

Review Article

AMPK: A Bridge between Inflammation and Metabolism

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Abstract

Hypercholesterolemia and low-grade inflammation are both basic factors that contribute to the genesis and progression of atherosclerosis. AMP-activated protein kinase (AMPK) is proposed to be a key regulator of cellular and organismal metabolism. Increased evidence shows that AMPK signaling can inhibit inflammatory responses. The macrophages play a diverse array of roles in atherogenesis, such as scavenger, immune modulation, and as a source of chemotactic molecules and cytokines. It has been considered that macrophages are central to all stages of atherosclerosis. AMPK lies at the crossroads of metabolically driven macrophage inflammation. In this review we propose to introduce the roles of AMPK and macrophage in the early stage of atherosclerosis. A comprehensive understanding in the role of AMPK between energy metabolism and inflammation in atherosclerosis may contribute to development of novel approaches in anti-atherosclerosis treatment.

Keywords

- AMPK
- Macrophage
- Inflammation
- Energy metabolism
- Atherosclerosis

ABBREVIATIONS

AMPK: AMP-Activated Protein Kinase; MCP-1: Monocyte Chemokine Protein-1; CCR2: Chemokine Receptor 2; MIF: Monocyte Migration Inhibitory Factor; LOX-1: Lectin Like Oxidized Low Density Lipoprotein Receptor-1; ABCG1: ATP Binding Cassette Transporter G1; ABCA1: ATP Binding Cassette Transporter A1

INTRODUCTION

Collectively, cardiovascular diseases are significantly associated with mortality and morbidity in modern human society and atherosclerosis is one of the main culprits [1,2]. The link between atherosclerosis and hyperlipemia has been widely studied and recognized. However, inflammatory mediators and vascular inflammation are also considered to be another important factor affecting the process of atherosclerosis [3]. Importantly, macrophages play an important role in the occurrence and development of atherosclerosis [4]. Monocyte recruitment into the vascular wall is one of the early events of atherosclerosis. Whereas monocytes activate into macrophages in the inner membrane, as an important inflammatory mediator in atherosclerosis, through production of a series of cytokines, oxygen free radicals, proteases and complement factors induced local inflammatory reaction. As antigen presenting cells, macrophages were also involved in the immune response [5]. Another important function of macrophages is a combination and modification of low density lipoprotein clearance, excessive intake will lead to the formation of intracellular cholesterol ester

accumulation in macrophage derived foam cells, which are an important marker for early atherosclerotic lesions [6]. In addition, due to the secretion of macrophages matrix metalloproteinases also affect the remodeling of arterial plaque, resulting in plaque rupture and lead to the occurrence of clinical cardiovascular events, such as ischemic stroke [7]. Therefore, macrophages are considered to be a potential target for treatment of atherosclerosis [8]. AMPK is a highly conserved multi-substrate serine/threonine protein kinase, which is called "energy sensor" [9]. It is mainly controlled by energy anabolism and catabolism pathways in order to maintain homeostasis in vivo. AMPK will be activated and phosphorylate a series of metabolism-related enzymes when intracellular energy is reduced or calcium ion is activated, thus accelerating ATP production and with reduced ATP consumption [10]. Long term activation of AMPK can enhance the effect through phosphorylation of transcription factors and co-activators. Besides energy states, AMPK activity is also affected by multiple cytokines secreted from immune cells and tissues. The centrally positioned regulatory roles of AMPK are reflected by an increasing volume of research efforts in recent years. Discussions of this review focus on the effects of AMPK on macrophages in the early stage of atherogenesis.

AMPK and monocyte recruitment

One of the early signs of atherosclerosis is monocyte recruitment [11]. The rise of circulating cholesterol and glucose impairs endothelial dysfunction through environmental stresses and promotes the production of cell adhesion molecules such

as ICAM, VCAM, endothelial monocyte adhesion molecule ELAM, P selectin and E selectin. The activation of circulating monocyte receptor results in monocyte integrin dependent adhesion to endothelium and subsequent transmigration to the sub endothelium. The factors that lead to the up regulation of endothelial cell adhesion molecules are complex. Studies have indicated that atherosclerosis was improved by reducing VCAM or ICAM knockout in atherosclerotic mice [12].

