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Linking fetal hemoglobin gamma - chain variants to gestational diabetes: a CRISPR–Cas9 investigative model

Abstract

Gestational diabetes mellitus (GDM) is characterized by progressive insulin resistance and enhanced hepatic gluconeogenesis during pregnancy. Elevated alanine aminotransferase (ALT) levels are associated with increased GDM risk. Fetal hemoglobin (HbF, $\alpha_2\gamma_2$) contains γ-globin variants at position 136, where glycine (Gγ) or alanine (Aγ) residues are present. We propose that γ-chain composition may influence erythrocyte metabolic function and indirectly modulate systemic alanine–pyruvate flux rather than serving as a direct amino acid source. This hypothesis integrates γ-globin polymorphisms with erythrocyte metabolic signaling, ALT-mediated alanine transamination, and hepatic metabolic adaptation during pregnancy. A CRISPR–Cas9 investigative framework is proposed using patient-derived $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) from women with GDM. Multiple genome-editing strategies—including HBG1 knock-in, BCL11A erythroid enhancer disruption, and promoter editing—are discussed. Evaluation of metabolic flux, insulin signaling, and erythroid function, alongside assessment of long-term efficacy and safety, may provide insight into a previously unexplored link between fetal hemoglobin composition and gestational metabolic dysregulation.

Keywords: Gamma-globin variants, alanine–pyruvate metabolism, erythrocyte metabolism, $CD34^+$ cells, CRISPR–Cas9 genome editing

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Abbreviations: HbF, fetal hemoglobin; GDM, gestational diabetes mellitus; HSPCs, hematopoietic stem and progenitor cells

Introduction

Gestational diabetes mellitus (GDM) develops during the second half of pregnancy and is characterized by progressive insulin resistance and increased hepatic glucose production.[1] Elevated alanine aminotransferase (ALT) levels—even within the upper normal range—are independently associated with increased GDM risk.[2] ALT catalyzes the reversible transamination of alanine to pyruvate, a central step in hepatic gluconeogenesis.[3,4] Fetal hemoglobin (HbF, $\alpha_2\gamma_2$) differs structurally from adult hemoglobin and contains two γ-globin variants (Gγ and Aγ), distinguished by a glycine-to-alanine substitution at position 136.[5,6] Although this substitution does not significantly alter oxygen affinity, it represents a subtle biochemical variation within erythroid cells.[5] Rather than acting as a direct contributor to circulating amino acids, we hypothesize that γ-globin polymorphisms may influence erythrocyte intracellular metabolism, redox balance, and amino acid handling.[7] These changes may indirectly affect systemic alanine–pyruvate cycling (Cahill cycle), thereby modulating hepatic gluconeogenesis and insulin sensitivity during pregnancy.[3,4]

Proposed mechanism

Erythrocyte metabolic modulation: Erythrocytes play an active role in systemic metabolism through redox regulation and metabolite exchange.[7] Variations in γ-globin structure may subtly influence intracellular amino acid handling, redox balance, and metabolic flux.[7]

Systemic alanine–pyruvate flux: Alanine is a key gluconeogenic substrate transported to the liver, where ALT catalyzes its conversion to pyruvate.[3] Alterations in erythrocyte-mediated metabolite exchange may influence circulating alanine availability and flux.[4,7]

Hepatic insulin resistance: Increased pyruvate availability may enhance gluconeogenesis and lipogenesis, contributing to hepatic insulin resistance a hallmark of GDM.[1,4]

Model system: patient-derived $CD34^+$ HSPCs

Patient-derived $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) from pregnant women with GDM provide a physiologically relevant model to investigate this hypothesis.[8,11] These cells preserve patient-specific metabolic programming and can be differentiated into erythroid lineages in vitro.[8] $CD34^+$ cells may be isolated from peripheral or cord blood using magnetic or flow cytometric sorting and differentiated into erythroblasts under controlled conditions.[8] This system enables evaluation of γ-globin expression, HbF levels, and intracellular metabolite profiles, including alanine and pyruvate.[7,8] Importantly, comparison between GDM and normoglycemic pregnancies allows assessment of disease-specific metabolic signatures and their interaction with γ-globin variants.[1,2]

CRISPR–Cas9 investigative strategies

CRISPR–Cas9 enables targeted genome editing via RNA-guided DNA cleavage, followed by repair through non-homologous end joining or homology-directed repair.[9,11]

HBG1 knock-in strategy: Precise editing of the HBG1 gene to introduce the Ala136→Gly substitution allows direct testing of the proposed mechanism.[6,9] However, homology-directed repair efficiency in HSPCs remains limited and may affect cell viability.[11]

BCL11A erythroid enhancer disruption: BCL11A is a key repressor of γ-globin expression. Disruption of its erythroid-specific enhancer results in robust HbF induction and represents a highly efficient and clinically validated strategy.[10] This approach enables functional amplification of γ-globin–related metabolic effects.[10,11]

HBG promoter editing: Editing promoter regions to mimic hereditary persistence of fetal hemoglobin (HPFH) can increase γ-globin expression but may carry risks of genomic instability due to locus homology.[6,11]

Emerging editing technologies: Base editing and prime editing offer precise modification without double-strand breaks, reducing genotoxicity and improving safety profiles.[13,14]

Evaluation metrics

Molecular and editing efficiency

I. On-target editing efficiency (NGS-based).[11]

II. Off-target mutation profiling.[12]

Hematologic outcomes

I. HbF percentage.[10]

II. γ-globin expression.[5,6]

III. Erythroid differentiation capacity.[8]

Metabolic assessment

I. Alanine and pyruvate concentrations.[3,4]

II. ALT activity.[2]

III. Stable isotope tracing of metabolic flux.[7]

Functional assays

I. Hepatocyte co-culture models

II. Glucose production assays.[4]

III. Insulin signaling pathways.[1,4]

Long-term efficacy and safety considerations

Long-term efficacy

Edited HSPCs must retain self-renewal capacity and demonstrate stable engraftment.[11] Sustained HbF expression has been demonstrated in clinical gene-editing studies.[10]

Genotoxicity risks

CRISPR–Cas9 editing may introduce off-target mutations, large deletions, or chromosomal rearrangements.[12] DNA damage responses, including p53 activation, may affect stem cell function.[12]

Immune responses

Potential immune reactions include pre-existing immunity to Cas9 proteins and inflammatory responses to edited cells.[11]

Clinical safety considerations

Myeloablative conditioning regimens and ex vivo manipulation introduce additional risks, including toxicity and genomic instability.[11,12]

Conclusion

We propose that γ-globin polymorphisms may influence erythrocyte metabolic signaling rather than directly contributing amino acids to systemic metabolism.[7] Through modulation of alanine–pyruvate cycling, these effects may contribute to hepatic gluconeogenesis and insulin resistance in GDM.[3,4] A CRISPR–Cas9-based investigative framework using patient-derived $CD34^+$ HSPCs provides a powerful platform to test this hypothesis.[8,9] Integration of genome editing, metabolomics, and functional assays may uncover a novel link between fetal hemoglobin composition and gestational metabolic regulation.

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None.

Conflicts of interest

The author declares that there are no conflicts of interest.

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