Ageing Research Reviews 9 (2010) 298–314

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Genetics vs. entropy: Longevity factors suppress the NF-κB-driven entropic aging process

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ARTICLE INFO

Article history:
Received 4 September 2009
Received in revised form 29 October 2009
Accepted 3 November 2009

Keywords:
Ageing
Hormesis
Inflammation
Longevity
NF-κB
SIRT1

ABSTRACT

Molecular studies in model organisms have identified potent longevity genes which can delay the aging process and extend the lifespan. Longevity factors promote stress resistance and cellular survival. It seems that the aging process itself is not genetically programmed but a random process involving the loss of molecular fidelity and subsequent accumulation of waste products. This age-related increase in cellular entropy is compatible with the disposable soma theory of aging. A large array of host defence systems has been linked to the NF-κB system which is an ancient signaling pathway specialized to host defence, e.g. functioning in immune system. Emerging evidence demonstrates that the NF-κB system is activated during aging. Oxidative stress and DNA damage increase with aging and elicit a sustained activation of the NF-κB system which has negative consequences, e.g. chronic inflammatory response, increase in apoptotic resistance, decline in autophagic cleansing, and tissue atrophy, i.e. processes that enhance the aging process. We will discuss the role of NF-κB system in the pro-aging signaling and will emphasize that several longevity factors seem to be inhibitors of NF-κB signaling and in that way they can suppress the NF-κB-driven entropic host defence catastrophe.

1. Introduction

Molecular studies on aging mechanisms in model organisms have identified several longevity genes which can delay the aging process and extend the lifespan. The human genome contains the homologs of these genes but their clear association to the regulation of longevity has not been established. On the other hand, a variety of observations support the hypothesis that the aging process itself is not genetically programmed but seems to be a random process involving the loss of molecular fidelity and subsequently the accumulation of waste products which disturb cellular homeostasis. The age-related increasing cellular entropy is compatible with the disposable soma theory of the aging process (Kirkwood and Holliday, 1979).

The aging models of *Saccharomyces cerevisiae* and *Caenorhabditis elegans* have proved to be a cornucopia of novel molecular mechanisms of longevity. The Sir2 family of genes in budding yeast exhaustion model (Sinclair et al., 1998) and the genes of DAF-2/insulin pathway in dauer larva formation (Kenyon et al., 1993) have provided novel insights into the genetic background of longevity. It seems that resistance against cellular stress and environmental insults can ensure a successful aging process and long lifespan. Interestingly, recent studies have demonstrated that lifespan can be extended by genetic, nutritional and pharmacological interventions in lower organisms (see Vijg and Campisi, 2008). However, caloric restriction appears to be the only common way to extend lifespan in all species (Bishop and Guarente, 2007).

It seems that during evolution the host defence and the aging processes have become linked together. A large array of different host defence systems has been connected to the NF-κB system which is an ancient signaling pathway specialized in the host defence, e.g. in the immune system. We will discuss below the role of the NF-κB system in the pro-aging signaling and we will argue that several longevity factors may well prove to be inhibitors of NF-κB signaling. We will propose that the aging process is NF-κB-driven entropic host defence catastrophe.

2. Aging: genetic vs. entropic process

The development of the organism is strictly genetically programmed but no genetic program has emerged to explain the aging process. In model organisms, several stress resistance and survival genes have been revealed which can delay the aging process

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doi:10.1016/j.arr.2009.11.001

and extend the lifespan, especially in harsh environmental conditions (Finch and Ruvkun, 2001; Vijg and Suh, 2005; Braeckman and Vanfleteren, 2007). The homologs of these genes are also present in the human genome which indicates that the genetic component in the human lifespan regulation could be caused by the variability in the survival genes. For instance, the protein interaction network of longevity genes shows a clear conservation of the aging processes between human and invertebrate species (Bell et al., 2009). Genetic studies have estimated that heritability accounts for about 20–25% in human longevity (Herskind et al., 1996).

