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Review

AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network

Antero Salminen[a,b,*], Kai Kaarniranta[c,d]

[a] Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland
[b] Department of Neurology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland
[c] Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland
[d] Department of Ophthalmology, Kuopio University Hospital, P.O. Box 1777, FIN-70211 Kuopio, Finland

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ABSTRACT

Efficient control of energy metabolic homeostasis, enhanced stress resistance, and qualified cellular housekeeping are the hallmarks of improved healthspan and extended lifespan. AMPK signaling is involved in the regulation of all these characteristics via an integrated signaling network. Many studies with lower organisms have revealed that increased AMPK activity can extend the lifespan. Experiments in mammals have demonstrated that AMPK controls autophagy through mTOR and ULK1 signaling which augment the quality of cellular housekeeping. Moreover, AMPK-induced stimulation of FoxO/DAF-16, Nrf2/SKN-1, and SIRT1 signaling pathways improves cellular stress resistance. Furthermore, inhibition of NF-κB signaling by AMPK suppresses inflammatory responses. Emerging studies indicate that the responsiveness of AMPK signaling clearly declines with aging. The loss of sensitivity of AMPK activation to cellular stress impairs metabolic regulation, increases oxidative stress and reduces autophagic clearance. These age-related changes activate innate immunity defence, triggering a low-grade inflammation and metabolic disorders. We will review in detail the signaling pathways of this integrated network through which AMPK controls energy metabolism, autophagic degradation and stress resistance and ultimately the aging process.

1. Introduction

Effective regulation of energy metabolism is a crucial requirement for cellular homeostasis. Disturbances in the maintenance of energy balance provoke diseases and jeopardize healthy aging. AMP-activated kinase (AMPK) is a highly conserved sensor of increased levels of AMP and ADP originating from ATP depletion (Steinberg and Kemp, 2009; Hardie, 2011; Mihaylova and Shaw, 2011). Mammalian AMPK is a serine/threonine protein kinase which is composed of a catalytic α subunit and regulatory β and γ subunits. There are some isoforms for both catalytic and regulatory subunits which are differently expressed and assembled in mammalian tissues. An elevated AMP/ADP concentration activates AMPK via allosteric regulation (Fig. 1). Several upstream kinases, e.g. serine/threonine kinase 11 (LKB1) (Hawley et al., 2003), Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) (Hurley et al., 2005) and transforming growth factor-β-activated kinase 1 (TAK1) (Momcilovic et al., 2006), can activate AMPK by phosphorylating the catalytic α subunit at Thr172. In turn, activated, phosphorylated AMPK can be inactivated by protein phosphatases (PP), e.g. PP2A, PP2Cα and Ppm1E (Marley et al., 1996; Gimeno-Alcaniz and Sanz, 2003; Voss et al., 2011) (Fig. 1). Many physiological and pathological conditions appear to stimulate AMPK signaling, e.g. exercise (Richter and Ruderman, 2009) and several diseases (Steinberg and Kemp, 2009). Moreover, some hormones, e.g. adiponectin, ghrelin and leptin, can either activate or inhibit AMPK signaling in a tissue-specific manner (Lim et al., 2010). In addition, the control of AMPK activation seems to be context-dependent in different developmental and environmental situations (Mantovani and Roy, 2011).

It is known that AMPK stimulates energy production from glucose and fatty acids during stress and inhibits energy consumption for protein, cholesterol and glycogen synthesis (Steinberg and Kemp, 2009; Hardie, 2011). It is not surprising that caloric restriction can stimulate AMPK activity whereas nutritional overload seems to impair AMPK activity and concurrently induce insulin resistance in many tissues thus promoting the appearance of the components of the metabolic syndrome i.e. obesity, diabetes and cardiovascular diseases (Lage et al., 2008; Steinberg and Kemp, 2009). Currently, AMPK is viewed as an important molecular

* Corresponding author at: Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland, P.O. Box 1627, FIN-70211 Kuopio, Finland. Tel.: +358 505740740; fax: +358 17162048.
E-mail address: antero.salminen@uef.fi (A. Salminen).

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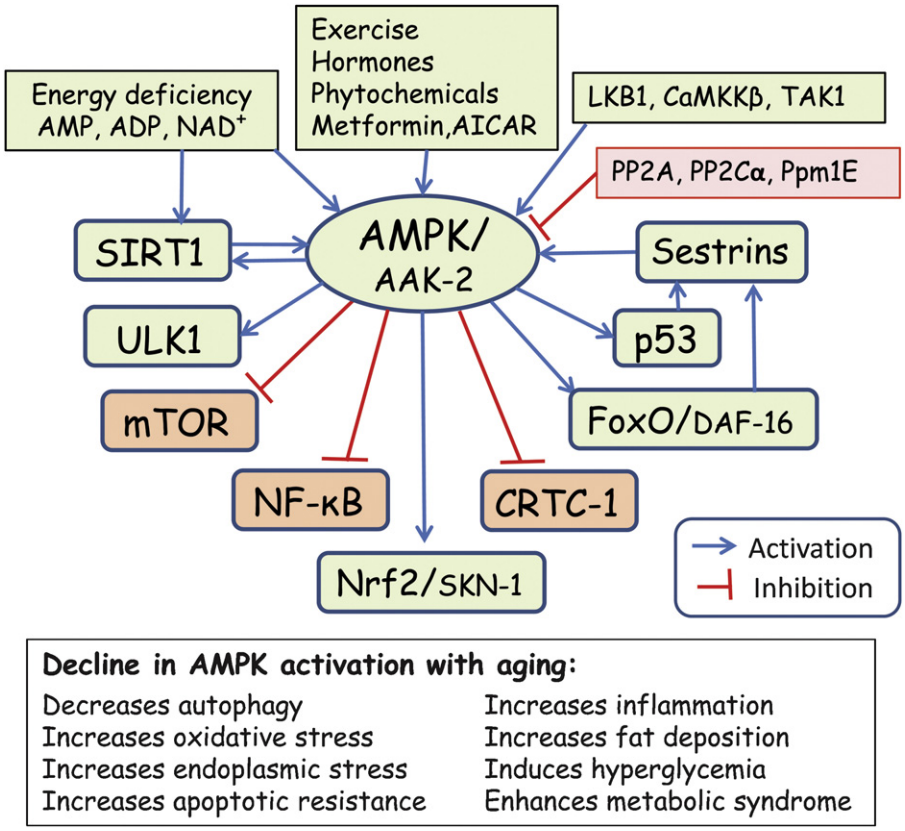

