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Review

Adiponectin as a potential therapeutic target for the treatment of restenosis

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ABSTRACT

Restenosis is a pathologic re-narrowing of a coronary artery lesion after mechanical injury. Its pathophysiological mechanisms have not been fully elucidated at present, but are thought to include inflammation, vascular smooth muscle cell (VSMC) proliferation, and matrix remodeling, beginning with insufficient endothelium healing. Restenosis presents with angina symptoms or acute coronary syndromes and lead to a revascularization, either with coronary artery bypass or repeat percutaneous coronary intervention. Some studies have reported that hypoadiponectinemia has been an independent risk factor for the onset of acute coronary syndromes and restenosis. Accumulating evidence shows that low concentrations of adiponectin may be involved in impairing endothelium functions, inflammation, and VSMC proliferation that lead to restenosis. Preclinical studies have proven that adiponectin promotes endothelium healing, effectively inhibits inflammation, and maintains contractile phenotypes of VSMCs, indicating that it may be developed as a new therapeutic target for the treatment of restenosis.

1. Introduction

Adiponectin, a protein mainly secreted by adipose tissue, exerts a protective role against the development of insulin resistance, diabetes, and atherosclerosis [1,2]. Hypoadiponectinemia is common in patients suffering from coronary artery diseases [3,4], and has a predictive value of future acute myocardial infarction and restenosis [5–7]. However, the molecular basis for association between hypoadiponectinemia and restenosis has not yet been completely elucidated. Low concentrations of plasma adiponectin may be involved in the exacerbation of atherogenesis through abnormal metabolism and promotion of inflammation [8]. Previous studies have suggested that adiponectin inhibits the activation of nuclear factor kappa B (NF-κB), macrophage-to-foam cell transformation, lipid accumulation in macrophages, and proliferation of vascular smooth muscles cells (VSMCs) [9,10]. Some researchers advocate that hypoadiponectinemia is responsible for the activation of the nucleotide-binding and oligomerization domain-like receptor, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome, resulting in diabetic vascular endothelial dysfunction [11]. In addition, adiponectin can attenuate endothelial cell injuries by decreasing NLRP3 inflammasome activity [11]. Therefore, because of the ability to protect endothelial cells, inhibit inflammation, and maintain contractile phenotypes of VSMCs, adiponectin may be developed as a new therapeutic approach in treating restenosis. The aim of this review is to provide an up-date on experimental and clinical studies that focus on adiponectin's potential therapeutic effects of improving restenosis and neointimal hyperplasia.

2. Biosynthesis of adiponectin and adiponectin receptors

Human adiponectin is encoded by the *Adipo Q* gene, which spans 17 kb on chromosome locus 3q27 [12,13]. *Adipo Q* gene expression is modulated by several factors. Key transcription factors, including peroxisome proliferator activator receptor γ (PPAR-γ), fork head box O1 (FoxO1), sterol-regulatory-element-binding protein-1c (SREBP-1c), and CCAAT/enhancer-binding protein-α (C/EBP-α) stimulate its expression, while reactive oxygen species (ROS), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6), are negative regulators [14]. Adiponectin is predominately, but not exclusively, produced by adipose tissue and secreted into the circulating blood. It is produced in part by epicardial fat, the liver, cardiomyocytes, skeletal muscle, the colon, salivary glands, placenta, and pituitary glands, although the contribution of these tissues is relatively small. In the plasma, it can be detected as three isoforms: low-molecular-weight (LMW) homotrimers, hexamers, and high-molecular-weight (HMW) multimers. Serum adiponectin levels in Japanese non-obese subjects were approximated at 3–30 u g/ml, which is inversely proportional to body mass index (BMI) and visceral adiposity [15,16]. Fifty percent of the total adiponectin in humans is HMW multimers, which is the active form [17,18].

Adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) are two predominant receptors through which adiponectin exerts its physiological effects. Consisting of seven trans-membrane

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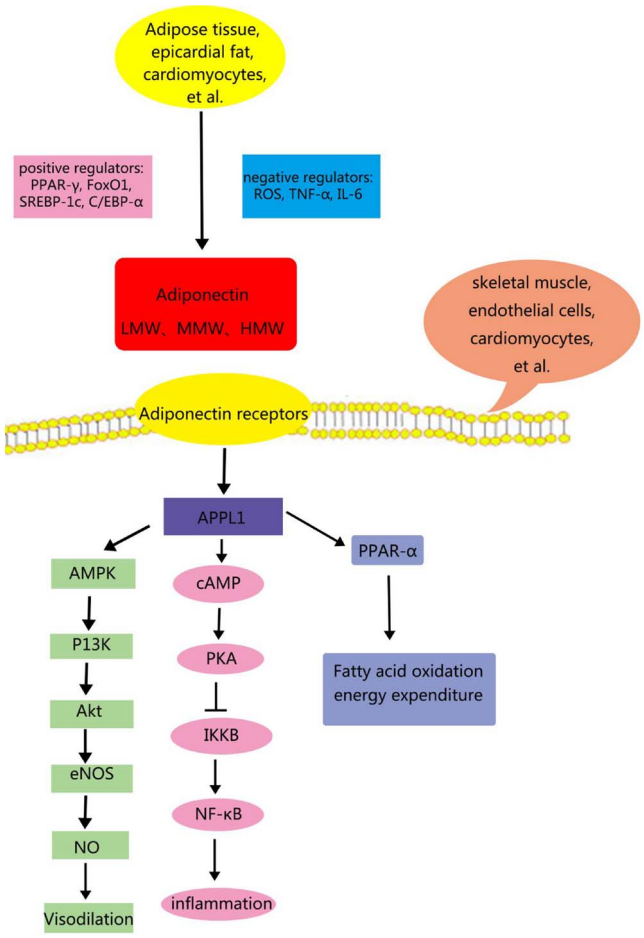

Fig. 1. Adiponectin, adiponectin receptors and their downstream signal pathways. Abbreviation: PPAR-γ, peroxisome proliferator-activated receptor-gamma; FoxO1, fork-head box O1; SREBP-1c, sterol-regulatory-element-binding protein-1c; C/EBP-α, CCAAT/enhancer-binding protein-alpha; ROS: reactive oxygen species; TNF-α: tumor necrosis factor alpha; IL-6: interleukin-6; AMPK: adenosine 5′-monophosphate (AMP)-activated protein kinase; Akt/PKB: Protein Kinase B; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; cAMP: cyclic adenosine monophosphate; PKA: Philippine Kendo association; IKKB: (inhibitor of nuclear factor kappa-B kinase subunit beta); NF-κB: Nuclear factor kB; PPAR-α, peroxisome proliferator-activated receptor-alpha.

domains, these two receptors are different from G-protein coupled receptors. AdipoR1 is abundantly detected in skeletal muscle and is also seen in endothelial cells [19], cardiomyocytes [20,21], and pancreatic-beta cells [22], and has a high affinity for globular adiponectin, whereas AdipoR2 is predominately expressed in the liver [23] and endothelial cells [24], with high affinity for the full-length form of adiponectin [25]. Actions of adiponectin are mediated by the activation of the cyclic adenosine monophosphate (cAMP)-dependent, AMP-activated protein kinase (AMPK), cyclooxygenase (COX)-2, and peroxisome proliferator-activated receptor (PPAR) alpha pathways [26–29] (Fig. 1). Similar to adiponectin, the expression of AdipoR1 and AdipoR2 was reduced in isolated monocytes from overweight patients with coronary artery disease [30]. Adiponectin-AdipoR1/2- Adaptor protein, phosphotyrosine interaction, pleckstrin homology domain, and leucine zipper-containing 1 (APPL1) axis was reported to suppress macrophage lipid accumulation and foam cell formation [31], suggesting that the axis may serve as a potential therapeutic target for preventing atherosclerosis. Apart from AdipoR1 and AdipoR2, T-cadherin, a glycosylphosphatidylinositol (GPI)-linked cell surface molecule, has also been reported to constitute a putative adiponectin receptor [32]. The expression of vascular T-cadherin was increased during neointima formation in experimental restenosis [33]. However, the specific mechanism remains unclear.

