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The role of circulating miR-20b-5p in diabetes

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Abstract

Circulating miRNAs are a class of non-coding RNA molecules that have the potential to become the biomarkers of diabetes. Among which, the recently studied circulating miR-20b-5p not only showed expression difference in both plasma and serum derived exosomes in patients with diabetes, but also associated with insulin signaling and angiogenesis. Here, we will discuss the role of circulating miR-20b-5p in diabetes, thereby to provide a better understanding of the significance of circulating miR-20b-5p and provide a theoretical basis for further research.

Introduction

Diabetes Mellitus(DM) is the most common metabolic disorder and is one of the fastest increasing disease worldwide. By the year 2040, 642 million people are expected to be affected by DM [1]. In order to early diagnosis and intervention of DM, recent studies have focused on mapping out miRNA expression profiles for the use of being disease biomarker.

miRNA is a type of small non-coding RNA and normally inhibit the process of translation by directly targeting specific mRNA [2]. miRNAs have been found in blood, breast milk, urine and so forth [3]. A proportion of which can be packaged in extracellular vesicles, like exosomes, to protect them from degradation [4]. Derived from almost all cells, exosomes are a class of extracellular vesicles with a diameter of 40 to 160nm and can be found in all body fluids such as blood and urine. They contain some proteins, lipids, nucleic acids and other substances, which have biological activity and can be absorbed by the recipient cells to realize the material transportation and information transmission between cells [5]. Therefore, circulating exosomal miRNAs are both regulators of cell-to-cell interaction and candidate biomarkers for disease pathogenesis.

miR-20b-5p is a kind of highly conserved miRNA among mouse, rat and human [6], its role in tumors has been widely studied. Apart from that, miR-20a-5p can promote adipocyte differentiation [7], modulate some inflammatory signals [8] and play a part in metabolic disease [9]. Currently, high level of circulating miR-20b-5p was found in patients with diabetes [8,9], however, whether it can be a candidate biomarker of diabetes is still not clear. Here, we aim to discuss the role of circulating miR-20b-5p in diabetes.

Circulating miR-20b-5p is associated with the incidence of diabetes

Recently, the role of miR-20b-5p in diabetes has been gradually elucidated. A short report showed that among Japanese Americans, plasma miR-20b-5p is relevant to incident diabetes over 10 years [10]. Compared with individuals without diabetes, those who developed diabetes after 10 years of follow-up have lower circulating miR-20b-5p. However, another study investigated that serum-derived exosomal miR-20b-5p instead of serum miR-20b-5p is altered in type 2 diabetes mellitus(T2DM), as the miRNA expression profiles of total serum RNA acquired from the same subject show no significant differences between the normal glucose tolerance subjects and T2DM patients [8]. Interestingly, the expression of miR-20b-5p was increased in serum exosome from individuals with T2DM, and the expression of miR-20b-5p in plasma exosomes of patients with T2DM also showed significant increases in miR-20b-5p levels [9]. A possible reason for this inconsistency may be the varied duration of diabetes as well as the differences between serum and plasma. According to previous study, higher miRNA expression was found in serum compared with plasma from the same blood sample, and the miRNA spectrum of plasma and serum is different [11]. In addition, due to the protective effect of exosomal vesicles, miRNAs in exosomes are more stable than in the peripheral blood.

Further, miR-20b-5p have an impact on glucose metabolism. In skeletal muscle, the overexpression of miR-20b-5p directly targets AKTIP to impairs insulin signaling and alter glycogen synthesis. When transfected with miR-20b-5p, the protein of glycogen synthase in skeletal muscle cells was reduced, which means reduced synthesize glycogen, resulting in a higher blood glucose level, which may be one of the causes of the incidence of diabetes. Besides, by directly targeting AKTIP, a protein known to enhance the phosphorylation of AKT, it can inhibit the process of AKTIP translation to reduce the stability of phospho-AKT and therefore decrease the insulin sensitivity for the fact that lowered insulin-stimulated increment in miR-20b-5p transfected cells with both basal and insulin-stimulated glucose uptake unaltered. However, in the subjects with impaired glucose tolerance and the T2DM cohort, the expression of exosome miR-20b-5p is not significantly correlated with clinical parameters [8].

Gestational diabetes mellitus (GDM) is another type of diabetes, characterized by carbohydrate intolerance that occurs during pregnancy. Previous studies suggest that up to 70% of GDM women will devel-

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op DM after pregnancy within 22–28 years [12,13]. It is reported that, compared with normal pregnancies mothers, those who experienced GDM-complicated pregnancies have significantly higher miR-20b-5p in whole peripheral blood 3 to 11 years postpartum with or without treatment(diet and/or therapy) [12]. However, in another similar high risk of developing diabetes, individuals with impaired glucose tolerance(IGT) have no significant change in serum exosomal miR-20b-5p [8]. Notably, the subjects with IGT are all men, the role of sex and gender has discussed before, and independent of age, IGT is more common in females than males [14], it is advisable to exam circulating exosomal miR-20b-5p in female individuals with IGT.

