Roles of adenosine monophosphate-activated protein kinase (AMPK) in the kidney

Na Zhu, Min Han

Department of Nephrology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei 430000, China.

To the Editor: The kidney is a highly energy-consuming organ and is prone to damage if there is an energy supply disorder. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a serine/threonine kinase that plays a critical role in metabolism, autophagy, inflammation, and mitochondrial homeostasis. AMPK is involved as an energy sensor in the physiological and pathological processes of the kidney.

AMPK is a heterogeneous complex comprising a catalytic subunit, α, and regulatory subunits, β and γ. AMPK activation can be induced by the increased ratio of AMP : adenosine triphosphate (ATP) or adenosine diphosphate (ADP) : ATP and upstream kinases, including liver kinase B1 (LKB1) and calcium/calmodulin-dependent protein kinase kinase beta (CaMKKβ). Other kinases like protein kinase B (AKT), protein kinase A (PKA), and transforming growth factor (TGF)-β-activated kinase-1 can also activate AMPK.

Activated AMPK inhibits fatty acid (FA) and cholesterol synthesis by suppressing the phosphorylation of acetyl-coenzyme A (CoA) carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), respectively. ACC is the rate-limiting step of FA synthesis, while HMGCR is the rate-limiting step of cholesterol synthesis. AMPK can also inhibit lipogenesis by suppressing sterol regulatory element-binding proteins1-c phosphorylation. AMPK promotes FA β-oxidation by suppressing the activity of carnitine palmitoyltransferase-1, which is regulated by the production of malonyl-CoA. Malonyl-CoA is generated by ACC. AMPK also participates in lipolysis by regulating adipose triglyceride lipase and hormone-sensitive lipase, which are the rate-limiting enzymes of lipolysis. Peroxisome proliferator-activated receptor gamma (PPARγ) has been demonstrated to be involved in lipid metabolism,[1] but the relationship between PPARγ and AMPK needs further investigation. AMPK also participates in lipotoxicity. FA enters the cell through FA translocase (CD36). The upregulation of CD36 leads to decreased AMPK activity and lipotoxicity.

AMPK is reportedly involved in glucose uptake, glycolysis, glycogen synthesis, gluconeogenesis, and insulin resistance.[2] AMPK increases glucose uptake by promoting *GLUT4* gene expression and translocation. AMPK also increases the expression of *GLUT1* in rat kidneys. The transient receptor potential regulation channel 6 (TRPC6)–AMPK pathway is involved in insulin-dependent glucose uptake.[3] AMPK stimulates glycolysis by activating phosphofructokinase 2, which is the rate-limiting enzyme of glycolysis. AMPK inhibits glycogen synthesis by suppressing glycogen synthases. AMPK regulates gluconeogenesis by inhibiting CREB-regulated transcription coactivator 2 (CRTC2) and HNF4α. CRTC2 is an activator of many gluconeogenic genes, such as phosphoenolpyruvate carboxykinase. AMPK participates in insulin resistance through the regulation of phosphatase and tensin homolog deleted on chromosome ten. The Sirt1–AMPK pathway is also necessary for insulin response.

AMPK helps maintain mitochondrial biogenesis, mitochondrial fission and fusion, and mitophagy. AMPK can activate PGC1α, which is an important regulator of mitochondrial biogenesis. PGC1α stimulates mitochondrial biogenesis through nuclear respiratory factors 1 and 2 (NRF1/2) and transcription factor A, mitochondrial (TFAM). AMPK is involved in mitochondrial dynamics by regulating the expression of a dynamin-like protein and mitofusin 1. Activated AMPK can enhance mitophagy by activating unc-51-like autophagy activating kinase 1 (ULK1) and inhibiting the mammalian target of rapamycin (mTOR). Moreover, AMPK also directly phosphorylates mitochondrial fission factor on Ser155 and Ser172, triggering fission and subsequently mitophagy.

Autophagy is a complex and highly regulated process of self-degradation of cellular components. In the kidney,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001831

Correspondence to: Dr. Min Han, Department of Nephrology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei 430000, China
E-Mail: minhan@tjh.tjmu.edu.cn

Chinese Medical Journal 2022;135(4)

Received: 26-03-2021; **Online:** 04-01-2022 **Edited by:** Yuanyuan Ji

basal autophagy flux is essential to maintain cellular homeostasis and renal function. AMPK mainly induces the expression of ULK1 and suppresses mTOR activity to promote autophagy. AMPK either directly phosphorylates mTOR or through phosphorylation of the tuberous sclerosis complex 2 protein to reduce mTOR activity. Activated AMPK leads to an increase in nicotinamide adenine dinucleotide (NAD), thus increasing SIRT1 activity. SIRT1 regulates autophagy by targeting *FOXO* in the nucleus.[1]

