***Minireview Article***

**AMP-activated protein kinase** (**AMPK) :cellular energy sensor and the guardian of metabolism**

***Abstract:*** ***AMPK is a important enzyme that plays a critical role in cellular energy metabolism. By activating AMPK through diet, lifestyle, and supplement strategies, individuals can improve their glucose and lipid metabolism, promote mitochondrial function and autophagy, and protect against oxidative stress and inflammation through activities of AMPK. However, it is important to point out that while AMPK activation can be beneficial for health, it should not be viewed as a only solution to prevent or treat disease. A comprehensive approach to health, includes a healthy diet, regular exercise, stress management, and regular medical checkups, is necessary to achieve good health and wellbeing.* *We review here a number of recent breakthroughs in the mechanistic understanding of AMPK function,***

***Key words****: AMP-activated protein kinase (AMPK),metabolism, cellular energy, fatty acid oxidation*

***Introduction***

One of the fundamental requirements of all cells is to balance ATP consumption and ATP generation. One of the central regulators of cellular metabolism in eukaryotes is the AMP-activated protein kinase (AMPK), a crucial enzyme, which is activated when intracellular ATP levels lower. AMPK responds to changes in intracellular adenine nucleotide (AMP) levels, and an increase in AMP/ADP/NAD+ activates AMPK, which in turn increases the rate of the catabolic (ATP production) pathway while decreasing the rate of the anabolic (ATP utilization) pathway. (Sheikh et al. , 2023, Kim et al. 2019). AMP-activated protein kinase (AMPK), controls systemic energy expenditure, glucose homeostasis, lipid metabolism and mitochondrial biogenesis.(Steinberg et al. 2023,;Morrison et al. 2022) AMP-activated protein kianse (AMPK) is a master sensor of cellular energy levels and a crucial regulator of nutrient metabolism such as the synthesis of fatty acids, glucose and protein as well as their oxidation to CO2 and water (Priya et al. 2018). Thus, AMPK signaling has important implications for fat deposition and glucose homeostasis in animals and humans. (Trefts et al. 2021)

AMPK is a phylogenetically conserved, heterotrimeric serine/threonine protein kinase. AMPK indirectly promotes fatty acid oxidation by reducing the production of malonyl-CoA, a molecule that inhibits carnitine palmitoyltransferase a key enzyme in fatty acid mitochondrial transport. AMPK plays a significant role in regulating lipid metabolism in various tissues, including liver, muscle, and adipose tissue, where it can influence the rate of fat storage and utilization depending on the energy needs of the body. (Wang et al. 2017, Misra et. al. 2011)AMPK directly phosphorylates and activates or inhibits various proteins involved in glucose metabolism, Further, AMPK can suppress gluconeogenesis (glucose production) in the liver by inhibiting the transcription factors responsible for the expression of gluconeogenic enzymes.

 AMPK plays critical roles in regulating growth and reprogramming metabolism, and recently has been connected to cellular processes including autophagy and cell polarity.(Agrawal et al. 2018, Cortez et al. 2018) Autophagy maintains cellular homeostasis during low energy states. According to the current understanding, glucose-depleted cells induce autophagy through AMPK, the primary energy-sensing kinase, to acquire energy for survival. In glucose-starved cells, autophagy induction may depend on the ability of the cells to obtain a minimum level of energy required for the process, which can be derived from stored energy reserves, such as lipids or glycogen, or other substrates. (Khalil et al. 2023) We review here a number of recent breakthroughs in the mechanistic understanding of AMPK function, focusing on a number of new identified downstream effectors of AMPK. The aim of this review is to provide a broad overview of some of the more recent developments within the AMP-activated protein kinase (AMPK) field.

**AMP-activated protein kinase (AMPK)**

The AMP-activated protein kinase (AMPK) acts as cellular metabolic sensor: when activated by increases in cellular AMP it promotes energy restoration and inhibits energy consumption. The AMP-activated protein kinase (AMPK) functions as a cellular energy sensor. (Xiao et al. 2024) Increases in cellular AMP : ATP ratios, starts the AMPK pathway, it acts to restore energy homeostasis by switching on catabolic pathways while switching off cell growth and proliferation thus influences cancer. ( Sheikh et al. 2023; Klepinin, A. et al 2020).

