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Epigenetics in hematology and transfusion

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Jianping Li
Division of Hematology/Oncology, University of Florida Health Cancer Center, USA

Correspondence: Jianping Li, Division of Hematology/Oncology, University of Florida Health Cancer Center Gainesville, FL, 280E, 2033 Mowry Road, USA, Email jli1@ufl.edu

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Introduction

In the nuclei of hematopoietic stem cells (HSCs), hematopoietic genes (DNA) are present in a complex called chromatin, where DNA is wrapped around an octamer of histones (H2A, H2B, H3 and H4). These gene expression defines the self-renewal and differentiation capacity of HSCs throughout the process of hematopoiesis. Beyond the genetic changes, epigenetics plays an indispensable role in hematopoiesis as well. Thanks to the dynamic chromatin architecture, the hematopoietic genes can be turned on or off at specific stages for the commitment of cellular lineages. Epigenetic regulators modulate gene expression through different ways, such as DNA methylation, histone modification, chromatin organization and remodeling. Epigenetic regulation is involved in all the processes of hematopoiesis, from HSCs, hematopoietic progenitor cells (HPCs), committed lineages to terminally differentiated mature cells (granulocytes, monocytes, lymphocytes, erythrocytes, and megakaryocytes). Aberrant epigenetic regulation at different time points or stages can result in the development of a variety of hematological disorders. Unlike genetic changes, epigenetic alterations are reversible and targetable. The results emerging from epigenetic studies in hematology are extending our knowledge of normal and abnormal hematopoiesis. Therefore, understanding the epigenetic mechanisms that control and regulate gene expression during hematopoiesis is pivotal for the diagnosis and treatment of hematological diseases.

Epigenetics and hematopoiesis

Dynamic epigenetic alterations enable HSCs to maintain the hematopoiesis through self-renewal and differentiation into a variety of blood cells. Histone modification and DNA methylation dynamically change the chromatin accessibility, allowing the transcription machinery complex move to a specific gene region and regulate the hematopoietic gene transcription. DNA methylation is modified by the DNA methyltransferases (DNMT3A, DNMT3B and DNMT1) to repress gene transcription while the DNA demethylases (ten-eleven translocation, TET) play an important role in DNA demethylation. Similar patterns occur in histone modification, which is modified by histone methyltransferases (HMTs), histone demethylases, histone acetyltransferases (HATs) and histone deacetylase (HDACs). The "writers" modify methylation and acetylation via addition of methyl and acetyl moieties, while the "erasers" alter the methylation and acetylation levels through demethylation and deacetylation respectively. Although these epigenetic regulators are not hematopoiesis-specific genes, the interaction between the "writers", "erasers" and "readers" dynamically change the chromatin accessibility where hematopoietic genes are located and modulate gene expression levels to maintain the homeostasis and continuous production of blood cells. The epigenetic interaction enables HSCs to differentiate into common myeloid progenitors (CMPs) by increasing the chromatin accessibility of myeloid-related genes and decreasing that of the lymphoid-related genes. In contrary, HSCs differentiate into common lymphoid progenitors (CLPs) due to the increased chromatin accessibility of lymphoid-related genes but closed chromatin accessibility of myeloid-related genes. Subsequent similar epigenetic regulations guide CMPs to differentiate into myeloid lineages and induces CLPs to differentiate into lymphoid lineages. Deletion of one of epigenetic regulators such as DNA methylation modifiers (DNMT3A, DNMT3B, DNMT1 and TET2) or histone. modifiers (EZH2, NSD2, P300, CREBBP, ASXL1, ASXL2) affects the hematopoiesis and demonstrates its requirement for HSCs self-renewal and differentiation.[1]