Many kidney diseases, including diabetes-associated chronic kidney disease, are characterized by inflammation and fibrosis. AMPK is involved in regulating inflammatory cell infiltration, oxidative stress, and fibrosis. AMPK activation can reduce macrophage infiltration and regulate macrophage polarization. Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases are one of the reactive oxide species (ROS) sources in renal cells. Activated AMPK can resist oxidative stress by inducing the expression of antioxidative genes, such as catalase and superoxide dismutase 2, and suppressing the production of NADPH oxidase 4 (NOX4), which is the most abundant NOX isoform in the kidney. The SIRT1–AMPK pathway is associated with the production of mitochondrial ROS; however, the direct interaction between AMPK and mitochondrial ROS has not been fully elucidated. AMPK exerts its anti-fibrosis effect through its interaction with CK2β.

The kidney tubules have many channels for transporting ions, such as the epithelial Na+ channel (ENaC), Na^+–K^+–ATPase (NKA), cystic fibrosis transmembrane conductance regulator (CFTR), and Na^+–K^+–2Cl-cotransporter (NKCC). AMPK is involved in the regulation of these ion channels. AMPK can enhance NKA activity by restoring NKA cell surface expression. AMPK indirectly regulates the activity of ENaC by influencing the interaction between neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4-2) and ENaC. NEDD4-2, the E3 ubiquitin-protein ligase, is engaged in regulating the activity of ENaC by promoting its internalization and degradation. AMPK can regulate CFTR activity through PKA. AMPK induces the activation of NKCC2, which is an NKCC isoform in epithelial cells.

