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Review Article

Noncoding RNAs: Emerging Modulators of β-Globin Regulation and β-Hemoglobinopathies

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Abstract

β-Hemoglobinopathies, including β-thalassemia and sickle cell anemia, are the most common autosomal recessive disorders, globally. Non-coding RNAs (ncRNAs) are derived from exons or introns of protein-coding genes or intronic regions of non-coding genes. There is significant evidence that these ncRNAs may act as protein decoys to impact a variety of biological functions, signaling, transcriptional regulators, cell differentiation, morphogenesis, and developmental regulation. The aberrant regulation of ncRNA expression serves as a hallmark of many hematological disorders, and there is solid evidence that these RNA species can play key roles in the pathogenesis of β-hemoglobinopathies. In the present review, we provide a summary of recent research findings about the role of ncRNA in *globin* gene regulation and β-hemoglobinopathies and their potential as therapeutic targets or prognostic and diagnostic biomarkers.

Keywords: ncRNA, hematopoiesis, β-thalassemia, sickle cell anemia, fetal hemoglobin, therapeutic targets

1. Introduction

A variety of non-coding RNAs (ncRNAs) that lack protein-coding potential has been identified to date. The ncRNAs are broadly categorized into two major classes based on sequence size including small ncRNAs (sRNAs) and long noncoding RNAs (lncRNAs), (Bartel, 2018; Dragomir et al., 2019; Maxwell & Fournier, 1995; Siomi, Sato, Pezic, & Aravin, 2011; Spizzo, Almeida, Colombatti, & Calin, 2012; Z. Zhang, Yang, & Xiao, 2018), they are further classified based on their function, as shown in Figure 1. Research interest in the molecular functions of ncRNAs has been steadily growing, particularly in the context of gene regulation through RNA/mRNA interaction. Following their initial discovery in the 1980s in the context of prokaryotic genome material, ncRNAs were subsequently detected in eukaryotic cells (Chen, Huang, Wang, & Shan, 2015; Hsu & Coca-Prados, 1979; Sanger, Klotz, Riesner, Gross, & Kleinschmidt, 1976).

β-hemoglobinopathies are the most common inherited disorders characterized by the aberrant production of hemoglobin (Hb) in the blood. The abnormal biochemical nature or lack of enough Hb in Red blood cells (RBCs), leads to a reduced supply of oxygen to tissues and organs. This may cause anemia and progress to more serious consequences, such as organ damage, which can

be life-threatening (Hamad Ali, Khan, & Musharraf, 2021a). These disorders are highly prevalent in African, Hispanic, Asian, Middle Eastern, West Indian, Italian, and Mediterranean ancestry (Kattamis, Forni, Aydinok, & Viprakasit, 2020)

