.).

Future Directions

Due to both the potential reversibility of epigenetic alterations and the capability to enhance specificity in treatments, developing therapeutic strategies to address hemolytic cancers has garnered greater attention. One approach is inhibiting DNA methyltransferases (DNMTs) that will add methyl groups to DNA and potentially silence tumor suppressor genes (K. Wang et al.). Since abnormal hypermethylation results in the regulation of cell growth and differentiation through the transcriptional silencing of genes that control such pathways, pharmaceuticals have started to be developed to inhibit DNMTs; azacitidine and decitabine are two such examples that are incorporated into DNA to trap DNMT2 and promote reactivity of tumor suppressor genes that would have been otherwise silenced. These pharmaceuticals have become approved for the treatment of myelodysplastic syndromes and acute myeloid leukemia (AML). Studies that administered azacitidine have demonstrated a median survival of 24.5 months post-treatment in AML patients, as 60% of the patients were able to successfully respond. (Z. Zhang et al.).

Contrarily, other potential research has approached acetylation as a potential target for developing therapies. Specifically, the research addresses histone deacetylase (HDAC) that causes closed chromatin states to repress gene transcription by removing acetyl groups (H. Han et al.). However, the facilitation of the expression of tumor suppression genes can be promoted by the application of HDAC inhibitors (HDACis) that allow chromatin to remain open (Karati et

al.). Hematological malignancies like cutaneous T-cell lymphoma (CTCL) have been treated with such drugs, in particular Vorinostat and romidepsin. Clinical trials in patients with relapsed or refractory peripheral T-cell lymphoma showed vorinostat inducing a response rate of 30% (J. Barankiewicz et al.). Thus, the inhibition of HDAC can restore gene expression by reversing aberrant epigenetic silencing found in hematological cancers through the promotion of reactivating tumor suppressor genes.

Targeting BET (bromodomain and extra-terminal domain) proteins is another promising therapeutic strategy. Integral to the regulation of the transcription of oncogenes, BET proteins like BRD4 can modulate epigenetic interactions and promote the progression of cancer. Inhibitors of BET (BETis) downregulate oncogenes that are prominent in cancer proliferation by binding the BET proteins to acetylate histones. Preclinical trials have shown that one such inhibitor, JQ1, has yielded efficacy when administered to cells with multiple variations of hematological malignancies. Along with a marked decrease in MYC expression, JQ1 reduced tumor burden in models of AML and multiple myeloma (J. Wang et al.).

Neddylation pathways that modulate cullin-RING ligases—enzymes that influence protein degradation—are a possible epigenetic therapy that approaches regulation post-transcription. Needylation pathways are a promising target since overactivation of the pathways is linked with cancer development. In preclinical models of AML, MLN4924 (pevonedistat), a neddylation inhibitor, demonstrated reduced tumor growth (Aubry et al.); the ability of prevonedistat to disrupt neddylation is relatively new, so an emphasis on how to practically implement therapeutics should be explored (Y. Zheng et al.).

Combining conventional therapies, including chemotherapy or immunotherapy, with epigenetic treatments could yield higher efficacy than either therapy individually and overcome resistant mechanisms. One study that applied both HDAC inhibitors and immunomodulatory drugs (IMiDs) in multiple myeloma reduced tumor proliferation and promoted rates of apoptosis (Ferro et al.). While possible side effects from such combinations must be addressed for the well-being of patients, the ability of combination therapies to address multiple pathways simultaneously makes the therapy enticing.

Conclusion

The processes of histone modifications, DNA methylation, and noncoding RNAs helped drive RBC evolution to control evolutionary adaptations, including utilization of oxygen transportation as well as erythropoiesis. The regulation of the administration of these epigenetic modifications maintains cellular identity and function across species. However, the pathogenesis and progression of cancers like leukemia result from aberrant epigenetic alterations. If interventions that focus on down-regulating the drivers of these harmful modifications—like inhibiting DNA

methyltransferases or BETs—the progression of the malignancy can halt. Therefore, new approaches must target the pathways in this manner to increase the efficacy of future cancer treatment.

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