AMPK stimulates glycolysis by activating phosphorylation of fructose-2,6-bisphosphatase and activating phosphorylation of glycogen phosphorylase, and it inhibits glycogen synthesis through inhibitory phosphorylation of glycogen synthase(Kjobsted et al. 2023). AMPK acts as a signal integration platform to control mitochondrial health. AMPK regulates at least three essential aspects of mitochondrial homeostasis: biogenesis. Exercise, hypoxia, calorie restriction, an increase in the AMP/ATP ratio  and certain phytochemicals in plants activate AMP-activated protein kinase (AMPK), an energy “sensor' that researchers describe as “the guardian of metabolism.” (Li et al. 2017, Qin et al. 2017)AMPK is activated whenever there's an energy shortage. When food is scarce, AMPK activation promotes the breakdown of stored nutrients like glycogen and fat to maintain energy levels. Further AMPK can be activated by oxidative stress, and its activation can help mitigate damage by regulating antioxidant defenses. AMPK is also activated in adipose tissue, liver, and perhaps other organs during exercise (Afinanisa et al. 2021)

AMPK coordinates the changes in the activity of enzymes of lipid metabolism and regulates the partitioning of fatty acid between oxidative and biosynthetic pathways AMPK stimulates glucose uptake and lipid oxidation to produce energy, while turning off energy-consuming processes including glucose and lipid production to restore energy balance. (Chen et al. 2022,Yan et al. 2021)

When activated, AMPK initiates metabolic changes like increased glucose uptake, fatty acid oxidation, and glycogen breakdown to generate ATP while inhibiting processes like protein synthesis and lipid synthesis that consume energy. (Janzen et al. 2021)Activation of AMPK  promotes glucose transport and fatty acid oxidation while suppressing glycogen synthase activity and protein synthesis. AMPK activity decreases with age. Studies show that activating AMPK not only reduces abdominal fat, but also reduces the inflammation and other damage caused by it.

In the hypothalamus, AMPK is stimulated by fasting, and manipulation of hypothalamic AMPK activity influences energy balance.  numerous polyphenols have been found to activate AMPK in cell and animal tissues.(Sengupta et al. 2016) These include: Resveratrol from red grapes . Quercetin from many plants including fruits, vegetables, and grains Polyphenol-rich foods, such as fruits, vegetables, and tea, can activate AMPK and improve glucose and lipid metabolism.( Xu et al. 2018 Lin et al. 2018, Lee et al. 2017, 2016, Hsu et al. 2016,) Supplement with AMPK activators: Certain supplements, such as berberine, (Kim et al. 2015 )omega-3 fatty acids, curcumin and resveratrol, can activate AMPK and improve glucose and lipid metabolism.( Liu et al. 2018, Song et al. 2018; Gu et al. 2018; Lin et al. 2018; Inoki et al. 2012,).  In addition, AMPK can also regulate cellular survival in conditions of hypoxic stress.

5' AMP-activated protein kinase (AMPK) is an enzyme (EC 2.7. 11.31) that plays a role in cellular energy homeostasis,(Kim et al. 2019) It activates glucose and fatty acid uptake and oxidation when energy level in cell is low. It has been found that resveratrol through AMPK activation improved cardiac function and decreased the risk of CVD development.(Kim et al. 2015, Chen et al. 2017) Several studies have indicated that natural AMPK activators can prevent the development of cardiac hypertrophy and resveratrol can control hypertrophic growth.(Janzen et al. 2021)

Various phytochemicals, such as polyphenols from fruits and vegetables and resveratrol and berberine, (Schaffer et al. 2012, Lee et al. 2017 Kishi et al. 2015) also support AMPK and/or SIRT1 activity. Fiber-rich foods, such as fruits, vegetables , green tea, ginseng and ginsenosides , capsaicin from chili peppers ,and whole grains, can activate AMPK and improve glucose and lipid metabolism.  Many clinical studies on ginseng have been performed to characterize its therapeutic properties, which include improving physical performance  and diabetes  (Hsu et al. 2016, Kim et al. 2018).Healthy fats, such as omega-3 fatty acids and monounsaturated fats, can activate AMPK and improve glucose and lipid metabolism.(Cordero – Herrea 2018).

