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Review Article

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Noncoding RNA-Mediated Control of HbF Switching: From Molecular Mechanisms to Clinical Translation

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Abstract

Noncoding RNAs (ncRNAs) serve as critical epigenetic regulators of fetal hemoglobin (HbF) switching, offering promising therapeutic opportunities for the treatment of β-hemoglobinopathies, including sickle cell disease and β-thalassemia. Despite significant advances, the exact role of ncRNA-mediated regulatory networks within existing models of transcriptional and epigenetic regulation of γ-globin expression remains unclear. This review summarizes the roles and interplay of microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and PIWI-interacting RNAs (piRNAs) in controlling γ-globin expression, as well as their interactions with key regulators such as BCL11A, KLF1, and various epigenetic modifiers. miRNAs, including miR-15a, miR-16-1, miR-486-3p, and miR-210, have been found to regulate key transcription factors that act as either enhancers or suppressors of HbF production. lncRNAs, such as BGLT3 and NR_120526, exert diverse regulatory functions through chromatin remodeling, transcriptional regulation, and protein interactions. circRNAs, including hsa-circRNA-100466 and hsa-circRNA-0008102, indirectly affect HbF, as they are thought to act as molecular sponges for miRNAs. The precise mechanisms by which piRNAs contribute to HbF switching remain unclear. Future studies should focus on mapping the comprehensive regulatory networks of ncRNAs, elucidating their molecular interactions, and evaluating therapeutic strategies in advanced preclinical and clinical settings for the treatment of β-hemoglobinopathies. Together, this review moves beyond the descriptive classification of ncRNA-mediated switching mechanisms toward an integrated regulatory model of HbF switching, and examines the therapeutic potential of targeting these networks to develop novel, next-generation treatment approaches for β-hemoglobinopathies.

Keywords:
noncoding RNAs; fetal hemoglobin (HbF); β-hemoglobinopathies; microRNAs (miRNAs); long noncoding RNAs (lncRNAs); circular RNAs (circRNAs); piwiRNA (piRNA)

1. Introduction

Human hemoglobin (Hb) is a tetrameric protein composed of two pairs of globin polypeptide chains, with each pair encoded by genes belonging to a distinct globin gene family. The human alpha-like globin genes (ζ, α_1, and α_2) are found on chromosome 16, whereas the beta-like globin genes (ε, Gγ, Aγ, δ, and β) are found on chromosome 11 [1]. Six distinct hemoglobin types form during development as a result of successive changes in the alpha- and beta-like globin clusters [2]. During the early stages of embryonic development, hemoglobin production begins in the yolk sac, resulting in the formation of three types of hemoglobins: Hb Gower 1 ($\zeta_2\varepsilon_2$), Hb Portland ($\zeta_2\gamma_2$), and Hb Gower 2 ($\alpha_2\varepsilon_2$) [3]. From 10–12 weeks of pregnancy, there is a shift of erythropoiesis from the yolk sac of the embryo to the fetal liver, and fetal hemoglobin (HbF; $\alpha_2\gamma_2$) becomes the most abundant type of hemoglobin throughout pregnancy because of erythroid precursor cells produce HbF to the first six months after

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birth [4]. HbF includes two alpha and two gamma subunits ($\alpha_2\gamma_2$), and differs from adult hemoglobin in its oxygen-delivery characteristics, which are crucial for fetal circulation [5]. Throughout development, a complex hemoglobin switch occurs, in which HbF is progressively replaced by adult hemoglobin (HbA, $\alpha_2\beta_2$) postnatally. Hemoglobin A_2 (HbA_2; $\alpha_2\delta_2$) is also produced during development and becomes a minor adult hemoglobin after birth [6]. This transition is significant because the persistence of HbF can benefit patients with β-globin disorders, such as β-thalassemia.

1.1. Clinical Significance of HbF in β-Hemoglobinopathies (SCD, β-Thalassemia)

The role of HbF in β-thalassemia is associated with the constant activation of the γ-globin gene, which helps to correct the imbalance of globin chains by enabling the γ-globin produced to bind with the remaining unbound α-globin chain [7]. Similarly, in sickle cell disease (SCD), elevated HbF levels are associated with less severe symptoms because deoxygenated red blood cells take a longer time to sickle [8]. The underlying pathological process of SCD involves the polymerization of deoxygenated sickle hemoglobin in hypoxia due to altered physicochemical properties, which is inhibited by increased levels of HbF [9]. Both HbF and its hybrid tetramer ($\alpha_2\gamma\beta S$) cannot engage in the polymerization of deoxygenated sickle hemoglobin (HbS); thus, the consequent and detrimental damage to cellular structures from HbS polymerization is prevented [10]. In both forms of hemoglobinopathy, enhanced regulation of the γ-globin gene is recognized as a modulating factor in the phenotype of the disease. Thus, understanding the intricate mechanisms associated with γ-globin gene regulation can be anticipated to have direct clinical implications, and potential application in the therapeutic development of β-hemoglobinopathies [11].

1.2. Noncoding RNAs as Emerging Epigenetic Regulators

Noncoding RNAs (ncRNAs) play a significant role in regulating β-globin expression and HbF production, making them promising targets for treating β-hemoglobinopathies [12]. MicroRNAs (miRNAs) are especially crucial in globin regulation because of their post-transcriptional gene silencing activities [13]. Specific miRNAs including miR-15a, miR-16-1, miR-23a, miR-26b, miR-27a, and miR-451, are capable of targeting key transcription factors, including Myeloblastosis Oncogene (MYB), B Cell Lymphoma 11A (BCL11A), GATA binding protein 1 (GATA1), Kruppel-Like Factor 3 (KLF3), and Sp1 (Specificity Protein 1) and thus cause increased γ-globin synthesis and production of HbF [14]. These ncRNAs serve as protein decoys; they interact with many aspects of biological processes and serve as markers for hematological disorders. Understanding these molecular mechanisms is key for developing ncRNA-based therapy for β-thalassemia and SCD [15].

Besides numerous miRNAs, a few long noncoding RNAs (lncRNAs) have been discovered that are associated with HbF regulation; however, the whole regulatory network of these ncRNAs involved in hemoglobin switching remains incomplete. Furthermore, the functions of lncRNAs, circular RNAs (circRNAs), and piwi-interacting RNAs (piRNAs) have not been widely explored, and there is a need for more thorough and advanced research on these topics as well as the development of new treatment approaches. This review addresses this gap by summarizing recent findings on how ncRNA regulate HbF, emphasizing the intertwined regulatory networks governing γ-globin expression, and exploring the potential for ncRNA-based therapeutic strategies. Furthermore, this review highlights existing challenges, limitations, and future research priorities necessary for the clinical implementation of ncRNA-targeted therapies for β-hemoglobinopathies.