Human genome-wide genetic analyses have revealed only a few age-related association loci and polymorphic longevity genes (Puca et al., 2001; Capri et al., 2006; Lunetta et al., 2007). In model organisms, e.g. in yeast, *C. elegans*, *Drosophila* and lower animals, several longevity genes have been discovered and thoroughly characterized. The most popular research topics have been Sirtuins, Sir2 homologs discovered in budding yeast model (see Section 4.2.1) and FoxOs, daf-16 homologs in *C. elegans* dauer model (see Section 4.2.2). However, these are clearly survival genes rather than the genes involved in determining the aging process. Functional genomics, i.e. expression profiling studies, have revealed a group of genes which are differentially expressed during aging (e.g. Weindruch et al., 2001; De Magalhaes et al., 2009). However, the results have been difficult to interpret because they represent both the survival process and the entropic aging process.

Epigenetic changes also affect the results on the expression profiling of age-related differences. Recently, Calvanese et al. (2009) and Sinclair and Oberdoerffer (2009) have reviewed the latest insights into the epigenetics of the aging process. The typical age-associated epigenetic alterations include (i) global hypomethylation, (ii) promoter-specific hypermethylation, and (iii) chromatin alterations (Calvanese et al., 2009). The DNA-methylation status has a crucial effect on the transcriptional activity of several genes containing CpG islands. There is still uncertainty about whether epigenetics could regulate the aging process since several factors can regulate DNA-methylation, e.g. environmental insults and diet. Furthermore, there are clear intra-individual alterations in the DNA-methylation status over time (Bjornsson et al., 2008). However, recent studies have demonstrated that DNA damage and the repair process itself can induce epigenetic changes, particularly those observed during aging (Sinclair and Oberdoerffer, 2009).

Human progeroid syndromes have provided an interesting approach for studying the human aging process. The genetic defects in the Werner syndrome and Hutchinson-Gilford syndrome have been characterized and their pathogenesis is basically understood. The mutated Werner gene, *WRN*, codes for a member of RecQ family of DNA helicases (Yu et al., 1996) whereas mutations in lamin genes cause laminopathies, e.g. Hutchinson-Gilford syndrome (Capell and Collins, 2006). RecQ helicases have an important role in the maintenance of genomic integrity and Werner syndrome patients exhibit defects in DNA stability and DNA repair (Bohr, 2005). In laminopathies, deficiencies in nuclear lamina affect the maintenance of DNA integrity, inducing defects in DNA replication and repair processes which subsequently cause DNA damage (Capell and Collins, 2006). It has been generally believed that DNA damage accumulating during aging, i.e. genotoxic stress, has an important role in the normal aging process (see Section 4.1.2).

During aging, the amount of DNA damage increases not only in nuclear DNA but also in mitochondrial DNA (mtDNA) (e.g. Khrapko and Vijg, 2008; Kukat and Trifunovic, 2009). Production of reactive oxygen species (ROS) and inefficient DNA repair expose the mitochondria to the accumulation of mutations in mtDNA. The heteroplasmy of mtDNA can propagate mutations and disturb oxidative metabolism during aging. There is still the question of whether these changes represent the cause or consequence of aging. Recently, Trifunovic et al. (2004) created a mtDNA-mutator mouse which expresses defective mtDNA polymerase and can evoke a prominent increase in the numbers of point mutations and deletions in mtDNA. Strikingly, these mice have a premature aging phenotype (Trifunovic et al., 2004; Trifunovic and Larsson, 2008; Kukat and Trifunovic, 2009). These observations clearly indicate that mitochondrial dysfunction can enhance the aging process.

In summary, it seems that the aging process is not genetically programmed but on the contrary, damage to nuclear and mitochondrial DNA can decrease the molecular fidelity and subsequently increase the accumulation of defective cellular components which impact unfavourably on physiological function. The decline in DNA integrity is one of the random processes which disturb cellular fidelity and cause senescence both at the cellular and organismal levels. This process represents the age-related increase in entropy (Hayflick, 2007). On the other hand, the genome contains a variety of stress resistance and survival genes which organize the cellular and organismal defence in order to combat long-term environmental stress and maintain cellular homeostasis. This survival effect consists of e.g. autophagic uptake mechanisms, chaperone systems and DNA repair mechanisms. Apoptotic cleansing of damaged cells and immune system are some examples of the host defence at the organismal level. Hayflick (2007) has recently reviewed some elements of entropic aging process and genetic determinants of longevity.

