Metabolism Open 22 (2024) 100266

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Beta cell-derived nanovesicle MicroRNAs promote insulin resistance

ARTICLE INFO

Keywords
Type 2 diabetes
T2DM
Nanovesicle
MicroRNAs
miR-503-5p
β cell

Type 2 diabetes mellitus (T2DM) is a metabolic syndrome characterized by hyperglycemia, insulin resistance and chronic inflammation. Previous research has revealed that the pancreas and beta cells play significant role among the initiators of chronic low-grade inflammation in T2DM [1]. Moreover, clinical studies targeting T2DM with anti-IL-1β interventions have demonstrated noteworthy improvements in the functionality of pancreatic beta cells. However, these drugs display restricted efficacy in addressing long-term insulin insufficiency and insulin resistance [2,3]. Therefore, gaining a comprehensive understanding of the secretion spectrum modulated by chronic inflammation in beta-cell function is crucial for unveiling the pathological mechanisms underlying insulin resistance and beta-cell dysfunction in T2DM. This knowledge offers potential targets for precision treatment of T2DM.

MicroRNAs (miRNAs), a subset of small non-coding RNAs (~22 nucleotides), are known to play crucial roles in the regulation of diabetes metabolism including insulin secretion, insulin resistance, glucose metabolism pathway, inflammation and oxidative stress. Firstly, three kinds of miRNA, including miR-375, miR-9, and miR-124a, have been shown to inhibit glucose-induced insulin secretion in pancreatic islet cells, thereby affecting blood glucose homeostasis [4]. Secondly, miR-128a targets genes associated with the insulin signaling pathway, including INSR and IRS1, thereby affecting insulin resistance [5]. Thirdly, miR-122, which is highly expressed in the liver, promotes the expression of enzymes involved in hepatic gluconeogenesis. Moreover, various other miRNAs can impact glucose absorption, utilization, and storage, consequently influencing blood glucose levels [6]. Fourthly, previous research found that miR-29 mediates pancreatic inflammation and destroys islets, thereby promoting systemic inflammation and the development of diabetes [7,8]. Taken together, miRNAs play diverse pathological roles in the development of diabetes, influencing insulin secretion, regulating insulin resistance, affecting glucose metabolism pathways, and modulating inflammation and oxidative stress responses.

Nanovesicles (NVs), ranging in size from 30 to 150 nm, are located within late endosomes/multivesicular bodies (MVBs) [9,10]. Upon secretion into extracellular spaces, NVs effectively deliver cargo consisting of proteins, lipids, and RNAs to acceptor cells [9]. Among the critical elements conveyed by NVs are exosomal miRNAs, which are known to be involved in the development of T2DM [11,12]. Exosomal miRNAs not only mediate signal communication between cells, but also play a key role in the regulation of oxidative stress, apoptosis, autophagy, and fibrosis. Previous studies indicate that plasma-derived exosomal miRNAs serve as biomarkers for diabetes and other metabolic diseases, highlighting the potential for innovative non-invasive diagnostic methods for these pathologies [4].

Han Xiao's latest research article published in *Diabetes* has provided novel insights into the regulation of miRNA expression and secretion by the inflammatory factor IL-1β, particularly in relation to miR-503-5p released by β cells [13]. This study reports that miR-503-5p induces insulin resistance and β cell dysfunction, thereby promoting the development of diabetes, particularly T2DM in elderly individuals. The authors identified decreased methylation in the miR-503 promoter region in the β cells of individuals with T2DM. Following stimulation with IL-1β, β cells initiate transcription, processing, and release of miR-503, thereby contributing to the development of T2DM [14]. Of note, the authors discovered that miR-503 is primarily transcribed in β cells under metabolic stresses such as aging and HFD (high-fat diet)-induced obesity. Their findings were further supported by experiments utilizing β cell-specific miR-503 transgenic (βTG) mice, which exhibited hyperglycemia and insulin resistance. Conversely, whole-body knockout of miR-503-5p in mice counteracted the HFD-induced T2DM.

