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SIRT1 improves VSMC functions in atherosclerosis

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ABSTRACT

Despite advancements in diagnosis and treatment of cardiovascular diseases (CVDs), the morbidity and mortality of CVDs are still rising. Atherosclerosis is a chronic inflammatory disease contributing to multiple CVDs. Considering the complexity and severity of atherosclerosis, it is apparent that exploring the mechanisms of atherosclerotic formation and seeking new therapies for patients with atherosclerosis are required to overcome the heavy burden of CVDs on the quality and length of life of the global population. Vascular smooth muscle cells (VSMCs) play a dominant role in functional and structural changes of the arterial walls in response to atherogenic factors. Therefore, improvement of VSMC functions will slow down the development of atherosclerosis to a large extent. Given its protective performances on regulation of cholesterol metabolism and inflammatory responses, SIRT1 has long been known as an anti-atherosclerosis factor. In this review, we focus on the effects of SIRT1 on VSMC functions and thereby the development of atherosclerosis.

Contents

1. Introduction

According to the World Health Organization (WHO), 17.5 million people die annually from cardiovascular diseases (CVDs) and account for estimated 31% of all deaths worldwide (WHO). Additionally, four out of five CVD deaths are due to heart attacks and strokes. Atherosclerosis is a complex, multi-step process through luminal stenosis or thrombogenesis that obstructs blood flow to the heart (coronary heart disease), brain (ischemic stroke) or lower extremities (peripheral vascular disease) to cause CVDs (Bentzon et al., 2014). The generation of atherosclerosis is usually initiated with endothelial dysfunction followed by modified low density lipoprotein (LDL) infiltration into the arterial walls, invasion of macrophages and vascular smooth muscle cells (VSMCs) and their transformation to fat-laden foam cells, and extracellular matrix remodeling in response to atherogenic factors (Rafieian-Kopaei et al., 2014). Considering the complexity and severity of atherosclerosis, it is apparent that exploring the mechanisms of atherosclerotic formation and seeking new therapies for patients with atherosclerosis are required to overcome the heavy burden of CVDs

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SIRT1, a member of the sirtuins (SIRT1-7) or silent information regulator 2 (Sir2) proteins, has been identified as a highly conserved nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase (Frye, 2000). By interacting with a number of target proteins, not restricted to histones, SIRT1 can affect a wide range of cellular functions involving energy, lipid, insulin and glucose homeostasis and neuron function (Chaudhary and Pfluger, 2009; Haigis and Guarente, 2006). SIRT1 has gained earlier extensive attention as a mediator of health and longevity in response to calorie restriction (Guarente and Picard, 2005). Besides, accumulating studies have recently found that SIRT1 plays a protective role in the CVDs (Ma and Li, 2015; Winnik et al., 2015). Some reviews (Corbi et al., 2013; Kotas et al., 2013; Luo et al., 2014; Ma and Li, 2015; Ota et al., 2010; Stein and Matter, 2011) highlight the potential role of SIRT1 on CVDs and expound the mechanisms including reduction of inflammation, defense against oxidative stress, improvement of endothelial function, delay of cellular senescence, promotion of autophagy and inhibition of foam cell formation. And for exactly these beneficial effects, the mechanisms of SIRT1 on atherosclerosis are starting to become clearer.

VSMCs of the media migrate into the intima and undergo modifications to inflammatory phenotype in atherosclerosis, becoming the main cell type in early arterial intimal thickening (Orekhov et al., 1986). Moreover, VSMCs are the important source of foam cells besides macrophages, and contain a much larger burden of the excess cholesterol in human coronary atherosclerosis (Allahverdian et al., 2014; Rosenfeld and Ross, 1990). Therefore, improvement of VSMC functions will slow down the development of atherosclerosis to a large extent. The emergence of SIRT1 as an important regulator in atherosclerosis has attracted increasing attention on the molecular mechanisms of VSMC-dependent pathways. Thus, this review presents the current knowledge of SIRT1 in improving VSMC functions in atherosclerosis.

1.1. SIRT1 and atherosclerosis

Endothelial cell-specific SIRT1 transgenic (SIRT1-Tg) mouse is a well-accepted model to study the effects of SIRT1 on vascular functions. In SIRT1-Tg mice, high fat-induced damage in endothelium-dependent vasodilation was improved compared with that of wild-type littermates (Zhang et al., 2008). Moreover, the SIRT1-Tg/apolipoprotein E (apoE)-deficient mice developed less atherosclerotic lesions compared with that of apoE-deficient controls (Zhang et al., 2008). The SIRT1 activator treatment decreases plasma levels of LDL-cholesterol and total cholesterol, and reduces atherosclerosis in apoE$^{-/-}$ mice (Miranda et al., 2015). SIRT1 exerts the atheroprotective effects in angiotensin II (AngII)-infused mice, characterized by suppressing the expression levels of proinflammatory factors including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), reducing serum free fatty acid, triglycerides, total cholesterol and blood glucose concentrations, and inhibiting inflammatory cell infiltration in atherosclerotic plaques (Chen et al., 2015). Given its protective performances on regulation of blood lipids metabolism and endothelial functions, SIRT1 has long been known as an anti-atherosclerosis factor (Brandes, 2008; Yu et al., 2009).