The relationship between circulating miR-20b-5p and diabetic complications

Currently, another report also explained the role of circulating exosomal miR-20b-5p in diabetes [9]. It suggested that exosomes derived from patients with T2DM hinder wound healing in mice by locally injecting exosomes to wounds on the mice backs, with the observation of a significantly reduced wound closure rate when injected diabetic exosomes. By using the miR-20b-KO diabetic mice, further investigation found that it is miR-20b-5p packaged in exosomes that slowed wound healing rate. Apart from that, we know angiogenesis is one of the key process essential for diabetic wound healing [15], when following treatment with agomiR-20b-5p in HUVECs, the proliferation ability of HUVECs was inhibited, and there was also a significant reduction in tube formation, through biometric analysis and experimental verification, it was found that the wnt/β-catenin signaling pathway which is closely related to angiogenesis [16] was suppressed by miR-20b-5p overexpression. Notably, HUVECs can take up exosomes in vitro, which means vascular endothelial cell may be one of the recipient cells to receive circulating exosomes. In addition, miR-20b-5p is part of the miR-17 family known to target STAT3 and HIF-1α, thereby regulating the VEGF expression [17,18]. Whereas impairment of endothelial function is one of the hallmarks of T2DM [19], which can lead to the diabetic microvascular complications such as diabetic retinopathy and diabetic nephropathy.

The role of VEGF in diabetic microvascular complications has been recognized [20], however, whether circulating miR-20b-5p is associated with diabetic microvascular complications is not clear. Recently, the association between diabetic retinopathy(DR) and miR-20b-5p has been discussed. DR is characterized by endothelial cells dysfunction and pathological neovascularization. Whereas miR-20b-5p is related to regulate angiogenesis, cell proliferation and apoptosis [21,22]. Zhu et al. [6] found that the expression of miR-20b-5p was increased in both high-glucose treated human retinal microvascular endothelial cells and the fibrovascular membrane in DR patients. By targeting BAMBI, a mediator of angiogenesis and capillary growth [23], the overexpressed miR-20b-5p down-regulates the expression of tight junction-related protein and then contributes to microvascular leakage and the blood-retina barrier dysfunction, exacerbating retinal damage. Notably, the human retinal microvascular endothelial cells express higher miR-20b-5p level after high-glucose treatment, whether it is possible for these upregulated miR-20b-5p to be released to circulation in the form of extracellular vesicles like exosomes? However, there is neither study on circulating miR-20b-5p expression and DR, nor did the study investigate whether miR-20b-5p has the ability to be the biomarker indicating DR progression. In the absence of effective treatment of diabetic microvascular complications, it is advisable to focus on early detection and intervention. Therefore, further researches are needed to explore the exact role of circulating miR-20b-5p in diabetic microvascular complications.

As for diabetic heart disease, the role of miR-20b-5p may be beneficial. In a study carried out by Zhou et al. [24], the expression of miR-20b-5p was decreased in both serum of Ischemia-reperfusion patients and H9c2 cells under hypoxia, and the overexpression of miR-20b-5p could attenuate cardiomyocyte apoptosis induced by hypoxia. Based on the high level of circulating miR-20b-5p in patients with diabetes discussed before, the up-regulated miR-20b-5p can more or less be benefit to the heart. Nevertheless, no such study discussed circulating miR-20b-5p and diabetic heart disease, it is still needed to be verified.

Conclusion

It is certain that circulating miR-20b-5p is closely linked to diabetes, but there are still problems need to be solved. Exosomes packaged miR-20b-5p come from cells and released into circulation, thereafter, functional exosomal miRNAs are delivered to target cells. The regulation mechanisms of this process, including the origin of these exosomal miRNAs, their delivery location and delivery manner, remain uncertain. On the other hands, the differences between the miR-20b-5p of whole peripheral blood, serum, plasma, and exosomes need to be discovered for the sake of better use of miR-20b-5p act as disease biomarkers. Still, it is encouraging that the abnormal expression of circulating miR-20b-5p can identify a group of people at high risk of development of diabetes and meanwhile they would benefit from the implementation of early prevention strategies and long term follow-up.

Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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Dr Songtao Yang and Jie Cao contributed equally as co-first authors.

