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Mechanisms of Poor Fetal Hemoglobin (Hb F) Induction by Hydroxyurea in Sickle Cell Disease and β-Thalassemia: A Review

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Abstract

Hydroxyurea (HU) is the cornerstone pharmacologic agent for inducing fetal hemoglobin (Hb F) in sickle cell disease (SCD) and β-thalassemia. Although it has demonstrated substantial clinical benefits, a subset of patients exhibits suboptimal Hb F response, limiting its therapeutic efficacy. This mini-review summarizes current knowledge on the mechanisms of poor Hb F induction with HU, focusing on genetic polymorphisms in key quantitative trait loci (BCL11A, HBS1L-MYB, and HBG2), epigenetic regulation of γ-globin gene expression, and pharmacokinetic variability driven by differences in drug metabolism and clearance. We also discuss the clinical implications of these resistance mechanisms and potential strategies to enhance HU responsiveness, including precision medicine approaches and emerging adjunct therapies. Understanding these factors is essential for optimizing Hb F induction and improving outcomes in hemoglobinopathies.

Introduction

Sickle cell disease (SCD) and β-thalassemia are among the most prevalent inherited hemoglobinopathies worldwide, contributing significantly to global morbidity and mortality, especially in sub-Saharan Africa, the Middle East, and South Asia **[1,2]**. SCD results from a point mutation in the β-globin gene (HBB), leading to sickle hemoglobin (Hb S) production, erythrocyte sickling, vaso-occlusion, and chronic hemolysis **[3,4]**. β-Thalassemia arises from mutations causing reduced or absent β-globin synthesis, resulting in ineffective erythropoiesis, anemia, and iron overload due to transfusion dependence **[5]**.

Fetal hemoglobin (Hb F; $\alpha_2\gamma_2$) has long been recognized as a major disease modifier. Its continued expression inhibits Hb S polymerization and ameliorates the ineffective erythropoiesis of β-thalassemia **[6,7]**. Patients with elevated Hb F levels due to hereditary persistence of fetal hemoglobin (HPFH) or pharmacologic induction often experience fewer complications and better survival outcomes **[8]**.

Hydroxyurea (HU) is the first and only FDA-approved disease-modifying therapy for SCD and is widely used off-label in β-thalassemia intermedia **[9]**. HU increases Hb F by inducing stress erythropoiesis, altering erythroid differentiation, and potentially affecting nitric oxide signaling and γ-globin gene activation **[10-13]**. Clinical trials have demonstrated that HU reduces painful crises, acute chest syndrome, and transfusion needs while improving survival in SCD **[14,15]**. However, inter-patient variability in HU response remains a major clinical challenge, with approximately 20–30% of patients demonstrating suboptimal Hb F induction **[16,17]**.

This variability in response is multifactorial. Genetic determinants, including single nucleotide polymorphisms (SNPs) in BCL11A, HBS1L-MYB, and the XmnI site (−158 C>T), influence baseline Hb F levels and response to HU **[18,19]**. Epigenetic mechanisms such as DNA methylation and histone modifications maintain γ-globin silencing and may limit HU's efficacy **[20,21]**. Furthermore, microRNAs (miRNAs) have emerged as key post-transcriptional regulators of γ-globin gene expression **[22]**. Pharmacokinetic factors, influenced by polymorphisms in genes such as CYP2D6, CAT, and SLC14A1, can also affect HU bioavailability and therapeutic outcomes **[23,24]**.

This mini-review explores these mechanisms of HU resistance and highlights current and future strategies to overcome them.