3. Restenosis

Restenosis is a pathologic re-narrowing of a coronary artery lesion after percutaneous coronary intervention (PCI), with or without stenting. Binary angiographic in-stent restenosis (ISR) is defined as diameter stenosis > 50% at the stent segment or its edges (5 mm segments adjacent to the stent) [34]. Patients experiencing ISR may present with associated clinical symptoms or cardiovascular events, including target lesion revascularization, angina pectoris, myocardial infarction, and sudden cardiac death [35]. Routine angiographic surveillance was conducted 6–8 months after stent implantation in one study, revealing ISR rates of 30.1%, 14.6%, and 12.2% for bare-metal stents (BMS), first-generation drug-eluting stents (DES), and second-generation DES, respectively [36]. DES has minimized the limitations of BMS. However, DES is associated with a steady increase in very late stent thrombosis (VLST; > 1year post-stent implantation) due to delayed re-endothelialization or a hypersensitivity reaction to the stent polymer. Although infrequent, stent thrombosis remains an important concern because of its sequelae, including myocardial infarction and death in up to 80% of affected patients [37]. Bioresorbable scaffold (BRS) technology was introduced more than 2 decades ago with the goal of avoiding the adverse events related to permanent metallic stents, such as stent thrombosis, restenosis, and neo-atherosclerosis. An unexpectedly high incidence of scaffold thrombosis early following implantation of coronary BRS was found in studies [38,39]. Nevertheless, ISR remains a serious concern as a late stent complication.

Pathophysiological mechanisms of restenosis have not been completely elucidated. It is an outcome of a series of complex and partial responses (Fig. 2). Briefly, balloon dilatation and stent implantation procedures cause endothelium denudation and inflammation response, following migration and proliferation of a large number of VSMCs, and increased secretions of extracellular matrix, which ultimately formed intimal hyperplasia [40]. Application of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) confirmed the existence of intimal hyperplasia, which is particularly common in ISR of BMS. However, in-stent neo-atherosclerosis (ISNA), characterized by accumulation of lipid-laden foamy macrophages within the neointima

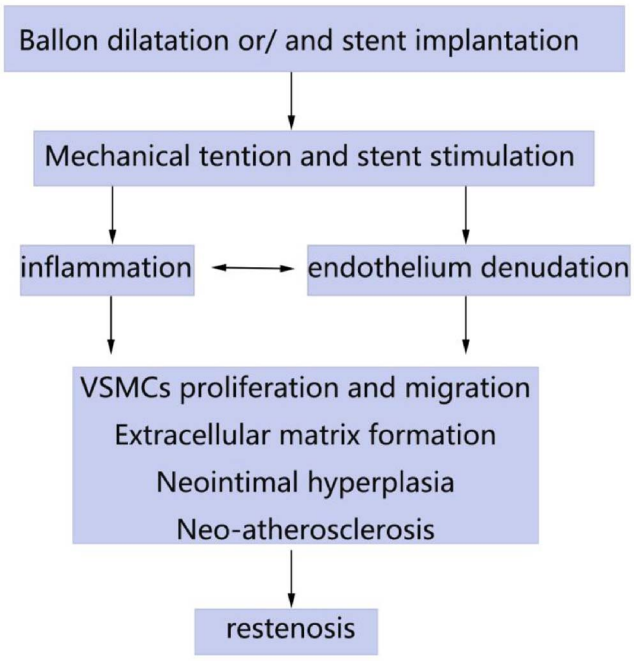

Fig. 2. Pathophysiology of restenosis. Endothelium denudation, inflammation and VSMC proliferation and migration mainly contribute to restenosis. VSMCs: vascular smooth muscle cells.