Fig. 1. Schematic overview of the signaling pathways targeted by AMPK activation. AMPK activity can be stimulated by energy deficiency and several physiological and chemical agents, e.g. metformin and many phytochemicals. Currently, it is known that AMPK can be activated by LKB1, CaMKKβ and TAK1 kinases. Protein phosphatases PP2A, PP2Cα and Ppm1E can inhibit AMPK phosphorylation and its activation. AMPK can trigger activating downstream signaling via SIRT1, ULK1, Nrf2/SKN-1, FoxO/DAF-16 and p53 pathways. AMPK inhibits the signaling of CRTC-1, mTOR, and NF-κB. The decline in the sensitivity of AMPK activation with aging can decrease cellular autophagy, increase cellular stress and provoke inflammation. In addition, it can disturb energy metabolic balance and promote the appearance of metabolic diseases during aging. *Abbreviations*: AAK-2, AMP-activated kinase-2; AICAR, 5-aminoimidazole-4-carboxamide riboside; AMPK, AMP-activated protein kinase; CaMKKβ, Ca^{2+}/calmodulin-dependent protein kinase kinase β; CRTC-1, cyclic AMP-regulated transcriptional co-activator-1; DAF-16, abnormal dauer formation protein-16; FoxO, forkhead box protein O; LKB1, serine/threonine kinase 11; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; Nrf2, nuclear factor-erythroid 2-related factor 2; PP, protein phosphatase; SIRT1, silent information regulator 1; SKN-1, skinhead-1; TAK1, transforming growth factor-β-activated kinase 1; ULK1, UNC-51-like kinase 1.

target since it is believed that novel AMPK activators may be useful in the therapy of metabolic and neurodegenerative diseases (Zhou et al., 2009a; Fogarty and Hardie, 2010). Metformin is a clinically used activator of AMPK reducing glucose level in type 2 diabetes. Moreover, 5-aminoimidazole-4-carboxamide riboside (AICAR), statins, thiazolidinediones and many phytochemicals, e.g. berberine, quercetin and resveratrol, have also been reported to activate AMPK signaling (Hwang et al., 2009; Steinberg and Kemp, 2009).

There are emerging studies indicating that the function of AMPK is not restricted to the maintenance of energy metabolism during increased energy consumption but it can coordinate several housekeeping mechanisms, e.g. autophagocytosis of damaged structures (Mihaylova and Shaw, 2011), and alleviate stress by increasing tissue stress resistance. The activation of AMPK reduces oxidative stress by upregulating the expression of thioredoxin (Li et al., 2009). Moreover, AMPK activity can repress endoplasmic reticulum stress (Dong et al., 2010) and inflammatory disorders (Salminen et al., 2011). Interestingly, these are the characteristics which are affected by aging, i.e. oxidative stress (Muller et al., 2007) and endoplasmic stress (Naidoo, 2009; Salminen and Kaarniranta, 2010a) are augmented with aging, autophagic capacity is impaired (Salminen and Kaarniranta, 2009) and a low-grade inflammation appears during aging (Franceschi et al., 2007). Moreover, metabolic diseases are more common in old people. These observations imply that the activation capacity of AMPK may decline during aging. Recent studies have confirmed that the responsiveness of AMPK to different insults is clearly suppressed in aged tissues (Section 2). Since AMPK coordinates a large signaling network of transcription factors (Canto and Auwerx, 2010; Mihaylova and Shaw, 2011), we will review here in detail the role of AMPK in the regulation of the aging process via this integrated signaling network.

2. Role of AMPK in the regulation of aging process

The crucial role of metabolic rate of animals in the regulation of aging process was already appreciated one century ago (see Hulbert et al., 2007). The rate-of-living theory of aging emphasizes that energy metabolism maintains homeostasis in the organism whereas excessive consumption of energy enhances the aging process. Decades ago it was observed that dietary restriction extended the lifespan of rodents (McCay, 1947; Berg and Simms, 1960; Ross, 1961, 1972). Subsequently, a plethora of studies have confirmed in a variety of species that controlled caloric restriction (CR) can delay the aging process and moreover, several regulatory signaling pathways have been identified (Anderson and Weindruch, 2009; Canto and Auwerx, 2009; Greer and Brunet, 2009; Fontana et al., 2010). It seems that this type of lifespan extension is mostly linked to the signaling pathways controlled by AMPK (Section 3). However, it needs to be clarified whether the increase in activation of AMPK associated with CR represents a common way to delay the aging process and what is the role of AMPK-linked signaling network in the aging process.

Studies on model organisms have revealed that mammalian AMPK and its orthologue in *Caenorhabditis elegans*, AMP-activated kinase-2 (AAK-2), have a crucial role in the regulation of longevity. Overexpression of AAK-2/AMPK and its activation by metformin extends the lifespan in some species, e.g. in *C. elegans* (Apfeld et al., 2004; Curtis et al., 2006; Onken and Driscoll, 2010) and *Drosophila* (Funakoshi et al., 2011). In mice, the knockout of AMPKα2 induced many disturbances in metabolism thus jeopardizing both the healthspan and lifespan (Viollet et al., 2003). In contrast, metformin treatment in rodents has prevented cancer incidence and cardiovascular diseases and in that way it can extend the lifespan (Anisimov, 2010; Anisimov et al., 2011). However, Kalender et al. (2010) demonstrated that metformin inhibited mTOR complex-1 function with AMPK-independent manner via RagGTPase and thus some of its health benefits are not related to AMPK signaling. It seems that in mammals, the appropriate, inducible activation of AMPK, e.g. after physical exercise (Richter and Ruderman, 2009), has profound effects on health but persistent overactivation, e.g. in stroke (McCullough et al., 2005) and myocardial ischemia (Dyck and Lopaschuk, 2006), can have deleterious effects and aggravate pathological damage.

Several research approaches have revealed that the responsiveness of AMPK activation declines during the aging process, Reznick et al. (2007) demonstrated that AICAR treatment and physical exercise clearly increased AMPKα2 activity in the muscles of young rats whereas in old rats these insults induced no response in AMPKα2 activity. Moreover, the decrease in energy metabolite levels in skeletal muscles evoked by a β-guanidinopropionic acid (β-GPA) diet clearly elevated AMPKα2 activity in the muscles of young rats but the increase was blunted in old animals. β-GPA treatment also increased mitochondrial biogenesis, a downstream effect of AMPK activation, in young rats but not in old animals. In agreement with the above observations, Ljubicic and Hood (2009) demonstrated that the activation of AMPK induced by muscle contractions was repressed in the old muscles. The decline in the sensitivity of AMPK activation with aging can provoke many age-associated diseases, e.g. cardiovascular diseases and metabolic syndrome. For instance, Qiang et al. (2007) reported that aging impaired AMPK activation and suppressed insulin-stimulated glucose uptake into rat skeletal muscles which could enhance the development of metabolic syndrome. Furthermore, Turdi et al. (2010) observed that the deficiency of AMPK exacerbated aging-induced myocardial dysfunction. In mouse brain, Liu et al. (2011a) demonstrated that the baseline activity of AMPK was higher in old animals compared to their younger counterparts. However, cerebrovascular stroke stimulated a robust increase in AMPK activity in young mice whereas it was unaffected in the old mice.