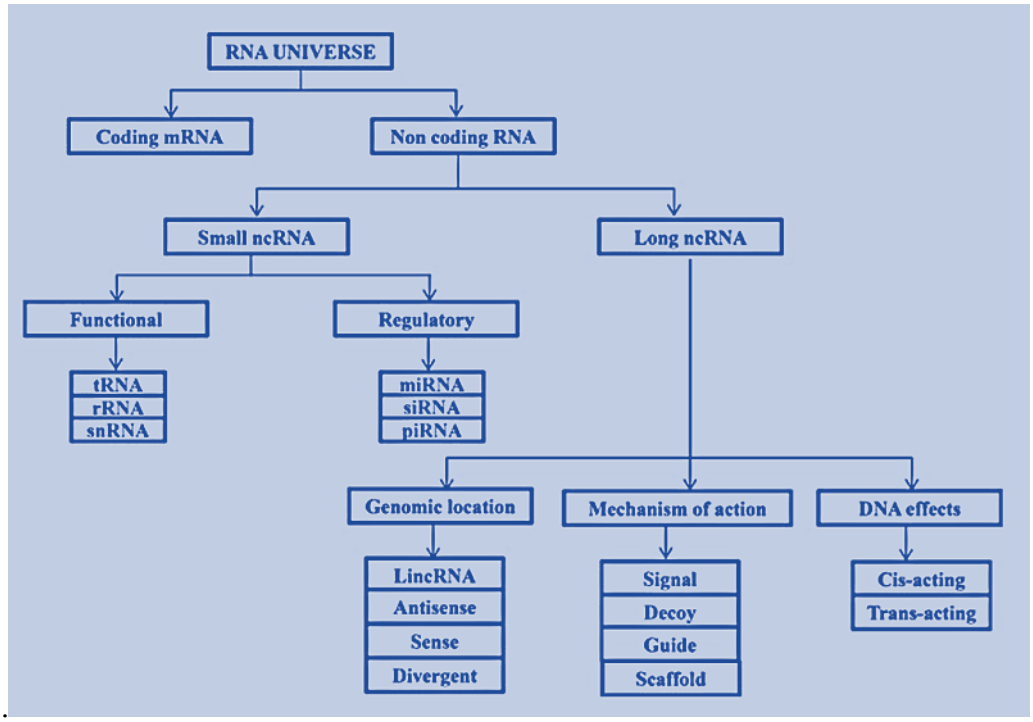

Figure 1: Classification of ncRNA (Srijyothi, Ponne, Prathama, Ashok, & Baluchamy, 2018).

Sickle cell disease (SCD), a β-globin disorder caused by the abnormal variant of hemoglobin called hemoglobin S (HbS) in red blood cells, which impart an abnormal, sickle shape to RBCs that are stiff and sticky, compromises the integrity of and ability of RBCs to transport oxygen associated with vasooclusive crises (Pecker & Lanzkron, 2021). β-thalassemia, a diverse group of β-hemoglobinopathies, is caused by reduced or lack in the production of functionally normal hemoglobin leading to ineffective erythropoiesis and anemia(F. Khan, Ali, & Musharraf, 2020; Thein & Wood, 2009).

Children with the β-thalassemia genotype experienced an asymptomatic condition during their first two years of life due to the continuing production of fetal hemoglobin (HbF). However, the transition to adult hemoglobin (HbA) develops the β-thalassemia phenotype which is characterized by severe anemia and may be fatal, if left untreated (Badawy, Beg, Liem, Chaudhury, & Thompson, 2021). At the molecular level β-hemoglobinopathies are caused either by direct mutation in the *β-globin* (*HBB*) gene or indirectly in *cis*-regulatory elements, or *trans*-acting elements and/or aberrant mRNA processing (Farashi & Harteveld, 2018; Lee, Im Cho, Park, & Seong, 2021). A transversion mutation (T > A) in the *HBB* gene encodes valine in place of glutamic acid in its β-globin subunits which leads to the production of hemoglobin S and sickle cell phenotype (Sundd, Gladwin, & Novelli, 2019). While Some *HBB* mutations either lead to decreased production of β-globin or completely inhibit the RBCs to synthesize β-globin and give rise β-thalassemia phenotype. β-hemoglobinopathies are autosomal

recessive, to be affected, a child should have to inherit both alleles with *HBB* mutation (Kavanagh, Fasipe, & Wun, 2022). A specific combination of *globin* gene mutations reflects the onset and severity of the phenotype, ranging from life-threatening to symptom-free phenotype. Hereditary persistent fetal hemoglobin (HPFH), a trait in which fetal hemoglobin continues to be expressed in adulthood, may confer a normal phenotype even in individuals with homozygous *HBB* mutations (Ju et al., 2022; Thein, 2005).

