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EDITORIAL

Exercise Improves the Function of Endothelial Cells by MicroRNA

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Abstract

Vascular diseases induced by diabetes and obesity (e.g., atherosclerosis) are associated with insulin resistance (IR), which leads to endothelial cell dysfunction due to metabolic disorder and oxidative stress. Research conducted by Cai showed that exercise prevented the formation of aortic plaque by regulating miR-429 and its target resistin, thus might be a novel potential therapeutic strategy for cardiovascular diseases.

Keywords Exercise · Aortic plaque · MicroRNA

Introduction

Diabetes is a common disease. It was estimated that there were 425 million diabetics in 2017 worldwide. The rising prevalence of obesity further leads to a rapid increase in the number of diabetes cases. It is well known that unhealthy lifestyles, including lack of exercise, can lead to cardiovascular diseases. In particular, macrovascular diseases, such as atherosclerosis (AS), are usually associated with hyperglycemia and hyperinsulinemia.

A previous study has shown that physical activity is able to reverse and prevent diabetes-related AS by stabilizing atherosclerotic plaque [1]. Similarly, in a recent study, Cai et al. proved that swimming exercise was helpful to inhibit the formation of aortic plaques [1]. At this stage, it has been confirmed that physical activity is an important way to prevent and treat cardiovascular diseases [2]. Although the underlying mechanisms for the beneficial effects of exercise in cardiovascular diseases remain elusive, strong evidence of the benefits of exercise in AS lead to its widespread use in AS treatment.

Risk Factors for Cardiovascular Disease

Diabetes is caused by insufficient insulin resistance (IR) in the maintenance of blood glucose homeostasis. IR is frequently associated with endothelial dysfunction, which may cause further cardiovascular diseases. Decades of studies have shown that IR-induced accumulation of reactive oxygen species (ROS) inhibits endothelial NO synthase (eNOS), and sufficient bioavailability of eNOS is critical in cardiovascular health status [3].

Overproduction of ROS is associated with diabetes-induced vascular complications. In the presence of diabetes, IR-induced hyperglycemia contributes to the activation of NADPH oxidase and protein kinase C (PKC), and subsequently, increases the generation of downstream ROS [3]. (Fig. 1 left half).

Moreover, hyperglycemia is not the only symptom of diabetes, for instance, type 2 diabetes is usually accompanied by hyperlipidemia. In Cai's study, ApoE-/- mice fed with a high-fat diet had significantly thickened vascular and increased plaque volume, in addition to lipid metabolism disorders with elevated levels of free fatty acid (FFA), total cholesterol (TC), triglyceride (TG) and low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL) [1]. The increased plasma FFA concentration binds Toll-like receptor (TLR)

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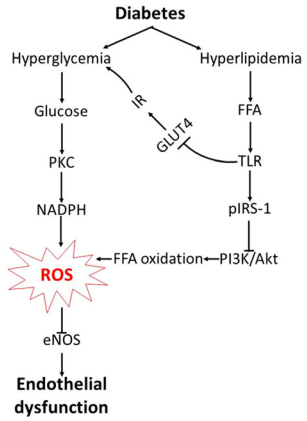

Fig. 1 The pathway of diabetes-induced endothelial dysfunction. PKC, protein kinase C; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; eNOS, endothelial NO synthase; FFA, free fatty acid; TLR, Toll-like receptor; pIRS-1, phosphorylation of insulin receptor substrate-1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, protein kinase B; GLUT4, glucose transporter 4; IR, insulin resistance

and induces phosphorylation of insulin receptor substrate-1 (IRS-1) and then downregulates glucose transporter 4 (GLUT4), which ultimately causes IR and hyperglycemia [3] (Fig. 1 right half). Hyperlipidemia-induced IR also plays a role in inhibiting PI3-kinase/Akt pathway, leading to increased generation of ROS by oxidation of surplus FFA [3] (Fig. 1 bottom).

MicroRNA Mediates the Beneficial Effects of Exercise

The progression of diabetes is generally considered to be irreversible; nevertheless, diabetes-induced cardiovascular diseases can be controlled. It has been shown that exercise helps to inhibit IR and to enhance endothelial function by increasing the activity of eNOS [1]. Therefore, in the context of AS, Cai et al. suggested that swimming could reduce hyperlipidemia and decrease the volume of plaques. In addition, miR-429 has also been found to be upregulated by swimming [1]. miRNAs are small noncoding RNAs which has been widely recognized to be crucially involved in the development and progression of AS. Some of them, such as miR-126-5p, miR-26a, and miR-19a, attenuate endothelial cell proliferation and/or inhibit endothelial apoptosis by regulating the target of endothelial cells, thus suppressing the genesis of atherosclerosis [4]. In contrast, other miRNAs, including miR-155, miR-92a, and miR-33, prompts the progression of AS, which turn out to enhance the inflammatory response or disturb lipid metabolism in macrophages in an AS animal model [4].

MiR-429, as a major microRNA in miR-200 family, has been mainly investigated in cancer therapies, for its regulatory roles on downstream factors including VEGFA, moesin, and PKCα [5]. Recent evidences demonstrated that miR-429 would be a potential mediator of glucose responses involved in endothelial cell function. However, the regulation mechanism of its downstream effector is still relatively vague. In the study conducted by Cai et al., high-fat diet caused a downregulation of miR-492 and an increase in the expression level of resistin in the aortic endothelial of AS model mice. They proved that miR-492 directly affect against resistin. Resistin, as a determinant of obesity, can indirectly lead to insulin resistance and contribute to the early development of AS. Additionally, they also found for the first time that exercise can increase the expression level of miR-492, which proved once again miRNAs' important role in the protective influence of exercise training on the cardiovascular system. However, the other target genes and its upstream triggers remain to be explored. In addition, the current study has not provided evidences about the role of miR-429 in vivo. However, administration of miR-492 and its targets in a signaling pathway that regulates insulin resistance might be new intervention agents in improving cardiovascular diseases, which may contribute to potential therapeutic strategy [3].

Conclusion

In the diabetic population, IR, hyperglycemia, and hyperlipidemia have been suggested to aggravate oxidative stress and dysfunction caused by energy substrate metabolic disorder. This study shows that exercise-mediated miRNAs inhibited the development of diabetes-induced AS by protecting the endothelial cell function.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent This article does not contain any studies with human participants.

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