Cell. Mol. Life Sci. 65 (2008) 1049 – 1058
1420-682X/08/071049-10
DOI 10.1007/s00018-008-7461-3

Cellular and Molecular Life Sciences

Review

Interaction of aging-associated signaling cascades: Inhibition of NF-κB signaling by longevity factors FoxOs and SIRT1

A. Salminen[a,b,*], J. Ojala[a], J. Huuskonen[a], A. Kauppinen[a], T. Suuronen[a] and K. Kaarniranta[c]

[a] Department of Neuroscience and Neurology, University of Kuopio, P.O. Box 1627, 70211 Kuopio (Finland), Fax: +358 17162048, e-mail: antero.salminen@uku.fi
[b] Department of Neurology, University Hospital of Kuopio, P.O. Box 1777, 70211 Kuopio (Finland)
[c] Department of Ophthalmology, University of Kuopio, P.O. Box 1627, 70211 Kuopio (Finland)

Received 4 October 2007; received after revision 7 November 2007; accepted 9 November 2007
Online First 15 January 2008

Abstract. Research on aging in model organisms has revealed different molecular mechanisms involved in the regulation of the lifespan. Studies on *Saccharomyces cerevisiae* have highlighted the role of the Sir2 family of genes, human Sirtuin homologs, as the longevity factors. In *Caenorhabditis elegans*, the daf-16 gene, a mammalian homolog of FoxO genes, was shown to function as a longevity gene. A wide array of studies has provided evidence for a role of the activation of innate immunity during aging process in mammals. This process has been called inflamm-aging. The master regulator of innate immunity is the NF-κB system. In this review, we focus on the several interactions of aging-associated signaling cascades regulated either by Sirtuins and FoxOs or NF-κB signaling pathways. We provide evidence that signaling *via* the longevity factors of FoxOs and SIRT1 can inhibit NF-κB signaling and simultaneously protect against inflamm-aging process.

Keywords. Aging, FoxO, NF-κB, sirtuins, inflamm-aging, inflammation.

Introduction

Traditionally, aging research has attempted to devise plausible mechanisms to explain the aging process. During the last decade, molecular research has focused on the aging mechanisms of several model organisms, such as the budding yeast *Saccharomyces cerevisiae* and the nematode *Caenorhabditis elegans*. This approach has been profitable in unraveling the complex molecular mechanisms behind the aging process in these model organisms. The Sir2 family of genes governs the budding exhaustion in *S. cerevisiae* [1, 2] and the daf-16 gene regulates lifespan extension in *C. elegans* [3, 4]. Both of those genes are conserved during evolution and several homologs of Sirtuins and FoxOs (daf-16 homologs) have been cloned in mammals. The relevance of these models for illustrating mammalian aging has been criticized [5–7]. For instance, the yeast model seems to mimic better cellular senescence rather than organism aging. Since *C. elegans* is a continuously growing organism, it may be more useful in elucidating the role of signaling pathways specialized in growth and cellular resistance, such as insulin/IGF/PI3K pathway. Furthermore, germline signaling occurs in *C. elegans* [8], but this does not probably take place in mammals.

Several studies have highlighted the direct correlation between cellular resistance and lifespan of lower organisms [9–12]. This is attributable to hormesis and

* Corresponding author.

resistance to age-related stress. Effective defense mechanisms against inherent cellular stress and environmental attacks are essential for successful aging process and long lifespan. Innate and adaptive immunity are the major defense mechanisms in the higher organisms. Innate immunity is already present in unicellular organisms but novel mechanisms of adaptive immunity have developed during evolution in the defense capabilities of multicellular organisms [13]. The pattern recognition receptors and signaling pathways involved in innate immunity have been highly conserved during evolution. The master regulator of innate immunity is the evolutionary ancient NF-κB signaling system [14]. Interestingly, the efficiency of adaptive immunity significantly declines during aging, whereas innate immunity is clearly activated. This induces a pro-inflammatory condition called inflamm-aging [15–17]. The role of NF-κB signaling is important in organism defense since it links the inherent system with that devoted to responding to environmental danger signals and in that way organizes the cellular defense [18–20].

Simultaneously with the discoveries in molecular aging mechanisms, enormous progress has been made in our understanding about cellular signaling cascades and interactions of different pathways in the regulation of gene expression. Several key players have been discovered in aging research that are important participants in signaling networks: FoxOs and NF-κB are transcription factors, and Sirtuins are the protein deacetylases that regulate the activity of FoxOs and NF-κB (Fig. 1). In this review, we postulate that the aging-associated signaling cascades regulate each other and all interactions affect the final outcome of the signaling network. Aging-associated signaling may represent the lifespan extending, longevity regulation, or the age-related degenerative, pro-aging signaling. We propose that the signaling cascades mediated *via* Sirtuins and FoxO represent the lifespan extending, anti-aging type of regulation. Conversely, NF-κB signaling enhances the tissue atrophy and inflammation and supports inflamm-aging. We also provide evidence that the signaling *via* longevity factors FoxOs and SIRT1 can inhibit the NF-κB signaling and simultaneously protect against inflamm-aging.

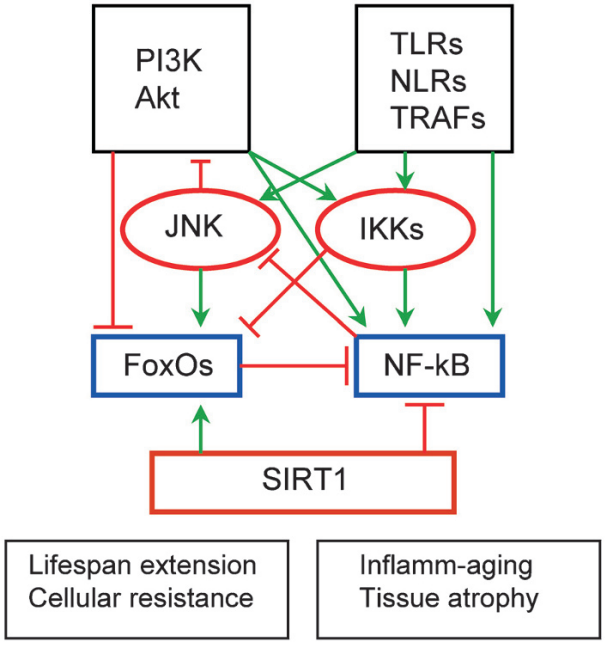

Figure 1. Schematic representation of the molecular interactions between longevity signaling mediated by FoxOs and inflamm-aging signaling involving NF-κB system. More details are presented in the text.