All these observations indicate that there is a clear deficiency in the sensitivity of AMPK activation in aged tissues. Currently, the mechanism to explain this effect is unknown but it seems possible that there are age-related changes in the function of protein phosphatases, i.e. PP2A, PP2Cα and Ppm1E, which could be involved in the suppression of AMPK activation with aging (Fig. 1). AMPK signaling can be inhibited e.g. by nutritional factors, some hormones and inflammatory signals (Viollet et al., 2010). In particular, the low-grade inflammation which is present in aging tissues may be one phenomenon suppressing AMPK signaling (Section 3.5).

3. AMPK controls the anti-aging signaling network

Aging research has revealed several signaling pathways which have been experimentally demonstrated to be involved in the regulation of aging process and promoting longevity of lower organisms. The first discovered and the most extensively studied pathway is the abnormal dauer formation protein-16 (DAF-16)/forkhead box protein O (FoxO) pro-longevity pathway, in particular in *C. elegans* (Section 3.3). Studies on mammalian aging and cellular senescence have revealed the role of p53 and nuclear factor-κB (NF-κB) signaling pathways and their versatile cross-talk (Sections 3.4 and 3.5). The yeast model of aging has clarified the role of Sir2/Sirtuins in energy metabolism and as a prolonging factor in yeast and lower organisms (Section 3.2). More recent studies have highlighted the role of cyclic AMP-regulated transcriptional co-activator-1 (CRTC-1)/cyclic AMP-responsive element-binding protein (CREB) (Section 3.1) and nuclear factor-erythroid 2-related factor 2 (Nrf2)/skinhead-1 (SKN-1) (Section 3.6) in the regulation of the aging process. These pathways have many common characteristics, e.g. AMPK can regulate the function of all these pathways and many of them target the regulation of autophagy and oxidative stress, functional hallmarks of the aging process. In addition, it seems that different signaling pathways are organized in an integrated network which has also positive feedback effects on the activity of AMPK.

3.1. CRTC-1/CREB signaling

There has been an intensive search for the signaling targets of AMPK/AAK-2 and their role in the regulation of the aging process during the last ten years. Recently, Mair et al. (2011) demonstrated that CRTC-1, a cytoplasmic co-activator of CREB, is a direct phosphorylation target of AAK-2/AMPK in *C. elegans*. In mammals, it is known that CRTCs are co-activators of CREB-mediated gene expression (Altarejos and Montminy, 2011). The inactive, phosphorylated CRTC can be activated in cytoplasm via the dephosphorylation e.g. by calcineurin (protein phosphatase 2B), after which it is translocated into the nucleus where it binds to CREB factors and promotes the transcription of target genes (Screaton et al., 2004). Mair et al. (2011) demonstrated that AAK-2/AMPK induced the phosphorylation of CRTC-1 which blocked its nuclear translocation and thus inhibited the transactivation of CRH-1, an orthologue of the mammalian CREB transcription factor. Interestingly, the inhibition of the CRTC–CREB pathway by AAK-2/AMPK signaling extended the lifespan of *C. elegans*, to the corresponding level observed in CRH-1 null worms (Fig. 1). In addition, Mair et al. (2011) observed that the inhibition of TAX-6, an orthologue of calcineurin, also extended the lifespan of *C. elegans*. This landmark study implied that those factors inhibiting the CRTC-induced CREB activation pathway play a key role in the regulation of aging process and longevity.

Currently, it is known that caloric restriction and heat stress can block the CRTC–CREB pathway and extend lifespan, at least in *C. elegans* (Mair et al., 2011). However, it needs to be clarified whether other AMPK activators, e.g. metformin, some hormones and phytochemicals, or certain protein kinases can also increase the phosphorylation status of CRTCs and block the pro-aging signaling via the CREB pathway. In addition to CRTC, there are several other pathways which can activate CREB-mediated transcription. For instance, many kinases, e.g. protein kinase A, Ca^{2+}/calmodulin-dependent protein kinases II/IV and p90 ribosomal S6 kinase (p90RSK), stimulate CREB-mediated gene expression (Takemori et al., 2007; Altarejos and Montminy, 2011). The CREB pathway has several important functions, e.g. in synaptic plasticity and memory, but on the other hand, it has been associated with many pathological conditions in the brain (Saura and Valero, 2011). Recent studies have indicated that the inhibition of protein kinase A signaling, whether or not this is mediated by CREB, can enhance healthy aging (Enns et al., 2009; Yamazaki et al., 2010). Some studies have also linked the activation of calcineurin through Ca^{2+} dysregulation with an accelerated aging process (Foster et al., 2001; Norris et al., 2005). Dwivedi et al. (2009) observed that calcineurin deficiency clearly increased the level of autophagy and extended the lifespan in *C. elegans*. In particular, *bec-1* and *atg-7* genes were crucial in

the extension of lifespan in the TAX-6/calcineurin null mutants. It is known that AMPK signaling can enhance autophagy and in that way, extend lifespan (Section 3.7). Whether or not the age-related CRTC–CREB signaling is associated with autophagic regulation is still unclear.

3.2. SIRT1 signaling

The AMPK and Silent information regulator 1 (SIRT1) signaling pathways are evolutionarily conserved energy sensors in cells responding to the increase in cellular AMP and NAD^+ concentrations, respectively (Ruderman et al., 2010). Mammalian SIRT1 is included in the Sirtuin family of seven genes which encode the class III protein deacetylases targeting histones and several transcription factors (Haigis and Guarente, 2006; Haigis and Sinclair, 2010). SIRT1 is a major regulator of cellular energy metabolism and many components of cell survival, e.g. apoptosis, cell proliferation and inflammation. SIRT1 regulates stress resistance by directly modulating the functions of FoxO, p53 and NF-κB signaling (Giannakou and Partridge, 2004; Salminen et al., 2008; Yi and Luo, 2010). Canto et al. (2009) demonstrated that the activation of AMPK stimulated the functional activity of SIRT1 by increasing the intracellular concentration of NAD^+ (Fig. 1). Consequently, SIRT1 activated several downstream targets, e.g. PGC-1α, FoxO1 and FoxO3. For instance, PGC-1α is a potent inducer of mitochondrial biogenesis. SIRT1 also enhanced the expression of Nampt which subsequently increased the level of NAD+ and thus potentiated SIRT1 activity (Nakahata et al., 2009). Interestingly, Lan et al. (2008) observed that SIRT1 was able to deacetylate LKB1 kinase which subsequently increased its activity. Since LKB1 is an upstream activator of AMPK, this signaling pathway stimulates the activation of AMPK. One can postulate that this positive feedback loop between SIRT1 and AMPK can also potentiate the function of the other AMPK-activated signaling pathways described below. The close relationship between AMPK and SIRT1 is evidence that energy balance effectively controls cellular responses via an integrated signaling network.