There are several diet, lifestyle, and supplement strategies that can help to better activate AMPK. Noncommunicable diseases (NCDs) caused 71% of all deaths (41 million) worldwide in 2018, reaching pandemic proportions. Regular exercise is indisputably the most powerful intervention for prevention and treatment of most NCDs.Regular exercise, particularly endurance exercise, is one of the most effective ways to activate AMPK.(Chen et al. 2018, Priya et al. 2018). Intermittent fasting has been shown to increase AMPK activity and improve glucose and lipid metabolism. Cycling exercise of moderate intensity (90 min) in humans resulted in increased AMPK activity and phosphorylation in muscle biopsies (Trefts et al. 2021; Gonzalez et al. 2020)

 A low-carbohydrate diet has been shown to activate AMPK and improve glucose and lipid metabolism.(Gu et al. 2018, Mohammadi et al. 2017, Pan et al. 2018) Many [biochemical](https://en.wikipedia.org/wiki/Biochemical) adaptations of skeletal muscle that take place during a single bout of [exercise](https://en.wikipedia.org/wiki/Exercise) or an extended duration of [training](https://en.wikipedia.org/wiki/Training), such as increased [mitochondrial biogenesis](https://en.wikipedia.org/wiki/Mitochondrial_biogenesis) and capacity, One of the effects of [exercise](https://en.wikipedia.org/wiki/Exercise) is an increase in [fatty acid metabolism](https://en.wikipedia.org/wiki/Fatty_acid_metabolism), which provides more [energy](https://en.wikipedia.org/wiki/Energy) for the cell. Muscle contractions during exercise lead to increases in calcium, nitric oxide, reactive oxygen species, and AMP/ADP as cues of stress, which in turn activate AMPK and signaling pathway ,AMPK Activation of these signaling pathways contributes to not only increased glucose and fatty acid uptake and oxidation as a fuel source to maintain exercise but also adaptative processes critical for enhanced muscle contractile and metabolic functions in the long run. (Xiao 2024, Chen et al. 2022) One of the key pathways in AMPK's regulation of [fatty acid oxidation](https://en.wikipedia.org/wiki/Fatty_acid_oxidation) is the phosphorylation and inactivation of [acetyl-CoA carboxylase](https://en.wikipedia.org/wiki/Acetyl-CoA_carboxylase).

[Insulin](https://en.wikipedia.org/wiki/Insulin) is a [hormone](https://en.wikipedia.org/wiki/Hormone) which helps regulate [glucose](https://en.wikipedia.org/wiki/Glucose) levels in the body. When blood glucose is high, insulin is released from the [Islets of Langerhans](https://en.wikipedia.org/wiki/Islets_of_Langerhans).(Afinanisa et al. 2021) Insulin, among other things, will then facilitate the uptake of glucose into cells via increased expression and [translocation](https://en.wikipedia.org/wiki/Protein_targeting) of glucose transporter [GLUT-4](https://en.wikipedia.org/wiki/GLUT-4) Under conditions of exercise, however, [blood sugar](https://en.wikipedia.org/wiki/Blood_sugar) levels are not necessarily high, and insulin is not necessarily activated, yet muscles are still able to bring in glucose.(Kjobsted et al. 2023) AMPK seems to be responsible in part for this [exercise](https://en.wikipedia.org/wiki/Exercise)-induced glucose uptake.