The available therapeutic strategies for β-hemoglobinopathies are few and mostly symptomatic to treat the anemia, including RBC transfusion, iron chelation, splenectomy, and fetal hemoglobin (Finotti & Gambari, 2014). Currently, bone marrow transplantation (BMT) is the only definitive treatment; however, allogenic BMT is not applicable in all circumstances, and the success rate of BMT is dependent on pre-transplantation conditions, the availability of an HLA-matched donor, transplant rejection, and the expense of the procedure (H. Ali et al., 2019; Gaziev & Lucarelli, 2003; La Nasa et al., 2005; H. Li et al., 2021). HbF induction, a pharmacological or druggable gene editing approach, is a molecular therapy for β-hemoglobinopathies. Only hydroxyurea (HU) got FDA approval as an HbF inducer, however, about 40% of the patients are typically non-responders to HU, and fail to achieve the desired level of HbF, while others are susceptible to myelosuppression which further worsens the condition (Hamad Ali, Khan, & Musharraf, 2021b; Sankaran, 2011)

The disease manifestations cannot be described exclusively by *HBB* mutations, since related mutations may create markedly distinct phenotypes. In addition to *globin* gene mutations, other molecular modifiers, such as epigenetic regulations, may impact the balance of hemoglobin subunits (Ardekani & Naeini, 2010; Bianchi et al., 2012). Epimutations tend to be stochastic, reversible, and mosaic; their incidence and inheritance principles diverge from Mendelian genetics (Chapelle & Silvestre, 2022; Peaston & Whitelaw, 2006). ncRNAs are one of the major contributors to the epigenetic process (Cao, 2014). The role of ncRNAs has been reported to be implicated in hematopoiesis and the pathogenesis of blood diseases (Alvarez-Dominguez & Lodish, 2017; Qiu, Xu, & Huang, 2021; Wilkes, Repellin, & Sakamoto, 2017).

Better insight into the molecular mechanisms governing the onset, pathophysiology, and severity of β-hemoglobinopathies is an unmet need to identify new diagnostic, therapeutic, and prognostic strategies suited to the management of this global healthcare burden. In this review, we focused on the regulatory roles and clinical implications of ncRNAs in β-hemoglobinopathies and reviewed the current state of research, enlightening the potential of the ncRNA pathways as therapeutic targets for sickle cell anemia and β-thalassemia.

2. Biological Functions of ncRNAs

ncRNAs are involved in a vast array of biological processes in health and sickness (Gayen, Maclary, Buttigieg, Hinten, & Kalantry, 2015), including X-chromosome inactivation (Gayen et al., 2015; Siniscalchi, Di Palo, Russo, & Potenza, 2022), telomere maintenance (Luke & Lingner, 2009), genomic imprinting (MacDonald & Mann, 2020), transcriptional interference, immunological response (Fok, Davignon, Fanucchi, & Mhlanga, 2019), epigenetic modifications, cell differentiation, cellular developmental processes (Dhanoa, Sethi, Verma, Arora, & Mukhopadhyay, 2018; Fok et al., 2019), and other biological functions, as shown in Figure 2. Some ncRNAs serve directly as regulators of transcription or splicing, whilst others function indirectly as miRNA sponges, protein decoys, or molecules capable of sequestering certain proteins (Kulcheski, Christoff, & Margis, 2016). ncRNAs have crucial regulatory and functional implications in cellular gene expression (Dykes & Emanueli, 2017).

