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PERSPECTIVE Article

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[1]. 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[2]. 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[3]. 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[3].

Caloric restriction was shown to protect against senescence by increasing autophagic activity and reducing oxidative damage[4]. These mechanisms are at least in part mediated by caloric restriction-induced activation of AMPK and its downstream signaling pathways[5]. Dietary restriction can at least in part mediate longevity by activating the AMPK-FOXO axis[6-8].

At least five clinical trials (Table 1) with AMPK activators, such as resveratrol[9-11], metformin[12] and exercise[13,14], investigate their impact on human aging-related characteristics, tissue homeostasis and metabolic dysfunctions[15].

Table 1. Clinical trials investigating the impact of AMPK activators (such as resveratrol, metformin and exercise) on human aging-related characteristics, tissue homeostasis and metabolic dysfunctions

Study name	Status (Dec. 2015)	Conditions	Purpose	Ref.
Beneficial Effects of Exercise and Healthy Diets on Muscle and Adipose Tissue	Recruiting	Metabolic Syndrome	Intends to verify if physical exercise and/or Mediterranean diet, in middle aged individuals with metabolic syndrome, preserve adequate adipose tissue functionality and delay skeletal muscle *aging*; *AMPK* is one of the studied markers	[16]
Effect of Age on Glucose and Lipid Metabolism	Active, not recruiting	Metabolism Disorders	Tests the hypotheses that the decrease in muscle fat oxidation from elderly human individual is secondary to an *age-mediated reduction in AMPK signaling*, in vivo, and exercise-induced *increase in the AMPK signaling* will result in/correlate with improved insulin action, increased fat oxidation & reduced intramyocellular lipids	[17]
Metformin and Longevity Genes in Prediabetes	Completed	*Aging*, Insulin Resistance, Prediabetes, Inflammation	Investigates the effects of the *AMPK pathway activation on longevity genes* and inflammation in the setting of pre-diabetes in vivo and in vitro	[18]
Metformin in Longevity Study (MILES)	Ongoing	*Aging*	Examine the effects of metformin treatment on the potential of changing the gene expression profile of older adults with impaired glucose tolerance, to that of young healthy subjects	[19]
Resveratrol to Enhance Vitality and Vigor in Elders (REVIVE)	Not yet recruiting	Physical and Mitochondrial function	Investigates if resveratrol improves the mitochondrial function within the skeletal muscles of elders; *AMPK* is one of the studied markers	[20]

AMPK activation protects against aging and elongates lifespan in several species

Recent reports demonstrated that AMPK can exert pro-longevity effects in several species[21]. AMPK activation in gastrointestinal tract increases Drosophila melanogaster's lifespan by 30%, from six weeks to eight weeks[21]. Caloric restriction-induced AMPK activation protects against senescence by increasing autophagic activity and reducing oxidative damage in rats[4]. This process is at least in part executed by the AMPK-FOXO signaling pathway, as shown in C. elegans[6]. 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[22].

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,

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[23] and acts as a pro-longevity axis in C. elegans[3]. 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[23-25]. 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[26,27].

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[2,28]. Several other AMPK downstream signaling pathways with potential involvement in aging were previously described[3].

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[1]. 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[1]. Metotrexate was also recently shown to activate AMPK, promoting glucose uptake and lipid oxidation in skeletal muscle[27].

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[19]. 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[28-31]. Interestingly, metformin mimics some of the benefits of calorie restriction without a decrease in caloric intake. It improves physical performance, reduces cholesterol and low-density lipoprotein levels and increases sensitivity to insulin[32]. Both metformin and rapamycin can prolong lifespan in mice[32,33]. AMPK was previously shown to mediate the anti-aging effects of metformin[32], while autophagy was proposed to be involved in inducing the anti-aging effects of rapamycin[34,35].

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

key tissues such as the brain, can slow aging in a non-cell autonomous manner[21]. 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[21]. Autophagy, which is a bulk protein degradation process[35,36], was previously proposed to be involved in inducing the anti-aging effects of rapamycin[34,35]. Thus, AMPK-induced autophagic clearance and increased resistance to stress are major players involved in lifespan elongation in lower organisms.

Recent reports[3,21,37] 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.