Epigenetics and hematological malignancies

Imbalance of interactions between the "writers", "erasers" and "readers" due to gene mutations or other gene alterations can cause the dysregulation of hematopoiesis-specific gene expression which can further lead to the development of blood disorders by themselves or in combination with other gene mutations. The aberrant DNA methylation driven by mutations of DNA methyltransferases (DNMT3A, DNMT3B and DNMT1) or TET2 alter the status of methylation at cytosine-phosphate-guanine (CpG) islands within the hematopoietic genes. As a result, these epigenetic regulator mutations lead to clonal hematopoiesis and hematological malignancies. Currently, mutations of DNMT3A are considered as a hallmark of clonal hematopoiesis and are frequently seen in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and T cell leukemia/lymphoma.[1,2] Similarly, the abnormal histone methylation driven by mutations of HMTs and histone demethylases activate or silence hematopoietic genes leading to leukemia or therapy resistance. For instance, mutations of HMT (enhancer of zeste homolog 2, EZH2) in lymphoid malignancies alter the repressive histone mark H3K27me3 and can lead to the development of tumors. Similarly, mutations of nuclear receptor binding SET domain protein 2 (NSD2), a histone methyltransferase specific to H3K36me2, are related to the relapse of pediatric acute lymphoblastic leukemia (ALL) and glucocorticoid resistance.[3] The mutations of HATs like P300, associated with active marker H3K27ac, have been frequently identified in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).[1,2] In addition, mutations of other epigenetic regulators such as ASXL family (ASXL1 and ASXL2) and cohesin complex (SMC1 and SMC3), indirectly affect the main modification groups, impact the chromatin architecture and can cause the hematological malignancies.

Epigenetic therapies

Given that many of the chromatin modifier mutations impact the hematopoiesis-related gene expression and contribute to the pathogenesis of hematological malignancies, therapeutic strategies targeting aberrant epigenetics is becoming a novel approach in the treatment of blood cancers. By targeting DNA methylation, DNA

hypomethylating azanucleosides (5-azacitidine and decitabine) exhibit their efficacy in the treatment of intermediate-risk to high-risk MDS and AML and have been approved by FDA (4). They are also used to reverse glucocorticoid resistance in pediatric ALL. Additionally, several epigenetic inhibitors have been developed that target histone methylation/demethylation (EZH2, DOT1L, PRMT5 and LSD1) or histone acetylation/deacetylation (BET and HDAC).[4] Among them, histone methyltransferase EZH2 inhibitors have been used in the treatment of FL and DLBCL, and approved by FDA to treat FL. In addition, EZH2 inhibitors have been shown to repress the tumor growth of MM and reverse the glucocorticoid resistance in ALL with *NSD2* mutation as well (3). DOT1L and LSD1 inhibitors selectively kill MLL-rearranged AML or induce the leukemic cell differentiation, while PRMT5 inhibitors have shown anti-tumor effects in AML and lymphoma. BET inhibitors, especially BRD4 inhibitors, target histone acetylation and cause anti-leukemic effects in MLL-rearranged AML, NPM1-mutant AML and high-risk MDS. On the other hand, HDAC inhibitors employ different strategy to restore histone acetylation and promote the differentiation and apoptosis in lymphoid malignancies (lymphoma and multiple myeloma). Although hematopoietic stem cell transplantation (HSCT) is still the most efficient therapy and the novel CAR-T therapies show promising efficacy in hematological malignancies, many epigenetic studies have shown that epigenetic drugs can significantly enhance HSCT and CAR-T therapy and attenuate graft versus host disease (GVHD), establishing the premise for the use of combination therapies.[5,6]

Epigenetics and transfusion

As one of current therapeutic approaches for hematological diseases, blood cell transfusion is of great importance in the treatment of malignant and non-malignant diseases. However, the blood donations are often outstripped by the clinical demand, especially that of red blood cells (RBCs) and platelets. Additional innovation to obtain enough blood cells and improve blood transfusion for the patients have become an important and challenging project for the scientists and physicians. Based on the comprehensive role of epigenetic regulation in erythropoiesis and megakaryopoiesis,[7] understanding the mechanisms of RBCs and platelets production and developing novel artificial manufacturing processes can be a potential viable approach to significantly improve blood transfusion.

In conclusion, gene transcription is modulated partly by chromatin regulators to maintain the hematological homeostasis. Aberrant alteration or mutations of epigenetic regulators disturb the highly organized chromatin architecture and cause hematological malignancies. Targeting the reversible epigenetic alterations provides us a novel therapeutic strategy to treat hematological diseases.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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