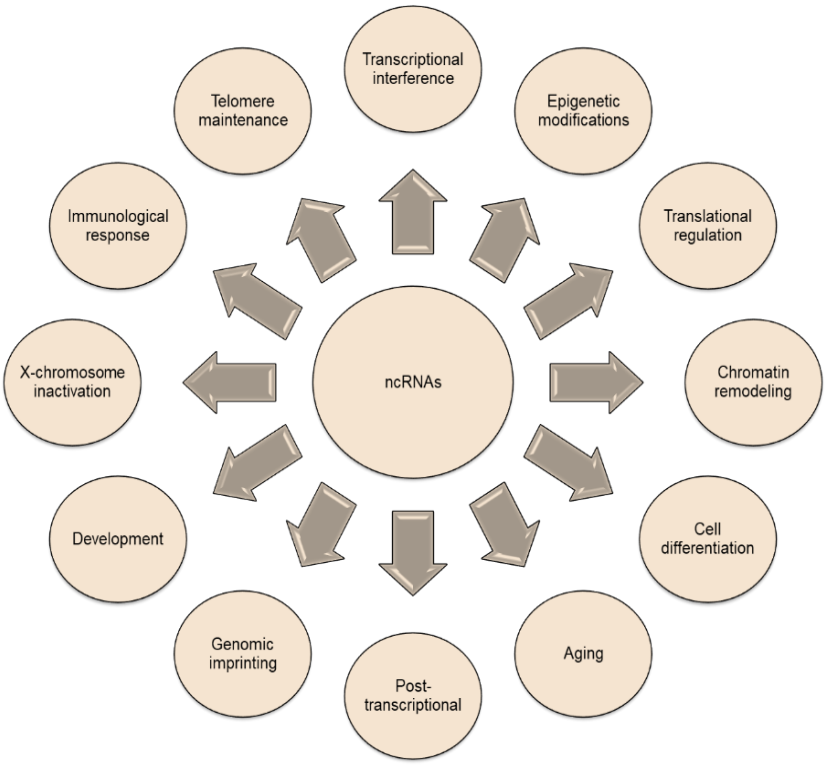

Figure 2: The biological roles of ncRNAs.

2.1. Role of ncRNA in Transcription Regulation

By blocking RNA polymerase II (pol II)recruitment or promoting chromatin remodeling, ncRNAs transcribed from an upstream promoter may have a favorable or negative impact on the expression of the downstream gene (Goodrich & Kugel, 2006). In eukaryotes, the telomeres are the functional nucleoprotein complexes that protect chromosome ends against breakdown and DNA damage responses. Genomic stability, senescence, and the aging process are all maintained by it (Luke & Lingner, 2009). In heterochromatin, telomeres are transcriptionally inactive DNA-protein complexes. Telomeres are transcribed in numerous species (e.g. *Homo sapiens, Mus musculus, Danio rerio*, yeast, plants) and produced lncRNA termed telomere repeat-containing RNA (TERRA). TERRA molecules regulate telomere length, telomerase activity, and chromosomal end heterochromatin. Changes in these molecules' expression may cause chromosomal instability and cell senescence (Redon, Reichenbach, & Lingner, 2010; Rossi & Gorospe, 2020). The majority of ncRNAs control transcription either directly or through competing with linear RNAs during splicing. By promoting RNA pol II elongation activity, ncRNA may regulate the transcription of the parental genes from which they are derived (Y. Zhang et al., 2013). Similarly, noncoding RNAs have cis-regulatory actions on their respective genes and may thus alter gene expression (Z. Li et al., 2015). The RNA pol II complex may interact with other ncRNAs, such as c-sirt7, to inhibit the expression of certain target genes, such as ankyrin repeat domain 52 (ANKRD52) and sirtuin 7 (SIRT7) (Rong et al., 2017). These previous findings suggest the capacity of certain ncRNAs to interact with the RNA pol II complex and other transcription-regulating proteins, therefore directly or indirectly regulating transcription.

2.2. Role of ncRNA in Translation Regulation

Since the majority of ncRNAs are expressed in the cytoplasm, they can function as post-

transcriptional regulators. miRNAs, which are short (22 nucleotides) noncoding RNAs that influence gene expression in several physiologic and pathologic conditions, and play well-established regulatory roles (Gebert & MacRae, 2019). By functioning as miRNA sponges or competing endogenous RNAs (ceRNAs), non-coding circRNAs may bind to and sequester miRNAs, preventing them from interacting with their target mRNAs to inhibit gene expression (Bak & Mikkelsen, 2014; Ebert & Sharp, 2010; Kulcheski et al., 2016).

Several ncRNAs may influence cellular physiology by engaging with certain RNA-binding proteins (RBPs) and functioning whether as protein decoys to restrict protein activity or as scaffolds to allow the interactions between the other proteins, therefore indirectly controlling transcriptional activity. RBPs have a regulatory function in practically all cellular processes, influencing cellular proliferation, growth, and survival in a variety of conditions (J. Liu, Liu, Wang, & He, 2017). As a decoy, lncRNAs bind target molecules such as trans-acting factors, chromatin remodelers, other regulatory factors, and RBP, as well as RNA molecules such as miRNAs. By interacting with lncRNAs, all these target molecules will stay functionally silent (W. Li, Ren, Si, Wang, & Yu, 2018).