2. Molecular Basis of HbF Switching

The transition from fetal to adult hemoglobin is regulated by complex transcriptional mechanisms, which are governed by negative regulation of the fetal γ-globin genes and positive regulation of the adult β-globin genes during development [16]. These transcriptional mechanisms are important for γ-globin gene regulation. With the advancement of biological technologies, numerous factors have been found and studied extensively [17,18]. One key component now well established in modulating γ-globin activation is the zinc-finger protein BCL11A, a strong repressor of γ-globin expression [19]. Research indicates that BCL11A interacts with DNA methyltransferase 1 (DNMT1), the nucleosome remodeling and deacetylase complex (NuRD), GATA1, and SRY-box 6 (SOX6) to inhibit the expression of γ-globin by binding to its distal and proximal promoters [18,20].

Another important repressor is ZNF410, a zinc-finger protein that acts as an indirect HbF repressor by promoting chromodomain helicase DNA binding protein 4 (CHD4) transcription. CHD4 is a core component of the NuRD complex, which mediates repression of γ-globin expression [21]. Studies have shown that MYB binds to the promoter of the β-globin activator Kruppel-

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Like Factor 1 (KLF1), increases KLF1 expression, and subsequently triggers activation of the γ-globin repressor GATA-1, making MYB a potent γ-globin repressor. Each globin promoter is associated with a locus control region (LCR) that can loop back to the promoter to enhance transcription [22].

Recent preclinical and clinical studies indicate that epigenetic changes involving DNA methyltransferases (DNMTs), histone methyltransferases (HMT), demethylases, histone deacetylases (HDACs), and histone acetyltransferases (HATs), and changes in the levels of miRNAs, influence the transition from γ-globin to β-globin synthesis [23]. After birth, changes take place in which the γ-globin genes are suppressed. Since epigenetic marks are reversible, they offer promising targets for therapies aimed at reactivating fetal hemoglobin genes [24]. Earlier methods for inducing HbF were mostly empirical and of limited effectiveness, but identifying specific molecular targets has opened new possibilities for developing more effective, rationally designed treatments [25].

DNA methyltransferases (DNMTs) are enzymes that catalyze the methylation of cytosine residues on DNA. Three functional DNMTs have been discovered in mammalian cells: DNMT1 for maintenance methylation, and DNA methyltransferase 3A (DNMT3A) and DNA methyltransferase 3B (DNMT3B) for de novo methylation [26]. These enzymes attach a methyl group to the 5th position of cytosine in CpG dinucleotides, using S-adenosylmethionine as a donor. 5-methylcytosine in the regulatory regions of certain genes may influence the interaction of transcription complexes with DNA [27]. Moreover, 5-methylcytosine can associate with silencing proteins, such as methyl-DNA-binding proteins, HDAC, and HMT, which modify chromatin architecture. Both mechanisms suppress genes with methylated regulatory elements [28].

Another epigenetic mechanism is histone modification. Histones undergo numerous post-translational modifications, such as acetylation, methylation, phosphorylation, ADP-ribosylation, and ubiquitination, which can alter chromatin structure due to their high lysine residues in their N-terminal tails [16,29]. Increased acetylation of histones is highly correlated with increased γ-globin expression. In particular, acetylation of lysine residues within histones H3 and H4 and binding of RNA polymerase II to the γ-globin enhancer led to the increase of HbF [30]. Acetylation of lysine residues in the N-terminal tails of histones H3 and H4 has been shown to modulate γ-globin expression, by causing chromatin to relax and thus promoting transcriptional activation, whereas histone deacetylation is usually linked to chromatin condensation and transcriptional repression [31].

Methyltransferases are also responsible for methylating histone amino acid residues, including lysine methyltransferase (KMT) and protein arginine methyltransferase (PRMT), which may result in an open chromatin configuration that is responsible for activating genes, or a more condensed chromatin state that represses gene expression [32]. These investigations suggest that the interaction between histone modifications and the recruitment of factors that ultimately control globin gene expression at the HBB locus is complex [32].

3. Overview of Noncoding RNAs

NcRNAs are a large class of regulatory RNA molecules that do not encode protein but play an increasingly recognized and critical role in gene expression regulation in eukaryotic cells [33,34]. These are crucial regulators of HbF switching, thereby influencing the transition from fetal to adult globin gene expression during erythropoiesis [35]. They mediate environmental responses, chromatin remodeling, transcriptional regulation, and post-transcriptional modulation of transcripts, contributing to new therapeutic possibilities in hemoglobinopathies such as SCD and β-thalassemia [36]. NcRNAs are divided into two broad groups: short ncRNAs, which contain miRNAs, small interfering RNAs (siRNAs), and piRNAs; and lncRNAs, which include long intergenic ncRNAs (lincRNAs) and circRNAs [37]. The interplay of ncRNAs with DNA as well as other RNAs and proteins can regulate gene activity to adjust the expression of genes in several biological pathways, making them important regulators of gene expression [38]. The regulatory functions of ncRNAs are manifested at different levels: transcriptional, post-transcriptional, or even epigenetic regulation, related to functions of chromatin-modifying complexes, for activation or repression of target genes [39].

3.1. MicroRNAs in HbF Switching

MiRNAs are small noncoding RNAs, typically 19 to 25 nucleotides long, that regulate gene expression at the post-transcriptional level. They typically achieve this by forming either perfect or partial base-pairing with the 3′ UTR of the target mRNA [40]. When miRNAs bind to target mRNA, they can influence gene expression through several mechanisms. One common method is translation suppression, where the miRNA-RISC complex obstructs ribosome attachment to the mRNA [41]. Moreover, miRNAs may mediate mRNA degradation through the promotion of deadenylation, decapping, and exonucleolytic decay. They may also play a role in mRNA stability by either safeguarding target mRNAs from degradation or boost-

ing their stability [42]. Increasing evidence shows that miRNAs are important in erythropoiesis. Some miRNAs are directed at major transcriptional repressors, including BCL11A and MYB, or epigenetic regulators, including DNMT, and can relieve the repression of γ-globin, resulting in enhanced HbF synthesis. Transcription factors of the fetal-to-adult hemoglobin switch are important regulators of BCL11A, SOX6, MYB, KLF1, and KLF3, and in normal conditions, these factors are inhibitory to HbF levels in adult erythropoiesis [43].

Reactivation of the switch and increased HbF production, along with the developmental activation of globin gene expression, have been associated with several miRNAs [44]. In particular, Bianchi et al. found that high HbF levels in an erythroid stem cell patient with thalassemia are associated with increased miR-210; mithramycin was shown to target miR-210 and induce γ-globin activation in K562 cells [45]. In one study of SCD patients receiving HU, the activity of miR-26b and miR-151-3p was linked with HbF levels at the maximum tolerated dose [46]. Another study showed that miR-34a suppressed Signal Transducer and Activator of Transcription 3 (STAT3), a recognized inhibitor of γ-globin, to cause HbF production in K562 cells [47].