Chemokines are low molecular weight chemokine protein that induce monocyte recruitment to inflammatory site. Based on the first cysteine residue, the chemokines have been found to be divided into four subtypes. Monocyte chemokine protein-1 (MCP-1) belongs to the chemokine CC subfamily, its receptor is chemokine receptor 2 (CCR2). Researchers have indicated that monocyte recruitment and arterial plaque were decreased simultaneously in CCR2 and ApoE deficient mice. Similar results have been reported in MCP-1^{-/-} mice [13]. IL-8 is a major neutrophil chemokine, which is also expressed in macrophage derived foam cells of human atherosclerotic plaques. Chemokine receptor CXCR2 is for IL-8, GRO α and other CXC chemokine. AMPK agonist AICAR significantly reduced TNF-induced monocyte adhesion as well as expression of cell adhesion molecule ICAM-1, VCAM-1 and E selectin. In human arterial endothelial cells, the activation of AMPK could inhibit monocyte infiltration by reducing MCP-1 expression (Figure 1) [14].

Monocyte migration inhibitory factor (MIF) is another important factor that influences the migration and differentiation of monocytes and regulates the level of inflammatory response by mediating the release of other pro inflammatory factors. MIF is expressed in a wide variety of cells, including monocytes / macrophages, vascular smooth muscle cells and cardiac muscle cells. MIF is involved in the pathological process of a number of inflammatory diseases, such as atherosclerosis and rheumatoid arthritis. The severity of atherosclerosis is positively associated with an increased level of MIF. The lack of MIF showed protective effects on atherosclerosis in LDL^{-/-} mice. In the unstable plaque, the MMP-9 level increased with MIF over

expression. Administration of MIF antibody protects vascular damage in ApoE^{-/-} and LDL^{-/-} mice. Recent studies indicate that CXCR2 and CXCR4 are functional receptors for MIF. Meanwhile, the CXCR2 and CD74 receptor complexes were also observed in the inflammatory lesions of blood vessels of patients with atherosclerosis. A study published in 2008 was the first time to demonstrate that MIF was released in the process of myocardial ischemia, and that AMPK activation by CD74 promotes glucose uptake in protecting myocardial ischemia reperfusion injury, building a new connection to inflammatory and metabolic regulation [15].

AMPK and atherosclerosis inflammation

Monocytes enter the endothelium and differentiate into macrophages, including type M1 and type M2 macrophages. Type M1 is inflammatory macrophage, which secretes a variety of inflammatory cytokines, such as TNF, IL-6, IL-1, iNOS, etc. Type M2 is an anti-inflammatory macrophage, secreting anti-inflammatory cytokines including IL-10, TGF- β 1. AMPK could regulate the differentiation of monocytes and the release inflammatory cytokines in macrophages [16]. AMPK exists as heterotrimeric complexes comprising α 1, β 1 and γ 1 subunits in macrophages, pro inflammatory factors such as LPS significantly reduce AMPK activity [17,18]. With LPS stimulation, the phosphorylation level of AMPK and its downstream target ACC was significantly decreased in RAW 264.7 [18]. LPS stimulated bone marrow macrophages also decreased the phosphorylation level of AMPK, which was mainly due to decreased expression of AMPK α 1. On the other hand, the down regulation of macrophage AMPK increased the mRNA expression of LPS induced inflammatory cytokines TNF- α , IL-6, COX-2. AMPK regulates the expression of these inflammatory cytokines by inhibiting transcriptional activation of NF- κ B. Relative, constitutive activation AMPK (CA-AMPK) or pharmacological AMPK activation significantly reduce the expression of these inflammatory factors. Adiponectin activated AMPK in macrophages reducing LPS induced inflammatory cytokines TNF α , IL-6 and INF γ , while increasing the anti-inflammatory factor IL-10 levels (Figure 2) [19,20].

