AMPK activation can delay aging

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ABSTRACT

AMPK controls the regulation of cellular homeostasis, metabolism, resistance to stress, cell survival and growth, cell death, autophagy, which are some of the most critical determinants of aging and lifespan. Specific AMPK activation was recently shown to delay aging and prolong lifespan in Drosophila melanogaster. Indirect AMPK activators, such as resveratrol, metformin and exercise, are currently in clinical trials for studying their impact on human aging-related characteristics, tissue homeostasis and metabolic dysfunctions. In this minireview, I am briefly discussing the recent advances on AMP involvement in aging and lifespan elongation.

Keywords:
AMP-activated protein kinase, lifespan, energetic metabolism;

Abbreviations:
AMP-activated protein kinase (AMPK); US Food and Drug Administration (FDA); Forkhead box protein O (FOXO); Silent mating type information regulation 2 homolog 1 (SIRT1);

Introduction

As a sensor of cellular energy status, AMP-activated protein kinase (AMPK) is expressed in almost all eukaryotic cells. Activation of AMPK is able to restore the energy balance when the energy state of a cell is decreased. This is performed by stimulating catabolic processes that generate ATP and by inhibiting anabolic processes that consume ATP. AMPK controls the regulation of cellular homeostasis, metabolism, resistance to stress, cell survival and growth, cell death, autophagy which are some of the most critical determinants of aging and lifespan. AMPK can integrate critical cellular signals and controls many signaling pathways that regulate these processes. Recent studies show that the AMPK activation and AMPK responsiveness decrease with age, which may explain the altered metabolic regulation, resulting in reduced autophagic clearance of unnecessary products and an increase in oxidative stress.

Caloric restriction was shown to protect against senescence by increasing autophagic activity and reducing oxidative damage. These mechanisms are at least in part mediated by caloric restriction-induced activation of AMPK and its downstream signaling pathways. Dietary restriction can at least in part mediate longevity by activating the AMPK-FOXO axis.

At least five clinical trials (Table 1) with AMPK activators, such as resveratrol, metformin and exercise, investigate their impact on human aging-related characteristics, tissue homeostasis and metabolic dysfunctions.
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Recent reports demonstrated that AMPK can exert pro-longevity effects in several species. AMPK activation in gastrointestinal tract increases Drosophila melanogaster’s lifespan by 30%, from six weeks to eight weeks. Caloric restriction-induced AMPK activation protects against senescence by increasing autophagic activity and reducing oxidative damage in rats. This process is at least in part executed by the AMPK-FOXO signaling pathway, as shown in C. elegans. Moreover, metformin was shown to prevent sedentariness-related damages in mice, a process which may be related to AMPK activation. In mice, metformin activated signaling mediated by AMPK and CAMKII, while inactivating ERK, thus modulating hepatic stress. In mouse skeletal muscle, metformin-induced phosphorylation of Akt and its activation, process important for skeletal muscle mass maintenance.

### AMPK signaling and aging

AMPK is shown to be a central regulator and integrator for several intracellular signaling pathways controlling cellular homeostasis, metabolism, response to stress, oxidative damage proliferation, cell growth, cell death, autophagy,
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AMPK activation/responsiveness decreases with age, resulting in:
- reduced autophagic clearance of unnecessary products
- an increase in oxidative stress
- a decrease resistance to cellular stress

AMPK-mediated autophagic clearance and increased resistance to stress are major players involved in lifespan extension in lower organisms.

cellular polarity and cellular senescence. Some of these pathways were shown to promote longevity in lower organisms.

It is now well known that DAF-16/FoxO transcription factor can be regulated by AMPK and acts as a pro-longevity axis in C. elegans. FoxO family of transcription factors are well known for the regulation a broad range of biological critical processes, such as apoptosis, cell cycle progression, resistance to oxidative stress, metabolism, differentiation and senescence. Moreover, muscle aging can be delayed by modulating the muscle-specific dFOXO/4E-BP/activin signaling, which can induce autophagy. These events are related to extended organismal lifespan.

Other groups have reported the involvement of p53 tumor suppressor, NF-kB signaling pathway and Sirtuins in cellular senescence and aging of mammalian organisms. SIRT1 is well known for inducing signaling changes that mediate caloric restriction-induced lifespan elongation. Several other AMPK downstream signaling pathways with potential involvement in aging were previously described.

Targeting AMPK activation to increase lifespan

Discovery of AMPK’s critical cellular functions has led to the identification of a huge number of products that can (most of them indirectly) activate AMPK. To date, over 100 natural products (many used in Asian medicine) are uncovered. Very few of them directly modulate AMPK, however, even those are expected to have AMPK-independent effects. For example, salicylate is shown to directly bind AMPK, although it also binds and modulates the activity of other cellular enzymes. Some of these compounds, indirectly activate AMPK by inhibiting mitochondrial respiratory chain: berberine, galegine etc. Moreover, at least two of these compounds, salicylate and metformine, are some of the most used drugs worldwide for the treatment of common pathologies. Although these drugs can activate AMPK, involvement of AMPK in their therapeutic effects is not yet well characterized. Metotrexate was also recently shown to activate AMPK, promoting glucose uptake and lipid oxidation in skeletal muscle.

In 2015, the US Food and Drug Administration (FDA) has given the green light for human clinical trials evaluating the potential metformin-induced elongation of human lifespan. In addition to its well characterized effects of regulating the glucose metabolism, being used in the treatment of type 2 diabetes for many years, metformin can influence a wide range of cellular processes critical in aging process and the development of age-related conditions, such as apoptosis, autophagy, cellular senescence, oxidative damage and inflammation. Interestingly, metformin mimics some of the benefits of caloric restriction without a decrease in caloric intake. It improves physical performance, reduces cholesterol and low-density lipoprotein levels and increases sensitivity to insulin. Both metformin and rapamycin can prolong lifespan in mice. AMPK was previously shown to mediate the anti-aging effects of metformin, while autophagy was proposed to be involved in inducing the anti-aging effects of rapamycin.

Conclusions

AMPK is a sensor of cellular energy status and a critical regulator of cellular homeostasis, metabolism response to stress, oxidative damage and many other processes involved in aging. We now know, that localized activation of AMPK in
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key tissues such as the brain, can slow aging in a non-cell autonomous manner. AMPK activation in the Drosophila’s nervous system induces autophagy both in the brain and the intestinal epithelium, which is related to the anti-aging effects and extended lifespan. Autophagy, which is a bulk protein degradation process, was previously proposed to be involved in inducing the anti-aging effects of rapamycin. Thus, AMPK-induced autophagic clearance and increased resistance to stress are major players involved in lifespan elongation in lower organisms.

Recent reports established that AMPK activation and AMPK responsiveness decrease with age, which may explain the altered metabolic regulation, resulting in reduced autophagic clearance of unnecessary products (via mTOR), an increase in oxidative stress and decrease resistance to cellular stress (potentially due to DAF-16/FoxO and/or p53 signaling pathways downregulation). Thus, finding efficient strategies of increasing AMPK responsiveness and activation may be of important use as anti-aging treatments and for lifespan elongation. Metformin, resveratrol and exercise are the leading examples currently tested in human clinical trials.

Conflict of Interest:
The author declares that there are no conflicts of interest.

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