Further functional studies showed that, upon introduction of both normal and sickle erythrocytes, miR-144 silenced transcription of Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) and, consequently, γ-globin. However, this suppression was inhibited in a dose-dependent manner by treatment with miR-144 antagomir [48]. In cultured adult primary erythroid cells, overexpression of the tumor-promoting LIN28B led to decreased miR-Let-7 levels and increased expression of the γ-globin gene and HbF levels, partly due to its effect on BCL11A expression [49]. Let-7 directly targets and represses HIC2, which in turn functions as a transcriptional repressor of BCL11A [50]. Furthermore, miR-486-3p facilitated HbF synthesis in adult erythroid progenitors by suppressing BCL11A expression [51].

The heightened expression of miR-15a and miR-16-1 in human erythroid cells is linked to repression of MYB and upregulation of fetal and embryonic Hb genes, as a mechanism of delayed switching [52]. Both miR-221 and miR-222 have been demonstrated to modulate expression of the kit receptor in erythroid cells and to influence HbF expression [53]. MiR-29b induces HbF by directly targeting DNMT3A/3B mRNAs, resulting in decreased DNA methyltransferase expression, DNA hypomethylation at the γ-globin gene, and reactivation of fetal globin. miR-29b mimics enhance the γ/β globin mRNA ratio and increase HbF-positive cell populations both in vitro (human CD34+ and SCD erythroid progenitors) and in vivo (SCD mouse models), with significant reductions in pathological sickling [54]. In an intriguing in vitro study, miR-96 was found to immediately suppress γ-globin gene expression, and there was an inverse relationship between the amount of HbF and the amount of miR-96 in the umbilical cord blood and adult blood reticulocytes [55]. Figure 1 depicts miRNA-mediated transcriptional and epigenetic regulation of fetal-to-adult hemoglobin switching.

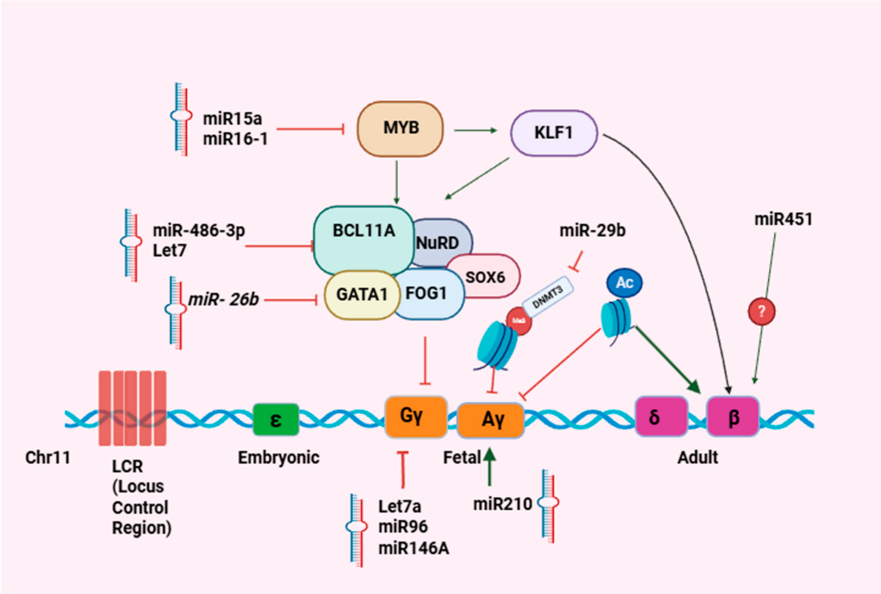


Figure 1: miRNA-mediated transcriptional and epigenetic regulation of fetal-to-adult hemoglobin switching. Created in BioRender. Mallik, S. (2026) https://BioRender.com/2ues9fj.

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A schematic representation of the miRNA-transcription factor-epigenetic network involved in switching the globin genes at the β-globin locus on chromosome 11 is presented. miR-15a/16-1 inhibits MYB, which results in decreased KLF1-driven activation of BCL11A, a crucial suppressor of γ-globin. miR-486-3p and Let-7 directly target BCL11A, whereas miR-26b influences GATA1 activity. BCL11A is involved in establishing a repressive chromatin state at the fetal gamma globin genes (Gγ and Aγ) in association with the NuRD complex, GATA1, FOG1, and SOX6. Conversely, miR-29b and miR-210 facilitate chromatin acetylation and the reactivation of γ-globin. This comprehensive regulatory network controls HbF suppression and adult β-globin expression.

3.2. Long Noncoding RNAs in HbF Switching

LncRNAs are the most prevalent and variable members of the ncRNA family. They represent the majority of ncRNA transcripts, and their lengths are greater than 200 nucleotides [56,57]. Some lncRNAs act as guides to lead chromatin remodelers (including SWI/SNF (Switch/Sucrose Non-Fermentable) family members and NuRD complex components) as well as histone-modifying enzymes (including HATs, HDACs, methyltransferases, and demethylases) to the β-globin locus, facilitating the creation or alteration of repressive chromatin structures [58]. Additionally, they can also act as competing endogenous RNAs (ceRNAs) to indirectly control the expression of other genes [59,60]. In addition, certain lncRNAs have been observed to be able to inhibit miRNAs, both intronic and exonic sequences during miRNA maturation [61]. Given their central role in biological processes, lncRNAs are expected to contribute to the pathogenesis of many diseases, including malignancies and hematologic disorders such as hematopoietic stem cell disorders [62]. The most likely mechanisms suggested so far are: (i) activation of histone proteins in epigenetic modulation; (ii) scaffolding of transcription factors; and (iii) activation of the interaction between activators and promoters [63]. High levels of HbF have been linked to dysregulated lncRNAs and miRNAs expression in carriers of β-thalassemia and hereditary persistence of fetal Hb (HPFH) [64]. High levels of HbF could be induced by the activation of hematopoietic cell lineage-inducible molecules and Hemoglobin Subunit Epsilon 1 (HBE1) by lncRNA as one of the possible mechanisms [44]. Mechanistically, this lncRNA interacts directly with the promoter of the ERF (Ets2 Repressor Factor) gene and brings DNMT3A into action to promote hypermethylation of the ERF promoter, effectively silencing ERF, which is recognized as a repressor of γ-globin [65].