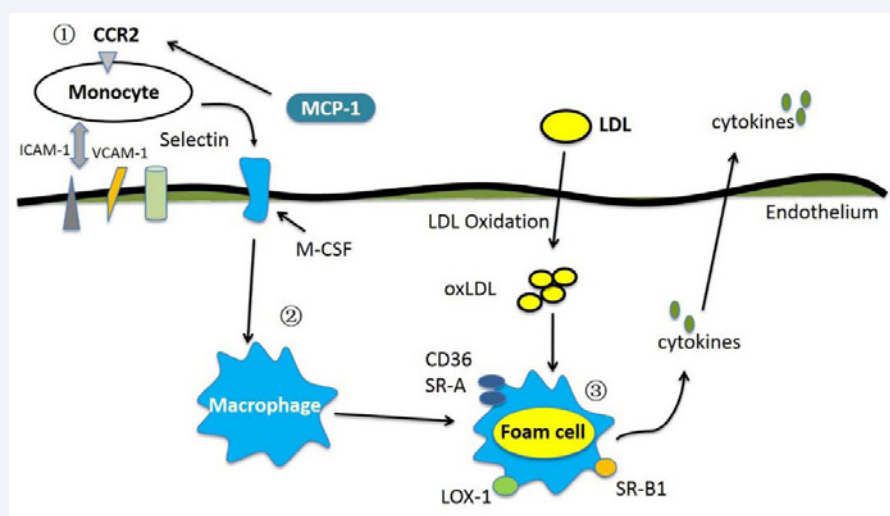


Figure 1 mononuclear cells migration in the early stage of atherosclerosis, macrophages differentiation, foam cells formation.

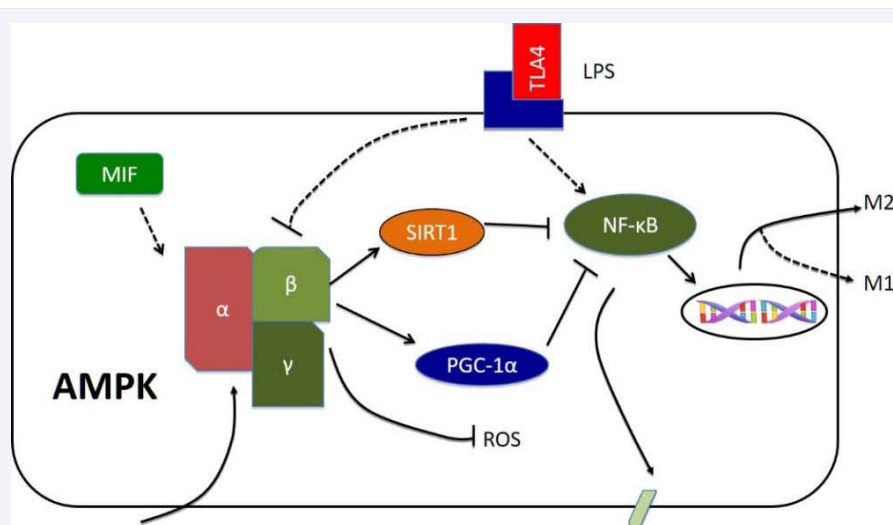


Figure 2 AMPK and macrophage inflammatory regulation.

