AMPKα2 Regulates Hypoxia-Inducible Factor-1α Stability and Neutrophil Survival to Promote Vascular Repair After Ischemia

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Circulating cytokines/chemokines and growth factors regulate endothelial function and influence the development of cardiovascular diseases. Cardiovascular diseases are characterized by endothelial dysfunction, vascular smooth muscle cell (VSMC) proliferation, and inflammatory cell migration, leading to obliteration or excessive enlargement of vascular lumens. Endothelial dysfunction is induced by cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, and smoking, all of which trigger a variety of vascular disorders. Recently, AMP-activated protein kinase (AMPK) has been demonstrated as an important regulator of metabolic functions, including the regulation of cellular energy homeostasis and metabolism. AMPK is an evolutionarily conserved serine/threonine kinase that functions as an important energy sensor and plays a crucial role in vascular homeostasis. Moreover, AMPK is a master regulator that senses cellular energetics in part through the AMP/ATP ratio and mitochondrial reactive oxygen species production and coordinates cell-autonomous responses to metabolic stress. Importantly, AMPK has an antipapoptotic effect in endothelial cells and a proapoptotic effect in VSMCs, which are critical for vascular remodeling. The interactions between endothelial cells, VSMCs, adventitial cells, and inflammatory cells play crucial roles in the development of vascular diseases. Both endothelial nitric oxide (NO) production and NO-mediated signaling in endothelial cells and VSMCs are targets and effectors of the AMPK signaling pathway. Furthermore, AMPK regulates many other stimuli modulating vascular functions, including reactive oxygen species, that promote VSMC proliferation by auto/paracrine growth mechanisms. AMPK is a heterotrimeric complex consisting of a catalytic subunit (α) and 2 regulatory subunits (β and γ), each having ≥2 isoforms (α1, α2, β1, β2, γ1, γ2, and γ3) that are differentially expressed in various tissues and subcellular locations. In the vascular endothelium, both α-subunits of AMPK are expressed, although AMPK-α1 is expressed to a greater extent than AMPK-α2. Endothelium-dependent vasodilatation is a vital mechanism of blood flow regulation in response to increased metabolic demand (Figure). We have demonstrated that endothelial AMPK plays an important role in microvascular homeostasis and regulation of systemic arterial pressure in mice in vivo. As a metabolic sensor, endothelial AMPK plays an important role in the metabolic regulation of blood flow, which is regulated by endothelial NO synthase through the activation of the AMPK-α1 subunit (Figure). Endothelial-specific AMPK-knockout mice and the resultant endothelial dysfunction induce increased expression of inflammatory cell adhesion molecules. Accumulated inflammatory cells generate an oxidizing environment, which involves abundant reactive oxygen species, inflammatory cytokines/chemokines, and growth factors that contribute to aortic aneurysm formation, which is also regulated by AMPK-α2 in VSMCs. Oxidative stress and a shift in the cellular redox balance have been linked with endothelial dysfunction at the early stages of cardiovascular diseases. In contrast, AMPK can inhibit reactive oxygen species formation through NADPH oxidase and stimulate NO production by endothelial NO synthase. Indeed, AMPK has been suggested to phosphorylate the p47phox subunit and thus prevent its translocation to the plasma membrane.

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Arteriogenesis and angiogenesis are determined by endothelial cells and by circulating inflammatory cells. It has been suggested that AMPK-α1 and AMPK-α2 may play different roles in endothelial function and inflammatory cell survival during hypoxia. Therefore, it will be of great interest to develop novel strategies targeting the inflammatory cells migrating to the vascular tissues. In this issue of Circulation Research, Abdel Malik et al assessed the role of AMPK, particularly the AMPK-α2 subunit, in the regulation of vascular repair in vivo in a model where the outcome is largely dependent on local responses to hypoxia and the mobilization and recruitment of monocytes and neutrophils. The authors demonstrated that AMPK-α2 regulates α-ketoglutarate generation, hypoxia-inducible factor-1α stability, and neutrophil survival, which in turn determines further myeloid cell recruitment and repair potential. The authors concluded that AMPK-α2 activation in neutrophils is a decisive event in the initiation of vascular repair after ischemia. Why is this article so intriguing and important? First, to understand the specific role of the AMPK-α2 subunit in myeloid cells in vascular repair, the authors performed an in vivo study using mice lacking the AMPK-α1 or the AMPK-α2 subunits specifically in myeloid cells and in endothelial cells. The authors found that the recovery of blood flow in ischemic hindlimbs was markedly attenuated in myeloid cell–specific AMPK-α2-knockout mice compared with that in their wild-type littermates. Next,
the authors used in vitro and ex vivo approaches and showed that AMPK-α2 is linked to an increase in early neutrophil infiltration, the upregulation of inflammatory cytokines, and adhesion molecule expression. Finally, the authors precisely demonstrated the molecular mechanism by which the AMPK-α2 in neutrophils is required for protection against apoptosis under hypoxic conditions via regulating hypoxia-inducible factor-1α hydroxylation and stabilization and hypoxia-inducible factor-1α–dependent responses (Figure). Unlike the AMPK-α1 subunit, AMPK-α2 can translocate to the nucleus and affect gene and protein expression by several mechanisms. Therefore, this study provides novel information about the role of AMPK-α2 in neutrophils, which serves as an important multifunctional regulator in cardiovascular diseases. On the basis of this study and previous reports, AMPK-α1 and AMPK-α2 modulate endothelial function, VSMC proliferation, and inflammatory cell activation through many intracellular and extracellular mechanisms. These data will augment the possibilities of AMPK activators in cardiovascular diseases therapy.

Clinical Significance

Several drugs and molecules activate AMPK, all of which could be potentially protective against the development of vascular diseases.13 AMPK activation by statins and metformin has been proposed to contribute to the pleiotropic effects of this compound class.6 In addition, pharmacological interventions that include aspirin, 5-aminoimidazole-4-carboxamide riboside, thiazolidinediones, and the phytochemicals berberine, quercetin, and resveratrol have the ability to activate AMPK signaling by raising the (AMP+ADP)/ATP ratio as a consequence of mitochondrial electron transport and glycolysis inhibition.6 In this study, the authors have shown that AMPK-α2 activation in neutrophils is a decisive event in the initiation of vascular repair after ischemia.14 These findings may have great therapeutic impact, leading to the development of novel therapeutic strategies using AMPK activators against cardiovascular diseases. Indeed, AMPK activation by oral administration of metformin has been shown to inhibit pulmonary VSMC proliferation and ameliorate the development of pulmonary hypertension.1 The pathobiology of cardiovascular diseases includes endothelial dysfunction,
VSMC proliferation, and inflammatory cell migration. Thus, AMPK may represent a novel therapeutic target against endothelial dysfunction, VSMC proliferation, inflammation, and vascular repair after ischemia. The present findings also suggest that AMPK activation may represent a novel strategy to target vascular repair and angiogenesis in response to hypoxia. Thus, we expect that a highly selective, tissue-specific AMPK activator will be developed in the near future.

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Disclosures
None.

References


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