H19 is an abundant lncRNA and plays a critical role in controlling hemoglobin expression. It has a greater effect on the cell during critical developmental periods, such as the transition from fetal to adult hemoglobin and embryogenesis [66,67]. H19 showed characteristic locations in the cell: in K562 cells, it was principally in the nucleus, whereas in HUDEP-2 cells, it was principally in the cytoplasm [66]. The presence of H19 in the cytoplasm of erythroid precursor-2 (HUDEP-2) cells from human umbilical cord blood opens the interesting possibility that it may be a competing endogenous RNA (ceRNA) which may mediate the interaction of microRNAs or mRNAs in regulating the expression of the γ-globin gene [15,66].

The intergenic long noncoding RNA HBS1L-MYB (HMI-lncRNA) is a possible regulator of the γ-globin gene. This lncRNA has been investigated as an enhancer RNA (eRNA) involved in the association between the remote activator and promoter of MYB [68].

Recent studies have drawn attention to the role of Beta globin locus transcript 3 (BGLT3) lncRNA, which is transcriptionally activated by hypoxia-inducible factor 1 (HIF1) under hypoxia or following von Hippel-Lindau (VHL) gene disruption [69]. HIF1 attaches to hypoxia response elements (HREs) in the BGLT3 locus, inducing chromatin changes to stimulate expression of the γ-globin gene. This is achieved through recruitment of GATA1, p300, and increased H3K27ac, an enhancer mark, resulting in long-range looping between the BGLT3 region and globin loci, ultimately leading to HbF upregulation [70].

The presence of NR_120526 was found to be strongly associated with HbF levels, and a variety of lncRNAs were found to be differentially expressed between individuals with high HbF levels. NR_120526 is hypothesized to negatively regulate the expression of the γ-globin gene and thus presents an attractive therapeutic target for increasing HbF in β-thalassemia patients. Targeting such negative regulators could help enhance HbF levels in β-thalassemia and other disorders [71].

Seven β-thalassemia patients with high HbF levels underwent microarray profiling, and the lncRNAs uc002fcj.1 and NR_001589 showed considerably higher average expression. This evidence supports a positive correlation of the lncRNAs and HbF. Further functional studies of the lncRNAs uc002fcj.1 and NR_001589 would help shed light on the molecular pathways involved in β-thalassemia. It is hypothesized that the lncRNAs have the potential to work as ceRNAs, where they regulate the up-regulation of the γ-globin gene through the sequestration of certain miRNAs, thus promoting HbF production in β-thalassemia [72]. The role of ncRNAs in the regulation of fetal hemoglobin is summarized in Table 1 [23,44–48,51,52,55,69,73–78].

Table 1: The roles and mechanisms of noncoding RNAs in fetal hemoglobin regulation.

Noncoding RNAs	Target	Effect of γ-Globin	Molecular Mechanism	References
		miRNAs		
Let-7a	γ globin	γ globin gene switching	Indirectly modulating erythroid maturation and γ-globin repression pathways	[73]
miR-486-3p	BCL11A	Increases expression of γ globin gene	Modulates erythroid differentiation signaling pathways, indirectly affecting γ-globin expression	[51]
miR-96	γ globin (CDSregion)	Suppress γ-globin gene expression	Directly targets γ-globin mRNA, suppressing its translation	[55]
miR-29b	DNMT, MYB	Increases expression of γ-globin gene	leading to hypomethylation of the γ-globin promoter	[23]
miR-144	NRF2	Decrease HbF (negative regulator)	Targets NRF2 and oxidative stress response pathways, indirectly influencing HbF regulation	[48]
miR-26b	GATA1	Increases γ globin gene expression	Modulates chromatin regulators and erythroid transcriptional programs	[46]
miR-210	γ globin	γ globin gene switching	Hypoxia-induced miRNA influencing erythroid differentiation and metabolic adaptation	[45]
miR-23a	SP1	Increases γ and ε globin expression	Targets components of the γ-globin repressor network, including erythroid transcription regulators	[74]
miR-27a	KLF3	Regulates HbF expression	Regulates erythroid differentiation pathways affecting globin gene expression	[74]
miR-34a	STAT3	γ-globin activation	Indirectly activating γ-globin through silencing of the repressor STAT3	[47]
miR-15a/-16-1	MYB	Increase γ-globin gene expression	Suppress MYB expression, resulting in γ-globin de-repression	[52]
		LncRNAs		
BGLT3	γ globin	Increase HbF	Promotes chromatin accessibility and LCR–γ-globin interaction	[69]
AlncRNA-EC7	γ-globin regulatory network	Increases γ-globin gene expression	Supports erythroid transcriptional program	[75]
HMI-lncRNA	MYB → BCL11A	Increases γ-globin gene expression and HbF	Suppresses MYB, reducing BCL11A-mediated repression	[68]
NR_001589, and T315543	γ-globin regulatory regions Potential	Increase γ-globin gene expression	Associated with epigenetic regulation in HbF-high states	[44]
NR_120526	γ-globin regulatory regions Potential	Decrease γ-globin gene expression	Associated with HbF level	[71]

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Table 1: *Cont.*

Noncoding RNAs	Target	Effect of γ-Globin	Molecular Mechanism	References
		CircRNAs		
hsa_circ RNA_100466	miR-19b-3p SOX6	Associated with decreased γ-globin/HbF	Acts as a miRNA sponge, modulating erythroid regulatory pathways linked to γ-globin expression	[76]
hsa_circ RNA_0008102	MiR-425-3p GATA2 (GATA-binding factor 2)	Associated with increase γ-globin/HbF	Regulates erythroid gene expression through miRNA sequestration and transcriptional network modulation	[77]

3.3. Circular RNAs in HbF Switching

CircRNAs are a class of endogenous Noncoding RNA molecules recognized for their role in regulating gene expression [77]. These circRNAs are innovative, endogenous, single-stranded ncRNAs produced by a process called back-splicing. Unlike their linear counterparts, circRNAs have a covalently closed-loop structure and lack both a 5′ cap and a 3′ tail; they range from 100 nucleotides to over 4 kilobases [78]. A covalently closed loop structure and superb stability, with an absence of a 5′ cap and 3′ tail, render circRNAs less sensitive to degradation by nucleic acid exonucleases. Predominantly found in the cytoplasm and not the nucleus, circRNAs act like a sponge for miRNAs, thereby regulating the target gene expression and reducing the suppressive effects of miRNAs on target RNAs [79]. They serve as competitive endogenous RNAs (ceRNAs); through miRNA binding, this miRNA-sequestering activity of circRNAs can affect target gene expression [80]. CircRNAs can also interact with RNA-binding proteins (RBPs) and modulate their functions. This interaction may alter RBP stability, localization, and function and subsequently influence gene expression [68].

