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EDITORIAL

New mediators in diabetes pathogenesis: Exosomes and metabolites

Type 2 diabetes is a systemic disorder characterized by metabolic impairment in multiple organs[1]. Various factors trigger insulin resistance in muscle, liver and adipose tissue resulting in increased insulin demand and de-repression of hepatic gluconeogenesis. When pancreatic β-cells fail to compensate their mass and function to the increased insulin demand, β-cell apoptosis and dedifferentiation occurs, which leads to hyperglycemia. As the diabetes progresses, systemic complications involving microvessels (retinopathy, nephropathy and neuropathy) and macrovessels (cardiovascular, cerebrovascular and peripheral vascular diseases) develop, which leads to increased mortality. As simple it might seem, the mechanism of how diabetes develops and progresses has not been fully elucidated. Cumulative evidence suggests that inter-organ communicating factors, such as exosomes (or extracellular vesicles) or metabolites, might participate in the process of developing type 2 diabetes and its complications (Figure 1).

Exosomes are 30–100 nm sized lipid bi-layered vesicles containing proteins, lipids, carbohydrates and nucleic acids (micro ribonucleic acids, long non-coding ribonucleic acids and messenger ribonucleic acids)[2]. Exosomes are formed through the endosomal pathway and can be secreted by most cell types. Importantly, exosomes secreted from a certain cell can be delivered to adjacent or distant cells in an autocrine, paracrine or endocrine manner to serve as an intercellular communicator. Interestingly, the circulating exosome level was significantly higher in patients with diabetes compared with euglycemic controls, suggesting the potential role of exosome in diabetes[3]. A well-designed rodent study showed that adipose tissue is an important source of circulating exosomes[4]. Along with adipokines or free fatty acids, exosomes are one of the important mediators of how adipose tissues contribute to the systemic insulin resistance. Adipose tissue-derived exosomes can develop insulin resistance by stimulating macrophages to express inflammatory cytokines (interleukin-6, tumor necrosis factor-α)[5]. Exosomal micro ribonucleic acid-27a from adipocytes can induce insulin resistance in muscles[6]. Adipose tissue macrophage derived exosomal micro ribonucleic acid-155 has the potential to impair insulin signaling in muscle, liver and adipose tissue by peroxisome proliferator-activated receptor γ suppression. Muscle-derived exosomes also play an important role in systemic metabolism. Muscle-derived exosomes from high palm oil-fed mice can incorporate to the pancreatic β-cells to regulate β cell mass[7]. Muscle-derived exosomes can also modulate myoblast proliferation and differentiation in a paracrine manner[8]. Research on pancreatic islets and exosomes have been heavily focused on the effect of other tissue-originated exosomes on pancreatic islets or β-cells. However, some evidence suggests that pancreatic islets also excrete exosomes, which act in a paracrine manner to regulate glucose homeostasis. Exosomal neutral ceramidase are secreted from β-cells when treated with pro-inflammatory cytokines, which protects β-cells from palmitate- or cytokine-induced apoptosis[9]. Healthy human donor islet-derived exosomes suppress amyloid deposition in a paracrine manner, which is impaired in islets of patients with type 2 diabetes[10]. Exosomal Lnc-364 from β-cells can regulate insulin secretion and β-cell proliferation[11]. As such, exosomes from various tissues can modulate biological processes in cells in an endocrine or paracrine manner, which can trigger insulin resistance and β-cell failure to develop type 2 diabetes. As many of the exosome studies were carried out *in vitro* or *ex vivo*, more carefully designed *in vivo* or translational research should be carried out.

Along with the exosomes, metabolites are circulating biomolecules that have the potential to activate biological processes in various tissues. Metabolomics studies in prospective cohorts suggest the potential role of various metabolites on the development and progression of type 2 diabetes. A large-scale metabolomics study in the Framingham Offspring cohort suggested that five branched chain amino acids (tyrosine, isoleucine, leucine, phenylalanine and valine) are highly associated with the development of diabetes[12]. A metabolomics study showed the association between specific metabolites (branched chain and aromatic amino acids, triacylglycerol in very low-density lipoprotein, non-esterified cholesterol in high-density lipoprotein and linoleic n-6 fatty acid) and diabetes risk[13]. Also, serum levels of metabolites (phospholipids, adenosine monophosphate) were associated with the preventative (pharmacological and lifestyle intervention) effect on the development of type 2 diabetes[14]. Despite epidemiological studies strongly suggesting the role of metabolites in the pathogenesis of diabetes, the mechanism of how these metabolites affect whole-body glucose metabolism is poorly understood. Recently, radioisotope-tracing combined metabolomics study enabled researchers to understand the physiological or pathological flux of metabolites[15]. This technological advancement will encourage researchers to further study the mechanism how metabolites affect whole-body glucose metabolism.

In conclusion, exosomes and metabolites are the new emerging mediators of diabetes development. Recently, a novel subclassification of newly diagnosed diabetes patients was documented[16]. This new subclassification (severe autoimmune, severe insulin deficient, severe insulin resistant, mild obesity-related and age-related) was based on pathophysiological

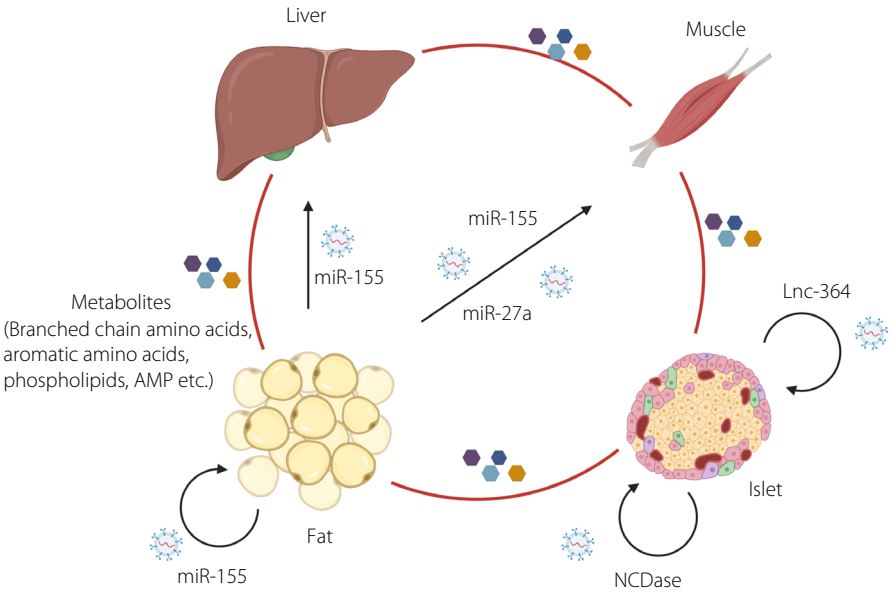

Figure 1 | Examples of the role of exosomes and metabolites in the pathogenesis of diabetes. Circulating exosomes and metabolites mediate inter-communicating signals between endocrine organs (liver, muscle, fat, islets), which are associated with the development type 2 diabetes. AMP, adenosine monophosphate; miR, micro ribonucleic acid; NCDase, neutral ceramidase.

heterogeneity, and this heterogeneity was shown to exist even before the development of diabetes[16,17]. Future studies comparing the difference of exosomes and metabolites between different diabetes subclasses might show valuable information regarding the pathogenesis of diabetes. These novel mediators might serve their role as a biomarker to predict the development and progression of diabetes. Future well-designed mechanistic studies will encourage the development of therapeutic targets associated with these novel mediators.

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DISCLOSURE

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