Longevity regulation: Signaling *via* FoxOs and Sirtuins

Daf-16/FoxO family of *C. elegans* longevity genes

C. elegans is a nematode that has been extensively studied in aging paradigms [21]. *C. elegans* has a short lifespan and it is able to enter a developmental diapause state, *i.e.*, the dauer larva stage, in unfavorable environmental conditions [22, 23]. The formation of the dauer stage involves the induction of alternate metabolism regulated by endocrine changes [4]. Over 30 dauer pathway genes have been cloned and named as *daf* genes [24, 25]. The most extensively studied and important of dauer pathways is the DAF-2 pathway, which includes DAF-2 (homolog to mammalian insulin/IGF-1 receptor), AGE-1 (PI-3K), DAF-18 (PTEN) and DAF-16 (FoxOs). Mutations in the genes of the DAF-2 pathway considerably extend the lifespan and can induce a dauer stage in the larva [23, 25, 26]. The DAF-2 pathway is an analog to mammalian insulin/IGF pathway and DAF-16 (the homolog to mammalian FoxOs) seems to be a key factor in the longevity regulation in *C. elegans*. DAF-16 is a transcription factor that has numerous target genes, many of which regulate stress resistance and longevity [27–29]. Assurance of energy availability may be the main function of DAF-16 in *C. elegans* supporting the disposable soma theory of aging [30]. The mammalian FoxO gene family contains four members: FoxO1 (earlier FKHR), FoxO3 (FKHRL1), FoxO4 (AFX) and FoxO6 [31, 32]. The function of FoxOs is regulated by phosphorylation, acetylation and ubiquitination [31–33] with phosphorylation being the most critical since it regulates the nucleo-cytoplasmic shuttling of most FoxO factors, except that of FoxO6 which is a nuclear factor. The

insulin/IGFs/PI-3K/Akt pathway phosphorylates FoxO proteins ensuring their retention in cytosol in a complex with 14–3-3 protein. Mutations in the genes or a decline in insulin/IGF signaling induce the translocation of FOXO proteins to the nucleus and the activation of target gene transcription [31–34]. In addition to the major FoxO kinase, AKT kinase, several other kinases, such as SGK (serum and glucocorticoid-regulated kinase), JNK (c-N-Jun terminal kinase), IKK (IκB kinase), CK1 (casein kinase), CDK2 (cyclin-dependent kinase-2) and DYRK (dual-specificity regulated kinase) can phosphorylate all or, in a specific manner, some of the FoxO proteins, affecting not only the translocation but probably also the transactivation efficiency of FoxO proteins [31–35]. Interestingly, FoxO proteins can link together different aging-associated transduction pathways, such as AKT, JNK and IKK regulated pathways (see below).

With respect to aging, it seems that the DAF-2/DAF-16 connection has been conserved during evolution. The insulin/IGF pathway may have a profound role in the regulation of mammalian aging process either directly *via* transactivation of the FoxO target gene or *via* FoxO-dependent inhibition of NF-κB signaling (Fig. 1). Klotho mice may represent a good mammalian example of the role of the insulin/FoxO cascade in the pathway to extending lifespan [36]. In 1997, Kuro-o et al. [37] cloned a *klotho* gene, the mutation of which leads to a progeroid syndrome resembling ageing in mouse. Importantly, the overexpression of a functional Klotho protein extended the lifespan of mice and hence Klotho can be viewed as an aging suppressor gene [38].

Recently, it was observed that Klotho functions as a cofactor that activates FGF-23 signaling [39]. This observation indicates that it is not Klotho deficiency, which is the primary cause of accelerated aging but rather its absence, which leads to the impaired FGF-23 signaling [40]. Studies attempting to determine the Klotho-dependent receptors and signaling are currently ongoing. Kurosu et al. [38] observed that Klotho represses the intracellular signaling of insulin and IGF-1, and hence can activate FoxO signaling and induce the resistance to oxidative stress, one of the hallmark functions of FoxO proteins [41].

Long-lived dwarf mice may be another example of the role of insulin/IGF-1 regulation in mammalian longevity [36, 42]. Lack of growth hormone (GH) reduces hepatic synthesis of IGF-1 and reduces insulin/IGF-1 signaling and causes a dwarf phenotype but does extend the lifespan. Ames and Snell dwarf mice as well as several transgenic mouse lines have been examined and links found between GH deficiency, insulin signaling and life extension. Bartke and Brown-Borg [42] have extensively reviewed the topic.

Summarizing, FoxO transcription factors are situated at a crossroads (Fig. 1) linking endocrine signaling and stress-related signals, *e.g.*, those from JNK and IKKs. The FoxO factors undertake interactions with several other transcription factors, *e.g.*, with NF-κB and p53, and thus can regulate the cellular survival responses, including metabolic, stress resistance and cell-cycle responses, and ultimately longevity [34, 43].

Sirtuins: Longevity regulation *via* protein acetylation

The seven mammalian sirtuins are yeast Sir2 (silent information regulator 2) homologs and an evolutionary conserved class III type of NAD-dependent protein deacetylases [44–46]. Sir2 is the gatekeeper to the budding type of aging in *Saccharomyces cerevisiae* [1, 2, 26]. Although mammalian aging does not proceed *via* the accumulation of extrachromosomal rDNA circles, as has been shown to be the case in *S. cerevisiae*, sirtuins have been demonstrated to be important regulators of cellular metabolism, survival and longevity [47–50].

SIRT1, the most extensively studied of the sirtuins, represents a perfect example of the interactions between aging-associated signaling cascades (Fig. 1). SIRT1 is a selective activator of FoxO signaling but simultaneously also an inhibitor of the NF-κB pathway [51–53]. This type of regulation can enhance the FoxO-dependent longevity functions, while inhibiting NF-κB-dependent pro-aging processes of inflamm-aging (see below). It seems that FoxOs/Daf-16 and sirtuins/Sir2 longevity genes have several overlapping activities both in *C. elegans* [54] and in mammalian systems [52, 55]. For instance, the interplay between FoxOs and SIRT1 potentiates the resistance to oxidative stress and enhances the cell-cycle arrest, two properties that promote cellular survival and longevity of organism. It seems that the sirtuins can affect longevity through different mechanisms. For instance, SIRT1 can enhance the nuclear translocation and trapping of FoxO1 [56] and probably promote target gene-specific transcription [53]. SIRT2 in turn increases the DNA binding of FoxO proteins [57]. Furthermore, sirtuins have also FoxO-independent longevity enhancing functions, *e.g.*, SIRT6 promotes the DNA repair [58].

Inflamm-aging: Pro-aging signaling *via* NF-κB system

Signaling *via* FoxOs and sirtuins represents the longevity regulation, which increases the cellular resistance and maintains homeostasis, and in that way can extend lifespan of the organism. Theoret-

ically, a deficiency of aging suppressors should lead to a premature aging phenotype and conversely the potentiation of longevity regulation *via* FoxOs and sirtuins should extend the lifespan but also produce an aging phenotype. However, the more probable scenario is that the signaling *via* FoxOs and sirtuins can protect against pro-aging signaling, *i.e.*, cascades that accelerate aging process. Aging research has devised several theories about pro-aging mechanisms, such as oxidative stress [59] and DNA damage [60, 61]. One common denominator, linked to evolutionarily conserved defense systems, might be the activation of innate immunity during aging. The major regulation pathways of innate immunity all impinge on the NF-κB system. Interestingly, longevity factors, FoxOs and sirtuins, are the inhibitors of NF-κB system (see below).

Activation of innate immunity during aging

Immunosenescence is a well-characterized decline in the function of the adaptive immune system occurring during aging [15–17, 62–65]. Age-related remodeling in adaptive immunity involves many facets, *e.g.*, thymic involution, alterations in T cell subsets, and reduction in antibody production. Although the efficiency of adaptive immunity declines, the incidence of autoimmune responses increases in the elderly [65]. Age-associated immunosenescence in adaptive immunity increases the burden on the activity of the innate immunity system. Antigenic stress, either external or inherent, associated with oxidative stress leads to a low-level but chronic pro-inflammatory phenotype. Franceschi et al. [16] termed this age-related immune status "inflamm-aging". Different research approaches have confirmed the presence of this age-associated pro-inflammatory phenotype [17, 67–70].