3. The role of ncRNA in Hematopoiesis

It has been suggested that miRNAs play a significant role in hematopoiesis, where they are involved in the determination of cell fate, proliferation, differentiation, as well as cancer pathogenesis and progression. (Bissels, Bosio, & Wagner, 2012; Garzon & Croce, 2008). Several miRNAs have been identified as potentially being important in the development and maturation of erythroid cells (Lawrie, 2010). It has been reported that erythropoiesis is promoted by miR-144 and miR-451 (Rasmussen et al., 2010), however, negatively regulated by miR-150, miR-221, miR-222, and miR-223 (Felli et al., 2005; Felli et al., 2009; Lu et al., 2008). It was found that the microRNAs miR-15b, miR-16, miR-22, and miR-185 all had a substantial positive association with the presence of erythroid surface markers and the production of hemoglobin (Lawrie, 2010; Noh et al., 2009). Altered expression of certain miRNAs may cause dramatic phenotypes, which can then lead to serious hematological abnormalities. On the other hand, targeted manipulation of miRNA expression has been proposed as a novel strategy for the development of new therapeutic interventions.

Li et.al., identified miR-199b-5p as a critical regulator of human erythropoiesis, and its transcription was up-regulated during K562 cells' erythroid maturation. Moreover, during erythropoiesis, miR-199b-5p levels increased in a GATA-1 (a master erythroid transcription factor) and Nuclear Factor-Erythroid-2 (NF-E2) dependent manner. GATA-1 and NF-E2 both are associated with the miR-199b gene and stimulated its transcription. miR-199b-5p induced expression in K562 cells influenced erythroid cell proliferation and maturation. It has been reported that the c-kit pathway is a direct target of miR-199b-5p in erythroid cells. suggesting new insights into the linkage of transcription and post-transcription regulation in erythroid development (Y. Li, Bai, & Zhang, 2014). Several other ncRNAs, including miR-15a, miR-16–1, miR-126, miR-144, miR-451, and miR-210, were shown to have a crucial role in erythroid development. Multiple processes associated with erythroid cells, including maturation and proliferation of early erythroid cells, expression of fetal -globin, and maturation, are controlled by these miRNAs. These revealed that erythroid-specific miRNAs serve as the foundation for the development of novel miRNA-based treatments based on both anti-miR compounds and miRNA substitution (Bianchi et al., 2012).

Table 1: lncRNA in Pathogenesis of β-Thalassemia.