Mitochondrial enzymes, such as [cytochrome c](https://en.wikipedia.org/wiki/Cytochrome_c), [succinate dehydrogenase](https://en.wikipedia.org/wiki/Succinate_dehydrogenase), [malate dehydrogenase](https://en.wikipedia.org/wiki/Malate_dehydrogenase), [α-ketoglutarate dehydrogenase](https://en.wikipedia.org/wiki/%CE%91-ketoglutarate_dehydrogenase), and [citrate synthase](https://en.wikipedia.org/wiki/Citrate_synthase), increase in expression and activity in response to exercises. In conditions where nutrients are scarce, AMPK acts as a metabolic checkpoint inhibiting cellular growth. (Malik et al. 2023)The most thoroughly described mechanism by which AMPK regulates cell growth. In addition to regulating cell growth, mTORC1 also controls autophagy, a cellular process of “self engulfment” in which the cell breaks down its own organelles (macroautophagy) and cytosolic components (microautophagy) to ensure sufficient metabolites when nutrients run low. (Xiao et al. 2024; Panwar et al. 2023; Khalil et al. 2023; Linde et al. 2023)AMPK has been reported to phosphorylate and regulate a number of transcription factors, coactivators, the acetyltransferase.(Batchuluun et al. 2022)

**Obesity and the metabolic syndrome**

Obesity and the metabolic syndrome is a major health problem in Western and developing countries. Keeping in view the role of AMPK in regulating energy balance at both the cellular and whole-body levels, this kinase occupies a central position in studies regarding obesity and diabetes. Metformin is known as one of the oldest, and most widely used oral medications in the treatment of type two diabetes or diabetes mellitus (Kjøbsted et al. 2023)Metformin can suppress gluconeogenesis and reduce blood sugar by activating adenosine monophosphate-activated protein kinase (AMPK) and inducing small heterodimer partner (SHP) expression in the liver cells. (Chen et al. 2017)The main mechanism of metformin’s action is related to its activation of the AMPK enzyme and regulation of the energy balance. apart from its significant role in the reduction of blood glucose level, metformin activates the AMPK enzyme that in turn has various efficient impacts on the regulation of various processes, including controlling inflammatory conditions.(Lee et al. 2016 ) In addition, altered metabolism of tumor cells is well recognized and AMPK is a potential target for cancer prevention.  Panax ginseng is known to be useful for treatment and/or prevention of cancer and metabolic diseases including diabetes(Li et al. 2017). The uncontrolled growth of cancer cells is supported by a corresponding adjustment of energy metabolism in a cell. A considerable number of these investigations have revealed that the capacity of metformin to activate AMPK and also the consequent activation or inhibition of different factors by metformin enable it to alter the pathological pathways of the disease,(Muraleedharan and Dasgupta 2023; Van deer Vaart et al. 2021; Afinanisa et al. 2021)

**Emerging themes and future directions**

 A wide range of studies in the past few years has begun decoding substrates of AMPK playing roles in a variety of growth, metabolism, autophagy, and cell polarity processes. An emergent theme in the field is that AMPK and its related family members often redundantly phosphorylate a common set of substrates on the same residues, though the tissue expression and condition under which AMPK or its related family members are active vary. AMPK was originally defined as the upstream kinase for the critical metabolic enzymes Acetyl-CoA carboxylase which serve as the rate-limiting steps for fatty-acid and sterol synthesis in wide-variety of eukaryotes.

Now with a more complete list of AMPK substrates, it is also becoming clear that there is a convergence of AMPK signaling with PI3K and Erk signaling in growth control pathways, and with insulin and cAMP-dependent pathways in metabolic control. Due to the activation of AMPK and its role in regulating several subcellular signaling pathways, AMPK can be effective in altering the cells’ proliferation and differentiation pathways and eventually in the prevention and treatment of certain diseases. Moreover, several studies have confirmed the role of the AMPK pathway in the reduction of lipid mass of the body and improvement of NAFLD by inducing liver fatty acid oxidation. Due to its role in regulating lipid metabolism, AMPK is a potential therapeutic target for conditions like obesity and metabolic syndrome, where dysregulation of lipid metabolism contributes to disease progression.  Further Research suggests AMPK may play a role in protecting neurons from stress-induced damage, making it a potential target for neurodegenerative conditions.

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