CircRNAs have become important regulators in the fetal-to-adult hemoglobin switch, mainly via what is known as their interaction with miRNAs and RNA-binding proteins in erythroid cells. They bind miRNAs like sponges and regulate gene expression. CircRNAs can sequester miRNAs and prevent them from binding to their target mRNAs, resulting in the enhanced stability and expression of target mRNAs [80]. CircRNAs can also attach to RNA-binding proteins (RBPs) and influence their activity. This interaction may alter the stability, localization, and/or function of RBPs and subsequently influence gene expression involved in the HbF to HbA transition [81,82]. For instance, hsa-circRNA-100466 is downregulated in individuals who are carriers of β-thalassemia with high levels of HbF and promotes HbF levels by upregulating miR-19b-3p, thereby reducing SOX6 expression, a known repressor of γ-globin [76]. Another circRNA, has_circ-0008102, is upregulated in pediatric patients with β-thalassemia and is linked to γ-globin activation via miRNA regulation [77]. Figure 2 below describes the interaction between miRNAs, lncRNAs, and circRNAs in fetal hemoglobin regulation.

3.4. PIWI-Interacting RNAs in Hemoglobin Switching

PIWI-interacting RNAs (piRNAs) are a unique type of ncRNAs that range from 24 to 31 nucleotides long and are associated with members of the PIWI (P-element Induced Wimpy Testis) protein family (PIWIL1-PIWIL4) [83]. They may help preserve genome stability and regulate chromatin organization by interacting with PIWI proteins [84]. No direct experimental evidence links piRNAs to the regulation of HbF or the hemoglobin switching process, although piRNAs have been identified in somatic tissues and are believed to play a role in epigenetic gene silencing [85]. Nevertheless, indirect evidence points to a possible connection, as piRNA-PIWI complexes are known to engage in chromatin remodeling, histone modifications, and interactions with epigenetic regulators such as the NuRD complex, which is recognized for repressing γ-globin expression. These findings suggest that piRNAs could affect HbF expression via epigenetic mechanisms. As a result, the role of piRNAs in regulating HbF remains relatively understudied, and additional mechanistic and functional research is needed to determine whether piRNAs directly influence HbF induction.

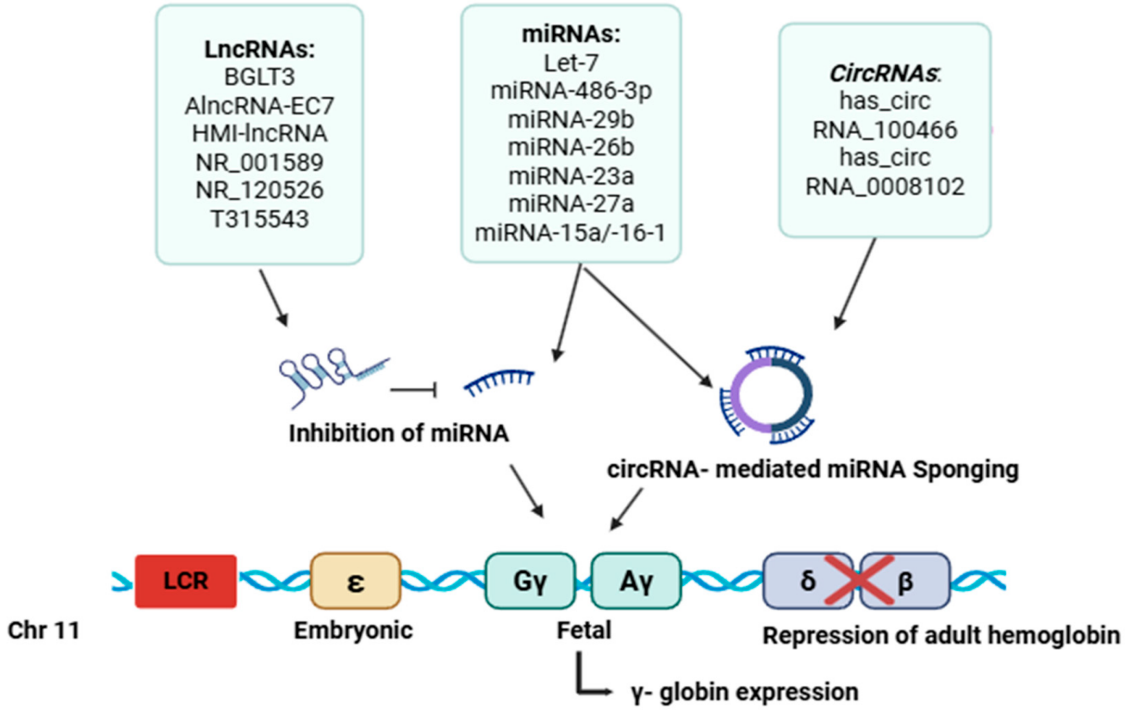


Figure 2: Cross-talk between miRNAs, lncRNAs, or circRNAs in fetal hemoglobin regulation. Created in BioRender. Mallik, S. (2026) https://BioRender.com/7pucn93. The schematic diagram (Figure 2) illustrates how noncoding RNAs work together to regulate globin gene expression at the β-globin locus on chromosome 11. Various microRNAs (miRNAs) including Let-7, miR-486-3p, miR-29b, miR-26b, miR-23a, miR-27a, and miR-15a/16-1, along with long noncoding RNAs (lncRNAs) like BGLT3, AlncRNA-EC7, HMI-lncRNA, lncRNA-GT, NR_001589, NR_120526, and T315543, and circular RNAs (circRNAs) including hsa_circRNA_100466 and hsa_circRNA_0008102, engage in miRNA–lncRNA–circRNA interactions to influence globin gene switching. This network affects the locus control region (LCR) and increases transcriptional activation of fetal γ-globin genes (Gγ and Aγ) while suppressing of adult β-globin expression. This ncRNA-driven regulation supports continued or renewed γ-globin expression, resulting in elevated fetal hemoglobin levels. This process provides therapeutic potential for use in the treatment of hemoglobinopathies including SCD and β-thalassemia.

4. Noncoding RNA–Based Therapeutic Strategies for HbF Switching

Reactivating HbF in adults has the potential to treat patients with all hemoglobinopathies. Clinical strategies for reactivating HbF pharmacologically have been used to treat β-hemoglobinopathies [62]. The existence of HPFH syndrome with an asymptomatic phenotype demonstrates this positive association between elevated HbF production and the amelioration of severe cases of β-hemoglobinopathies [85]. Therefore, understanding of the HbF switch is of critical importance for successful attempts to express the γ-globin gene in human expression systems [86]. Despite extensive investigations of hemoglobin switching, some of the regulatory mechanisms, particularly those involving epigenetic regulation, still remain obscure.