lncRNAs	Role in thalassemia/β -globin regulation	References
UCA1	Heme metabolism regulation in human erythroid cells. UCA1 may target the RNA-binding protein PTBP1, and the resultant complex can stabilize the ALAS2 mRNA.	(Jinhua Liu et al., 2018)
BGLT3	γ-Globin transcription regulation by interacting with the β-locus control region	(Ivaldi et al., 2018)
ShincRNA-EC6	Promote erythroid enucleation by inhibiting Rac1 and its downstream target PIP5K expression.	(C. Wang et al., 2015)
AlncRNA-EC7	*Band 3* gene expression is regulated to promote erythrocyte maturation and subsequent enucleation.	(Alvarez-Dominguez et al., 2014)
LincRNA-Saf	Promote the maturation of RBC by binding GATA-1 and KLF1.	(Villamizar et al., 2016)
LincRNA-EPS	Decreasing apoptosis and increasing differentiation.	(Hu, Yuan, Flygare, & Lodish, 2011)
Antisense noncoding RNA in the Inhibitors of CDK4 (*INK*) locus (ANRIL)	Hematopoietic differentiation, proliferation, and stress response. Identifying the etiology and phenotypic characteristics of people with the β-thalassemia.	(Fakhr-Eldeen, Toraih, & Fawzy, 2019)
Myocardial infarction associated transcript (MIAT)	Increased MIAT expression in β-thalassemia is related to dysfunctional endothelium. The higher severity of β-thalassemia may be connected with upregulated expression.	(Fakhr-Eldeen et al., 2019) (Tsuiji et al., 2011)
Metastasis associated Lung adenocarcinoma transcript 1 (MALAT1)	MALAT1 expression as an adaptive response to increased DNA damage is one of the key contributors to the phenotype and consequences of thalassemia. Identifying the etiology and phenotypic characteristics of people with the β-thalassemia.	(Fakhr-Eldeen et al., 2019)
HMI-lncRNA	Role in triggering HbF	(Morrison et al., 2018)
lincRNA-TPM1	Control the β-thalassemia clinical phenotypes	(Ma et al., 2017)
XIST	Control the β-thalassemia clinical phenotypes	(Ma et al., 2017)
DQ583499	Control the β-thalassemia clinical phenotypes	(Ma et al., 2017)
lincRNA-RUNX2- 2	Control the β-thalassemia clinical phenotypes	(Ma et al., 2017)
MRFS16P	Control the β-thalassemia clinical phenotypes	(Ma et al., 2017)
lncRNA-αGT	Regulating the expression of *α-globin*	(Arriaga-Canon et al., 2014)
NR_001589, NR_120526 and T315543	Elevated HbF. *Epsilon-1 globin (HBE1)* activation and hemopoietic cell lineage-inducible factors inhibit the expression of apoptosis-inducible proteins	(Lai, Jia, Yu, Luo, & He, 2017)
HMI-lncRNA (*MYB* enhancer RNA)	Downregulation increased *γ-globin* *Gene (HBG)* expression in erythroid cells	(Morrison et al., 2018)

4. Implications of ncRNA in β-thalassemia Phenotype

Even though a similar mutation might on occasion yield a dramatically different phenotype, the phenotypes that are associated with β-thalassemia cannot be entirely explained by mutations in the *β-globin* gene. Other molecular modifiers, such as epigenetic controls, may also affect the production or equilibrium of hemoglobin molecules (Hanly, Esteller, & Berdasco, 2018; Ma, Liu, Du, Ma, & Xiong, 2017). Epimutations tend to be random, reversible, and heterogeneous (Martin, Ward, & Suter, 2005). The family of non-coding RNAs, lncRNAs, is one of the most

important players that contribute to the epigenetic process
(Engreitz, Ollikainen, & Guttman, 2016; Hanly et al., 2018). In addition to this, there have been reports that it has a role in the process of hematopoiesis as well as the pathogenesis of blood diseases (Nobili, Lionetti, & Neri, 2016). It has been reported that lncRNAs have a relation to the clinical phenotype of β-thalassemia through the implications they have with their target genes in several phenotype-related pathways, Table 1. These pathways include the response to hypoxia and the development of muscle organs, which contribute to the emergence of histanoxia. Histanoxia is caused by elevated HbF levels and dysontogenesis in β-thalassemia major patients (Ma et al., 2017).

