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## Regulation of hepatic metabolism by AMPK

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- (1) The AMP-activated protein kinase (AMPK) is an evolutionary conserved serine/threonine protein kinase that functions as a major regulator of cellular and whole-body energy homeostasis coordinating multiple metabolic pathways to adapt cellular processes to the energy status. AMPK is a heterotrimeric complex composed of one catalytic ( $\alpha$ ) and two regulatory subunits ( $\beta$  and  $\gamma$ ). AMPK activation requires phosphorylation on Thr172 within the activation loop of the catalytic  $\alpha$ -subunit by upstream kinase, identified as the liver kinase B1 (LKB1).
- (2) AMPK is activated in response to a variety of physiological processes and pathological stresses that typically change the cellular AMP/ATP ratio caused by increasing ATP consumption or reducing ATP production. Activated AMPK switches cells from an anabolic to a catabolic state, shutting down the ATP-consuming synthetic pathways and initiating ATP-producing pathway to restore energy balance. In addition, adipokines such as adiponectin and resistin, that regulates whole-body energy balance, may also affect hepatic AMPK activity and could contribute to the fed-to-fasted transition from anabolism to catabolism in the liver [1].
- (3) As well as responding to metabolic stresses, AMPK is activated by various pharmacological and phytochemical products including the antidiabetic drug metformin, AICAR and resveratrol. Recent evidence confirms that these compounds behave as indirect AMPK activators by causing a mild impairment of ATP synthesis [2-4]. Intriguingly, AMPK is dispensable for the effects of metformin and AICAR on hepatic gluconeogenesis, acting directly by reducing energy charge through inhibition of the respiratory-chain complex I [2, 3].
- (4) AMPK controls the fate of fatty acids by reducing intracellular malonyl-CoA content which is both a critical precursor for biosynthesis of fatty acids and a potent inhibitor of mitochondrial fatty acid oxidation via the allosteric regulation of carnitine palmitoyltransferase 1 (CPT1) which catalyzes the entry of long-chain fatty acyl-CoA into mitochondria. AMPK phosphorylates and inhibits acetyl-CoA carboxylase (ACC) and increases malonyl-CoA decarboxylase (MCD) activity resulting in lower malonyl-CoA levels and therefore promoting mitochondrial  $\beta$ -oxidation while simultaneously suppressing fatty acid synthesis. The activity of glycerol-3-phosphate acyltransferase

(GPAT), the first committed step in triacylglycerol synthesis, is also regulated by AMPK activation. The cholesterol biosynthesis is controlled by AMPK through direct phosphorylation and inhibition of the rate limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase [1].

- (5) Although the action of AMPK is achieved by rapid and direct phosphorylation of key metabolic enzymes, long-term effects have been clearly demonstrated on the expression of a number of gene sets. AMPK promotes the induction of the transcriptional mitochondrial gene program and the inhibition of lipogenesis gene expression by direct phosphorylation of transcription factors and co-activators [1, 3, 5]. Interestingly, AMPK influences the NAD<sup>+</sup>-dependent SIRT1 deacetylase activity by modulation of NAD<sup>+</sup> levels following induction of fatty acid oxidation and thus may indirectly modulate the acetylation and activity of certain transcriptional regulators in addition to direct phosphorylation events [6]. AMPK phosphorylates the transcriptional coactivator peroxisome proliferator-activated receptor- $\gamma$  coactivator-1  $\alpha$  (PGC-1  $\alpha$ ), which controls the expression of multiple transcription factors to induce mitochondrial biogenesis, and results in greater mitochondrial oxidative capacity by increasing PGC1- $\alpha$  expression and activation through PGC1- $\alpha$  promoter autoregulation and SIRT1-mediated deacetylation, respectively [6, 7]. AMPK participates in the regulation of lipogenesis gene expression by phosphorylation of the carbohydrate response element binding protein (ChREBP), reducing its DNA binding capacity and nuclear translocation, and down-regulating sterol regulatory element-binding protein-1c (SREBP-1c) gene expression and stability probably through SIRT1-dependent deacetylation [1, 5]. Lastly, the phosphorylation of CREB-regulated transcription coactivator 2 (CRTC2) by AMPK promotes CRTC2 binding to 14-3-3 proteins in the cytoplasm and prevents its translocation to the nucleus, thereby reducing CREB-dependent expression of the gluconeogenesis genes [1], although this effect was recently challenged [2].
- (6) AMPK activation also inhibits other ATP-consuming anabolic pathways such as protein synthesis. This occurs by multiple mechanisms including inhibition of the mTOR/S6K1 pathway, that stimulates translational initiation, through sequential phosphorylation of the TSC2 tumor suppressor by the kinases AMPK and GSK3 as well as AMPK-dependent phosphorylation of the critical mTOR-binding subunit raptor [8] and activation of eEF2 kinase which inhibits the elongation step.
- (7) Under nutrient starvation, the liver initiates the process of autophagy (lysosomal breakdown of cellular proteins and organelles) to provide amino acids for gluconeogenesis. Recent evidence indicates that AMPK is required for autophagy in hepatocyte, revealing a direct connection between energy status and autophagy initiation [9].
- (8) The mTOR/S6K1 pathway exerts a negative feedback loop on insulin signaling promoting insulin resistance via inhibitory serine phosphorylation of IRS1. Pharmacologic enhancement of AMPK activity has been shown to improve insulin sensitivity and AMPK-induced inhibition of the mTORC1/S6K1 pathway may alleviate hepatic insulin resistance. Additionally, AMPK activation may also modulate insulin's metabolic action by increasing fatty acid oxidation, thereby reducing hepatic lipotoxicity and insulin resistance [5, 10]. Therefore, the efficacy of AMPK activation to reverse many metabolic disorders has provided the rationale for the development of new pharmacological but also nutritional AMPK activators.

## Conflicts of interest

The Authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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