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SHORT COMMUNICATION

MicroRNAs: Diagnostic and Therapeutic Implications in Diabetes Mellitus

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ABSTRACT

Introduction:
MicroRNAs are a class of RNA (ribonucleic acid) that bind to mRNAs, leading to a decreased or complete cessation of protein synthesis. Dysregulation in microRNAs (miRNAs) has been associated with the development of diabetes mellitus. MiRNA-133a is responsible for the anti-apoptotic mechanism within the heart, and is thus cardioprotective via means of repression of cardiac fibrosis. In the kidney, the overexpression of miR-192 leads to increased collagen formation and deposition in the extracellular matrix (ECM). miR-34a is also overexpressed, leading to the suppression of anti-apoptotic proteins and an increase in reactive oxygen species (ROS), thereby promoting podocyte apoptosis. In terms of diagnosis, serum miR-126 has demonstrated high specificity and sensitivity in distinguishing progressive from non-progressive diabetic retinopathy.

Conclusion:
Understanding the action of modulating specific miRNAs can be beneficial for treating or reducing inflammation or fibrosis, thus preventing complications and aggravation in diabetic patients.

Keywords
MicroRNAs, Circulating MicroRNA, RNA, Nucleic Acids, Diabetes Complications

Introduction

MicroRNAs are a class of RNA (ribonucleic acid) that bind to mRNAs, leading to a decrease or complete cessation of protein synthesis. Dysregulation in microRNAs (miRNAs) has been associated with the development of many diseases, including diabetes mellitus, cardiovascular diseases, and others. There are various techniques for quantifying circulating miRNA, namely northern blot, qRT-PCR, ddPCR, and miRNA microarrays [1]. Different circulating miRNAs can serve as markers for early detection of DM complications [2]. Gene expression can also be manipulated to reduce the risk of complications.

Pathogenesis of Complications in Diabetes Mellitus

The heart expresses many miRNAs that play important roles in cardiogenesis, cardiac physiology, and disease pathogenesis. miRNAs can activate gene expression by direct or indirect processes. miRNAs such as miRNA-1/-133a work in early phases of cardiogenesis, while miRNA-208 and miRNA-499 function in later stages. Alterations in miRNA expression drive the pathogenesis of heart disease in diabetic patients. miR-133a mediates anti-apoptotic signaling in the heart and is thus cardioprotective by repressing cardiac fibrosis. MiRNA-133a is notably downregulated in the diabetic heart. Other abnormalities in normal heart function and rhythm can occur due to the deletion of miRNA-1; hypertrophy of cardiac muscle occurs due to the upregulation of miRNA-208a and miRNA-22; and an upregulation of miRNA-21 increases fibrosis [3].

In the pathogenesis of diabetic kidney disease, MiR-21 increases inflammation and fibrosis and suppresses anti-fibrotic regulators. An overexpression of miR-192 leads to increased collagen formation and deposition in the ECM. miR-34a is also overexpressed, leading to the suppression of anti-apoptotic proteins and an increase in reactive oxygen species (ROS), thereby triggering podocyte apoptosis and the destruction of the kidney's microarchitecture. miR-217 causes fibrosis by inhibiting SIRT1, which, under normal conditions, protects against oxidative stress, apoptosis, and fibrosis. In chronic conditions, miR-423-5p can lead to sclerosis and kidney dysfunction [4].

In the pathogenesis of diabetic retinopathy, miR-155, miR-146a, and miR-21 regulate pro-inflammatory pathways. They increase inflammation and reduce anti-inflammatory proteins. miR-126, miR-200b, miR-21 and miR-155 also have a role in neovascularization.

When miR-155 is upregulated, it decreases the expression of SH2-containing inositol 5-phosphatase 1 (SHIP1), which, in turn, causes new vessel formation (neovascularization). miR-146a and miR-21 cause fibrosis in retinal vessels [5].

Dysregulated miRNAs and associated complications

A study by Kura et al. has shown an association between cardiac-enriched miRNAs (e.g., miRNA-208, miRNA-499, miRNA-22, miRNA-17-92) and hypertrophied cardiac muscle and heart dysfunction. These miRNAs are greatly elevated in Diabetic patients with cardiovascular diseases [5]. A study by Yu et al. also showed a significant elevation in miRNAs (miR-130B-3p, miR-30d-5p, miR-126a-5p, and miR-133a) in patients with diabetic cardiomyopathy or myocardial infarction, which was associated with increased heart fibrosis [6].

A study by Rodzon-Norwicz et al. showed that miRNAs (e.g., miR-21, miR-193, miR-155, miR-34a, miR-217, miR-423-5p) play a role in apoptosis, oxidative stress, inflammation, and fibrosis in the kidney. An increase in expression of these miRNAs leads to increased pro-inflammatory molecules, chronic inflammation, increased oxidative stress, and fibrosis. The activity of anti-apoptotic proteins is also inhibited, leading to increased synthesis and deposition of these proteins in the ECM. All of these changes then lead to the development of Diabetic kidney disease. In chronic phases, renal failure can occur [4].

Among the various microvascular complications found in diabetes mellitus, diabetic retinopathy is the most common. miRNAs (e.g., miR-155, miR-146a, Mir-21, miR-126, miR-204-5p, miR-1273g-3p) are involved: they increase pro-inflammatory molecules, endothelial dysfunction, apoptosis, vascular inflammation, retinal neovascularization, and ultimately fibrosis. All of these changes will initially cause a decrease in vision and, over time, lead to a progressive or non-progressive case of diabetic retinopathy [7].

Therapeutic applications and biomarkers

It has been shown that certain miRNAs protect the kidney, namely miR-126-3p, miR-29, miR-451, miR-30a, miR-146a, and miR-215. These miRNAs, when modulated, help keep inflammation in check, prevent endothelial dysfunction, and prevent ECM deposition [4]. A study conducted by Kura et al. also showed that an overexpression of miRNA-1 and miRNA-24-3p causes a reduction in the number of proliferating cardiac fibroblasts and collagen and thus causes an improvement in the heart’s structure [3]. In terms of diagnosis, serum miR-126 has shown high specificity and sensitivity in differentiating progressive from non-progressive Diabetic retinopathy and is used to screen for retinal endothelial injury. Also, overexpression of miR-126 was shown to decrease ROS production and apoptosis in microvascular endothelial cells [7]. The use of miRNAs as biomarkers is a non-invasive method compared to tissue biopsy [1].

Conclusion

Some miRNAs cause progression in the complications associated with Diabetic patients, namely, cardiovascular disease, diabetic kidney disease, and diabetic retinopathy.

Hence, levels of specific serum miRNAs can serve as biomarkers to monitor the risk of developing complications and their progression, thereby preventing further disease progression. Furthermore, understanding the action of modulating specific miRNAs can be beneficial for treating or reducing inflammation or fibrosis, thus preventing further complications in such diabetic patients.

Abbreviations

Diabetes mellitus (DM), microRNAs (miRNAs), extracellular matrix (ECM), reactive oxygen species (ROS), ribonucleic acid (RNA)

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Authors' contribution

a. Study planning: KM, IB
b. Interpretation: KM, IB, JR
c. Manuscript writing: KM, IB, JR
d. Manuscript revision: KM, IB, JR
e. Final approval: KM, IB, JR
f. Agreement to be accountable for all aspects of the work: KM, IB, JR

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