We have observed that the DNA-binding activity of nuclear NF-κB complexes is increased in the tissues of old mice and rats [71–73]. However, the nuclear DNA-binding pattern of the NF-κB complexes was similar in young and old animals, indicating that aging does not affect the protein composition of the NF-κB complexes. The DNA-binding activity of several other transcription factors was unaffected or decreased, *e.g.*, those of AP-1 and Sp1 factors [71–73]. In agreement with the EMSA results, the protein levels of p52 and p65 were also clearly increased in the nuclear but not in cytoplasmic fractions in old rodents [73]. Ageing did not affect the protein levels of the main IκB inhibitors, IKK subunits, or NIK protein. The expression levels of p52 and p65 mRNAs, as well as those of IκB α/β mRNAs were unaffected by aging [73]. These observations imply that the retention of NF-κB proteins in the nuclei may increase during aging.

Toll-like receptors (TLRs) are the major host defense receptors recognizing a variety of pathogen-associated molecular patterns, either invading pathogens (PAMPs) or damage-associated molecular structures (DAMPs) [74, 75]. TLR signaling is linked to the NF-κB system *via* a variety of adapter proteins and kinases. Most inflammatory signals, either mediated *via* TLRs or cytokine receptors, occur due to activation of the IKKα/IKKβ kinase complex [19, 74]. The signaling of several other PAMP (or DAMP) receptors, such as NODs and NALPs, is also connected to the NF-κB system [76, 77]. It seems that an ancient host defense signaling system, NF-κB signaling, sits at the crossroads receiving signals from PAMPs and DAMPs and inducing inflammatory responses to maintain the viability of organism.

Signaling *via* NF-κB: All roads lead to NF-κB

Over 20 years ago, Lenardo and Baltimore [78] proposed that the NF-κB system is a pleiotrophic mediator of inducible and tissue-specific gene control – a truly remarkable insight. There are several similarities but also distinct differences in the signaling between FoxOs and NF-κB systems [20, 31–34, 79–82]. Both factors are normally trapped in the cytoplasm, FoxOs to 14–3-3 protein and NF-κB components to IκB proteins. However, NF-κB becomes activated after phosphorylation, while FoxOs are inactivated, *e.g.*, by PI-3K/Akt (Fig. 1). Only a few kinases can phosphorylate IκB proteins and release the cytoplasmic NF-κB factors from their inhibitors. The IKKs are the major kinases, but CKII (induced by UV stress) and JNK (induced, *e.g.*, by oxidative stress) can also activate the NF-κB system [20, 81].

The IKK complexes, consisting of IKKα, IKKβ and their regulator protein NEMO, are the major integrators of signals from different pathways [80–84]. The canonical pathway involves the signals from TLRs and several cytokine receptors that are mediated *via* IKKβ and inactivate IκB proteins. Atypical pathway, the NEMO-mediated signaling, involves the genotoxic signals from the nuclei. This pathway is linked to IKK activation *via* ATM [82]. The non-canonical pathway mediating signals from CD40, lymphotoxin and BAFF/BLys receptors is IKK dependent but IκB independent, and regulates NF-κB activation *via* the p100 (NF-κBp52) processing. There are several kinases upstream from IKKs, such as ATM, TAK1, MEKK3, NIK, NAK, and, interestingly, PI-3K/AKT, an inhibitor of FoxOs, linking several growth factor receptors to the activation of IKKα [83, 84]. IKKα and IKKβ have very different upstream signaling and downstream targets [81]. In general, IKKβ mediates the innate immunity responses, as well as cancer signals *via* a variety of distinct upstream and down-

stream pathways [20]. Interestingly, IKKβ phosphorylates and thus inactivates FoxO3 protein, a tumor suppressor, and in this way can increase cell proliferation [20].

Several protein kinases, *e.g.*, GSK-3β, MSK1, RSK1, PKA, PKCζ and PI-3K/AKT can also phosphorylate NF-κB proteins directly, mostly the RelA (p65) component, and regulate their transcriptional function [76, 79, 80]. Furthermore, the site-specific acetylation of RelA (p65) protein *via* PCAF and p300/CBP enhances the transcriptional efficiency of the NF-κB complexes [79]. Interestingly, SIRT1 can deacetylate RelA protein and inhibit the signaling *via* NF-κB (see below). Protein sumoylation also regulates the efficiency of NF-κB signaling. The response can either enhance or inhibit the transactivation efficiency, depending on the protein component sumoylated [85].

Pro-aging output of NF-κB signaling: Inflammation and tissue atrophy

The NF-κB transcription factor system is very complex both at the upstream signaling level and the transcriptional downstream level. A multitude of signals as well as the co-activators and repressors regulate the transactivation specificity and expression level. The question arises, how can such a pleiotrophic factor regulate pro-aging responses? The major function of NF-κB system is to induce inflammation and innate immunity responses [81, 84, 86]. TLR-induced signals, as well as inherent DAMPs, can expand and interact in signaling networks, *e.g.*, *via* cytokine production, the activation of different cytokine receptors, and their downstream signaling, such as *via* the JAK-STAT pathway [87]. Furthermore, RIP kinases can integrate the signals from different pathways and activate NF-κB and JNK signaling [88]. It is difficult to predict the genome-wide response of this kind of self-supporting enhancing mechanism. Several profiling studies related to NF-κB-dependent gene networks have been reported (*e.g.*, [89]) but the responses have appeared to be highly specific for different inducers and cell types.

In addition to the regulation of innate immunity, NF-κB factors are essential for the development and functions of T and B lymphocytes, dysregulation of these cells causes many diseases [64, 90, 91]. Kumar et al. [90] have listed the genes whose expression is regulated by NF-κB, as well as the major diseases associated with functional changes in NF-κB system. Most of the diseases are chronic and aging-associated degenerative diseases. For example, the role of NF-κB signaling *via* the RANKL-RANK (receptor activator of NF-κB) is recognized in the development of osteoporosis [92]. Furthermore, the activation of NF-κB signaling may be the major signaling pathway causing tissue atrophy associated with cachexia and sarcopenia [93, 94]. Cytokine TNF-α, earlier known as cachectin, promotes NF-κB signaling to activate the expression of MuRF1, E3 ubiquitin ligase, which enhances the proteasome-mediated tissue atrophy in muscle. In addition, FoxO pathway also regulates the expression of atrogin-1, another E3 ubiquitin ligase, and enhances muscle proteolysis and atrophy [95].

NF-κB signaling has a major role in the anti-apoptotic signaling and the development of cellular resistance against apoptosis [96–98]. However, increased resistance to apoptosis may expose dividing cells to cancerous proliferation. Thus, NF-κB signaling represents the link between inflammation and cancer development and progression [99]. Inhibition of apoptosis is mediated by the expression of IAPs (inhibitor proteins of apoptosis), such as c-FLIP, Bcl-xL, c-IAP1, c-IAP2 and XIAP. NF-κB inhibits also apoptosis by inhibiting the function of JNK [100]. The resistance to apoptosis has been believed to be a double-edged sword, since any decline in apoptosis can lead to the accumulation of functionally defective proteins and activate danger-recognizing DAMP receptors. It seems that the activation of innate immunity, increased NF-κB signaling and the apoptotic resistance could induce the age-related accumulation of cellular waste products, the so-called "garbage-can hypothesis" of aging [101, 102].