The potential mechanism of inhibiting inflammatory response through AMPK activation is a topic of interest. Long term studies suggest that the activation of AMPK mainly inhibits NF- κ B mediated proinflammatory signaling pathway. CA-AMPK or pharmacological activation of AMPK in RAW264.7 macrophages could increase NAD⁺/NADH and activate SIRT1, leading to SIRT1 mediated NF- κ B deacetylation and inhibition of NF- κ B activation. PGC-1 is one of the important energy metabolism regulators. PGC-1 alpha can be combined with the NF- κ B p65 subunit, activation of the NF- κ B signaling pathway enhanced p65 and PGC-1 alpha interaction, resulting in decreased expression of PGC-1 alpha protein [21]. AMPK phosphorylates PGC-1 to trigger the effects of SIRT1 mediated acetylation and PGC-1 activation. Kim et al. showed that the increase of PGC-1 could inhibit NF- κ B activation and NF- κ B mediated inflammatory response induced by TNF- α [22]. The Fox O family and p53 are transcription factors that has a variety of functions, including regulation of energy metabolism and inflammation. The p53 comes into antagonism with NF- κ B signaling [23]. Levine et al. demonstrated that p53 inhibited the NF- κ B signaling pathway, while lacking the gene significantly increased NF- κ B activity [24]. There is an elevation in NF- κ B activity and inflammatory response in p53 knockout mice. AMPK phosphorylates p53 transcription activation domain Ser15 and Ser20, where the binding sites are closely related to inflammation and play an anti-inflammatory effects [24]. FoxO family consists of FOXO1, FOXO3a, FOXO4 and FOXO6 transcription factors [25]. Mammalian AMPK can phosphorylate FOXO3a at 6 regulatory sites and activates transcription of specific genes. FOXO3a deficient in mice induced inflammatory response, while FOXO3 inhibited activation of nuclear factor NF- κ B in T cells [26]. FOXO4 is an endogenous inhibitor of NF- κ B and FOXO4 deletion induces chronic inflammation in mice [27]. Moreover, SIRT1 bind to FOXO4 to increase its transcriptional activity [28]. These data suggest that AMPK may affect the function of FOXO by direct phosphorylation or indirectly effect through SIRT1. In addition, AMPK may directly phosphorylate transcriptional co activator P300 Ser89 to inhibit its activity, thereby inhibiting NF- κ B signaling and inflammatory reaction. However, AMPK

inactivation leads to increased activity of P300 up regulation of acetylation NF- κ B and transcription activity.

AMPK and macrophage-derived foam cell

Maintenance of cellular cholesterol homeostasis is a challenge to peripheral tissues, maintaining cholesterol homeostasis in macrophages is particularly important. Macrophages transform in to foam cells is mainly due to the excessive intake of modified low density lipoprotein [30,31]. This process involves the regulatory actions of macrophage scavenger receptors, different from LDLR, which is not controlled by the cellular cholesterol content [32]. Scavenger receptors expressed in macrophages of atherosclerotic plaques mainly includes SR-A1, SR-AII, CD36, SR-B1, CD68, lectin like oxLDL receptor-1 (LOX-1) [33] and SR-PSOX(34). SR-A and CD36 dominate in seven of all the scavenger receptors (35). Deletion of SR-A and CD36 genes may delay the development of atherosclerosis in mice. SR-B1 and CD36 belong to the type B scavenger receptor family. Similarly, SR-B1 combined with a variety of scavenger receptor ligands, such as acLDL and oxLDL, and its importance and special feature is the double role in reverse cholesterol transport [36]. In addition to cholesterol intake, SR-B1 is involved in cholesterol efflux. Another important scavenger receptor, LOX-1, was first identified from endothelial cells in 1997 [37]. Subsequent studies showed that LOX-1 were expressed in monocytes/macrophages, smooth muscle cells, myocardial cells, fibroblasts, adipocyte and platelets medium, especially in the atherosclerotic plaques in the human or animal [38,39]. In the physiological state LOX-1 is expressed in relatively low levels in endothelial cells, while LOX-1 expression can be significantly increased by stimulating inflammatory cytokines. The expression of LOX-1 could be significantly increased in various disease states, such as hypertension, hyper lipidemia, diabetes and ischemic injury [40,41]. LOX-1 transgenic mice fed high fat diet showed increase of oxLDL uptake, oxidative stress and macrophages infiltration [42]. The over expression of LOX-1 promotes the development of atherosclerosis [43]. On the contrary, LOX-1^{-/-}/LDLR^{-/-} mouse shows reduced artery plaque formation [44]. In addition, heterotopic liver expression

LOX-1 attenuates the development of atherosclerosis in Apo E^{-/-} mice. The mechanism may be attributed to their removal of circulating oxLDL by hepatic LOX-1 to decrease peripheral lipid accumulation and oxidative stress [45]. These pieces of evidence suggest that LOX-1 plays an important role in oxLDL uptake and the development of atherosclerosis.