Caloric restriction is a unified condition which can extend lifespan in different species through the evolutionary range from budding yeast to mammals (Bordone and Guarente, 2005; Bishop and Guarente, 2007). Several studies have indicated that SIRT1 signaling is associated with the extension of lifespan although it seems that SIRT1-independent factors are also involved (Longo and Kennedy, 2006; Canto and Auwerx, 2009). The increase in SIRT1 activity during caloric restriction can enhance the cellular stress resistance which is a well-known defence mechanism against the aging process (Le Bourg, 2009). Recent studies have emphasized the role of autophagy in the extension of lifespan (Hariharan et al., 2010; Kume et al., 2010; Madeo et al., 2010). It is a well-known observation that the autophagic capacity declines during aging (Salminen and Kaarniranta, 2009). Kume et al. (2010) demonstrated that caloric restriction increased SIRT1 expression in the kidneys of old mice. They observed that SIRT1 could attenuate the hypoxia-induced damage by stimulating the FoxO3-induced expression of Bnip3, known as a potent inducer of autophagy. Hariharan et al. (2010) revealed that SIRT1 deacetylated FoxO1 which subsequently triggered autophagy by inducing the expression of Ras-related protein Rab7 in cardiac myocytes and Rab7 could stimulate lysosomal fusion with autophagosomes. Starvation-induced cardiac autophagy was clearly reduced in mice with cardiac-specific deletion of FoxO1 which also impaired cardiac function in these mice. In addition to the FoxO-mediated mechanisms, SIRT1 could also induce autophagy by directly deacetylating AuTophaGy (ATG) proteins, e.g. Atg5, Atg7 and Atg8 (Lee et al., 2008). The deacetylation of these proteins potentiated the autophagosome formation. Lee et al. (2008) demonstrated that the embryonic fibroblasts from $SIRT1^{-/-}$ mouse could not stimulate autophagy during starvation. They also emphasized that both the $SIRT1^{-/-}$ and $Atg5^{-/-}$ mice displayed deficiencies in the clearance of damaged organelles, such as mitochondria. These studies imply that SIRT1 can also directly stimulate autophagic uptake which is a crucial housekeeping mechanism, in particular during the aging process.

Recently, Chau et al. (2010) demonstrated that fibroblast growth factor 21 (FGF21) activated LKB1-AMPK-SIRT1 signaling pathway in mouse adipocytes. This is an interesting observation, since FGF21 requires β-Klotho protein as an obligatory co-receptor for the activation of FGF receptors (Kurosu and Kuro-o, 2009). The deficiency of β-Klotho protein induced a premature aging phenotype in mice (Kuro-o, 2009). FGF21 was able to stimulate extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling which subsequently activated LKB1 (Sapkota et al., 2001). However, β-Klotho protein is predominantly expressed in liver, pancreas and adipose tissue where FGF21 regulates metabolic functions, e.g. by activating AMPK-SIRT1 signaling. One major function of FGF21 is to regulate the adaptive responses to caloric restriction (Kliewer and Mangelsdorf, 2010) but the role of AMPK-SIRT1 signaling needs to be clarified in the premature aging process induced by β-Klotho deficiency.

Originally, it was reported that yeast Sir2, an orthologue to mammalian Sirtuins, could extend the longevity of budding yeast (Kaeberlein et al., 1999). Later it was revealed that *sir-2* gene could also extend lifespan in *C. elegans* (Tissenbaum and Guarente, 2001) and in *Drosophila* (Rogina and Helfand, 2004). This has almost become a kind of dogma but just recently, Burnett et al. (2011) was not able to confirm these effects on the lifespan and it now seems that the genetic background and mutagenic effects of transgene insertions may have affected the results of earlier studies. However, different approaches have clearly demonstrated that mammalian SIRT1 can improve the healthspan and in that way alleviate many age-related degenerative diseases, e.g. cardiovascular and neurodegenerative diseases (Longo and Kennedy, 2006; Canto and Auwerx, 2009; Haigis and Sinclair, 2010).

3.3. FoxO axis

The mammalian FoxO family of Forkhead transcription factors consists of four members, i.e. FoxO1, FoxO3a, FoxO4 and FoxO6, which are involved in the regulation of several crucial cellular functions, e.g. apoptosis, cell cycle, stress resistance, glucose and lipid metabolism and inflammation (Greer and Brunet, 2008; Nakae et al., 2008; Peng, 2008). In 1997, it was observed in *C. elegans* that DAF-16, an orthologue of mammalian FoxOs, was a key player in longevity regulation (Lin et al., 1997; Ogg et al., 1997). The DAF-2 pathway, corresponding to mammalian insulin/IGF-1 signaling (IIS) (Section 4), down-regulated the activity of FoxO/DAF-16 transcription factor, both in mammals and *C. elegans*. In mammals, it has been reported that AKT kinase phosphorylates FoxO factors at three sites and triggers their binding to the 14-3-3 chaperone which promotes the export of FoxO proteins from the nuclei and retains FoxOs in the cytoplasm (Greer and Brunet, 2008). Lin et al. (1997) and Ogg et al. (1997) observed that the loss-of-function mutations of DAF-2 pathway could double the lifespan of *C. elegans*. They also revealed that the lifespan extension was dependent on the activation and nuclear translocation of DAF-16. The 14-3-3 genes of *C. elegans*, *ftt-1* and *ftt-2*, may regulate lifespan by both DAF-16-dependent and -independent mechanisms (Araiz et al., 2008). The independent mechanism has been postulated to be associated with the AMPK-dependent, UNC-51-like kinase 1 (ULK1)-induced autophagy (Mihaylova and Shaw, 2011) (Section 3.7).

Greer et al. (2007b) demonstrated that AMPK directly phosphorylated FoxO3 protein at six threonine/serine residues in the transactivation domain in mouse fibroblasts. They also revealed

that AMPK induced the activation of FoxO3-mediated transcription without affecting the subcellular location of FoxO3 protein. Recently, Greer et al. (2007a) revealed that the AMPK-FoxO/DAF-16 axis was involved in the lifespan extension induced by dietary restriction in *C. elegans*. They also generated transgenic worms expressing a constantly active mutant of AMPKγ2 in order to study the effect of AMPK-FoxO/DAF-16 axis on longevity regulation. Interestingly, they observed that continuously active AMPK promoted the organismal resistance to oxidative stress and extended the lifespan of the worms. These effects of constant activation of AMPK required the presence of intact DAF-16 protein. Several studies have examined the genes activated by FoxO/DAF-16 (Murphy et al., 2003; Greer et al., 2007b; van der Vos and Coffer, 2011). The target genes of AMPK-FoxO3 pathway, associated with increased longevity, include several genes which are involved in defence against oxidative stress, e.g. thioredoxin (Li et al., 2009) and uncoupling protein UCP2 (Greer et al., 2007b), and against DNA damage, e.g. Gadd45a (Tran et al., 2002; Greer et al., 2007b).