Host defence is not a random process but utilizes a multilayer signaling network between danger recognition and the transcriptionally mediated adaptive response. There is an extensive literature demonstrating that the NF-κB signaling system is at the focal point linking the danger recognition to the acute transcriptional responses (see Sections 3 and 4.1). It is not surprising that the NF-κB system is activated during aging and age-related diseases (see Section 3) since most of the pro-aging signals and conditions are well-known inducers of NF-κB system, e.g. oxidative stress (see Section 4.1.1), DNA damage (Section 4.1.2), and immune defence (Section 4.1.3). However, in order to achieve homeostasis, a brake needs to be placed on the excessive activation of NF-κB signaling. Strikingly, many of the longevity factors are inhibitors of NF-κB signaling, either directly or indirectly. Some of the longevity factors which are NF-κB inhibitors will be discussed in Section 4.2. During aging, the amount of destructive insults increases and a sustained activation of NF-κB system can also have harmful responses, e.g. chronic inflammatory responses, increased apoptotic resistance, decline in autophagic cleansing, and tissue atrophy. All these responses enhance the entropic aging process (see Section 6, Fig. 1).

3. NF-κB signaling linked to aging process

The developmental determination genes, e.g. MyoD, were first discovered over twenty years ago (Davis et al., 1987). Determination genes are transcription factors, i.e. sequence specific DNA-binding proteins which can regulate the transcription of a number of inducible genes required to establish a distinct cellular phenotype. NF-κB (nuclear factor-κB) is also transcription factor but it is a pleiotropic mediator of gene expression which can interact with the sequences observed first in the immunoglobulin enhancer (Sen and Baltimore, 1986). The structural and functional characteristics of the NF-κB system have been extensively studied during the last twenty years (e.g. Siebenlist et al., 1994; Hayden and Ghosh, 2004; Perkins, 2007; Vallabhapurapu and Karin, 2009). The mammalian Rel/NF-κB family includes three Rel proteins, RelA/p65, c-Rel and RelB, as well as two NF-κB components, p50 (and its precursor p105) and p52 (and the precursor p100). These components form dimeric complexes with each other which are trapped into the cytoplasm

