Advancing Early Prediction of Gestational Diabetes Mellitus with Circular RNA Biomarkers

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Abstract

Gestational diabetes mellitus (GDM) is a common pregnancy complication associated with adverse maternal and neonatal outcomes. Early prediction is crucial for implementing timely interventions. Circular RNAs (circRNAs), a novel class of endogenous non-coding RNAs with covalently closed loop structures, have emerged as promising biomarkers due to their high stability, abundance in plasma, and tissue specificity. This review explores the potential of circRNAs as diagnostic tools for early prediction of GDM. We analyze the mechanisms through which circRNAs modulate glucose metabolism and insulin sensitivity, highlight recent studies identifying specific circRNA signatures in early pregnancy, and discuss their potential clinical applications. The integration of circRNA profiling in prenatal care could revolutionize GDM prediction, enabling precision medicine approaches to maternal health.

Keywords: Gestational diabetes mellitus; Circular RNA; biomarkers; Early prediction; Pregnancy; Insulin resistance; Non-coding RNA; Precision medicine; Gene regulation; Molecular diagnostics

INTRODUCTION

Gestational diabetes mellitus (GDM) affects 7–14% of pregnancies globally and is characterized by glucose intolerance first recognized during pregnancy [1]. GDM poses risks such as preeclampsia, macrosomia, and future development of type 2 diabetes mellitus (T2DM) in both the mother and child [2]. Conventional screening using the oral glucose tolerance test (OGTT) is typically performed in the second trimester, limiting the window for early intervention.

Recent advancements in molecular biology have shifted attention toward non-invasive biomarkers detectable in early pregnancy. Among these, **circular RNAs (circRNAs)** have gained prominence. CircRNAs are single-stranded, covalently closed-loop RNA molecules generated by back-splicing events of pre-mRNAs [3]. They are highly stable in peripheral blood, making them attractive candidates for biomarker discovery.

This article discusses the biological roles of circRNAs, summarizes current evidence linking circRNA dysregulation to GDM, and explores their potential as early predictive tools in clinical obstetrics.

DESCRIPTION

Circular RNAs: characteristics and biological functions

CircRNAs differ from linear RNAs in structure and function. Their circular configuration renders them resistant to exonuclease-mediated degradation, conferring greater stability in bodily fluids [4]. They are derived from coding and non-coding genes and often regulate gene expression by acting as microRNA (miRNA) sponges, modulating transcription, or interacting with RNA-binding proteins [5].

Pathophysiology of GDM and potential circRNA involvement

GDM is primarily caused by progressive insulin resistance and inadequate compensatory insulin secretion during pregnancy. Inflammatory cytokines, placental hormones, and metabolic stress contribute to these alterations [6]. CircRNAs may influence these processes through miRNA sponging, affecting genes involved in insulin signaling, beta-cell function, and glucose metabolism.

Results

Recent transcriptomic studies have identified differentially expressed circRNAs in the plasma and placental tissue of GDM patients.

- Chen profiled circRNA expression in first-trimester plasma and identified circ_0008285 as significantly upregulated in women who later developed GDM [7].
- Liu found circHIPK3 downregulated in placental tissues of GDM patients, suggesting its role in beta-cell dysfunction and glucose transport [8].
- Zhang conducted a longitudinal cohort study and reported a predictive circRNA signature composed of circ_0054633, circ_0008726, and circ_0088196, showing an AUC of 0.87 for early GDM prediction [9].

In vitro assays demonstrated that silencing certain circRNAs altered insulin signaling and inflammatory gene expression in trophoblast cell lines, indicating potential mechanistic roles.

DISCUSSION

The findings support the feasibility of using circRNAs as non-invasive biomarkers for early GDM detection. CircRNAs can be isolated from maternal blood samples collected in the first trimester, well before hyperglycemia manifests. Their expression profiles correlate with known metabolic pathways involved in GDM pathogenesis.

Moreover, the integration of circRNA data with clinical variables and other omics data (e.g., proteomics, metabolomics) can improve predictive accuracy. Machine learning approaches can further enhance biomarker selection and validation [10].

However, challenges remain:

- **Standardization**: Variability in sample collection, RNA extraction, and sequencing platforms hampers reproducibility.
- **Validation**: Most studies are limited to small, ethnically homogeneous cohorts.
- **Mechanistic insights**: Functional studies are needed to confirm causal roles of candidate circRNAs in GDM development.

Despite these limitations, the translational potential of circRNAs is significant. Their stability, early detectability, and disease specificity make them ideal candidates for next-generation prenatal diagnostics.

CONCLUSION

CircRNAs represent a promising frontier in the early prediction of gestational diabetes mellitus. Their unique properties, including structural stability and

regulatory functions, enable their use as reliable, non-invasive biomarkers. Current evidence supports the inclusion of circRNA profiling in first-trimester screening protocols. Future large-scale, multicentric studies and functional validations are essential to transition these discoveries from bench to bedside and improve maternal-fetal health outcomes.

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