In addition, FoxO factors are integrated into the functions of other longevity factors. For instance, it is known that FoxO3a can inhibit NF-κB signaling via the induction of inhibitory κB genes, IκBβ and IκBε, thus preventing the age-related inflammatory responses (Lin et al., 2004). On the other hand, the upstream kinases of NF-κB signaling, IKKα and IKKβ, can phosphorylate FoxO3a protein which triggers ubiquitination and degradation of this protein (Hu et al., 2004). It is known that p38α kinase, a well-known inducer of cellular senescence, could inhibit AMPK-FoxO3a signaling (Chiacchiera et al., 2009). They also observed that the pharmacological blockade of p38α triggered the presence of FoxO3a in the nuclei and increased the expression of phosphatase and tensin homolog (PTEN), a potent inhibitor of IIS/DAF-2 pathway and thus an inducer of nuclear translocation of FoxO3a. This positive feedback loop potentiates the activity of AMPK-FoxO3a axis. Although AMPK can stimulate autophagy through the ULK1/mammalian target of rapamycin (mTOR) regulation (Section 3.7), FoxO factors also stimulate the expression of several inducers of autophagy, e.g. Bnip3, LC3, ATG12 and Gabarabl1 (van der Vos and Coffer, 2011). There are studies demonstrating that FoxO1 and FoxO3a promote autophagy e.g. in cardiomyocytes (Sengupta et al., 2009) and skeletal muscle (Mammucari et al., 2007). Moreover, SIRT1 augmented the FoxO3a-mediated autophagy during caloric restriction (Kume et al., 2010). Recently, Demontis and Perrimon (2010) demonstrated that FoxO/4E-BP signaling could stimulate autophagic uptake and maintain proteostasis in aging muscles in *Drosophila*. It seems that AMPK can enhance autophagy through both the FoxO and ULK1/mTOR pathways.

FoxO factors and p53 exist in a complex interaction network (You and Mak, 2005; van der Horst and Burgering, 2007). Interestingly, both of these proteins can induce the expression of Sestrins in cellular stress, e.g. oxidative stress, hypoxia and genotoxic stress (Chen et al., 2010; Lee et al., 2010a; Budanov, 2011) (Fig. 1). Stress-inducible Sestrins, three SESNs in mammals, have antioxidative capabilities but all of their functions are not known (Budanov, 2011). Remarkably, Lee et al. (2010b) demonstrated that FoxO was a potent activator of AMPK in *Drosophila* and in that way they established a positive feedback loop between FoxO factors and AMPK signaling. p53 also activated AMPK which subsequently inhibited mTOR and triggered autophagy (Budanov and Karin, 2008) (Section 3.7). Lee et al. (2010b) demonstrated that the loss of Sestrin resulted in age-associated pathological changes, e.g. mitochondrial dysfunction, muscle degeneration and lipid accumulation. These effects of Sestrin depletion were most likely attributable to the increased TOR activity and the associated decrease in autophagic uptake since these pathologies were prevented by the activation of AMPK by AICAR and the inhibition of TOR by rapamycin. This means that FoxOs, as well as p53, can be considered as inducers of the Sestrin-induced negative feedback loop for mTOR signaling which operates via the activation of AMPK and is able to translate cellular stress signals into bolstering the autophagic defence which can extend the organismal lifespan (Fig. 1).

3.4. p53 pathways

The p53 protein has been the focus of studies on aging and cellular senescence since the early experiments of Wright and Shay (1992). The p53 transcription factor is an important tumor suppressor protein but recently, its major role in the regulation of metabolism and autophagy has been appreciated (Vousden and Ryan, 2009; Balaburski et al., 2010; Feng and Levine, 2010). It is known that different stressors can trigger the phosphorylation of Ser-20 at the transactivation domain in p53 protein (Maclaine and Hupp, 2009). AMPK is one of the kinases targeting this site which occurs in response to energy deficiency. Jones et al. (2005) demonstrated that AMPK promoted the p53 activity by phosphorylating at Ser-15 which induced cell cycle arrest. Okoshi et al. (2008) observed that the enforced expression of AMPKα2 increased the transcription of p53 gene and enhanced the phosphorylation of p53 protein at Ser-46 which triggered apoptotic cell death. In contrast, the down-regulation of AMPKα2 attenuated the Ser-46 phosphorylation and decreased the expression of p53. These studies indicate that p53 protein is one of the target proteins of AMPK controlling both the expression level of p53 and its transactivation capacity.

There is conflicting literature on the role of p53 in cellular senescence and organismal aging (Donehower, 2009; de Keizer et al., 2010; Feng et al., 2011; Liu and Xu, 2011). Matheu et al. (2007) demonstrated that the activation of Arf/p53 pathway clearly delayed the aging process and reduced age-related damage in mice. This was probably attributable to the increased expression of antioxidant genes (Matheu et al., 2007). Several studies have revealed that p53 is a potent inducer of antioxidant proteins and thus could decrease aging-associated oxidative stress (Sablina et al., 2005). Recent studies have indicated that p53 has a major impact on the regulation of longevity but this occurs in a context-dependent process which is attributable to its versatile role in cellular metabolism. For instance, p53 is an effective regulator of autophagy but its response is dependent on its localization within the cell, i.e. while present in the cytoplasm, p53 represses autophagy whereas if it reaches the nuclei, it can stimulate autophagy via the transcription of DNA-damage regulated autophagy modulator 1 (DRAM1) and Sestrin 2 proteins (Kroemer et al., 2010). Moreover, the effects of p53 on autophagy are dependent on the activation level of mTOR and production of reactive oxygen species (ROS) (Galluzzi et al., 2010; Vigneron and Vousden, 2010). There is clear evidence that the effects of p53 on organismal aging are mediated by autophagy (Tavernarakis et al., 2008; Feng et al., 2011). The increased autophagy could extend the organismal lifespan whereas its repression would increase the accumulation of waste material, jeopardizing healthspan and longevity (Meijer and Codogno, 2009; Kroemer et al., 2010; Rubinsztein et al., 2011). Mitochondria are the major target of several p53 activities, e.g. mitochondrial biogenesis (Saleem et al., 2009) and in this way, p53 regulates mitochondrial energy metabolism (Maddocks and Vousden, 2011) and apoptosis (Vaseva and Moll, 2009). Recent studies have indicated that p53 can also control mitochondrial integrity through the induction of Mieap, a protein which eliminates oxidized protein within mitochondria (Kitamura et al., 2011).

It has been difficult to elucidate the functional role of p53 *in vivo* during aging. Feng et al. (2007) demonstrated that the efficiency of p53 response to cellular stress significantly declined in the tissues of aging mice. They observed that the transcriptional activity of p53 factor as well as the p53-dependent apoptosis clearly decreased with aging. They did not study the effects of aging on

AMPK activity (Section 2) but the age-related deficiency in AMPK activation could suppress p53 signaling. The decline in p53 function was reported to induce similar phenomena as observed during aging, e.g. decrease in autophagy (Kroemer et al., 2010), increase in inflammatory responses via the stimulation of NF-κB signaling (Kawauchi et al., 2009; Salminen and Kaarniranta, 2011) and increase in oxidative stress (Liu and Xu, 2011). Moreover, p53 and NF-κB have antagonistic effects i.e. increased NF-κB activity during aging (Section 3.5) can down-regulate many functions of p53 (Salminen and Kaarniranta, 2011). A decrease in the p53 transactivation capacity with aging could also diminish the sestrin-driven activation of AMPK and enhance the appearance of age-related pathological changes (Section 3.3).