Another mechanism to maintain cholesterol homeostasis is cellular cholesterol efflux. Two major cholesterol efflux pathways include SR-B1 and ATP binding cassette transporter ABCG1, ABCA1 mediated cholesterol efflux [46,47]. ApoA-1 promotes the flow of phospholipids and cholesterol to lipid deficient ABCA1 by direct binding to ABCA1. Whereas SR-B1 and ABCG1 increases cholesterol efflux to mature HDL [48,49]. Cholesterol homeostasis is essential for the maintenance of endothelial and immune cell functions in atherosclerosis. Existing research has shown that AMPK can affect the balance between cholesterol uptake and efflux. The activation of AMPK in primary cultured macrophages could inhibit the proliferation of oxLDL induced macrophage [50]. Recently, the author's research group found that the expression of AMPK and LOX-1 is closely related to oxLDL uptake in macrophages. AMPK activation significantly reduced the LOX-1 expression and oxLDL uptake in macrophages, while the inhibition or silencing of AMPK induced an up regulation of LOX-1 expression. Mechanistically, AMPK suppresses NF- κ B signaling by PP2A-mediated dephosphorylation RelA/p65 [51]. Other research reported that AICAR significantly inhibited oxLDL uptake, but the mechanism remains undefined [52]. In addition, AMPK inhibits foam cell formation by promoting cell cholesterol efflux. AICAR activated AMPK decreased intracellular cholesterol ester accumulation through increasing ABCG1 mediated cholesterol efflux from macrophages and endothelial cell, the mechanism is independent of LXR regulation with the increase ABCG1 mRNA stability [53,54]. Berberine activated AMPK may increase ABCA1 mediated cholesterol efflux and reduce the expression of scavenger receptor CD36 and LOX-1

in THP-1 derived macrophages [55]. AICAR also increased the expression of ABCA1 in THP-1 cells [52]. Admittedly, AMPK plays an important role in the maintenance of macrophage cholesterol homeostasis, whereas the exact mechanism still needs to be fully characterized. Using more specific AMPK activators or AMPK genetically modified animals may provide opportunities for future investigations (Figure 3).

Drug therapy and AMPK activation

Abnormal glucose and lipid metabolism cause hyperlipidemia and hyperglycemia, which are at least in part responsible for vascular inflammation and atherosclerosis. Energy metabolism disorder leads to AMPK energy sensing disorder and regulatory dysfunction. Elevated inflammation, in turn, further derails the regulatory roles of AMPK in energy metabolism, eventually contributing to a global imbalance that leads to the development of atherosclerotic lesions. Therefore, it is a plausible approach to maintaining the energy homeostasis to reverse atherosclerosis by restoring the function of AMPK.

Over the years, a large number of drugs have been investigated and used in treatment of metabolic and cardiovascular diseases. Many of these drug actions target directly or indirectly the functional aspects of AMPK. The cardiovascular protective effects of metformin, thiazolidinediones and statins are well documented [56]. In addition, studies have indicated that angiotensin II may induce AMPK inactivation, which may be the basis for vascular remodeling. Therefore, it was hypothesized that whether ACEI or ATII receptor antagonists might indirectly inhibit AMPK inactivation. Angiotensin II receptor antagonist telmisartan increased AMPK phosphorylation levels through PPAR δ pathway in skeletal muscle cells, but there still lacks investigations on vascular smooth muscle cells. Besides existing AMPK agonists, there may be a number of compounds specifically activate AMPK. AMPK agonist AICAR has been extensively studied. The pharmacokinetics of AICAR showed it has low oral bioavailability