References

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, et al. (2017) IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 128: 40-50. [Crossref]

2. Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. *Cell* 136: 215-233. [Crossref]

3. Párrizas M, Novials A (2016) Circulating microRNAs as biomarkers for metabolic disease. *Best Pract Res Clin Endocrinol Metab* 30: 591-601. [Crossref]

4. Huang-Doran I, Zhang CY, Vidal-Puig A (2017) Extracellular Vesicles: Novel Mediators of Cell Communication In Metabolic Disease. *Trends Endocrinol Metab* 28: 3-18. [Crossref]

5. Kalluri R, LeBleu VS (2020) The biology, function, and biomedical applications of exosomes. *Science* 367: eaau6977 [Crossref]

6. Zhu K, Hu X, Chen H, Li F, Yin N, et al. (2019) Downregulation of circRNA DMNT3B contributes to diabetic retinal vascular dysfunction through targeting miR-20b-5p and BAMBI. *EBioMedicine* 49: 341-353. [Crossref]

7. Zhu E, Zhang J, Zhou J, Yuan H, Zhao W, et al. (2018) miR-20a-5p promotes adipogenic differentiation of murine bone marrow stromal cells via targeting Kruppel-like factor 3. *J Mol Endocrinol* 60: 225-237. [Crossref]

8. Katayama M, Wiklander OPB, Fritz T, Caidahl K, El-Andaloussi S, et al. (2019) Circulating Exosomal miR-20b-5p Is Elevated in Type 2 Diabetes and Could Impair Insulin Action in Human Skeletal Muscle. *Diabetes* 68: 515-526. [Crossref]

9. Xiong Y, Chen L, Yan C, Zhou W, Endo Y, et al. (2020) Circulating Exosomal miR-20b-5p Inhibition Restores Wnt9b Signaling and Reverses Diabetes-Associated Impaired Wound Healing. *Small* 16: e1904044. [Crossref]

10. Wander PL, Enquobahrie DA, Bammler TK, Srinouanprachanh S, MacDonald J, et al. (2020) Short Report: Circulating microRNAs are associated with incident diabetes over 10 years in Japanese Americans. *Sci Rep* 10: 6509. [Crossref]

11. Wang K, Yuan Y, Cho JH, McClarty S, Baxter D, et al. (2012) Comparing the MicroRNA spectrum between serum and plasma. *PLoS One* **7**: e41561. [Crossref]

12. Hromadnikova I, Kotlabova K, Dvorakova L, Krofta L (2020) Diabetes Mellitus and Cardiovascular Risk Assessment in Mothers with a History of Gestational Diabetes Mellitus Based on Postpartal Expression Profile of MicroRNAs Associated with Diabetes Mellitus and Cardiovascular and Cerebrovascular Diseases. *Int J Mol Sci* 21: 2437. [Crossref]

13. Committee on Practice Bulletins—Obstetrics. (2018) ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol* 131: e49-e64. [Crossref]

14. Kautzky-Willer A, Harreiter J, Pacini G (2016) Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. *Endocr Rev* 37: 278-316. [Crossref]

15. Wang M, Wang C, Chen M, Xi Y, Cheng W, et al. (2019) Efficient Angiogenesis-Based Diabetic Wound Healing/Skin Reconstruction through Bioactive Antibacterial Adhesive Ultraviolet Shielding Nanodressing with Exosome Release. *ACS Nano* 13: 10279-10293. [Crossref]

16. Savage AM, Kurusamy S, Chen Y, Jiang Z, Chhabria K, et al. (2019) tmem33 is essential for VEGF-mediated endothelial calcium oscillations and angiogenesis. *Nat Commun* 10: 732.

17. Tanzer A, Stadler PF (2004) Molecular evolution of a microRNA cluster. *J Mol Biol* 339: 327-335. [Crossref]

18. Cascio S, D'Andrea A, Ferla R, Surmacz E, Gulotta E, et al. (2010) miR-20b modulates VEGF expression by targeting HIF-1 alpha and STAT3 in MCF-7 breast cancer cells. *J Cell Physiol* 224: 242-249. [Crossref]

19. Thomou T, Mori MA, Dreyfuss JM, Konishi M, Sakaguchi M, et al. (2017) Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature* 542: 450-455. [Crossref]

20. Wong TY, Cheung CMG, Larsen M, Sharma S, Simo R, et al. (2016) Diabetic retinopathy. *Nat Rev Dis Primers* 2: 16012. [Crossref]

21. Liang ZG, Yao H, Xie RS, Gong CL, Tian Y (2018) MicroRNA-20b-5p promotes ventricular remodeling by targeting the TGF-βSmad signaling pathway in a rat model of ischemia-reperfusion injury. *Int J Mol Med* 42: 975-987. [Crossref]

22. Zhang D, Yi Z, Fu Y (2019) Downregulation of miR-20b-5p facilitates Mycobacterium tuberculosis survival in RAW 264.7 macrophages via attenuating the cell apoptosis by Mcl-1 upregulation. *J Cell Biochem* 120: 5889-5896. [Crossref]

23. Guillot N, Kollins D, Gilbert V, Xavier S, Chen J, et al. (2012) BAMBI regulates angiogenesis and endothelial homeostasis through modulation of alternative TGFbeta signaling. *PLoS One* 7: e39406. [Crossref]

24. Zhou Z, Chen S, Tian Z, Deng S, Yi X, et al. (2020) miR-20b-5p attenuates hypoxia-induced apoptosis in cardiomyocytes via the HIF-1alpha/NF-kappaB pathway. *Acta Biochim Biophys Sin (Shanghai)* 52: 927-934. [Crossref]