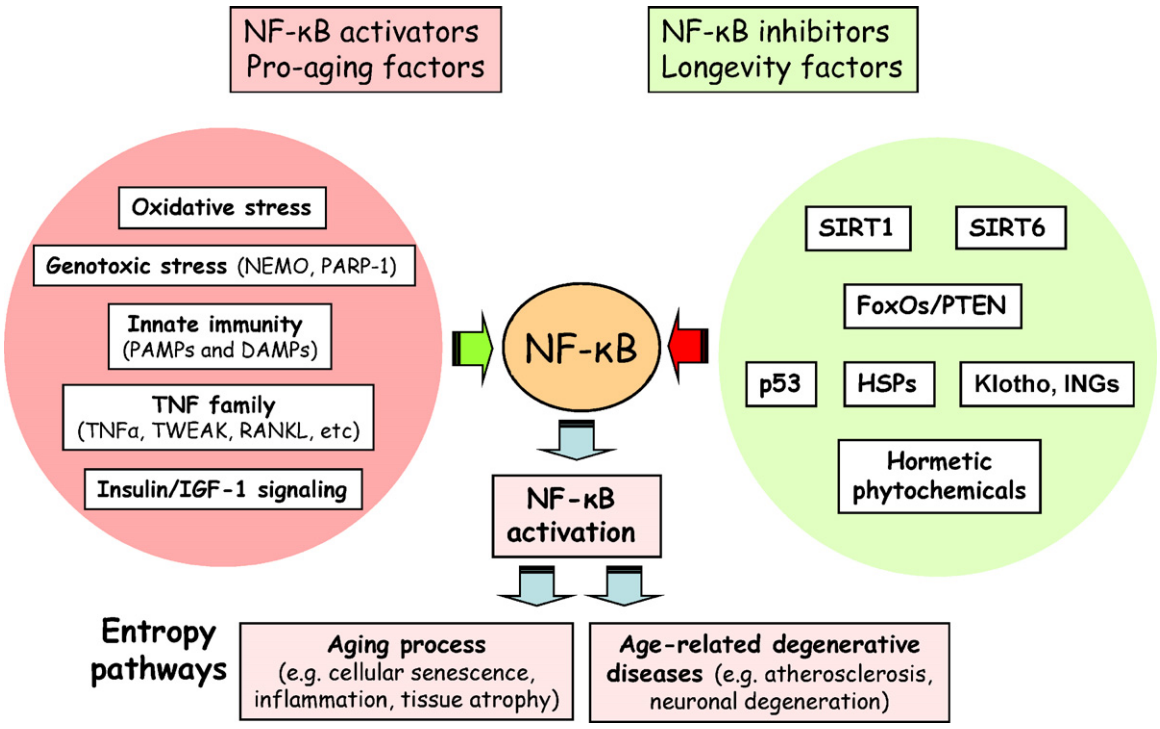

Fig. 1. NF-κB system is at the hub of aging network. Pro-aging factors are NF-κB activators whereas longevity factors are NF-κB inhibitors. A sustained NF-κB activation can elicit a host defence catastrophe which enhances the aging process and augments age-related degenerative diseases.

when they become bound to several inhibitory IκB proteins (IκBα, IκBβ, IκBε, IκBζ, and Bcl-3). Several upstream protein kinases can phosphorylate IκB proteins and in that way release NF-κB complexes from the IκB proteins. Subsequently, the complexes can be translocated to the nucleus where they can transactivate the expression of target genes, especially the inflammatory genes. IKKs (IκB kinases α and β) and NIK (NF-κB-inducing kinase) are the major protein kinases activating the NF-κB complexes. NEMO (an essential NF-κB modulator) protein is the regulatory subunit of the IκB kinase (IKK) complex and it can regulate the activation of the IKK kinase complex (Sebban et al., 2006). The Gilmore Laboratory (http://people.bu.edu/gilmore/NF-κB/lab/index.html) has collected a large information package on the Rel/NF-κB system, such as inducers, inhibitors, target genes and diseases associated with NF-κB system.

The mammalian NF-κB system represents an ancient host defence system which branched out into different signaling forms during evolution (Friedman and Hughes, 2002). In particular, NF-κB system is a cytoplasmic sensor which can be activated both by immune attacks (see Section 4.1.3) and by a plethora of external and internal danger signals, such as oxidative stress (see Section 4.1.1), genotoxic stress (see Section 4.1.2) and tissue injuries (see Section 4.1.3) (Schreck et al., 1992; Perkins, 2007; Vallabhapurapu and Karin, 2009). As a consequence of its duties in defence, the NF-κB system is crucially activated in several age-related diseases (Kumar et al., 2004). The NF-κB system can also regulate morphogenesis, e.g. the dorsal–ventral patterning of *Drosophila* embryo (Belvin and Anderson, 1996), as well as the differentiation of many cell types, particularly those of the immune system (Vallabhapurapu and Karin, 2009).

Progress in the search of developmental determination genes inspired aging researchers to unravel the determination genes related to aging process. Before the era of expression profiling, EMSA (electrophoretic mobility shift assay) afforded an opportunity to screen changes in the DNA-binding capacities of age-related transcription factors. The EMSA technique can reveal changes in many functional properties, such as protein modifications affecting complex formation and DNA binding affinities. Several years ago, we screened transcription factors to examine whether the aging process could affect their DNA-binding affinities in rodent tissues. Our screening revealed that the DNA-binding activity of NF-κB complex was the only transcription factor which demonstrated a consistent age-related upregulation in all rat and mouse tissues (Helenius et al., 1996a,b; Korhonen et al., 1997). These studies also disclosed that most of the factors were unaffected but some were also down-regulated, e.g. AP-1 and Sp1 in liver and cardiac muscle (Helenius et al., 1996a,b). Protein characterization revealed that the levels of p52 and p65 were clearly increased in the nuclear extracts of old rodents. Further studies revealed that the protein levels of IκB inhibitors as well as those of activating kinases IKKα, IKKβ and NIK were unaffected by aging (Helenius et al., 1996a,b, 2001). Strikingly, the expression levels of p52 and p65 were not increased at the mRNA levels during aging (Helenius et al., 2001). This clearly indicated that the retention of NF-κB proteins into the nuclei had been increased by aging. Subsequently, several microarray profiling studies support this conclusion since they have not detected any age-related changes in the expression levels of NF-κB or IκB component mRNAs.