5. The role of ncRNA in HbF Regulation.

Although HbF is the most predominant form of hemoglobin at the fetal stage, its levels gradually decrease after birth and are mostly replaced by adult Hb (HbA). At six months after birth, HbF accounts for less than five percent of the total Hb, and this percentage continues to fall, reaching an adult level of less than one percent by the age of two (Bou-Fakhredin, De Franceschi, Motta, Cappellini, & Taher, 2022; Mukherjee et al., 2021). Some pathological stages of β-thalassemia and non-pathological disorders such as HPFH keep HbF levels high, the patients may have mild phenotype and transfusion independent. High HbF levels may reduce the clinical and hematological severity of β-thalassemia major (Forget, 1998; Steinberg, 2020; Tuan, Murnane, DeRiel, & Forget, 1980). However, the molecular mechanisms of HbF induction in β-thalassemia remain obscure. Therefore, a better understanding of the relevant mechanism is critical for improved treatment of β-thalassemia major. Additionally, there is an urgent need to identify therapeutic targets focused on HbF. miRNAs regulate globin gene translation by post-transcriptional gene silencing during erythroid production and maturation (Bianchi et al., 2012; Peixeiro, Silva, & Romão, 2011; Saki et al., 2016). Several miRNAs such as miR-15a, miR-16-1, and miR-486-3p may stimulate *γ-globin* gene expression and HbF production by suppressing trans-acting factors, MYB and BCL11A, during *β-globin* gene expression (Eltaweel, ElKamah, Khairat, Atia, & Amr, 2021). Despite this, there have been no studies done so far that have compared β-thalassemia carriers who have high HbF levels to normal controls to examine the expression of miRNAs in HbF induction. The discovery of miRNA-mediated HbF induction pathways might be made by further investigation of abnormally expressed miRNAs in patients with HPFH and β-thalassemia minor who have high HbF.

Different types of miRNAs have been associated with the reactivation of the *γ-globin* gene and enhanced HbF production, as well as the developmental regulation of globin gene expression (Byon & Papayannopoulou, 2012; Lawrie, 2010). The HbF persistence varies substantially between adults, and this heterogeneity is mostly genetically determined. (Bauer, Kamran, & Orkin, 2012; Bou-Fakhredin et al., 2022; Sankaran, Xu, & Orkin, 2010). Over the past two decades, attempts to enhance HbF synthesis have been driven by the concept that increased HbF alleviates the severity of β-hemoglobinopathies (Hamad Ali et al., 2021b; Bou-Fakhredin et al., 2022).
High miR-210 levels were found to be associated with elevated γ-globin levels

(Bianchi, Zuccato, Lampronti, Borgatti, & Gambari, 2009), whereas the let-7 family has been linked to hemoglobin switching (Noh et al., 2009). Furthermore, miR-221 and miR-222, have been found as modulators of HbF production in erythropoietic cells through the kit receptor (Gabbianelli et al., 2010).

Sankaran et al., have shown that high levels of fetal and embryonic hemoglobin gene expression are caused by higher levels of miR-15a and miR-16-1 expression in human erythroid cells (Sankaran et al., 2011). The underline mechanism is partially mediated by the down-regulation of MYB, a *γ-globin* gene suppressor. miRNA-96 was demonstrated to be a negative regulator of HbF expression via the direct post-transcriptional regulation of *γ-globin* mRNA in erythroid precursors (Azzouzi et al., 2011).

BCL11A, a zinc finger protein, is involved in the ontogenic regulation of hemoglobin switching and suppression of *γ-globin* transcription in adults (Sankaran et al., 2008; Sankaran et al., 2009). BCL11A is necessary for proper lymphocyte development and is usually implicated in lymphoid cancers (P. Liu et al., 2003). BCL11A inhibition in erythroid cells promoted γ-globin and HbF synthesis without altering erythroid differentiation. Similar to MYB, BCL11A controls HbF levels by direct transcriptional regulation of the *γ-globin* gene, rather than via altering erythroid kinetics (Hamad Ali et al., 2021a; Faisal Khan, Ali, & Musharraf, 2022; Thein et al., 2007; Xu et al., 2010). Lulli et. al. reported the role of miR-486-3p in controlling HbF expression in adult $CD34^{+}$ erythroid cells through modulating BCL11A. The *human Ankyrin-1* (ANK1) gene on Chr. 8p11 encodes miR-486-3p along with miR-486-5p. It has been shown that miR-486-3p is expressed exclusively in adult erythroid cells, which directly targets BCL11A mRNA, and post-transcriptionally inhibits the BCL11A protein, modifying *γ-globin* expression during adult erythropoiesis (Lulli et al., 2013). Increased expression of miR-26b, miR-151-3p, miR-148a, and miR-494 has been found in SCD patients treated with hydroxyurea, an HbF-inducing drug (Walker et al., 2011; Walker, Steward, Wang, Smeltzer, & Ware, 2010). Overexpression of miR-26b, in particular, stimulated the expression of the *γ-globin* gene in K562 cells (F. Wang, Ling, & Yu, 2021).