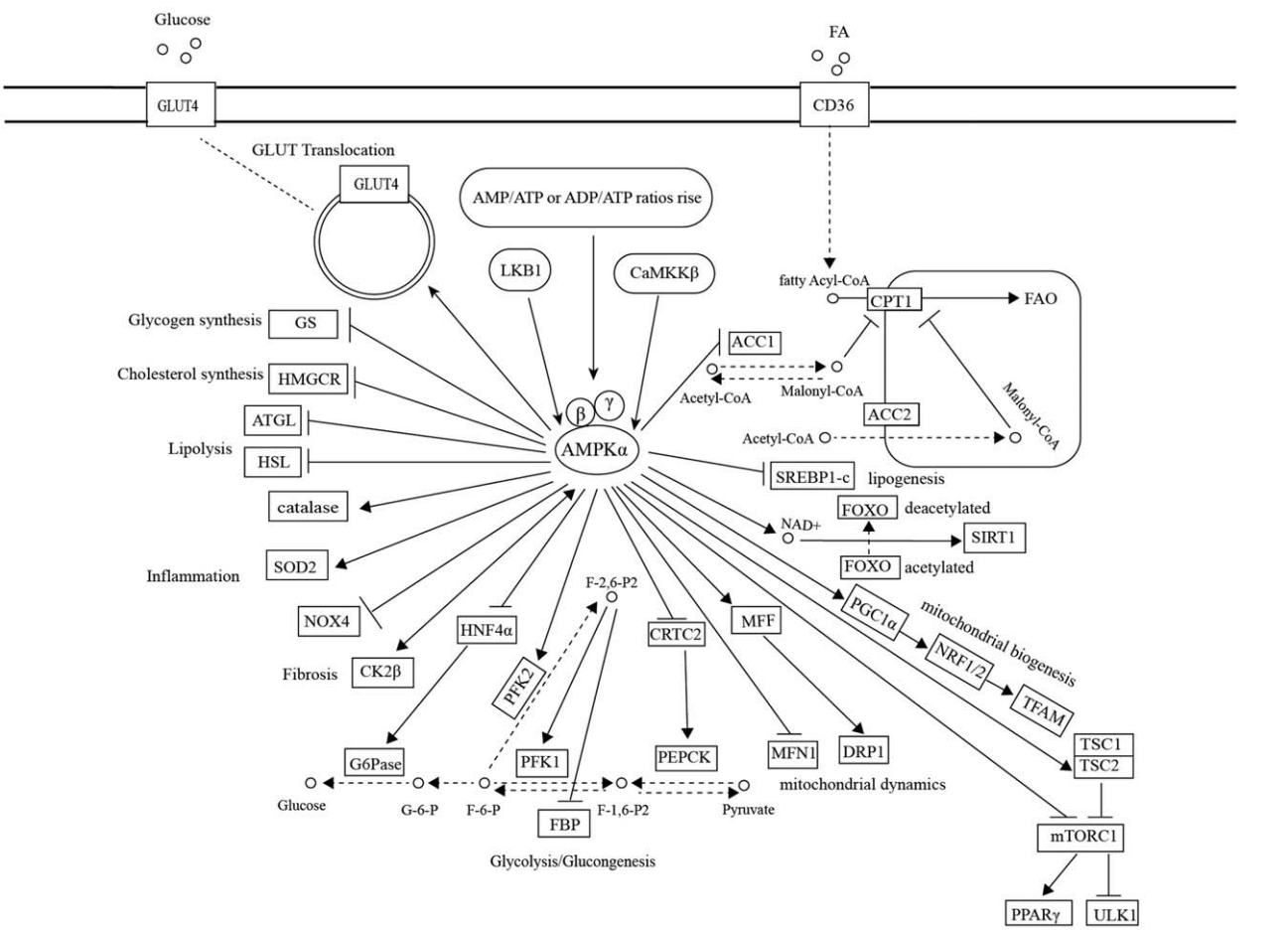

Figure 1: AMPK signaling in the kidney. ACC: Acetyl-CoA carboxylase; AMPK: AMP-activated protein kinase; ATGL: Adipose triglyceride lipase; CaMKKβ: Calcium/calmodulin-dependent protein kinase kinase beta; CPT-1: Carnitine palmitoyltransferase-1; FA: Fatty acid; GS: Glycogen synthases; HMGCR: 3-hydroxy-3-methylglutaryl-CoA reductase; HSL: Hormone-sensitive lipase; LKB1: Liver kinase B1; MFF: Mitochondrial fission factor; MFN1: Mitofusin 1; NRF1/2: Nuclear respiratory factors 1 and 2; PEPCK: phosphoenolpyruvate carboxykinase; PFK1: Phosphofructokinase 1; PFK2: Phosphofructokinase 2; PPARγ: Peroxisome proliferator-activated receptor gamma; SOD2: Superoxide dismutase 2; SREBP1-c: Sterol regulatory element-binding proteins; TFAM: Transcription factor A, mitochondrial; TSC1: Tuberous sclerosis complex 1; TSC2: Tuberous sclerosis complex 2; ULK1: Unc-51-like autophagy activating kinase 1.

AMPK, sirtuins, and PGC-1α form an energy-sensing network that regulates energy metabolism in the kidney. The AMPK/SIRT1/PGC1-α pathway is involved in maintaining mitochondrial homeostasis. AMPK can also directly activate PGC1α. PGC1-α can activate SIRT3, which plays an important role in fighting oxidative stress and promoting ATP synthesis. SIRT3 promotes ATP synthesis by acting on the electron transport chain, ATP synthase, and promoting FA oxidation.

The multiple roles of AMPK in the kidney reveal the potential of AMPK agonists in the treatment of kidney diseases. There are direct and indirect AMPK agonists. Metformin, polyphenol resveratrol, and canagliflozin are examples of indirect AMPK activators, while AICAR and A769662 are examples of direct activators. Both metformin and canagliflozin activate AMPK by inhibiting mitochondrial complex I, and both can be used in the treatment of type 2 diabetes-related kidney diseases. However, metformin is associated with a high risk of lactic acidosis, which limits its use. Polyphenol resveratrol activates AMPK through multiple mechanisms, including the inhibition of ATP synthase and the activation of SIRT1. Although polyphenol resveratrol and AICAR have been shown to slow the progression of kidney diseases, such as acute kidney injury and diabetic kidney disease, none of them have been incorporated in clinical practice. A769662 is the first drug to be identified to activate AMPK by binding to the interface of the α- and β-subunits; however, it has poor bioavailability. To conclude, AMPK plays various roles in the kidney [Figure 1], and it emerges as a promising therapeutic target, but the safety of its agonists needs to be further validated.

Conflicts of interest

None.

References

1. Juszczak F, Caron N, Mathew AV, Decleves AE. Critical role for AMPK in metabolic disease-induced chronic kidney disease. Int J Mol Sci 2020;21:7994. doi: 10.3390/ijms21217994.
2. Steinberg GR, Carling D. AMP-activated protein kinase: the current landscape for drug development. Nat Rev Drug Discov 2019;18:527–551. doi: 10.1038/s41573-019-0019-2.
3. Rachubik P, Szrejder M, Rogacka D, Audzeyenka I, Rychłowski M, Angielski S, *et al*. The TRPC6-AMPK pathway is involved in insulin-dependent cytoskeleton reorganization and glucose uptake in cultured rat podocytes. Cell Physiol Biochem 2018;51:393–410. doi: 10.1159/000495236.

How to cite this article: Zhu N, Han M. Roles of adenosine monophosphate-activated protein kinase (AMPK) in the kidney. Chin Med J 2022;135:488–490. doi: 10.1097/CM9.0000000000001831