Several research groups have verified the age-related constitutive activation of the NF-κB system (e.g. Spencer et al., 1997; Poynter and Daynes, 1998; Kim et al., 2000). Spencer et al. (1997) and Poynter and Daynes (1998) also studied whether dietary treatments with antioxidants and PPAR-α agonist could affect the age-related changes in DNA-binding capacity. Strikingly, they demonstrated that these therapies clearly reduced the increase in the DNA-binding activity of the NF-κB complex. They also verified that the reduction in the DNA-binding activity had functional effects since these treatments also decreased the expression levels of IL-6 and IL-12 cytokines (Poynter and Daynes, 1998). These studies clearly highlight the role of oxidative stress in the sustained activation of the NF-κB system during aging (see Section 4.1.1).

Recently, several studies have confirmed that the age-related changes in the DNA-binding activity of NF-κB complexes reflect

the activation of NF-κB signaling during aging rather than its repression. Adler et al. (2007) employed the motif module mapping technique to determine the most frequent transcription factor binding sites at the cis-regulatory motifs of differentially expressed genes which revealed aging changes in expression profiles. These workers demonstrated that the NF-κB binding domain was the site most strongly associated with age-related changes in many human and mouse tissues. Furthermore, Hutchinson-Guilford syndrome, a progeroid disease, revealed similar results (Adler et al., 2007). De Magalhaes et al. (2009) performed a meta-analysis of the expression profiles of published microarray data. Inflammatory and immune response genes were clearly overexpressed during aging confirming a role for age-related NF-κB activation.

In conclusion, all these observations support the scenario where the aging process increases the activation level of NF-κB system by inducing the retention of NF-κB complexes to nuclei where they can potentiate the transcription of a set of NF-κB-dependent genes, so-called age-related profile including inflammatory genes. Given that the NF-κB system is highly versatile, the age-related response can be specific in several steps, i.e. in the complex formation, retention to nuclei, interaction with coactivators and repressors, and finally as a role in association with chromatin level regulators.

4. NF-κB system is at the hub of aging network

The NF-κB system is an ancient defence system which is utilized to recognize danger signals and subsequently orchestrate the transcriptional defence responses. The aging process can consist of a variety of insults to homeostasis, e.g. oxidative stress, genotoxic stress, and an abundance of accumulating proteotoxic waste products. It is reasonable that the NF-κB system is intended to respond to these insults to protect the host. However, the maintenance of the homeostasis requires that the responses are not overwhelming and for that reason an efficient repressor system is required. Interestingly, it seems that longevity factors can inhibit the activation of NF-κB system (see below). We will speculate on the age-related signaling network where the pro-aging signals are the activators of NF-κB system and longevity factors are the endogenous inhibitors of NF-κB system.

4.1. Pro-aging signals are NF-κB activators

4.1.1. Oxidative stress

The free radical theory is the classical aging theory put forward by Denham Harman in 1956 (Harman, 1956). Oxygen has been a crucial molecule during the evolution of life based on aerobic respiration. However, the metabolic use of oxygen can generate a variety of reactive oxygen species (ROS), such as superoxide anions, hydrogen peroxide and hydroxyl radicals. Oxidative phosphorylation in mitochondria is the major endogenous producer of ROS but several enzymes, such as 5-lipoxygenase and NADPH oxidase, can also produce oxidant species in cells. ROS can react with DNA, proteins and lipids and produce toxic compounds. Moreover, recent studies have revealed that ROS can be messenger molecules in several signaling pathways (Gloire et al., 2006; Nakano et al., 2006). During evolution, a complex detoxification system of ROS, called the antioxidative system, has developed to counteract the oxidative stress in cells. The chemistry of ROS generation, their targets in cells, and the association to the aging process has been a popular topic for detailed reviews (e.g. Martin et al., 1996; Berlett and Stadtman, 1997; Beckman and Ames, 1998; Sohal et al., 2002).