The NF-κB system is a pleiotrophic signaling mediator (see above) and the output is most probably age dependent. Generally, inflammation and the activation of NF-κB system protect tissues and organisms against pathogen attacks and traumatic tissue damage. This is especially important in young organisms to protect the reproduction but later in the life the pleiotrophic functions of the NF-κB system may carry out the disposable soma program.

Antagonistic interactions between FoxOs and NF-κB pathways

FoxO/DAF-16 is involved in cellular resistance against different stresses, *e.g.*, against oxidative stress, as well as the extension of lifespan in *C. elegans* [28, 29]. The mechanism of how it extends lifespan is still largely unknown, although the resistance against several inherent and environmental stresses including anti-apoptotic and anti-mitotic responses is the major candidates for longevity. The key question is still whether a 1-mm worm represents a valid model of mammalian aging. Several critical opinions have been raised in this debate [6, 7, 103]. In this review, we emphasize that the immunity system of *C. elegans* is faint and less developed than the corresponding

system in mammals [104, 105], the NF-κB system is absent, and most importantly, in mammals FoxO proteins are important immune regulators [106, 107]. It seems that during evolution, FoxOs and NF-κB, two ancient regulators of gene expression, have established interactive signaling connections. Here we demonstrate that two ancient longevity factors, DAF-16/FoxOs and SIRT1, are directly or indirectly the inhibitors of NF-κB function (Fig. 1). This antagonistic regulation supports the inflamm-aging theory of aging in mammals.

FoxOs inhibit NF-κB signaling

Stanford Peng and his colleagues [107, 108] have studied the regulation of mammalian immune system by FoxO proteins. They have observed that FoxO3a deficiency in mice leads to a spontaneous proliferation in lymphoid organs and elevated inflammation in several tissues. Autoinflammation was associated with the presence of hyperactivated helper T cells that secreted a higher amount of Th1 and Th2 cytokines. They convincingly displayed that FoxO3a protein can inhibit NF-κB activation (Fig. 1) and that the autoinflammation encountered in FoxO3a-deficient mice was due to the overactivity of the NF-κB system and the activation of helper T cells [108]. They also observed that the protein levels of inhibitor proteins of NF-κB, IκBβ and IκBε, were significantly reduced in the T cells of FoxO3a-deficient mice. The effect of FoxO3a on the expression of IκB proteins is probably indirect and mediated *via* Foxj1, an anti-inflammatory transcriptional factor that is known to regulate the expression of IκB genes [107, 108]. These results are interesting with respect to aging since Spencer et al. [109] have observed that the constitutive activation level of NF-κB system was clearly increased in the major lymphoid tissues and cells, including spleen, bone marrow, and mesenteric and peripheral lymph nodes in old mice. T and B lymphocytes and macrophages isolated from the spleen of old mice displayed a prominent increase in nuclear DNA-binding activity of NF-κB factors compared to the cells from adult mice [109].

FoxO factors are important regulators of different kinds of stress resistance, including apoptotic stress and oxidative stress, as well as acting as metabolic regulators and cell-cycle inhibitors [34]. The inhibitory response of FoxO factors on the NF-κB system could be induced by some stress resistance factor, other than IκB proteins [110]. For instance, Hsp70 inhibits NF-κB system and attenuates inflammatory responses [111]. Furthermore, FoxO factors and the NF-κB system exhibit antagonistic effects in cell-cycle regulation. FoxO factors are potent cell-cycle inhibitors but the NF-κB system is a well-known tumor promoter [112, 113]. The interaction of FoxOs and NF-κB in tumorigenesis is largely unknown, although two mechanisms have been proposed: either insulin/IGF/PI3K/Akt-induced down-regulation of FoxO function relieves the activation of NF-κB (see above) or IKKβ activation in inflammation blocks the activation of FoxO factors [35, 113], which could potentiate NF-κB function, not only in inflammation but also in tumor progression (Fig. 1). The interaction between FoxO and NF-κB signaling could be a sensitive balance regulating the cellular fate between senescence and the risk of cancerous cell-cycle escape. This topic has been thoroughly reviewed by Campisi [114].

IKKs and JNKs: Opposite regulation of FoxOs and NF-κB

The function of FoxO factors and NF-κB system has been strictly regulated by post-translational regulation [20, 32–34, 79–84]. Both the FoxO proteins and NF-κB components have been regulated by phosphorylation, acetylation, and ubiquitination. The most interesting protein kinases with respect to aging are JNK and IKKs along with PI3K/Akt, which displays antagonistic effects in the regulation of FoxO and NF-κB. PI3K/Akt signaling inhibits FoxOs, but, in contrast, activates NF-κB [115] (Fig. 1). The logic of this type of regulation would be that it represents one way of maintaining the growth and survival of cells. Inhibition of FoxOs promotes growth and the activation of NF-κB prevents apoptosis. The risk of this kind of regulation is the cancerous escape of the cells, especially senescing cells. From the prospect of longevity, this has a synergistic benefit since any inhibition of the PI3K/Akt signaling activates FoxO and supports cellular resistance, while a reduction of NF-κB signaling might reduce the inflammatory and atrophic responses and combat against the process of inflamm-aging.

JNK and IKKs are the two major kinases mediating stress and inflammation signals to FoxOs and NF-κB, and both have connections to aging-associated signaling (Fig. 1). Stress-responsive JNK can extend the lifespan in *C. elegans* and *Drosophila* by activating FoxO factors [116, 117]. Furthermore, it is known that JNK can antagonize Akt-mediated signaling by phosphorylating 14–3-3 protein and promoting the translocation of FoxO3a to the nuclei [118]. Oxidative stress and several environmental insults can activate JNK, which activates FoxOs and hence mediates the protection against oxidative stress (*e.g.*, [119]). JNK also suppresses insulin/IGF signaling [119], which potentiates the FoxO response (Fig. 1). However, it is known that the FoxO regulation involves both cell-type and stimulus-specific responses. For instance, the MST-FoxO activation leads to cell death in mammalian neurons but to lifespan extension in *C. elegans* [120].

Inflammation cascades from TLRs and some cytokine receptors not only activate IKKs but also JNK *via* the TRAF/TRIF connection (Fig. 1). The integrating kinase is TAK1, which can activate both IKKβ and JNK [121]. The TAK1-mediated JNK activation is linked to the AP-1 activation, which provokes and maintains an inflammatory response. Furthermore, the inflammatory signals impinging on IKKβ can inhibit the FoxO3a factor, promoting cell proliferation and tumorigenesis in chronic inflammation [35]. There is also crosstalk between NF-κB and JNK [122]. NF-κB signaling activates the expression of Gadd45β which inhibits MKK7, an upstream kinase of JNK, and hence NF-κB can inhibit apoptosis *via* JNK signaling (Fig. 1). This control is especially important in inflammatory cells to protect these cells from undergoing apoptosis due to the presence of chronic inflammation. Overall, it seems that pro-inflammatory signaling can antagonize longevity regulation *via* JNK and FoxO. Simultaneously, the down-regulation of FoxOs exposes cells to the risk of proliferation and cancer progression.