3.5. NF-κB signaling

Fifteen years ago, our group observed that the DNA-binding activity of NF-κB complexes was significantly increased with aging in several tissues of mice and rats (Helenius et al., 1996a,b). We also verified that the increase in DNA-binding capacity was associated with the increase in the nuclear levels of p52 and p65 components of NF-κB complex (Helenius et al., 1996a, 2001). However, the expression levels of p52 and p65 mRNAs and the presence of proteins in the cytoplasmic fraction were unaffected by aging. Furthermore, we did not find any age-related changes in the protein levels of the main IκB inhibitors or major upstream kinases, IKKα, IKKβ and NIK (Helenius et al., 2001). These results clearly indicated that the retention of NF-κB components into the nuclei was elevated during aging or the increased NF-κB activity could originate in an expanded number of inflammatory cells in tissues with aging. Subsequent studies have indicated that both possibilities may well be correct. Adler et al. (2007) revealed with motif module mapping that the NF-κB motif was the most frequently associated module with expressed genes during aging in many human and mouse tissues. Recently, Kawahara et al. (2009, 2011) have demonstrated that SIRT6 could inhibit the expression of several NF-κB-driven genes by modulating their chromatin structures. Interestingly, the SIRT6 depletion in keratinocytes increased the expression of NF-κB-dependent genes and induced a premature aging phenotype.

Chronic inflammation associated with increased NF-κB signaling is a typical hallmark of several age-related metabolic disorders, e.g. obesity, type 2 diabetes and atherosclerosis (Baker et al., 2011). Activators of AMPK, e.g. metformin and AICAR, are potent energy metabolic enhancers but they also have anti-inflammatory properties. Several studies have demonstrated that the activation of AMPK can inhibit NF-κB signaling, a master regulator of inflammation, both *in vitro* and *in vivo* (Fig. 1). We have recently reviewed this topic in detail (Salminen et al., 2011). It seems that the activation of NF-κB in macrophages can initiate the inflammatory process which aggravates many metabolic diseases (Baker et al., 2011). Ko et al. (2009) observed that consumption of a high-fat diet decreased AMPK activity and increased macrophage proliferation and expression of interleukin-6 (IL-6) in mouse heart. It is known that metformin can inhibit NF-κB signaling and prevent inflammatory responses in endothelial cells in vascular walls (Hattori et al., 2006; Isoda et al., 2006). Moreover, some non-steroidal anti-inflammatory drugs, e.g. aspirin (Sung and Choi, 2011) and flufenamic acid (Chi et al., 2011), are potent activators of AMPK signaling.

Currently, it is not known whether AMPK can directly phosphorylate IKK kinases or NF-κB components. It seems that AMPK indirectly suppresses the signaling of NF-κB system (Salminen et al., 2011). Yeung et al. (2004) demonstrated that SIRT1 interacted with the RelA/p65 component of the NF-κB complex and cleaved the acetyl group from the Lys310. This deacetylation reaction inhibited the NF-κB signaling since the acetylation of Lys310 at p65 protein is a potent enhancer of NF-κB transactivation. The deacetylation of Lys310 can trigger the Set9-mediated methylation of Lys314 and Lys315 and subsequently the ubiquitination and degradation of the p65 protein (Yang et al., 2010a). Thus, it seems that the AMPK-SIRT1-NF-κB signaling pathway has a major role in the suppression of immune responses, e.g. by caloric restriction and dietary phytochemicals, and in that way may enhance healthspan and lifespan (Section 3.2). Several studies have also revealed that FoxO factors, FoxO3a (Lin et al., 2004) and FoxO4 (Zhou et al., 2009b), are effective inhibitors of NF-κB signaling and can prevent immune responses. AMPK is a potent activator of FoxO signaling (Section 3.3), and thus some of the FoxO responses may be mediated through the inhibition of NF-κB signaling. Moreover, one of the major targets of AMPK-mediated signaling, PGC-1α, can bind to the p65 subunit of NF-κB (Alvarez-Guardia et al., 2010). One can envisage that there is cross-talk between energy metabolism and inflammation since the activation of NF-κB increased the interaction of these factors and subsequently reduced the expression of PGC-1α (Alvarez-Guardia et al., 2010). Conversely, increased expression of PGC-1α inhibited NF-κB signaling and inflammatory responses in aortic smooth muscle and endothelial cells (Kim et al., 2007). These observations indicate that AMPK controls NF-κB signaling and thus the deficiency in AMPK signaling encountered during aging (Section 2) not only disturbs energy metabolism but also provokes inflammatory responses.

3.6. Nrf2/SKN-1 signaling

Capĭnĭcollar transcription factors mammalian nuclear factor erythroid-derived 2 (Nrf2) and *C. elegans* skinhead family member 1 (SKN-1) are potent inducers of cellular defence responses to oxidative stress (Sykiotis and Bohmann, 2010; Brigelius-Flohe and Flohe, 2011). Oxidative stress has been recognized as the hallmark mechanism of aging since Denham Harman presented his free radical theory of aging in 1956 (Harman, 1956). Mitochondria, 5-lipoxygenase and NADPH oxidase are the major sources of reactive oxygen species within mammalian cells. Several studies have indicated that the activation of signaling pathways mediated by Nrf2 and SKN-1, an orthologue in *C. elegans*, can extend the lifespan of model organisms (Tullet et al., 2008; Park et al., 2009; Leiser and Miller, 2010; Lewis et al., 2010; Sykiotis and Bohmann, 2010). On the other hand, it seems that these pathways are less active or dysregulated during aging and in age-related degenerative diseases (Przybysz et al., 2009; Sykiotis and Bohmann, 2010; Ungvari et al., 2011) which could obviously aggravate the oxidative stress in these conditions. Moreover, Nrf2 signaling can protect against inflammatory disorders (Kim et al., 2010) and accordingly any deficiency in Nrf2 signaling, such as that occurring with aging, could augment the inflammatory phenotype. Yu et al. (2011) demonstrated that the p65 component of NF-κB complex could bind to the Kelch-like ECH-associated protein 1 (Keap1) protein, an inhibitor of Nrf2 signaling, leading to increased localization of Keap1 into the nuclei and consequently reduced the binding of Nrf2 to its target sites. This implies that NF-κB signaling can antagonize Nrf2 activity, i.e. the increased NF-κB signaling that is encountered with aging (Section 3.5) can reduce Nrf2 signaling.