Hydroxyurea is a U.S.-approved pharmacological HbF inducer for moderate to severe SCD [87]. While the precise mechanisms by which hydroxyurea promotes HbF remain unclear, several studies have noted its effect on reducing BCL11A, MYB, and KLF1, underscoring that these genes are significant in the study of β-thalassemia as therapeutic targets [88]. 5-azacytidine is a DNA hypomethylating agent which was initially identified to stimulate production of HbF in SCD and β-thalassemia patients; however, due to its carcinogenic activity, it has limited applications for HbF therapies [89]. Recent clinical trials have demonstrated that the combination of decitabine, a less toxic chemical derivative of 5-azacytidine, and tetrahydrouridine (THU), which stabilizes decitabine, shows potential to be used in the treatment of sickle cell disease [89]. DNMT1 is well known for maintaining methylation on DNA during cell division. Moreover, DNMT1 is a common repressor that can be recruited by sequence-specific DNA-binding factors, such as DRED (TR2/TR4) and BCL11A, which regulate epigenetic silencing of γ-globin [90]. Additionally, recent investigations have revealed an HPFH-associated germline missense mutation in DNMT1, which directly

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demonstrated the role of DNMT1 as an important epigenetic co-repressor of the γ-globin gene, and also indicated that DNMT1 could be a therapeutic target for hemoglobinopathies [91,92].

Among the naturally occurring short-chain fatty acids, a popular HDAC inhibitor, butyrate, was reported to induce long-term HbF production in most patients with SCD [93]. Butyrate-induced upregulation of the γ-globin gene is typically attributed to enhanced acetylation at its promoter. Additionally, butyrate can activate the soluble guanylate cyclase and p38 MAP kinase pathways [94]. Nevertheless, the exact mechanisms by which these signaling pathways stimulate the activation of γ-globin genes remain unclear. Butyrate was more recently reported to stimulate production of HbF in SCD patients via an increase in the translation of γ-globin mRNA [95]. Although using butyrate can lead to notable improvements in anemia for individuals with β-thalassemia, most patients receiving treatment continue to experience considerable anemic symptoms [96].

The erythroid-specific enhancer and transcript benefit the erythroid-specific transcription factor BCL11A, which is associated with HbF, compared with other HbF transcription factors. The long form of the BCL11A gene, i.e., BCL11A-XL, has been the focus of functional studies highlighting its crucial role in the silencing of erythroid γ-globin and the repression of HbF during erythroid maturation [97]. MYB is autoregulated by enhancers for erythroid activation in the distal region of the HBS1L-MYB intergenic region, which influences HbF levels, and BCL11A is expressed only in its erythroid-specific isoform compared to MYB, which is far more accessible to miRNA [98]. Genome-wide association studies have identified BCL11A as the primary regulator of HbF production, and various studies have shown that reducing BCL11A expression positively impacts HbF levels [24]. Nevertheless, targeting only the coding region of BCL11A for genetic editing may not be an effective therapeutic approach, as this site is also crucial for the function of the hematopoietic stem cell reservoir and the progression of lymphoid development. In K562 cells in which BCL11A was disrupted using the CRISPR/Cas9 system, there was a notable reduction in BCL11A levels along with an increase in HbF expression [99]. KLF1 (EKLF) is a vital transcription factor required for the expression of β-globin, the process of definitive erythropoiesis, and the transition from HbF to HbA [100]. Reduced KLF1 levels decrease BCL11A expression, resulting in higher HbF levels [101].

Lentiviral gene therapy has become a potential curative approach, and it is now possible to introduce functional variants of β-globin into autologous hematopoietic stem cells (HSCs) with high fidelity, allowing production of normal hemoglobin levels [102]. Patients become transfusion independent and have lowered hemolysis markers when treated with lentiviral β-globin-transduced autologous hematopoietic stem and progenitor cells (HSPCs) in Sickle Cell Anemia (SCA) [103].

The induction of the globin gene by thalidomide and the production of HbF are correlated with both the activation of p38 MAPK and the acetylation of histone H4. Additionally, one study suggested that thalidomide triggers Reactive Oxygen Species (ROS) production in erythroid progenitor cells, leading to the expression of later globin genes through the involvement of p38 MAPK and the acetylation of histone H4 [104]. This is the first report that clarifies the role of ROS in thalidomide-induced globin expression [104].

Emerging research emphasizes the potential of ncRNAs, ranging from important biomarkers for diagnosing human diseases to promising therapeutic targets for preventing and treating hemoglobinopathies [12]. RNA therapeutics are a rapidly growing area of biotherapeutics and offer several advantages over conventional drugs. Therapies based on antisense RNA modifiers of targeted mRNA or protein expression or function, act within a cell or organ, either transcriptionally or translationally, to treat specific clinical conditions [39].

As mentioned earlier, miRNAs are single-stranded RNA molecules, and their therapeutic application of miRNAs consists of modifying and affecting pathological changes in miRNA expression using miRNA mimics and anti-miRs, respectively [104]. MiRNA-based therapeutics have two main advantages. First, miRNAs are naturally occurring in human cells, unlike synthetic RNAs such as ASOs; thus, their processing and target selection follow natural pathways. Secondly, miRNAs can regulate a wide variety of targets in various ways, including through complementary base-pairing mechanisms [40]. Consequently, miRNA may be an alternative to current siRNA/ASO RNA therapeutics and may offer enhanced therapeutic benefits over synthetic siRNAs/ASOs specific to one target gene [44]. The therapeutic potential of lncRNAs is evident due to their multifaceted functions; accordingly, targeting strategies must be tailored to their mode of action [105]. The inhibition of lncRNAs might occur at both the transcriptional and post-transcriptional levels through secondary structure variation or protein interactions; this can be achieved by introducing synthetic lncRNAs and by identifying key elements regulating lncRNA transcription, such as lncRNA-targeted miRNA sites, which can be edited using the CRISPR-Cas9 technique currently under investigation for the treatment of diseases of the β-hemoglobin chain, i.e., β-

hemoglobinopathies [106]. MiR-29b mimics or inhibitors of suppressive lncRNAs (e.g., NR_120526 antisense oligos) are the perfect candidates as next-generation epigenetic drugs for SCD and thalassemia because of their low toxicity demonstrated in preclinical models [107].

The high stability of circRNAs and their contribution to hemoglobin-switching pathways make them excellent biomarkers and therapeutic targets in hemoglobinopathies, including SCD and β-thalassemia [108]. They introduce a novel regulatory dimension by interacting with miRNAs and RNA-binding proteins, which may affect developmental gene switches in erythroid lineage cells. Beyond diagnostics, there has been a limited amount of research on circRNAs as therapeutic formulations for clinical trials, particularly for RNA therapeutics based on circRNA [77,109]. Additionally, engineered circRNAs have been shown to act as stable mRNA templates for protein synthesis, which could serve as an alternative to conventional RNA-based therapies [106].