Multiple experimental approaches have demonstrated that oxidative stress is linked to the aging process but the exact molecular mechanisms still need to be evaluated. Oxidative stress certainly increases the pressure on the housekeeping mechanisms, e.g. autophagy which declines with aging (Salminen and Kaarniranta, 2009), but recent studies have emphasized the role of ROS, along with reactive nitrogen species, as second messengers (Martindale and Holbrook, 2002), and in that way the increased presence of ROS during aging could disturb cellular signaling and potentiate the aging process. In the early 1990s, several workers demonstrated that the insults inducing oxidative stress simultaneously also activated the NF-κB signaling pathway (Schreck et al., 1992; Pahl, 1999) (Fig. 1). It was believed that oxidative stress via ROS could be the only signal capable of evoking the activation of the NF-κB system. However, subsequent studies have revealed that there are several other mechanisms which can trigger NF-κB signaling. The ROS-induced activation of NF-κB signaling seems to be highly specific for different cell types and also displays differences between distinct stimuli (Gloire et al., 2006). Furthermore, the level of oxidative stress can modulate the signaling pathways involved and the outcome of the stress (Gloire et al., 2006). In her review, Pahl (1999) gathered an extensive list of activators and target genes of NF-κB signaling.

The NF-κB system is a redox-dependent network which can be regulated by a complex set of different antioxidants (Kabe et al., 2005; Pantano et al., 2006). Inflammatory stress and ischemic-reperfusion insults are the major source of excessive oxidant stress. Cytokines, such as IL-1β and TNF-α, and the ligands to TLRs (Toll-like receptors) can activate the NF-κB system through the steps regulated by ROS (see Sections 4.1.3 and 4.1.4). ROS production via NADPH oxidase and 5-lipoxygenase can potentiate the cell-type specific NF-κB signaling induced by IL-1 receptors and TLRs (see Gloire et al., 2006). It seems that ROS enhance the NF-κB signaling via the classical pathway involving the activation of IKKs. Wuerzberger-Davis et al. (2007) demonstrated that oxidative stress, as well as genotoxic stress (see Section 4.1.2) and heat shock, can trigger the sumoylation-dependent NEMO cascade which activates the IKK complex. Several redox-dependent upstream kinases have been observed to be involved in ROS-dependent NF-κB signaling, such as ASK1, CK2, RIP1, RSK1 and Src (Kabe et al., 2005; Pantano et al., 2006; Gloire et al., 2006; Temkin and Karin, 2007). Several observations highlight the role of mitochondria in ROS generation in the regulation of NF-κB signaling (Temkin and Karin, 2007).

Oxidative stress can also activate JNK (c-Jun N-terminal kinase), a well-known kinase mediating apoptotic signals (Papa et al., 2004; Nakano et al., 2006). Interestingly, NF-κB signaling can inhibit the JNK-induced apoptosis by activating the expression of Gadd45β (growth arrest- and DNA damage-inducible gene) which inhibits the MKK7, an upstream kinase of JNK (Papa et al., 2004; Wullaert et al., 2006). NF-κB signaling also combats against apoptosis by inducing the expression of several antiapoptotic genes, e.g. c-FLIP, Bcl-xL, XIAP (Nakano et al., 2006). In conclusion, it seems that age-related oxidative stress activates the NF-κB system to defend cells against apoptotic cell death but on the other hand exposes cells to increasing problems in housekeeping, i.e. defective cells can survive which exposes them to an entropic host defence catastrophe (see Section 6).

