The Functional Link Between AMPK Pathway Activation and Atherosclerosis Progression

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Received: August 18, 2018; Published: August 29, 2018
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Abstract

The atherosclerosis is a complex pathological process that influences lipid deposition in the intima of middle- and large-sized arteries. AMP-activated protein kinase (AMPK) is a nutrient sensor that stimulates ATP production and fatty acid oxidation, but inhibits lipogenesis. Moreover, AMPK plays a key role in regulating oxidative stress, inflammation and vascular smooth muscle cells de-differentiation involved in atherosclerosis progression.

Keywords: Atherosclerosis; Oxidative stress; AMPK; Dyslipidemia

Abbreviations: ACC: Acetyl COA Carboxylase; AMPK: AMP-Activated Protein kinase; ECM: Extracellular Matrix; LDL: Low-Density Lipoprotein; NO: Nitric Oxide; NOX: NADPH Oxidase; VSMCs: Vascular Smooth Muscle Cells

Introduction

Atherosclerosis

Atherosclerosis is considered as one of causes of morbidity and premature disability in developed countries. Atherosclerosis is a complex chronic pathological disorder that affects many organs in human body causing ischemia of brain, extremities or heart leading to infarction depending on vessel involved [1]. It is characterized by the subendothelial accumulation of fibrous deposits in the intima of large arteries. Atherosclerosis was formerly regarded as a bland lipid storage disease, but recent studies have illustrated the role of inflammation, oxidative stress, immune system and endothelium on progression of atherosclerotic lesions [2]. Major risk factors for atherosclerosis involve hypercholesterolemia, dyslipidemia, hypertension, diabetes, inflammation, smoking, obesity, old age and family history of heart diseases [3].

Biochemical mechanisms of Atherosclerosis

Atherosclerosis is a progressive process that adversely influences the endothelial-lining of arteries. Additionally, vascular endothelium is considered as a functional barrier between blood stream and arterial wall. Vascular endothelium maintains the vascular homeostasis through secreting of contracting factors [e.g. endothelin and angiotensin II] and relaxing factors [e.g. nitric oxide (NO)] [4]. Imbalance of endothelial functions resulting in injury is called endothelial dysfunction, the initial stage of atherosclerosis. The process of atherosclerosis can be summarized as follow [2,3,5].

a) Injured vascular endothelial cells release chemokines and cytokines and also express adhesion molecules.

b) Monocytes are chemoattracted to the injured endothelium and penetrate into the subendothelial spaces where they differentiate into macrophages.

c) High blood levels of low-density lipoprotein (LDL) cholesterol infiltrates into subendothelial spaces where it is oxidized, modified and taken up by activated macrophages leading to foam cell formation.

d) Vascular smooth muscle cells (VSMCs) migrate into the intima, transform and proliferate into extracellular matrix (ECM) secreting cells. Moreover, oxidized LDL are taken up by transformed VSMCs gaining them atherogenic properties.

e) The increase in ECM secretion by proliferative VSMCs leading to the formation of fibrous scar and atherosclerosis.

f) The vital risks of atherosclerosis are that atherosclerotic plaques may block the vessels and obstruct blood flow, or they may rupture under the influence of biological and mechanical forces leading to thrombosis and clot formation [6].

AMPK Pathway

AMP-activated protein kinase (AMPK) is a metabolic key that maintains the balance of ATP production under many physiological
AMPK Activation and Dyslipidemia

Dyslipidemia is defined as elevated LDL cholesterol and triglyceride and/or decreased high density lipoprotein cholesterol and it is a primary factor inducing endothelial dysfunction [9]. The serine kinase AMPK plays a major role in lipid metabolism. In addition, AMPK mitigates lipogenesis and elevates fatty oxidation by affecting downstream signaling as ACC [10]. ACC has been regarded a key target in the treatment of metabolic diseases as type 2 diabetes and dyslipidemia owing to its role in lipogenesis [11]. Activated AMPK inhibits ACC activity through phosphorylation leading to a decline in malonyl CoA content and an increase in β-oxidation [12].

AMPK Activation and Oxidative Stress

Oxidative stress is characterized by the increase in reactive oxygen species and free radicals. Reactive oxygen species involve oxides and hydroperoxides, these compounds are produced during the oxidation-reduction reactions [13]. Recent studies have shown that AMPK has anti-oxidative activity that are partially attributed to the inhibition of NADPH oxidase (NOX) isoforms (NOX2; NOX4). As NOX is the enzyme responsible for reactive oxygen species generation [14]. In addition, AMPK activation regulates mitochondrial biogenesis and antioxidant defense gene expression. Furthermore, the expression levels of γ-glutamyl cysteine synthetase, catalase and superoxide dismutase, critical antioxidant enzymes, were downregulated after knockdown of the AMPK α1 subunit [15].

AMPK Activation and Macrophages

Circulating monocytes have a vital role in atherosclerosis formation and progression by influencing the plaque structure and the inflammatory response. AMPK activation reduces monocytes chemotaxation by suppressing chemokine production. Additionally, AMPK activation attenuates the number of macrophages in the atherosclerotic plaques [16]. Moreover, the phosphorylated AMPK suppresses the pro-inflammatory responses, macrophage polarization and inflammatory cytokine production [17]. Another study showed that activation of AMPK by phosphorylation plays anti-inflammatory activities through the AMPK/Nrf2 signaling pathways and its downstream target genes, (Hemoxygenase-1 and NADPH dehydrogenase quinone-1), in the macrophages, so preventing excessive macrophages-related responses in inflammation [18].

AMPK Activation and VSMCs

In healthy individuals, the arterial wall contains contraction-type VSMCs long-spindle shaped in the middle layer of intima. Although, in response to multiple stimuli, VSMCs dedifferentiate into proliferative and ECM-secreting cells [19]. Many studies have shown that AMPK can regulate cell differentiation through many downstream signaling pathways including endothelial nitric oxide synthase [20] and also promote re-differentiation of VSMCs [21]. Additionally, proliferative VSMCs enter S phase of the cell cycle, unlike the normal to be arrested in the G0/G1 phase of the cell cycle. AMPK activation was found to induce cell cycle arrest of VSMCs through p53 and p21 downstream [22].

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