At present, no direct evidence connects piRNAs to the HbF switch, as most studies have focused on miRNAs rather than piRNAs [110]. PiRNAs are widely known for their function in the silencing of genes, controlling the activity of transposons and genome stability, particularly in germline cells, while also playing regulatory roles in somatic cells [111–113]. In theory, piRNAs may influence HbF switching by altering the epigenetic status of globin gene loci or silencing transposons near key regulatory regions [112,113]. More focused research is needed to conclusively demonstrate whether piRNAs have a direct or indirect impact on HbF switching and regulation of globin genes in human erythroid cells. Table 2 describes some therapeutic approaches that regulate HbF expression [43,56,92,99,101,102,109,114–119].

Table 2: Therapeutic approaches that modulate fetal hemoglobin (HbF) expression.

Therapy/ Molecule	Molecular Target/Pathway	Mechanism of Action	Key Clinical Findings	References
Hydroxyurea	γ-globin gene regulation; NO–cGMP (Nitric oxide–cyclic guanosine monophosphate) signaling	Stimulates γ-globin expression via stress erythropoiesis and nitric oxide signaling; reduces BCL11A expression indirectly	Increases HbF (up to ~20–30%); reduces vaso-occlusive crises and mortality in SCD	[114,115]
BCL11A inhibition (CRISPR/Cas9 editing)	BCL11A erythroid enhancer	Destabilizes BCL11A binding → derepression of γ-globin gene	HbF induction (>30–40%); transfusion independence in β-thalassemia; reduced VOC in SCD	[99]
Lentiviral β-globin gene therapy	β-globin gene addition	Introduces functional β-globin or γ-globin–like variants → compensates for defective hemoglobin	Sustained hemoglobin production; reduced transfusion dependence	[102]
Histone deacetylase (HDAC) inhibitors	Epigenetic chromatin remodeling	Enhanced histone acetylation → opens γ-globin gene locus for transcription	Induces HbF in preclinical and early clinical studies	[116]
DNA methyltransferase (DNMT) inhibitors (e.g., Decitabine, Azacitidine)	DNA methylation at γ-globin promoters	Hypomethylation of γ-globin gene promoters → reactivation of HbF	Significant HbF induction in SCD patients; improved erythropoiesis	[92]
KLF1 modulation	KLF1 transcription factor	Downregulation of KLF1 reduces BCL11A expression → enhances HbF	Genetic and experimental evidence supports HbF induction	[101]

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Table 2: *Cont.*

Therapy/ Molecule	Molecular Target/Pathway	Mechanism of Action	Key Clinical Findings	References
MicroRNAs (e.g., miR-15a/16-1, miR-486-3p)	BCL11A, MYB, KLF1	Post-transcriptional repression of HbF repressors	Enhances γ-globin expression; potential therapeutic targets	[43]
Long noncoding RNAs (e.g., BGLT3, HMI-lncRNA)	γ-globin locus regulation	Regulates chromatin looping and transcription factor recruitment	Emerging regulators of HbF switching; therapeutic potential under investigation	[56]
Circular RNAs (circRNAs)	miRNA sponging networks (BCL11A/MYB axis)	Act as miRNA sponges → relieve repression of γ-globin activators or inhibit repressors	Emerging evidence: circRNA-mediated networks regulate erythroid differentiation and HbF levels; potential therapeutic targets	[109]
Short-chain fatty acids (e.g., Butyrate derivatives)	Epigenetic modifiers	Histone acetylation → activation of γ-globin gene	Moderate HbF induction; limited clinical use due to pharmacokinetics	[117]
Thalidomide	Transcriptional regulators	Modulates erythroid differentiation and γ-globin expression	Increases HbF; reduces transfusion requirement in β-thalassemia	[118,119]

5. Challenges and Future Directions

The role of ncRNAs in the transition to HbF is increasingly recognized, but there are still some barriers to overcome before they can be fully utilized for therapeutic purposes. Firstly, the regulatory mechanisms of ncRNAs are not fully known, especially lncRNAs and circRNAs, regarding their interaction with transcriptional repressors and chromatin modifiers, which remains under investigation. Secondly, most insights are derived from in vitro systems or small-scale animal research, which lack robust preclinical and clinical validation. Third, finding an effective and safe way to deliver ncRNA-based treatments to hematopoietic cells remains a great challenge that is complicated by issues of stability, off-target effects, and the complexity of many of the ncRNAs. These challenges highlight the necessity of careful optimization before clinical use. Key challenges include detecting and confirming specific ncRNA biomarkers and establishing effective, reliable methods to detect them. Furthermore, preclinical and clinical trials must consider in detail the off-target effects of agents targeting ncRNAs and determine the safety profile of these agents with long-term use.

Despite growing mechanistic interest, ncRNA-mediated regulation of HbF switching remains largely confined to preclinical and in vitro systems, and this stage gap is the central translational barrier facing the field. Unlike genome-editing approaches targeting BCL11A, which have already reached regulatory approval, none of the miRNA mimics, antagomirs, lncRNA-targeting antisense oligonucleotides, or circRNA-based constructs discussed in this review have advanced into clinical trials, reflecting unresolved challenges in delivering RNA therapeutics specifically to hematopoietic stem and progenitor cells rather than the liver, where most lipid nanoparticle systems are naturally tropic. Compounding this, synthetic RNA constructs carry inherent risks of immunogenicity and off-target silencing that require extensive toxicology work before first-in-human studies, while GMP-grade manufacturing of RNA therapeutics at clinically relevant scale remains costly and technically demanding. Trial design is further hampered by the lack of validated, mechanism-specific biomarkers to track ncRNA target engagement independent of HbF percentage, making it difficult to establish dose-response relationships or predict durability of effect. Finally, even if these scientific and regulatory hurdles are overcome, the populations bearing the greatest burden of sickle cell disease and β-thalassemia are concentrated in low- and middle-income regions of Africa and South Asia, where the cost and infrastructure demand of RNA-based or cell-based therapies pose a separate, equally consequential barrier to equitable access. Bridging these gaps—mechanistic validation, targeted delivery, safety profiling, and affordable manufacturing—will determine whether ncRNA-targeted HbF induction moves from a promising conceptual framework to a clinically deployable therapy.

In the future, comprehensive mapping of ncRNA regulatory networks using multi-omics and single-cell techniques will be crucial to understanding their role in erythropoiesis and HbF reactivation. Expanding studies beyond miRNAs to examine new lncRNAs and circRNAs could reveal new mechanistic insights and therapeutic opportunities. Advances in delivery systems, such as lipid nanoparticles and exosomes-based delivery systems, are showing promising approaches to increase specificity and stability.