SIRT1: Opposite regulation of FoxOs and NF-κB

Protein acetylation is an important post-translational regulation mechanism acting on FoxOs and NF-κB proteins [33, 34, 123]. SIRT1, a member of the sirtuin family of longevity factors, regulates the function of FoxOs and NF-κB by protein deacetylation. Interestingly, SIRT1 activates the function of FoxOs, whereas simultaneously SIRT1 is an inhibitor of NF-κB signaling [51–53] (Fig. 1). SIRT1 enhances the nuclear translocation of FoxOs and probably regulates the gene-specific transcription [53, 56], while SIRT2 can increase the DNA-binding efficiency of FoxO proteins [57]. SIRT1 can inhibit the NF-κB-mediated transactivation either by deacetylating the RelA/p65 subunit of NF-κB complex [51] or by interacting with TLE1, a transcriptional co-repressor, in the NF-κB complex [124]. This type of antagonistic regulation of SIRT1 between FoxOs and NF-κB would provide synergistic benefits for longevity. The activation of FoxO signaling can support the cellular viability, *e.g.*, by providing resistance against oxidative stress, whereas the inhibition of NF-κB signaling can reduce inflammatory and atrophic responses and combat against inflamm-aging.

Lifespan extension: *Via* enhancing longevity regulation or inhibiting pro-aging regulation?

Studies on the molecular mechanisms of longevity regulation originate from work done in *S. cerevisiae* and *C. elegans*. The families of Sir2 and FoxOs have expanded during evolution, but also new aspects in respect of aging process have emerged during aging. For instance, evolution has greatly intensified the power of the immune system in the host defense, at the same time as there has been an extension of lifespan. There is no NF-κB system in *C. elegans* and the immune system is not comparable to that of mammals. Also cancer does not appear in *C. elegans*, probably due to the life-long growth process in this organism. In these respects, it is relevant to remember that evolution has tipped to the reproduction and cellular resistance.

It seems that metabolism has been the consistent theme in lifespan regulation during evolution. Caloric restriction extends the lifespan in organisms from budding yeast to mammals [125–127]. However, the mechanism to explain this phenomenon is still unknown, although the longevity genes, especially SIRT1 has been proposed to be involved in *C. elegans*. In mammals, the mechanism may be more complex, since caloric restriction induces also resistance to inflammation [128] and causes hormonal changes, such as release of glucocorticoids [129] which are powerful inhibitors of NF-κB system and inflammation [130]. Energy availability, especially extreme dauer stage formation, may be crucial in the life of worms and flies [30] but in mammals the luxurious dauer state seems to be replaced with immunity defenses. Progeroid syndromes, such as the Werner and Hutchinson-Gilford syndromes, are not energy availability syndromes but originate due to the defects in DNA stability and repair [131]. Furthermore, several animal models of accelerated aging, such as Klotho and SAMP8 mouse models [40, 132, 133], are not energy deficiency syndromes, and most probably not related to Sir2-FoxO longevity regulation. It seems that the accelerated aging syndromes could be inherent danger syndromes and involve signaling *via* DAMP receptors to activate NF-κB system and inflamm-aging process [75, 134].

Acknowledgements. This study was financially supported by grants from the Academy of Finland and the University of Kuopio, Finland. The authors thank Dr. Ewen MacDonald for checking the language of the manuscript.

1 Sinclair, D., Mills, K. and Guarente, L. (1998) Aging in *Saccharomyces cerevisiae*. Annu. Rev. Microbiol. 52, 533–560.
2 Guarente, L. (2000) Sir2 links chromatin silencing, metabolism, and aging. Genes Dev. 14, 1021–1026.
3 Hsu, A-L., Murphy, C. T. and Kenyon, C. (2003) Regulation of aging and age-related disease by DAF-16 and heat-shock factor. Science 300, 1142–1145.
4 Baumeister, R., Schaffitzel, E. and Hertweck, M. (2006) Endocrine signaling in *Caenorhabditis elegans* controls stress response and longevity. J. Endocrinol. 190, 191–202.