There is an extensive literature indicating that AMPK activity can inhibit oxidative stress and inflammation (Xie et al., 2008; Li et al., 2009; Yang et al., 2010b; Salminen et al., 2011). For instance, Xie et al. (2008) revealed that AMPK signaling induced the expression of mitochondrial UCP-2 which repressed superoxide production in hyperglycemic endothelial cells. Furthermore, Li et al. (2009) demonstrated that the activation of AMPK induced the expression of thioredoxin, a disulfide reductase which prevents the cysteine oxidation of cellular proteins. The exact mechanisms of the AMPK-mediated antioxidative responses are still unclear but some recent

studies have indicated that AMPK can stimulate Nrf2/SKN-1 signaling (Fig. 1). Onken and Driscoll (2010) observed that the increased activity of AAK-2 by metformin extended the median lifespan of *C. elegans*. This phenomenon required both the presence of an intact AAK-2/AMPKα subunit and the SKN-1 transcription factor. Moreover, metformin triggered an AAK-2-dependent translocation of SKN-1 into the nuclei. Recently, Liu et al. (2011b) demonstrated that AMPK induced the expression of antioxidative heme oxygenase-1 gene via the Nrf2 signaling pathway in endothelial cells. They also observed that AICAR treatment rapidly stimulated the expression of Nrf2 which clearly was an AMPK-dependent process. The activation of Nrf2 signaling by AMPK acts in concert with the function of AMPK-FoxO3a axis (Section 3.3) in the generation of stress resistant phenotype of long-lived animals.

3.7. mTOR/ULK1 regulation

There is a growing literature that AMPK signaling is a major inducer of autophagy associated with the reduction of energy metabolism (Egan et al., 2011; Kim et al., 2011; Mihaylova and Shaw, 2011). Autophagy is a cellular housekeeping and protein quality control mechanism which can remove damaged or defective proteins and organelles, e.g. mitochondria. Several studies have demonstrated that the autophagic capacity to degrade harmful proteins in cells clearly declines with aging (Salminen and Kaarniranta, 2009; Rubinsztein et al., 2011). This triggers the accumulation of waste products, in particular into post-mitotic cells, during aging. Studies on the aging mechanisms in *C. elegans* have revealed that several autophagy genes, e.g. *bec-1*, *Atg-7* and *Atg-12*, are required for the extension of lifespan and autophagy is a crucial process in the longevity regulation (Melendez et al., 2003; Hars et al., 2007; Jia and Levine, 2007). Hansen et al. (2008) observed that the lifespan extension by dietary restriction was also associated with increased autophagy in *C. elegans*. In mammals, Cuervo and Dice (2000) were the first to demonstrate that chaperone-mediated autophagy clearly declined during aging in rat liver. This was attributed to the progressive decrease in the expression of lysosomal-associated membrane protein 2 (LAMP2) which is the receptor protein of chaperone-mediated autophagy. Later studies indicated that the prevention of the age-related decline of LAMP2 suppressed the accumulation of damaged proteins and maintained better hepatic function (Zhang and Cuervo, 2008). Moreover, the macroautophagy, e.g. mitophagy in the uptake of defective mitochondria, is also impaired with aging (Brunk and Terman, 2002; Bergamini et al., 2004; Yen and Klionsky, 2008). Autophagy can be activated by several stresses, e.g. caloric restriction, and seems to be associated with stress resistance. In addition, the decline in autophagy can induce cellular senescence in human fibroblasts (Kang et al., 2011). This dysfunction of autophagy has also been linked to several age-related neurodegenerative diseases, e.g. Alzheimer's disease (Li et al., 2010; Wong and Cuervo, 2010). As a conclusion, there is emerging evidence that autophagy has a crucial role in the longevity regulation (Cuervo, 2008; Yen and Klionsky, 2008; Salminen and Kaarniranta, 2009; Petrovski and Das, 2010).

AMPK can regulate the initiation of autophagosome formation via different signaling mechanisms (Yang and Klionsky, 2010; Mihaylova and Shaw, 2011). It has been known for some time that mTOR, a conserved Ser/Thr protein kinase, is a potent inhibitor of autophagy. mTOR is involved in the signaling pathways induced by growth factors, abundant nutrients and sufficient energy status. For instance, the growth factor signaling pathway, PI3K-AKT, activates the mTOR-mediated biosynthetic processes whereas simultaneously it represses autophagic degradation. AMPK can inhibit the activity of mTOR complex (mTORC1) via two different mechanisms, either by directly phosphorylating the Raptor, a regulatory component of mTORC1, or by the phosphorylation of tuberous sclerosis protein 2 (TSC2), which subsequently suppresses the activity of mTOR (Jung et al., 2010; Mihaylova and Shaw, 2011). Active mTORC1 becomes associated with the ULK1/ATG13/FIP200 complex and mTOR phosphorylates ULK1 and thus represses its protein kinase activity. AMPK is a positive regulator of autophagy by dissociating mTORC1 from the ULK1 complex via the phosphorylation of the Raptor component. Mammalian ULK1, an orthologue of yeast Atg1, is a gate keeper for autophagosome formation by binding to phagophoric membranes and enhancing the function of autophagic conjugation systems (Mizushima, 2010). The cross-talk between mTORC1 and ULK1 complexes regulates the metabolic balance between synthetic processes, e.g. protein and ribosome synthesis, and the catabolic processes via autophagy.

Recent studies have demonstrated that AMPK can stimulate autophagy by directly binding to the ULK1 complex and phosphorylating ULK1 (Lee et al., 2010c; Egan et al., 2011; Kim et al., 2011) (Fig. 1). There is still controversy about whether there are distinct phosphorylation sites in the ULK1 protein by AMPK. ULK1 is not the only regulator of autophagy. For instance, Lee et al. (2008) demonstrated that SIRT1 could complex with several autophagy components, e.g. Atg5, Atg7, and Atg8, and deacetylated these proteins. The absence of SIRT1 increased the acetylation level of these proteins. The tissues of SIRT1$^{-/-}$ mice revealed the accumulation of damaged organelles similar to the situation in Atg5$^{-/-}$ mice. It seems that the activation of AMPK can also enhance the later steps in autophagosome formation via the activation of SIRT1 signaling (Section 3.2). Moreover, the activation of FoxO1 and FoxO3a transcription factors could induce the expression of several autophagy-related genes and this could lead to enhanced autophagocytosis, in particular in cardiac and skeletal muscles (Zhao et al., 2007; Sengupta et al., 2009). These studies clearly emphasize the role of AMPK as a key activator of the signaling network which maintains cellular housekeeping by autophagy and in that way can extend the organismal health span and lifespan.