Future clinical studies should investigate combination and sequential strategies to reactivate HbF that target complementary aspects of γ-globin silencing. For example, epigenetic priming (inhibiting HDAC to enhance chromatin accessibility) followed by genome editing (disruption of BCL11A using CRISPR) could lower the CRISPR dosage needed and minimize off-target side effects, while also achieving greater HbF elevation. Implementing sequential miRNA inhibition (to decrease the most prevalent miRNAs that silence γ-globin) followed by lncRNA elevation (to sequester remaining miRNA pools) could exploit mechanistic synergies. These approaches require well-planned clinical trial designs with defined efficacy endpoints, safety monitoring procedures, and mechanistic biomarker assessments to enable real-time optimization.

The ability to adapt platforms to apply proven HbF-reactivation methods across various therapeutic avenues (such as gene therapy, base editing, prime editing, and ncRNA modulation) would allow different regions and healthcare systems to adopt strategies that align with their technological capabilities and financial limitations. Achieving this requires standardized evaluation of HbF-reactivation effectiveness and safety across different platforms, enabling regulatory bodies to compare new methods against recognized benchmarks instead of needing separate approvals for each new approach.

6. Conclusions

Noncoding RNAs have been identified as important epigenetic controllers in the switch-over of HbF and complement the known functions of transcription factors and chromatin modifiers. Studies about miRNAs, lncRNAs, and circRNAs have shown the role of these molecules in modulating γ-globin expression and influencing the clinical progression of β-hemoglobinopathies. Although promising, current understanding remains incomplete; the mechanistic basis of many ncRNAs, such as piRNA, is still poorly defined, and the amount of translational data is limited. Clinical advances in ncRNA-targeted HbF reactivation have achieved significant successes: therapies involving CRISPR-Cas9 editing of BCL11A have received FDA approval and demonstrate lasting positive effects in patients. To progress the field, the following priorities should be addressed: (1) finalize the exploration of ncRNA networks that regulate hemoglobin switching, particularly focusing on the less understood piRNA pathways and their feedback systems; (2) create in vivo methods for ncRNA modulation that eliminate the need for ex vivo manufacturing and lessen the toxicity associated with conditioning treatments; (3) adopt personalized profiling of ncRNA to enable treatment choices tailored to individual patients; (4) establish manufacturing systems and regulatory frameworks that ensure worldwide accessibility; (5) conduct long-term studies on safety and durability to provide data-driven assessments of risk and benefit. Achieving these goals will turn HbF reactivation from an expensive, specialized academic treatment into a practical, effective option for millions of patients with hemoglobin disorders worldwide.

List of Abbreviations

ADP	Adenosine Diphosphate
ASO	Antisense Oligonucleotide
BCL11A	B-cell Lymphoma/Leukemia 11A
BCL11A-XL	BCL11A Extra-Long Isoform
BGLT3	Beta-Globin Locus Transcript 3
Cas9	CRISPR-associated protein 9
CDS	Coding Sequence
ceRNA	Competing Endogenous RNA
cGMP	Cyclic guanosine monophosphate
CHD4	Chromodomain Helicase DNA-binding Protein 4
CircRNA	Circular RNA
CpG	Cytosine-phosphate-Guanine
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNMT	DNA Methyltransferase
DNMT1	DNA Methyltransferase 1
DNMT3A	DNA Methyltransferase 3A
DNMT3B	DNA Methyltransferase 3B
DRED	Direct Repeat Erythroid-Definitive Complex
EKLF	Erythroid Kruppel-Like Factor (KLF1)
ERF	ETS2 Repressor Factor
eRNA	Enhancer RNA
FDA	Food and Drug Administration
FOG1	Friend of GATA1
GATA1	GATA Binding Protein 1
GATA2	GATA-Binding Factor 2
H3K27ac	Histone H3 Lysine 27 Acetylation

HAT	Histone Acetyltransferase
Hb	Hemoglobin
HbA	Adult Hemoglobin
HbF	Fetal Hemoglobin
HBB	β-Globin Gene
HBE1	Hemoglobin Subunit Epsilon 1
HBG	Gamma-Globin Gene
HBG1/HBG2	Gamma-Globin Genes 1 and 2
HbS	Sickle Hemoglobin
HDAC	Histone Deacetylase
HIF1	Hypoxia-Inducible Factor 1
HMI-lncRNA	HBS1L-MYB Intergenic Long Noncoding RNA
HMT	Histone Methyltransferase
HPFH	Hereditary Persistence of Fetal Hemoglobin
HRE	Hypoxia Response Element
HSC	Hematopoietic Stem Cell
HSPC	Hematopoietic Stem and Progenitor Cell
HU	Hydroxyurea
HUDEP-2	Human Umbilical Cord Blood-Derived Erythroid Progenitor-2 Cells
KLF1	Kruppel-Like Factor 1
KLF3	Kruppel-Like Factor 3
KMT	Lysine Methyltransferase
LCR	Locus Control Region
LincRNA	Long Intergenic Noncoding RNA
LncRNA	Long Noncoding RNA
MAPK	Mitogen-Activated Protein Kinase
MiRNA	MicroRNA
mRNA	Messenger RNA
MYB	Myeloblastosis Oncogene
NcRNA	Noncoding RNA
NO	Nitric Oxide
NO–cGMP	Nitric Oxide–cyclic Guanosine Monophosphate
NRF2	Nuclear Factor Erythroid 2-Related Factor 2
NuRD	Nucleosome Remodeling and Deacetylase Complex
piRNA	PIWI-Interacting RNA
PIWI	P-element Induced Wimpy Testis
PIWIL	Piwi-like protein
PRMT	Protein Arginine Methyltransferase
RBP	RNA-Binding Protein
RISC	RNA-Induced Silencing Complex
ROS	Reactive Oxygen Species
SCA	Sickle Cell Anemia
SCD	Sickle Cell Disease
siRNA	Small Interfering RNA
SOX6	SRY-Box Transcription Factor 6
Sp1	Specificity Protein 1
STAT3	Signal Transducer and Activator of Transcription 3
SWI/SNF	Switch/Sucrose Non-Fermentable
THU	Tetrahydrouridine
TR2/TR4	Testicular Receptor 2/Testicular Receptor 4
UTR	Untranslated Region
VHL	Von Hippel–Lindau
VOC	Vaso-Occlusive Crisis
ZNF410	Zinc Finger Protein 410

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Conceptualization, writing—original draft preparation, visualization: S.M.; writing—review and editing: S.M., A.N.; supervision, project administration: S.S.N. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

During the preparation of this work, the authors used GPT 5.2 to provide grammar suggestions. After using this tool, the authors carefully reviewed and edited the content as required and take full responsibility for the content of the published article.

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