References:

1. Hardie DG. Regulation of AMP-activated protein kinase by natural and synthetic activator. Acta Pharmaceutica Sinica B; available online on 21 July 2015. doi: 10.1016/j.apsb.2015.06.002.
2. Ruderman NB, Xu XJ, Nelson L, Cacicedo JM, Saha AK, Lan F, Ido Y. AMPK and SIRT1: a long-standing partnership? Am J Physiol Endocrinol Metab. 2010 Apr;298(4):E751-60. doi: 10.1152/ajpendo.00745.2009. PMID: 20103737.
3. Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. Ageing Res Rev. 2012 Apr;11(2):230-41. doi: 10.1016/j.arr.2011.12.005. PMID: 22186033.
4. Ning YC, Cai GY, Zhuo L, Gao JJ, Dong D, Cui S et al. Short-term calorie restriction protects against renal senescence of aged rats by increasing autophagic activity and reducing oxidative damage. Mech Ageing Dev. 2013; 134(11-12): 570-9. doi: 10.1016/j.mad.2013.11.006. PMID: 24291536.
5. García-Prieto CF, Pulido-Olmo H, Ruiz-Hurtado G, Gil-Ortega M, Aranguez I, Rubio MA. Mild caloric restriction reduces blood pressure and activates endothelial AMPK-PI3K-Akt-eNOS pathway in obese Zucker rats. Vascul Pharmacol. 2015 Feb-Mar;65-66:3-12. doi: 10.1016/j.vph.2014.12.001.; PMID: 25530153.
6. Greer EL, Dowlatshahi D, Banko MR, Villen J, Hoang K, Blanchard D et al. An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in C. elegans. Curr Biol. 2007 Oct 9;17(19):1646-56. doi: 10.1016/ j.cub.2007.08.047. PMID: 17900900.
7. Greer EL, Banko MR, Brunet A. AMP-activated protein kinase and FoxO transcription factors in dietary restriction-induced longevity. Ann N Y Acad Sci. 2009 Jul;1170:688-92. doi: 10.1111/j.1749-6632.2009.04019.x. PMID: 19686213.
8. Greer EL, Brunet A. FOXO transcription factors at the interface between longevity and tumor suppression. Oncogene. 2005 Nov 14;24(50):7410-25. doi:10.1038/sj.onc.1209086. PMID: 16288288.
9. Chen S, Zhou N, Zhang Z, Li W, Zhu W. Resveratrol induces cell apoptosis in adipocytes via AMPK activation. Biochem Biophys Res Commun. 2015 Feb 20; 457(4): 608-13. doi: 10.1016/j.bbrc.2015.01.034. PMID: 25603053.
10. Chen S et al. Resveratrol inhibits cell differentiation in 3T3-L1 adipocytes via activation of AMPK. Can J Physiol Pharmacol. 2011 Nov;89(11):793-9. doi: 10.1139/Y11-077. PMID: 22017765.
11. Chen S, Xiao X, Feng X, Li W, Zhou N, Zheng L. Resveratrol induces Sirt1-dependent apoptosis in 3T3-L1 preadipocytes by activating AMPK and suppressing AKT activity and survivin expression. J Nutr Biochem. 2012 Sep;23(9):1100-12. doi: 10.1016/j.jnutbio.2011.06.003. PMID: 22137261.
12. Duca FA, Côté CD, Rasmussen BA, Zadeh-Tahmasebi M, Rutter GA, Filippi BM. Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats. Nat Med. 2015 May;21(5):506-11. doi: 10.1038/nm.3787. PMID: 25849133.
13. Fentz J, Kjøbsted R, Kristensen CM, Hingst JR, Birk JB, Gudiksen A. AMPKα is essential for acute exercise-induced gene responses but not for exercise training-induced adaptations in mouse skeletal muscle. Am J Physiol Endocrinol Metab. 2015 Dec 1; 309(11): E900-14. doi: 10.1152/ajpendo. 00157.2015. PMID: 26419588.
14. Lundberg TR, Fernandez-Gonzalo R, Tesch PA. Exercise-induced AMPK activation does not interfere with muscle hypertrophy in response to resistance training in men. J Appl Physiol (1985). 2014 Mar 15; 116(6): 611-20. doi: 10.1152/ japplphysiol.01082.2013. PMID: 24408998.

