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Commentary

AMP-activated protein kinase activation: therapeutic potential in human diseases

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AMP-activated protein kinase (AMPK), a conserved sensor of cellular energy under physiological and pathological conditions, has been in the spotlight for decades. It is typically activated upon energy deprivation. The consumption of ATP causes the increase of AMP/ATP ratio, which results in the phosphorylation of threonine 172 (Thr 172) in the AMPKα subunit and the activation of AMPK. In addition to its direct effects on cellular metabolism and energy homeostasis, AMPK regulates multiple biological processes, including restoring autophagy, inhibiting oxidative stress, and ameliorating inflammation. Here, we highlight recent significant advances in elucidating the protective role of AMPK in cardiovascular diseases (CVDs), ageing, diabetes mellitus, and cancer. Furthermore, we discuss its therapeutic potential for these conditions.

Most CVDs progress to heart failure. The heart is an organ with high energy requirements that turns over approximately 30 kg of ATP daily. Therefore, myocardial energy deficiency is a significant contributor to pathological cardiac hypertrophy and resulting in cardiac dysfunction. The α2 isoform of the AMPK catalytic subunit is the most abundantly expressed isoform in the heart, and is predominantly distributed in cardiomyocytes, whereas AMPKα1 is the major isoform expressed in non-myocytes [1]. In failing hearts, an AMPKα2 isoform to AMPKα1 isoform shift accompanied by mitochondrial dysfunction was observed [2]. Moreover, overexpression of AMPKα2 reversed phenylephrine-induced cardiac dysfunction by promoting cardiac mitophagy via the putative kinase-1-Parkin pathway [2]. Cardiac remodelling is generally accepted to be a critical process in the progression of heart failure. Increasing evidence supports that direct or indirect AMPK activators, such as 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), metformin, or A769662, can protect against cardiac remodelling by promoting autophagy, suppressing fibroblast proliferation, and inhibiting transforming growth factor (TGF)-β and ROS production [1]. Although the beneficial effects of AMPK in cardiac remodelling are unequivocal, the underlying molecular mechanism has not been fully elucidated.

Atherosclerosis is characterised by lipid deposition on vascular walls and is the critical cause of myocardial infarction and heart failure. AMPK activation remarkably prevents the progression of atherosclerosis, as manifested by amelioration of dyslipidemia, improvement in endothelial function, and reduction of atherosclerotic plaque formation. The underlying mechanisms include inhibition of endoplasmic reticulum stress, reduction of adipokine production, suppression of reactive oxygen species (ROS) and NADPH oxidase, and improvement of mitochondrial function [3]. AMPK also contributes to maintaining the stabilization of atheromatous plaques by promoting cholesterol efflux and inhibiting inflammation. AMPK activation promotes cholesterol efflux by increasing expression of cholesterol transport proteins (such as ATP-binding cassette transporter subfamily A member 1 [ABCA1], ABCG1, and scavenger receptor class B member 1 [SR-BI]) in macrophages, vascular smooth muscle cells, and endothelial cells [4]. AMPK activation inhibits LDL-induced macrophage proliferation and inflammasome formation by increasing autophagy [4]. Collectively, these data suggest AMPK activation not only prevents the atherosclerotic lesion formation, but also may enhance the stability of atherosclerotic plaques. Therefore, AMPK activators possess therapeutic potential for atherosclerosis.

Ageing is associated with the decline of various physiological processes, leading to an increase in the risk of CVDs. It is well accepted that AMPK activation in response to caloric restriction, exercise, or AMPK activators extends the lifespan of various animal models. In a mammalian model, mice with mitochondrial dysfunction exhibited signs of premature ageing, and accumulated senescent cells, as a result of decreased AMPK activation [5]. AMPK activity declines with advancing age in various murine tissues, particularly the aorta and cerebral arteries [6]. Endothelial dysfunction induced by lipopolysaccharide was ameliorated in ageing mice after treatment with the AMPK activator metformin [7]. Moreover, loss of sirtuin 2 (SIRT2), a cytosolic member of the sirtuin family, aggravated age-related cardiac hypertrophy by reducing AMPK activation [8]. Taken together, augmenting AMPK signalling can contribute to longevity and ameliorate age-related cardiovascular disease pathologies. However, further studies are warranted to provide enough direct

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evidence to support the notion that AMPK activation prolongs mammalian lifespans.