Further analysis revealed that miR-503-5p is packaged within NVs that are predominantly localized in insulin vesicles. These NVs are released in conjunction with insulin in response to elevated plasma glucose levels. Importantly, NVs secreted by pancreatic β cells primarily target the liver and adipose tissue, but not skeletal muscle. When mice were injected with βTG-NVs, which overexpress miR-503-5p, they exhibited significantly elevated blood glucose compared to control mice. Upon reaching the liver and adipose tissue, βTG-NVs release miR-503-

https://doi.org/10.1016/j.metop.2023.100266
Received 5 December 2023; Accepted 6 December 2023
Available online 19 December 2023

5p, which subsequently leads to the development of insulin resistance by targeting the INSR/P-AKT signaling pathway. Interestingly, miR-503-5p, when secreted by pancreatic β cells, can also exert autocrine effects by targeting the cells themselves. This autocrine effect inhibits β cell proliferation capability and glucose-induced insulin secretion by regulating the JIP2/MAPK signaling pathway. Notably, the use of a miR-503 cluster sponge significantly alleviates insulin resistance and defects in β cell secretion.

In summary, this research provides novel insights into the role of miR-503-5p-containing nanovesicles in promoting the development of T2DM under metabolic stresses, including HFD-induced obesity and aging. This extremely thrilling finding indicates that the insulin granule has been proposed to function as a signaling hub rather than simply serving as an insulin container. Furthermore, these results suggest that the use of microRNA sponge may serve as a promising therapeutic strategy for the simultaneous management of systemic insulin resistance and β cell dysfunction in T2DM.

CRediT authorship contribution statement

Junli Liu: Writing – review & editing.

References

[1] Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444(7121):860–7.
[2] Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest 2017;127(1):1–4.
[3] Rohm TV, et al. Inflammation in obesity, diabetes, and related disorders. Immunity 2022;55(1):31–55.
[4] Zhang AM, et al. Islet β cell: an endocrine cell secreting miRNAs. Biochem Biophys Res Commun 2018;495(2):1648–54.
[5] Kaur P, et al. Role of miRNAs in the pathogenesis of T2DM, insulin secretion, insulin resistance, and β cell dysfunction: the story so far. J Physiol Biochem 2020;76(4):485–502.
[6] Nemecz M, et al. Microvesicle-associated and circulating microRNAs in diabetic dyslipidemia: miR-218, miR-132, miR-143, and miR-21, miR-122, miR-155 have biomarker potential. Cardiovasc Diabetol 2023;22(1).
[7] Haidar M, et al. miR-126-5p by direct targeting of JNK-interacting protein-2 (JIP-2) plays a key role in -infected macrophage virulence. PLoS Pathog 2018;14(3).
[8] Sun Y, et al. Expression of miRNA-29 in pancreatic β cells promotes inflammation and diabetes via TRAF3. Cell Rep 2021;34(1).
[9] Suckalel J, Solimena M. The insulin secretory granule as a signaling hub. Trends Endocrinol Metabol 2010;21(10):599–609.
[10] van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 2018;19(4):213–28.
[11] Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. Nat Rev Endocrinol 2024;20(1):27–49.
[12] Guay C, et al. Lymphocyte-derived exosomal MicroRNAs promote pancreatic β cell death and may contribute to type 1 diabetes development. Cell Metabol 2019;29(2):348–+.
[13] Zhou Y, et al. Beta-cell MiRNA-503-5p induced by hypomethylation and inflammation promotes insulin resistance and β-cell decompensation. Diabetes; 2023.
[14] Eguchi K, Nagai R. Islet inflammation in type 2 diabetes and physiology. J Clin Invest 2017;127(1):14–23.

Ning Wang
Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200233, China

Suzhen Chen**
Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200233, China

Junli Liu*
Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, 200233, China

** Corresponding author. Shanghai JiaoTong University, Affiliated 6thPeople's Hospital and Shanghai, JiaoTong University School of Medicine, Shanghai, China.

* Corresponding author. Shanghai JiaoTong University, Affiliated 6thPeople's Hospital and Shanghai, JiaoTong University School of Medicine, Shanghai, China.
E-mail address: cszdream@163.com (S. Chen).
E-mail address: liujunli@sjtu.edu.cn (J. Liu).