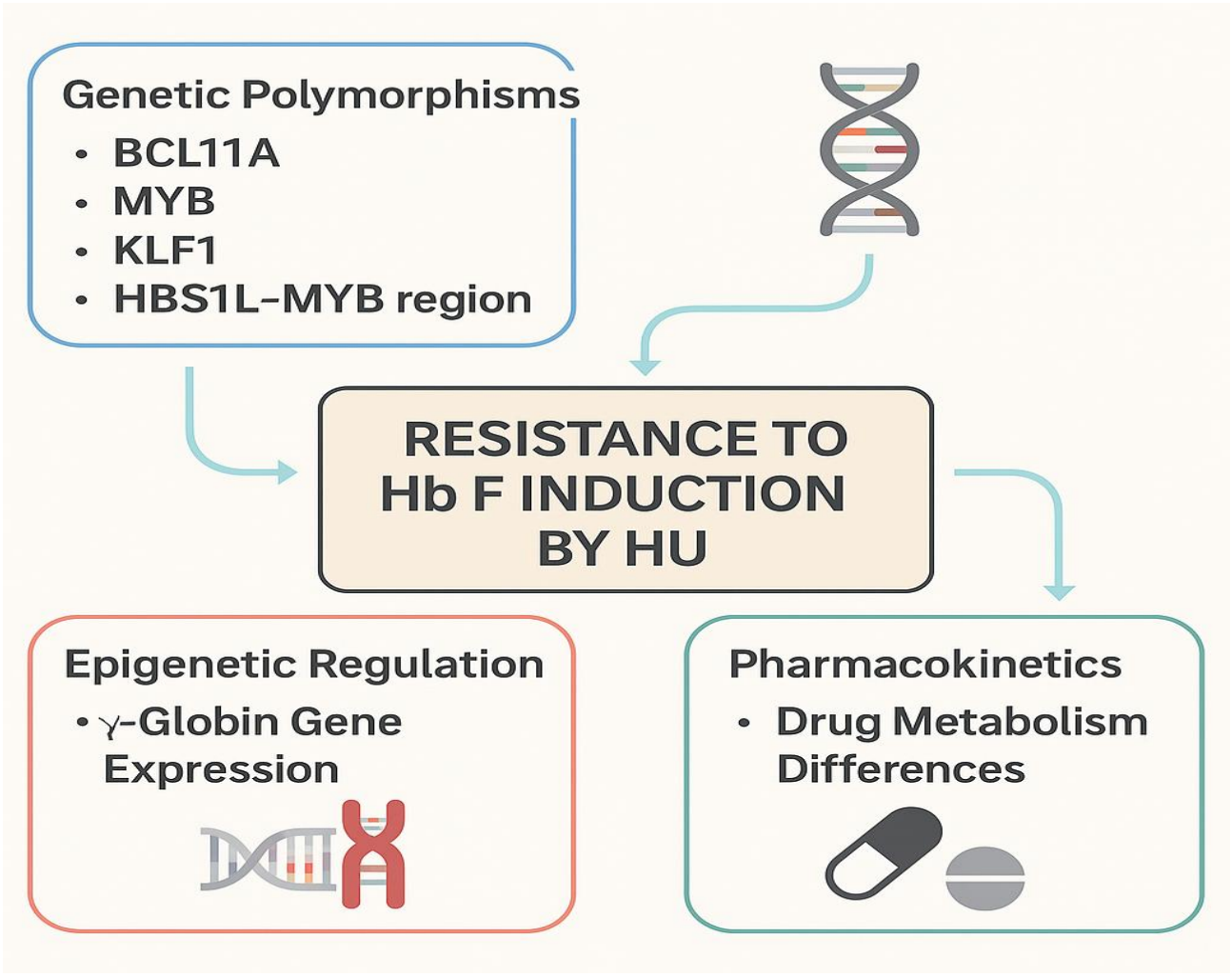

Figure 1. Mechanisms of Resistance to Hb F Induction by Hydroxyurea

Discussion

1. Genetic Determinants of HU Response

Genetic polymorphisms in Hb F-associated loci significantly influence HU response. Variants in BCL11A, a key γ-globin repressor, are strongly associated with higher baseline Hb F levels and improved HU responsiveness **[18]**. Similarly, SNPs in the HBS1L-MYB intergenic region modulate erythroid differentiation and Hb F expression **[19]**. The XmnI (−158 C>T) polymorphism upstream of HBG2 correlates with enhanced Hb F production in response to HU **[20]**. Studies have also implicated genes involved in stress erythropoiesis, such as ARG1, SAR1A, and NOS1, though findings remain heterogeneous **[21]**.

2. Epigenetic and Transcriptional Regulation

Epigenetic repression of γ-globin genes involves DNA methylation and histone deacetylation. HU may partially reverse these modifications by inducing stress erythropoiesis and activating pathways that downregulate repressors such as BCL11A and KLF1 **[22]**. miRNAs, including miR-15a, miR-26b, and miR-151-3p, have been identified as mediators of γ-globin reactivation via suppression of these transcriptional repressors **[23]**. However, inter-individual differences in epigenetic regulation may underlie resistance in some patients.

3. Pharmacokinetic Variability

HU bioavailability and metabolism vary widely among individuals. Polymorphisms in CYP2D6, CAT, and SLC14A1 can affect drug absorption, distribution, and clearance **[24,25]**. Rapid metabolism or poor absorption may lead to subtherapeutic HU levels, contributing to poor Hb F induction. Population pharmacokinetic models support the potential for genotype-guided HU dosing strategies to optimize therapy **[26]**.

4. Clinical Implications and Future Directions

The identification of genetic and epigenetic biomarkers for HU responsiveness has enabled the development of predictive algorithms to guide personalized therapy. Adjunct treatments, such as DNA methyltransferase inhibitors (decitabine) and histone deacetylase inhibitors, are under investigation to augment HU-induced Hb F production **[27]**. Gene-editing technologies targeting BCL11A and other repressors represent promising avenues for achieving sustained Hb F induction in poor HU responders **[28]**.

Conclusion

Poor Hb F induction with HU therapy in SCD and β-thalassemia is a complex phenomenon involving genetic, epigenetic, and pharmacokinetic factors. A precision medicine approach incorporating predictive genomics and pharmacogenetics may improve treatment outcomes. Further research into adjunct therapies and novel agents targeting Hb F repression pathways holds promise for patients who are resistant to HU.

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