15. ClinicalTrials.gov; accessed in December 2015: https://clinicaltrials.gov/ct2/results?term=AMPK%2C+aging&Search=Search
16. ClinicalTrials.gov registry of U.S. NIH; NCT01793896; accessed in December 2015: https://clinicaltrials.gov/ct2/show/NCT01793896
17. ClinicalTrials.gov registry of U.S. NIH; NCT01737164; accessed in December 2015: https://clinicaltrials.gov/ct2/show/NCT01737164
18. ClinicalTrials.gov registry of U.S. NIH; NCT01765946; accessed in December 2015: https://clinicaltrials.gov/ct2/show/NCT01765946
19. ClinicalTrials.gov registry of U.S. NIH; NCT02432287; accessed in December 2015: https://clinicaltrials.gov/ct2/show/NCT02432287
20. ClinicalTrials.gov registry of U.S. NIH; NCT02123121; accessed in December 2015: https://clinicaltrials.gov/ct2/show/NCT02123121
21. Ulgherait M, Rana A, Rera M, Graniel J, Walker DW. AMPK modulates tissue and organismal aging in a non-cell-autonomous manner. Cell Rep. 2014 Sep 25;8(6):1767-80. doi: 10.1016/j.celrep.2014.08.006. PMID: 25199830.
22. Senesi P, Montesano A, Luzi L, Codella R, Benedini S, Terruzzi I. Metformin Treatment Prevents Sedentariness Related Damages in Mice. J Diabetes Res. 2016; 2016: 8274689. doi: 10.1155/2016/8274689. PMID: 26697506.
23. Dumitrascu GR, Bucur O. Critical physiological and pathological functions of Forkhead Box O tumor suppressors. Discoveries 2013, Oct-Dec; 1(1): e5. doi: 10.15190/d.2013.5.
24. Plati J, Bucur O, Khosravi-Far R. Dysregulation of apoptotic signaling in cancer: molecular mechanisms and therapeutic opportunities. J Cell Biochem. 2008 Jul 1; 104(4): 1124-49. doi: 10.1002/jcb.21707. PMID: 18459149.
25. Singh A, Ye M, Bucur O, Zhu S, Tanya Santos M, Rabinovitz I et al. Protein phosphatase 2A reactivates FOXO3a through a dynamic interplay with 14-3-3 and AKT. Mol Biol Cell. 2010 Mar 15; 21(6): 1140-52. doi: 10.1091/mbc.E09-09-0795. PMID: 20110348.
26. Wang Y, Liang Y, Vanhoutte PM. SIRT1 and AMPK in regulating mammalian senescence: a critical review and a working model. FEBS Lett. 2011 Apr 6;585(7):986-94. doi: 10.1016/j.febslet.2010.11.047. PMID: 21130086.
27. Pirkmajer S, Kulkarni SS, Tom RZ, Ross FA, Hawley SA, Hardie DG et al. Methotrexate promotes glucose uptake and lipid oxidation in skeletal muscle via AMPK activation. Diabetes. 2015 Feb;64(2):360-9. doi: 10.2337/db14-0508. PMID: 25338814.
28. Anwar MA, Kheir WA, Eid S, Fares J, Liu X, Eid AH, Eid AA.. Colorectal and Prostate Cancer Risk in Diabetes: Metformin, an Actor behind the Scene. J Cancer. 2014 Oct 9;5(9):736-44. doi: 10.7150/jca.9726. PMID: 25368673.
29. Bhat A, Sebastiani G, Bhat M. Systematic review: Preventive and therapeutic applications of metformin in liver disease. World J Hepatol. 2015 Jun 28;7(12):1652-9. doi: 10.4254/wjh.v7.i12.1652. PMID: 26140084.
30. Na HJ, Park JS, Pyo JH, Jeon HJ, Kim YS, Arking R, Yoo MA. Metformin inhibits age-related centrosome amplification in Drosophila midgut stem cells through AKT/TOR pathway. Mech Ageing Dev. 2015 Jul;149:8-18. doi: 10.1016/j.mad.2015.05.004. PMID: 25988874.
31. Na HJ, Park JS, Pyo JH, Lee SH, Jeon HJ, Kim YS, Yoo MA. Mechanism of metformin: inhibition of DNA damage and proliferative activity in Drosophila midgut stem cell. Mech Ageing Dev. 2013 Sep; 134(9): 381-90. doi: 10.1016/j.mad.2013.07.003. PMID: 23891756.
32. Martin-Montalvo A, Mercken EM, Mitchell SJ, Palacios HH, Mote PL, Scheibye-Knudsen M. Metformin improves healthspan and lifespan in mice. Nat Commun. 2013;4:2192. doi: 10.1038/ncomms3192. PMID: 23900241.
33. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009 Jul 16;460(7253):392-5. doi: 10.1038/nature08221. PMID: 19587680.
34. Bjedov I, Toivonen JM, Kerr F, Slack C, Jacobson J, Foley A, Partridge L. Mechanisms of life span extension by rapamycin in the fruit fly Drosophila melanogaster. Cell Metab. 2010 Jan;11(1):35-46. doi: 10.1016/j.cmet.2009.11.010. PMID: 20074526.
35. Rubinsztein DC, Mariño G, Kroemer G. Autophagy and aging. Cell. 2011 Sep 2;146(5):682-95. doi: 10.1016/j.cell.2011.07.030. PMID: 21884931.
36. Bucur O, Ray S, Bucur MC, Almasan A. APO2 ligand/tumor necrosis factor-related apoptosis-inducing ligand in prostate cancer therapy. Front Biosci. 2006 May 1;11:1549-68. doi: 10.2741/1903. PMID: 16368536.
37. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. Cell Metab. 2014 Jul 1;20(1):10-25. doi: 10.1016/j.cmet.2014.03.002. PMID: 24726383

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