Poly (ADP-ribose) polymerase 1 (PARP1), an abundant nuclear enzyme, has an important impact on numerous cellular processes. Accumulating studies have established a novel concept that PARP1 inhibition or *PARP1* deletion decreases atherosclerosis by reducing expression of adhesion molecules, inhibiting inflammation and diminishing features of plaque vulnerability (Pacher and Szabó, 2007; von Lukowicz et al., 2008; Xie et al., 2009). In addition, pharmacologic inhibition of PARP1 selectively promotes foam cell death and protects endothelial cells and VSMCs from injury (Hans et al., 2008; Zhang et al., 2015a). PARP1 is a major NAD^+-consuming enzyme, and attenuation of PARP-1 is found to increase cellular NAD^+ levels and thereby enhance SIRT1 activity (Bai et al., 2011). It is acceptable that the beneficial effects of PARP1 inhibition on attenuating atherosclerosis is at least partly associated with the activation of SIRT1. However, the interconnection between PARP1 and SIRT1 in atherosclerosis is very complicated, not just the competition for the common NAD^+ substrate (Xu et al., 2014).

Since the first report of the “French paradox” which states low mortality from coronary heart disease despite a high-fat diet in French people may be attributable in part to high consumption of wine, the potential protective role of resveratrol in preventing CVD has been broadly studied (Renaud and de Lorgeril, 1992). Resveratrol is a natural polyphenol produced by many different plant species especially grapevine, which is the main material of red wine. Resveratrol has been shown to be antiatherogenic in many conditions observed in cardiovascular cells and atherosclerotic apoE knockout mice (Catalgol et al., 2012; Wang et al., 2012). Among the diverse intracellular targets of resveratrol, SIRT1 is best described and well-known (Pervaiz and Holme, 2009). Resveratrol significantly increases the SIRT1 activity (Howitz et al., 2003) and has been shown to reduce thrombosis, lower lipids accumulation and slow down the atherosclerosis development (Fukao et al., 2004; Zang et al., 2006). Resveratrol plays a significant role in preventing cardiac abnormalities induced by atherogenic diet (Meng et al., 2014) and inhibiting inflammasome activation induced by vascular injury (Deng et al., 2015) associated with the activation of SIRT1.

Observed in a recent study, metformin has a novel protective role to ameliorate the proinflammatory state in patients with carotid artery atherosclerosis, characterized by reducing the expression of IL-6 and TNF-α and attenuating nuclear factor-kappa B (NF-κB) DNA binding activity in mononuclear cells through SIRT1 induction (Xu et al., 2015b). In a word, SIRT1 should be expressed more accurately as the central molecule regulating the cholesterol metabolism and inflammatory responses, which are two key processes involved in the development of atherosclerosis.

1.2. SIRT1 and VSMC

In human VSMCs, endogenous SIRT1 is decreased with age and loss of this protein directly contributes to the induction of cellular senescence and deficits of cellular function including impaired stress response and reduced capacity for cell migration and proliferation (Thompson et al., 2014b). Overexpression of SIRT1 in VSMCs attenuates AngII-induced hypertension, vascular remodeling and related pathological changes in mice (Gao et al., 2014). Moreover, high SIRT1 expression in VSMCs retards neointima formation through inhibiting VSMC proliferation and migration (Li et al., 2011b). And this research team speculated that Fas ligand (FasL), a death factor that induces apoptosis, might be involved in the neointima formation suppression by SIRT1 (Li et al., 2013). The inhibition of neovascularization of the vessel walls is also associated with the attenuated neointima formation induced by hypercholesterolemia in early atherosclerosis (Gossl et al., 2009). Hypoxia is one of the most potent stimuli for neovascularization, and impaired oxygen diffusion is present at depth in the atherosclerotic plaque (Björnheden et al., 1999; Doyle and Caplice, 2007). Hypoxia inducible factor-1 (HIF-1), a heterodimeric transcription factor with HIF-1α and HIF-1β subunits, mediates adaptive responses to hypoxia (Wang et al., 1995). It was found that SIRT1-mediated HIF-1α deacetylation inactivated HIF-1α even in