5 Gershon, H. and Gershon, D. (2000) The budding yeast, *Saccharomyces cerevisiae*, as a model for aging research: A critical review. Mech. Ageing Dev. 120, 1–22.
6 Gershon, H. and Gershon, D. (2002) *Caenorhabditis elegans*-a paradigm for aging research: Advantages and limitations. Mech. Ageing Dev. 123, 261–274.
7 Johnson, T. E. (2003) Advantages and disadvantages of *Caenorhabditis elegans* for aging research. Exp. Gerontol. 38, 1329–1332.
8 Mukhopadhyay, A. and Tissenbaum, H. A. (2007) Reproduction and longevity: Secrets revealed by *C. elegans*. Trends Cell Biol. 17, 65–71.
9 Munoz, M. J. (2003) Longevity and heat stress regulation in *Caenorhabditis elegans*. Mech. Ageing Dev. 124, 43–48.
10 Rattan, S. I. (2004) Aging, anti-aging, and hormesis. Mech. Ageing Dev. 125, 285–289.
11 Cypser, J. R., Tedesco, P. and Johnson, T. E. (2006) Hormesis and aging in *Caenorhabditis elegans*. Exp. Gerontol. 41, 935–939.
12 Morley, J. F. and Morimoto, R. I. (2004) Regulation of longevity in *Caenorhabditis elegans* by heat shock factor and molecular chaperones. Mol. Biol. Cell 15, 657–664.
13 Danilova, N. (2006) The evolution of immune mechanisms. J. Exp. Zool. (Mol. Dev. Evol.) 306B, 496–520.
14 Friedman, R. and Hughes, A. L. (2002) Molecular evolution of the NF-kappaB signaling system. Immunogenetics 53, 964–974.
15 Franceschi, C., Bonafe, M. and Valensin, S. (2000) Human immunosenescence: The prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine 18, 1717–1720.
16 Franceschi, C., Valesin, S., Bonafe, M., Paolisso, G., Yashin, A. I., Monti, D. and De Benedictis, G. (2000) The network and the remodeling theories of aging: Historical background and new perspectives. Exp. Gerontol. 35, 879–896.
17 Franceschi, C., Capri, M., Monti, D., Giunta, S., Olivieri, F., Sevini, F., Panourgia, M. P., Invidia, L., Celani, L., Scurti, M., Cevenini, E., Castellani, G. C. and Salvioli, S. (2007) Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. Mech. Ageing Dev. 128, 92–105.
18 Karin, M. and Lin, A. (2002) NF-kappaB at the crossroads of life and death. Nat. Immunol. 3, 221–227.
19 Doyle, S. L. and O'Neill, L. A. J. (2006) Toll-like receptors: From the discovery of NF-kappaB to new insights into transcriptional regulations in innate immunity. Biochem. Pharmacol. 72, 1102–1113.
20 Perkins, N. D. (2007) Integrating cell-signalling pathways with NF-kappaB and IKK function. Nat. Rev. Mol. Cell Biol. 8, 49–62.
21 Olsen, A., Vantipalli, M. C. and Lithgow, G. J. (2006) Using *Caenorhabditis elegans* as a model for aging and age-related diseases. Ann. N. Y. Acad. Sci. 1067, 120–128.
22 Tatar, M. and Yin, C.-M. (2001) Slow aging during insect reproductive diapause: Why butterflies, grasshoppers and flies are like worms. Exp. Gerontol. 36, 723–738.
23 Burnell, A. M., Houthoofd, K., O'Hanlon, K. and Vanfleteren, J. R. (2005) Alternate metabolism during the dauer stage of the nematode *Caenorhabditis elegans*. Exp. Gerontol. 40, 850–856.
24 Mooijaart, S. P., Brandt, B. W., Baldal, E. A., Pijpe, J., Kuningas, M., Beekman, M., Zwaan, B. J., Slagboom, P. E., Westendorp, R. G. and van Heemst, D. (2005) *C. elegans* DAF-12, nuclear hormone receptors and human longevity and disease at old age. Ageing Res. Rev. 4, 351–371.
25 Vanfleteren, J. R. and Braeckman, B. P. (1999) Mechanisms of life span determination in *Caenorhabditis elegans*. Neurobiol. Aging 20, 487–502.
26 Guarente, L. and Kenyon, C. (2000) Genetic pathways that regulate ageing in model organisms. Nature 408, 255–262.
27 Barthel, A., Schmoll, D. and Unterman, T. G. (2005) FoxO proteins in insulin action and metabolism. Trends Endocrinol. Metab. 16, 183–189.
28 Jensen, V. L., Gallo, M. and Riddle, D. L. (2006) Targets of DAF-16 involved in *Caenorhabditis elegans* adult longevity and dauer formation. Exp. Gerontol. 41, 922–927.
29 Murphy, C. T. (2006) The search for DAF-16/FOXO transcription targets: Approaches and discoveries. Exp. Gerontol. 41, 910–921.
30 McElwee, J. J., Schuster, E., Blanc, E., Thornton, J. and Gems, D. (2006) Diapause-associated metabolic traits reiterated in long-lived daf-2 mutants in the nematode *Caenorhabditis elegans*. Mech. Ageing Dev. 127, 458–472.
31 Van der Heide, L. P., Hoekman, M. F. M. and Smidt, M. P. (2004) The ins and outs of FoxO shuttling: Mechanisms of FoxO translocation and transcriptional regulation. Biochem. J. 380, 297–309.
32 Huang, H. and Tindall, D. J. (2007) Dynamic FoxO transcription factors. J. Cell Sci. 120, 2479–2487.
33 Vogt, P. K., Jiang, H. and Aoki, M. (2005) Triple layer control. Phosphorylation, acetylation and ubiquitination of FOXO proteins. Cell Cycle 4, 908–913.
34 Van der Horst, A. and Burgering, B. M. T. (2007) Stressing the role of FoxO proteins in lifespan and disease. Nat. Rev. Mol. Cell Biol. 8, 440–450.
35 Hu, M. C.-T., Lee, D.-F., Xia, W., Golfman, L. S., Ou-Yang, F., Yang, J.-Y., Zou, Y., Bao, S., Hanada, N., Saso, H., Kobayashi, R. and Hung, M.-C. (2004) IκB kinase promotes tumorigenesis through inhibition of Forkhead FOXO3a. Cell 117, 225–237.
36 Bartke, A. (2006) Long-lived Klotho mice: New insights into the roles of IGF-1 and insulin in aging. Trends Endocrinol. Metab. 17, 33–35.
37 Kuro-o, M., Matsumura, Y., Aizawa, H., Kawaguchi, H., Suga, T., Utsugi, T., Ohyama, Y., Kurabayashi, M., Kaname, T., Kume, E., Iwasaki, H., Iida, A., Shiraki-Iida, T., Nishikawa, S., Nagai, R. and Nabeshima, Y. I. (1997) Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 390, 45–51.
38 Kurosu, H., Yamamoto, M., Clark, J. D., Pastor, J. V., Nandi, A., Gurnani, P., McGuinness, O. P., Chikuda, H., Yamaguchi, M., Kawaguchi, H., Shimomura, I., Takayama, Y., Herz, J., Kahn, C. R., Rosenblatt, K. P. and Kuro-o, M. (2005) Suppression of aging in mice by the hormone Klotho. Science 309, 1829–1833.
39 Kurosu, H., Ogawa, Y., Miyoshi, M., Yamamoto, M., Nandi, A., Rosenblatt, K. P., Baum, M. G., Schiavi, S., Hu, M.-C., Moe, O. W. and Kuro-o, M. (2006) Regulation of fibroblast growth factor-23 signaling by klotho. J. Biol. Chem. 281, 6120–6123.
40 Lanske, B. and Razzaque, M. S. (2007) Premature aging in klotho mutant mice: Cause or consequence? Ageing Res. Rev. 6, 73–79.
41 Yamamoto, M., Clark, J. D., Pastor, J. V., Gurnani, P., Nandi, A., Kurosu, H., Miyoshi, M., Ogawa, Y., Castrillon, D. H., Rosenblatt, K. P. and Kuro-o, M. (2005) Regulation of oxidative stress by the anti-aging hormone klotho. J. Biol. Chem. 280, 38029–38034.
42 Bartke, A. and Brown-Borg, H. (2004) Life extension in the dwarf mouse. Curr. Top. Dev. Biol. 63, 189–225.
43 Accilli, B. and Arden, K. C. (2004) FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. Cell 117, 421–426.
44 Blander, G. and Guarente, L. (2004) The Sir2 family of protein deacetylases. Annu. Rev. Biochem. 73, 417–435.
45 Sauve, A. A., Wolberger, C., Schramm, V. L. and Boeke, J. D. (2006) The biochemistry of sirtuins. Annu. Rev. Biochem. 75, 435–465.
46 Moazed, D. (2001) Enzymatic activities of Sir2 and chromatin silencing. Curr. Opin. Cell Biol. 13, 232–238.