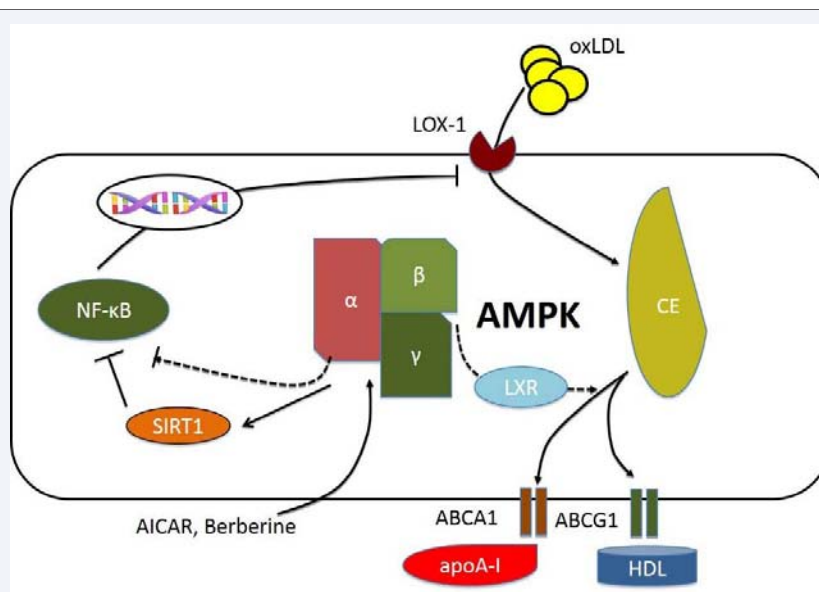


Figure 3 Effect of AMPK on the formation of macrophage derived foam cells in the process of atherosclerosis..

and is administrated only by vein injection, which limits its application as a vascular protective drug. Moreover, AICAR is more likely to be targeted to the ischemic tissue, thus avoiding unnecessary peripheral side effects. These properties exemplified a need to develop AMPK agonist with good bioavailability and high selectivity. However, the development of AMPK targeted therapeutic drugs is hampered because of the complex structure of AMPK and the interaction of AMPK complex with its upstream and downstream proteins. A-769662 provides a new possibility, where it specifically activates the AMPK β 1 subunit, which makes it possible to develop targeted AMPK agonist for clinical use [57]. In addition, A-769662 seems to have no effects on the glycogen domain of alpha and beta subunit as well as gamma subunit. But, its disadvantageous is similar with poor bioavailability of AICAR. Recent studies also questioned its selectivity on AMPK activation. The author's research group recently found a new AMPK agonist IMM-H007, which activates AMPK through binding AMPK γ 1 subunit and improves lipid metabolism *in vitro* and *in vivo* with good bioavailability [58,59]. Our studies have also found that IMM-H007 inhibits foam cell formation and inflammatory response in atherosclerosis [51].

Although AMPK is highly conserved, it plays multiple roles in different cell types, whether these compounds play a part in vascular protection is still need to further confirm. In addition, physical exercise is an effective, healthy "AMPK activator". Some research showed that moderate physical exercise improves insulin resistance and inflammation. Low-intensity exercise may promote the cycle of AMPK by activating PGC-1 α/β to promote the differentiation of mononuclear cells to the M2 type and thus ameliorate atherosclerosis [60].

DISCUSSION AND CONCLUSION

Inflammatory and metabolic disorders are two key factors in the pathogenesis of atherosclerosis. Between them AMPK plays a role as a bridge and coordinator. However, there are unsolved questions: The precise roles of AMPK in mono cyte adhesion, macrophage differentiation and foam cell formation need to be clearly defined. These investigations will help understand how AMPK activation plays a protective role in atherosclerosis. In conclusion, a better understanding of the regulatory roles of AMPK in metabolism and inflammation are the key to identifying an effective approach to treating atherosclerosis.

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