Hyperglycaemia is an independent risk factor of CVDs. Various studies have shown that AMPK activity is reduced in diabetes mellitus, accompanied by the attenuated cardiac function that is referred to as diabetic cardiomyopathy. Decreased autophagy due to reduced AMPK activity is an important mechanism of diabetic cardiomyopathy in type 2 diabetes. AMPK activation protects against mitochondrial dysfunction, and ultimately improves the diabetic cardiac function [9]. Metformin, a first-line medicine for diabetes, is also a well-known AMPK activator. A meta-analysis showed that metformin reduces the risk of acute myocardial infarction and stroke more than other non-insulin glucose-lowering drugs, or insulin therapy in diabetes patients [10]. The above results suggest the potential for AMPK activation to prevent cardiac events in patients with diabetes.

Epidemiological studies have suggested that diabetes is associated with an increased risk of cancer. AMPK activation by metformin has proven to efficiently inhibit tumour growth, promote the infiltration of immune cells into tumour tissue, and contribute to an increased survival rate of patients with breast cancer [11]. Nonetheless, AMPK has also been shown to advance the growth of some cancer cells, which can be partially explained by the promotion effect of AMPK on glucose absorption [12]. Thus, AMPK can either be a tumour suppressor or promotor depending on the pathological tumour type and context. Moreover, it is essential to clarify the role of AMPK at different stages of tumour progression.

Inflammatory injury is a common pathological feature of CVDs, diabetes, and cancer. Accumulating evidence has shown that AMPK can regulate immune cells through processes such as inhibiting proinflammatory cytokines secreted by macrophages, enhancing the phagocytic and cytotoxic functions of neutrophils, maintaining dendritic cell activity, and regulating the differentiation and functions of lymphocytes [13]. Knockdown of AMPKα1 increases expression of the inflammatory marker of M1-macrophages, C-C chemokine receptor 2, which facilitates inflammatory cell infiltration. In addition, AMPK activation not only suppresses the release of multiple proinflammatory cytokines and their downstream signalling pathways, but also reduces oxidative stress by inhibiting expression of inducible nitric oxide (NO) synthase, *cyclo*-oxygenase-2, and NADPH oxidase-2 [13]. Progressive inflammatory injuries are critical pahological responses in various diseases. The anti-inflammatory effect of AMPK might be the protective mechanism by which AMPK activation inhibits different pathological processes.

Several medicines activating AMPK have been developed or re-recognized. In particular, IMM-H007 is an activator of AMPK that was proven to be effective in reducing the oxidized low-density lipoprotein level and the lesion size of atherosclerosis in apolipoprotein E deficient mice [14]. Berberine (BBR), a natural compound extracted from several plants, has a long history of use in traditional Chinese medicine. Studies have identified that AMPK is one of the molecular targets of BBR. By activating AMPK, BBR can target various diseases, such as atherosclerosis, insulin resistance and diabetes mellitus, and non-alcoholic fatty liver disease [15].

In summary, the protective roles of AMPK have been demonstrated in CVDs, ageing, diabetes mellitus, and cancer. However, several issues on the application of AMPK activator need to be carefully examined. First, the mechanisms underlying its functions in multiple diseases remain poorly defined. Second, the mechanism that AMPK plays different regulatory roles in different tumours is still unknown. Third, there have been numerous clinical studies on the effects of metformin whose protective effects include AMPK-dependent and -independent pathways. Therefore, the long-term safety and efficacy of other specific AMPK activators also require further assessment. Further investigation focused on these questions would provide valuable information to researchers aiming to develop therapeutic strategies targeting AMPK for various diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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