47 Haigis, M. C. and Guarente, L. P. (2006) Mammalian sirtuins – Emerging roles in physiology, aging, and calorie restriction. Genes Dev. 20, 2913–2921.
48 Guarente, L. (2006) Sirtuins as potential targets for metabolic syndrome. Nature 444, 868–874.
49 Longo, V. D. and Kennedy, B. K. (2006) Sirtuins in aging and age-related disease. Cell 126, 257–268.
50 Yamamoto, H., Schoonjans, K. and Auwerx, J. (2007) Sirtuin functions in health and disease. Mol. Endocrinol. 21, 1745–1755.
51 Yeung, F., Hoberg, J. E., Ramsey, C. S., Keller, M. D., Jones, D. R., Frye, R. A. and Mayo, M. W. (2004) Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 23, 2369–2380.
52 Berdichevsky, A. and Guarente, L. (2006) A stress response pathway involving sirtuins, forkheads and 14–3-3 proteins. Cell Cycle 5, 2588–2591.
53 Giannakou, M. E. and Partridge, L. (2004) The interaction between FOXO and SIRT1: Tipping the balance towards survival. Trends Cell Biol. 13, 408–412.
54 Wang, Y. and Tissenbaum, H. A. (2006) Overlapping and distinct functions for a *Caenorhabditis elegans* SIR2 and DAF-16/FOXO. Mech. Ageing Dev. 127, 48–56.
55 Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., Tran, H., Ross, S. E., Mostoslavsky, R., Cohen, H. Y., Hu, L. S., Cheng, H. L., Jedrychowski, M. P., Gygi, S. P., Sinclair, D. A., Alt, F. W. and Greenberg, M. E. (2004) Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. Science 303, 2011–2015.
56 Frescas, D., Valenti, L. and Accili, D. (2005) Nuclear trapping of the forkhead transcription factor FoxO1 *via* Sirt-dependent deacetylation promotes expression of glucogenetic genes. J. Biol. Chem. 280, 20589–20595.
57 Wang, F., Nguyen, M., Qin, F. X. and Tong, Q. (2007) SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. Aging Cell 6, 505–514.
58 Mostoslavsky, R., Chua, K. F., Lombard, D. B., Pang, W. W., Fischer, M. R., Gellon, L., Liu, P., Mostoslavsky, G., Franco, S., Murphy, M. M., Mills, K. D., Patel, P., Hsu, J. T., Hong, A. L., Ford, E., Cheng, H. L., Kennedy, C., Nunez, N., Bronson, R., Frendewey, D., Auerbach, W., Valenzuela, D., Karow, M., Hottiger, M. O., Hursting, S., Barrett, J. C., Guarente, L., Mulligan, R., Demple, B., Yancopoulos, G. D. and Alt, F. W. (2006) Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell 124, 315–329.
59 Beckman, K. B. and Ames, B. N. (1998) The free radical theory of aging matures. Physiol. Rev. 78, 547–581.
60 Bohr, V. A. and Anson, R. M. (1995) DNA damage, mutation and fine structure DNA repair in aging. Mutat. Res. 338, 25–34.
61 Vijg, J., Busuttil, R. A., Bahar, R. and Dolle, M. E. (2005) Aging and genome maintenance. Ann. NY Acad. Sci. 1055, 35–47.
62 Globerson, A. and Effros, R. B. (2000) Ageing of lymphocytes and lymphocytes in the aged. Immunol. Today 21, 515–521.
63 Pawelec, G., Hirokawa, K. and Fulop, T. (2001) Altered T cell signalling in ageing. Mech. Ageing Dev. 122, 1613–1637.
64 Boren, E. and Gershwin, M. E. (2004) Inflamm-aging: Autoimmunity, and the immune-risk phenotype. Autoimmun. Rev. 3, 401–406.
65 Hasler, P. and Zouali, M. (2005) Immune receptor signaling, aging, and autoimmunity. Cell. Immunol. 233, 102–108.
66 Aw, D., Silva, A. B. and Palmer, D. B. (2007) Immunosenescence: Emerging challenges for an ageing population. Immunology 120, 435–446.
67 Johnson, T. E. (2006) Recent results: Biomarkers of aging. Exp. Gerontol. 41, 1243–1246.
68 Chung, H. Y., Kim, H. J., Kim, K. W., Choi, J. S. and Yu, B. P. (2002) Molecular inflammation hypothesis of aging based on the anti-aging mechanism of calorie restriction. Microsc. Res. Tech. 59, 264–272.
69 Gomez, C. R., Boehmer, E. D. and Kovacs, E. J. (2005) The aging innate immune system. Curr. Opin. Immunol. 17, 457–462.
70 Sarkar, D. and Fisher, P. B. (2006) Molecular mechanisms of aging-associated inflammation. Cancer Lett. 236, 13–23.
71 Helenius, M., Hänninen, M., Lehtinen, S. K. and Salminen, A. (1996) Changes associated with aging and replicative senescence in the regulation of transcription factor nuclear factor-kappa B. Biochem. J. 318, 603–608.
72 Helenius, M., Hänninen, M., Lehtinen, S. K. and Salminen, A. (1996) Aging-induced up-regulation of nuclear binding activities of oxidative stress responsive NF-κB transcription factor in mouse cardiac muscle. J. Mol. Cell. Cardiol. 28, 487–498.
73 Helenius, M., Kyrylenko, S., Vehviläinen, P. and Salminen, A. (2001) Characterization of aging-associated up-regulation of constitutive nuclear factor-kappa B binding activity. Antioxid. Redox Signal. 3, 147–156.
74 Kaisho, T. and Akira, S. (2006) Toll-like receptor function and signaling. J. Allergy Clin. Immunol. 117, 979–987.
75 Bianchi, M. E. (2007) DAMPs, PAMPs and alarmins: All we need to know about danger. J. Leukoc. Biol. 81, 1–5.
76 Strober, W., Murray, P. J., Kitani, A. and Watanabe, T. (2006) Signalling pathways and molecular interactions of NOD1 and NOD2. Nat. Rev. Immunol. 6, 9–20.
77 Mariathasan, S. and Monack, D. M. (2007) Inflammasome adaptors and sensors: Intracellular regulators of infection and inflammation. Nat. Rev. Immunol. 7, 31–40.
78 Lenardo, M. J. and Baltimore, D. (1989) NF-kappa B: A pleiotropic mediator of inducible and tissue-specific gene control. Cell 58, 227–229.
79 Chen, L.-F. and Greene, W. C. (2004) Shaping the nuclear action of NF-κB. Nat. Rev. Mol. Cell Biol. 5, 392–401.
80 Hayden, M. S. and Ghosh, S. (2004) Signaling to NF-kappaB. Genes Dev. 18, 2195–2224.
81 Dejardin, E. (2006) The alternative NF-κB pathway from biochemistry to biology: Pitfalls and promises for future drug development. Biochem. Pharmacol. 72, 1161–1179.
82 Sebban, H., Yamaoka, S. and Courtois, G. (2006) Posttranslational modifications of NEMO and its partners in NF-κB signaling. Trends Cell Biol. 16, 569–577.
83 Web-site for NF-κB signaling: www.cellsignal.com.
84 Scheidereit, C. (2006) IκB kinase complexes: Gateways to NF-κB activation and transcription. Oncogene 25, 6685–6705.
85 Mabb, A. M. and Miyamoto, S. (2007) SUMO and NF-κB ties. Cell. Mol. Life Sci. 64, 1979–1996.
86 Hoffmann, A. and Baltimore, D. (2006). Circuitry of nuclear factor κB signaling. Immunol. Rev. 210, 171–186.
87 Murray, P. J. (2007) The JAK-STAT signaling pathway: Input and output integration. J. Immunol. 178, 2623–2629.
88 Meylan, E. and Tschopp, J. (2005) The RIP kinases: Crucial integrators of cellular stress. Trends Biochem. Sci. 30, 151–159.
89 Tian, B. and Brasier, A. R. (2003) Identification of nuclear factor kappa B-dependent gene networks. Recent Prog. Horm. Res. 58, 95–130.
90 Kumar, A., Takada, Y., Boriek, A. M. and Aggarwal, B. B. (2004) Nuclear factor-κB: Its role in health and disease. J. Mol. Med. 82, 434–448.
91 Ponnappan, U. (1998) Regulation of transcription factor NF-kappaB in immune senescence. Front. Biosci. 3, 152–168.
92 Wada, T., Nakashima, T., Hiroshi, N. and Penninger, J. M. (2006) RANKL-RANK signaling in osteoglastogenesis and bone disease. Trends Mol. Med. 12, 17–25.
93 Cai, D., Frantz, J. D., Tawa, N. E. Jr, Melendez, P. A., Oh, B.-C., Lidov, H. G. W., Hasselgren, P.-O., Frontera, W. R., Lee, J., Glass, D. J. and Shoelson, S. E. (2004) IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. Cell 119, 285–298.
94 Kandarian, S. C. and Jackman, R. W. (2006) Intracellular signaling during skeletal muscle atrophy. Muscle Nerve 33, 155–165.