4. Insulin/IGF (IIS) pathway opposes the effects of AMPK on longevity

The fundamental studies on the long-lived *C. elegans* mutants revealed the first genes related to the regulation of longevity, i.e. *age-1*, *daf-2* and *daf-16* (Friedman and Johnson, 1988; Kenyon et al., 1993). This DAF-2 pathway is an analogue of the mammalian insulin/IGF-PI3K pathway and the DAF-2 protein is an orthologue of insulin/IGF-1 receptor and the AGE-1 protein that of PI3K (Guarente and Kenyon, 2000). The non-functional mutants of DAF-2 and AGE-1 stimulate DAF-16/FoxO -mediated lifespan extension (Section 3.3). The insulin/IGF pathway activates also mTOR kinase and consequently its downstream targets, eukaryotic initiation factor 4 (eIF4) and ribosomal protein S6 kinase 1 (S6K1), which regulate protein and ribosome biosynthesis. It is known that mTOR is a detrimental agent since it acts to accelerate the aging process (Blagosklonny, 2009; Wesierska-Gadek, 2010), probably because it is such a potent inhibitor of autophagy (Section 3.7). Recent studies have demonstrated that rapamycin, an inhibitor of mTOR, is able to extend the lifespan of old mice (Harrison et al., 2009) and also is beneficial in cancer-prone mice (Anisimov et al., 2010). Moreover, the inhibition of mTOR can attenuate nutrient-induced cell death and reduce hyperglycemic damage in primary endothelial cells (Panieri et al., 2010). Currently, it is not known whether the lifespan extension is caused by the activation of autophagy or by the inhibition of the other downstream targets of mTOR. Interestingly, Selman et al. (2009) demonstrated that the deletion of S6K1 kinase in mice increased their lifespan and prevented many age-related pathologies. Moreover, the gene expression patterns of these mice resembled those seen after caloric restriction and AICAR

treatment. These results imply that S6K1, a downstream target of insulin/IGF-mTOR pathway, could repress AMPK signaling and its deletion stimulated AMPK signaling including lifespan extension.

Insulin/IGF-1 signaling associated with growth hormone regulation represents a crucial somatotropic axis in mammals (Schneider et al., 2003; Bartke and Brown-Borg, 2004). Deficiencies in the function of this pathway lead to dwarfism, i.e. individuals having a reduced body size. Interestingly, all dwarf mice, e.g. Ames, Snell and Little mice, live longer than their wild type counterparts (Bartke and Brown-Borg, 2004). The extension of lifespan varies between 20% and 70% in the different dwarf models. Moreover, Kurosu et al. (2005) demonstrated that the overexpression of Klotho protein inhibited insulin/IGF1 signaling and increased lifespan whereas the functional deficiency of Klotho induced a premature aging. The molecular mechanisms of the insulin paradox still needs to be clarified but it seems that insulin/IGF pathway dominates, e.g. during development, and can suppress autophagy via mTOR signaling (Section 3.7). However, there are studies indicating that AKT, a key protein kinase in insulin/IGF pathway, could inhibit AMPK signaling (Kovacic et al., 2003; Horman et al., 2006; Ning et al., 2011). Horman et al. (2006) demonstrated that AKT induced the phosphorylation of AMPKα1 at Ser^{485}/Ser^{491} which subsequently inhibited the phosphorylation of AMPK at Thr^{172} by LKB1 and thus suppressed the activation of AMPK. This mechanism has been observed in cardiac muscle (Horman et al., 2006) and vascular smooth muscle (Ning et al., 2011). It is rational that the catabolic effects of AMPK will be blocked by anabolic insulin/IGF-1 signaling.

Insulin/IGF-1 and AMPK signaling pathways are mutually inhibitory since the insulin/IGF-1 pathway can also repress many targets of AMPK signaling. For instance, insulin/IGF-1 pathway directly inhibits FoxO longevity factors activated by AMPK (Section 3.3). AMPK signaling also inhibits NF-κB system (Section 3.5) whereas insulin/IGF-1 pathway can activate NF-κB signaling (Salminen and Kaarniranta, 2010b). Moreover, Tullet et al. (2008) demonstrated in *C. elegans* that insulin-like signaling (DAF-2 pathway) directly phosphorylated SKN-1/Nrf2 and by this mechanism inhibited the nuclear translocation of SKN-1 and the expression of SKN-1 target genes. AKT1/2 (protein kinase B) and serum/glucocorticoid regulated kinase 1 (SGK-1) were involved in the inhibition of SKN-1 function. A decrease in the DAF-2 signaling increased SKN-1 signaling and extended the lifespan of *C. elegans*. Ning and Clemmons (2010) revealed that AMPK activation suppressed the signaling of insulin/IGF-1 pathway by phosphorylating insulin receptor substrate-1 (IRS-1) at Ser794 and thus inhibited the signaling of insulin/IGF-1 pathway to AKT/mTOR/S6K1 in vascular smooth muscle cells.

Interestingly, the potent activators of AMPK, metformin and AICAR, can improve insulin sensitivity and thus enhance insulin/IGF-1 signaling and glucose uptake (Lee et al., 2011; Tao et al., 2010). There seems to be several mechanisms mediating this pleiotropy of AMPK function. Lee et al. (2011) observed that metformin and AICAR suppressed the expression of PTEN, an inhibitor of AKT function, in 3T3-L1 preadipocytes. The inhibition was AMPK dependent and mTOR was involved in the repression of PTEN promoter activity. It is well known that the deletion of DAF-18/PTEN shortens lifespan in *C. elegans* (Mihaylova et al., 1999). DAF-18/PTEN acts as a phosphatidylinositol 3,4,5-trisphosphate phosphatase and thus limits the activation of AKT1 and AKT2 (Mihaylova et al., 1999; Kishimoto et al., 2003). AMPK can also stimulate insulin/IGF-1 signaling by inhibiting mTOR/S6K1 activity (Section 3.7) since S6K1 induces a feedback inhibition of insulin/IGF-1 pathway by phosphorylating IRS-1 (Zhang et al., 2008). Chronic stimulation of S6K1 can provoke insulin resistance in obesity by inhibiting IRS-1 protein in the insulin/IGF-1 pathway (Tremblay et al., 2007). It seems that AMPK can enhance the function of insulin/IGF-1 signaling if it supports its metabolic functions, e.g. glucose uptake, but represses all energy-consuming synthetic pathways.

5. Conclusions

AMPK is a crucial regulator of energy metabolism, at both the cellular and whole-body levels. In addition, AMPK controls the autophagic degradation and many characteristics of cellular stress resistance. It is not surprising that increased AMPK activity can extend the lifespan in lower organisms. Currently, it is believed that efficient autophagic clearance and increased stress resistance are the major characteristics which can improve the healthspan and in that way also extend the lifespan. There are recent studies indicating that the sensitivity of AMPK to cellular stress declines with aging and this could impair downstream signaling and the maintenance of cellular energy balance and stress resistance. In particular, a deficiency in AMPK signaling could attenuate autophagic clearance via the mTOR and ULK1 pathways. Moreover, reduced activity of FoxO/DAF-16, Nrf2/SKN-1 and p53 pathways is known to impair the maintenance of resistance against cellular stressors. These difficulties in housekeeping can trigger innate immunity defence, in particular because the ability of AMPK to suppress NF-κB signaling is reduced with aging. In conclusion, AMPK controls an integrated signaling network which has a major role in the regulation of the aging process.

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