Disruptions of circRNA-miRNA-mRNA have been associated with several hematological diseases. In the context of β-globin disorders, Fang et, al. studied the circRNAs in the β-thalassemia trait with elevated HbF levels and compared them with those of healthy persons. There was a differential expression of 2,183 circRNAs, and their associations with hematological parameters were evaluated. For example, the Downregulation of hsa-circRNA-100466 revealed a substantial negative association with HbF and HbA2 levels. Furthermore, the hsa-circRNA-100466-miR-19b-3p-SOX6 axis was found to be involved and showed that hsa-circRNA-100466 and SOX6 were dramatically down-regulated whereas miR-19b-3p was significantly up-regulated, SOX6 is a well-known repressor for γ-globin (Hamad Ali et al., 2021a; Yang et al., 2022). While many more circRNAs have been identified to serve as miRNA sponges so far, only a portion of these regulating ceRNAs have been extensively explored, and further research is required to explore the roles of other circRNAs and their target miRNAs in the context of globin gene regulation and potential therapeutic targets for β-thalassemia.

6. Potential Role of ncRNA in Dignoisis of β-thalassemia

Currently, β-thalassemia is diagnosed using clinical history, physical exam, complete blood count (CBC), and electrophoresis or high-performance liquid chromatography of (HPLC) of hemoglobin. However, there is a need to enhance β-thalassemia detection and diagnosis. The abnormal transcription patterns of ncRNA in erythrocytes and their progenitors, as well as blood samples from β-thalassemia patients, have the potential to serve as diagnostic biomarkers for β-thalassemia. According to Abeer et al., molecular profiling of the three lncRNAs from serum samples showed that thalassemia patients had considerably greater expression levels of ANRIL, MALAT1, and MIAT compared to the control group (Fakhr-Eldeen et al., 2019). Other lincRNAs that control β-thalassemia phenotype include lincRNA-TPM1, XIST, DQ583499, lincRNA-RUNX2- 2, and MRFS16P (Ma et al., 2017). These ncRNA might help clinicians better grasp the disease's etiology and diagnosis.

7. Conclusions and Future Prospective

The high expression levels, stability, and aberrant expression patterns of ncRNAs during the pathological state make ncRNA promising candidates for use as prognostic and diagnostic biomarkers of blood disease. The direct regulatory involvement of some of the ncRNAs, mentioned in this review, in hematopoiesis and β-hemoglobinopathies may suggest promising new avenues for the treatment of β-globin disorders. In conclusion, there is mounting evidence that ncRNAs modulate crucial events during hematopoiesis, such as proliferation, cell cycle progression, differentiation maturation, apoptosis, and the regulation of the *β-globin* locus. As shown above, ncRNAs may influence the phenotype of thalassemia patients in a variety of ways and play a variety of regulatory functions in both healthy and diseased conditions. A better understanding of the functional significance and clinical relevance of these ncRNAs will be essential to facilitate their translational application for the diagnosis, prognosis, and therapeutic interventions for β thalassemia, clinically. However, there have only been a small number of studies specifically evaluating the impact of ncRNAs HbF induction and clinal implication in β-globin disorders. Future investigations of the potential of specific ncRNAs to influence this dynamic milieu may provide more intuitions into the molecular basis of β-globin disorders and discover additional treatment targets. Furthermore, new insights into these ncRNA species concerning β-globin disorders and a systematic understanding of the mechanisms responsible for ncRNA fate determination will help to direct the proposal of novel diagnostic, prognostic, and therapeutic interventions that will aid in extending the patient's survival and improved quality of life.

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Authors Contribution

HA conceptualized the review. HA and FK, did the literature search, collected relevant studies, and wrote the final manuscript. All

the authors have read and approved the final version of the manuscript

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