95 Sandri, M., Sandri, C., Gilbert, A., Skurk, C., Calabria, E., Picard, A., Walsh, K., Sciaffino, S., Lecker, S. H. and Goldberg, A. L. (2004) Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. Cell 117, 399–412.
96 Perkins, N. D. and Gilmore, T. D. (2006) Good cop, bad cop: The different faces of NF-kappaB. Cell Death Differ. 13, 759–772.
97 Dutta, J., Fan, Y., Gupta, N., Fan, G. and Gelinas, C. (2006) Current insights into the regulation of programmed cell death by NF-kappaB. Oncogene 25, 6800–6816.
98 Hunter, A. M., Lacasse, E. C. and Korneluk, R. G. (2007) The inhibitors of apoptosis (IAPs) as cancer targets. Apoptosis 12, 1543–1568.
99 Karin, M. and Greten, F. R. (2005) NF-κB: Linking inflammation and immunity to cancer development and progression. Nat. Rev. Immunol. 5, 749–758.
100 Papa, S., Bubici, C., Zazzeroni, F., Pham, C. G., Kuntzen, C., Knabb, J. R., Dean, K. and Franzoso, G. (2006) The NF-kappaB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. Cell Death Differ. 13, 712–729.
101 Wang, E. (1997) Regulation of apoptosis resistance and ontogeny of age-dependent diseases. Exp. Geront. 32, 471–484.
102 Zhang, Y. and Herman, B. (2002) Ageing and apoptosis. Mech. Ageing Dev. 123, 245–260.
103 Van Voorhies, W. A., Fuchs, J. and Thomas, S. (2005) The longevity of *Caenorhabditis elegans* in soil. Biol. Lett. 1, 247–249.
104 Engelmann, P., Cooper, E. L. and Nemeth, P. (2005) Anticipating innate immunity without a Toll. Mol. Immunol. 42, 931–942.
105 Gravato-Nobre, M. J. and Hodgkin, J. (2005) *Caenorhabditis elegans* as a model for innate immunity to pathogens. Cell. Microbiol. 7, 741–751.
106 Coffer, P. J. and Burgering, B. M. T. (2004) Forkhead-box transcription factors and their role in the immune system. Nat. Rev. Immunol. 4, 889–899.
107 Peng, S. L. (2007) Immune regulation by FoxO transcription factors. Autoimmunity 40, 462–469.
108 Lin, L., Hron, J. D. and Peng, S. L. (2004) Regulation of NF-kappaB, Th activation, and autoinflammation by the forkhead transcription factor Foxo3a. Immunity 21, 203–213.
109 Spencer, N. F., Poynter, M. E. Im, S.-Y. and Daynes, R. A. (1997) Constitutive activation of NF-kappa B in an animal model of aging. Int. Immunol. 9, 1581–1588.
110 Singh, V. and Aballay, A. (2006) Heat-shock transcription factor (HSF)-1 pathway required for *Caenorhabditis elegans* immunity. Proc. Natl. Acad. Sci. USA 103, 13092–13097.
111 Shi, Y., Tu, Z., Tang, D., Zhang, H., Liu, M., Wang, K., Calderwood, S. K. and Xiao, X. (2006) The inhibition of LPS-induced production of inflammatory cytokines by HSP70 involves inactivation of the NF-κB pathway but not the MAPK pathways. Shock 26, 277–284.
112 Perkins, N. D. (2004) NF-κB: Tumor promoter or suppressor? Trends Cell Biol. 14, 64–69.
113 Hu, M. C.-T. and Hung, M. C. (2005) Role of IκB kinase in tumorigenesis. Future Oncol. 1, 67–78.
114 Campisi, J. (2005) Senescent cells, tumor suppression, and organismal aging: Good citizens, bad neighbors. Cell 120, 513–522.
115 Gustin, J. A., Korgaonkar, C. K., Pincheira, R., Li, Q. and Donner, D. B. (2006) Akt regulates basal and induced processing of NF-kappaB2 (p100) to p52. J. Biol. Chem. 281, 16473–16481.
116 Oh, S. W., Mukhopadhyay, A., Svrzikapa, N., Jiang, F., Davis, R. J. and Tissenbaum, H. A. (2005) JNK regulates lifespan in *Caenorhabditis elegans* by modulating nuclear translocation of forkhead transcription factor/DAF-16. Proc. Natl. Acad. Sci. USA 102, 4494–4499.
117 Wang, M. C., Bohmann, D. and Jasper, H. (2005) JNK extends life span and limits growth by antagonizing cellular and organism-wide responses to insulin signaling. Cell 121, 115–125.
118 Sunayama, J., Tsuruta, F., Masuyama, N. and Gotoh, Y. (2005) JNK antagonizes Akt-mediated survival signals by phosphorylating 14–3-3. J. Cell Biol. 170, 295–304.
119 Erol, A. (2007) Insulin resistance is an evolutionarily conserved physiological mechanism at the cellular level for protection against increased oxidative stress. Bioessays 29, 811–818, 2007.
120 Lehtinen, M. K., Yuan, Z., Boag, P. R., Yang, Y., Villen, J., Becker, E. B. E., DiBacco, S., de la Iglesia, N., Gygi, S., Blackwell, T. K. and Bonni, A. (2006) A conserved MST-FOXO signaling pathway mediates oxidative-stress responses and extends life span. Cell 125, 987–1001.
121 Shim, J.-H., Xiao, C., Paschal, A. E., Bailey, S. T., Rao, P., Hayden, M. S., Lee, K.-Y., Bussey, C., Steckel, M., Tanaka, N., Yamada, G., Akira, S., Matsumoto, K. and Ghosh, S. (2007) TAK1, but not TAB1 or TAB2, plays an essential role in multiple signaling pathways *in vivo*. Genes Dev. 19, 2668–2681.
122 Papa, S., Bubici, C., Zazzeroni, F., Pham, C. G., Kuntzen, C., Knabb, J. R., Dean, K. and Franzoso, G. (2006) The NF-kappaB-mediated control of the JNK cascade in the antagonism of programmed cell death in health and disease. Cell Death Differ. 13, 712–729.
123 Chen, L.-F. and Greene, W. C. (2004) Shaping the nuclear action of NF-kappaB. Nat. Rev. Mol. Cell Biol. 5, 392–401.
124 Ghosh, H. S., Spencer, J. V., Ng, B., McBurney, M. W. and Robbins, P. D. (2007) Sirt1 interacts with transducin-like enhancer of split-1 to inhibit NF-kappaB mediated transcription. Biochem. J. 408, 105–111.
125 Weindruch, R. (1996) The retardation of aging by caloric restriction: Studies in rodents and primates. Toxicol. Pathol. 24, 742–745.
126 Bordone, L. and Guarente, L. (2005) Calorie restriction, SIRT1 and metabolism: Understanding longevity. Nat. Rev. Mol. Cell Biol. 6, 298–305.
127 Wolf, G. (2006) Calorie restriction increases life span: A molecular mechanism. Nutr. Rev. 64, 89–92.
128 Holloszy, J. O. and Fontana, L. (2007) Caloric restriction in humans. Exp. Gerontol. 42, 709–712.
129 Patel, N. V. and Finch, C. E. (2002) The glucocorticoid paradox of caloric restriction in slowing brain aging. Neurobiol. Aging 23, 707–717.
130 Smoak, K. A. and Cidlowski, J. A. (2004) Mechanisms of glucocorticoid receptor signaling during inflammation. Mech. Ageing Dev. 125, 697–706.
131 Kyng, K. J. and Bohr, V. A. (2005) Gene expression and DNA repair in progeroid syndromes and human aging. Ageing Res. Rev. 4, 579–602.
132 Takeda, T. (1999) Senescence-accelerated mouse (SAM): A biogerontological resource in aging research. Neurobiol. Aging 20, 105–110.
133 Nabeshima, Y. (2002) Klotho: A fundamental regulator of aging. Ageing Res. Rev. 1, 627–638.
134 Davis, T. and Kipling, D. (2006) Werner syndrome as an example of inflamm-aging: Possible therapeutic opportunities for a progeroid syndrome? Rejuvenation Res. 9, 402–407.