4.1.2. Genotoxic stress

Genomic instability seems to be a major stochastic mechanism of aging (Lombard et al., 2005; Vijg et al., 2005; Schumacher et al., 2008). This hypothesis is supported by much experimental evidence of which the human progeroid syndromes and transgenic animal models are the most convincing. DNA lesions appear during aging in both the nuclear DNA and mitochondrial DNA. Several studies have indicated that free radicals and oxidative stress are probably the most important source of age-related DNA mutations. DNA damage activates ATM (Ataxia Telangiectasia Mutated) and

ATR (ATM and Rad 3-related) kinases which trigger a complex host defence system, an attempt to repair the DNA damage and maintain cellular homeostasis (e.g. Harrison and Haber, 2006). The major signaling pathways induced by genotoxic stress are p53, NF-κB and PARP-1 (Sancar et al., 2004; Janssens and Tschopp, 2006; Schreiber et al., 2006).

Recently, it was demonstrated that the activation of NF-κB signaling is one of the cellular hallmarks evoked by DNA damage (Habraken and Piette, 2006; Janssens and Tschopp, 2006; Wu and Miyamoto, 2007). NEMO protein has a central role in the molecular cascade, inducing the activation of NF-κB signaling after DNA damage (Fig. 1). We have recently reviewed in detail this cascade called the NEMO shuttle (Salminen et al., 2008e). Briefly, genotoxic stress induces the formation of the complex between NEMO, PIDD (p53-induced protein with a death domain) and RIP1 (receptor interacting protein) kinase. This complex accumulates in nuclei after genotoxic insults. In nuclei, PIASy, a nuclear matrix-associated SUMO E3 ligase, can sumoylate the NEMO protein (Mabb et al., 2006). Oxidative stress and heat shock can also evoke the sumoylation of NEMO (Wuerzberger-Davis et al., 2007). Sumoylation is the prerequisite to allow ATM kinase to phosphorylate the NEMO protein (Mabb et al., 2006). Subsequently, the phosphorylated NEMO is desumoylated and mono-ubiquitinated on K277 and K309 residues. After that, the NEMO/ATM complex is exported from nuclei (Wu and Miyamoto, 2007). In cytoplasm, NEMO/ATM proteins bind with IKKs and ELKS, a scaffold protein of IKK kinases, and activate the IKK kinases which trigger NF-κB signaling (Scheidereit, 2006). It seems that the aim of NF-κB activation in genotoxic stress is to prevent the p53-induced apoptosis. This assumption is supported by the observation that IKKβ can phosphorylate p53 protein and subsequently induce its degradation by proteasomes (Xia et al., 2009).

The activation of PARP-1 [poly(ADP-ribose) polymerase-1] is another hallmark of DNA damage (Muiras, 2003; Burkle et al., 2005; Nguewa et al., 2005). PARP-1 is a ubiquitously expressed member of the PARP family of enzymes which can modify proteins by poly(ADP-ribosyl)ation. PARP-1 is a sensor of DNA damage and it maintains the genomic integrity by regulating DNA repair. PARP-1 is activated by NAD^+ and in that way PARP-1 can be triggered by an increased concentration of NAD^+ not only in several physiological conditions but also during pathological events, such as stroke and myocardial infarction (Nguewa et al., 2005; Beneke, 2008). Increased PARP-1 activity aggravates both inflammatory responses and infarctions and the inhibitors of PARP-1 can alleviate subsequent cell death (Beneke, 2008).

Recent studies have demonstrated that PARP-1 is a novel coactivator of NF-κB signaling (Hassa and Hottiger, 2002; Schreiber et al., 2006) and could potentiate the activation of NF-κB signaling in genotoxic stress (Fig. 1). PARP-1 can interact with p300/CBP protein which triggers the acetylation of PARP-1 (Hassa et al., 2005). Acetylated PARP-1 can bind to the p50 subunit of NF-κB complex and the association of p300/PARP-1 complex to NF-κB complex clearly potentiates the transactivation of the NF-κB-dependent target genes (Hassa et al., 2005). Interestingly, Rajamohan et al. (2009) demonstrated that SIRT1 longevity factor could deacetylate PARP-1 and the sumoylation of PARP-1 could even totally abrogate p300-mediated acetylation. These observations indicate that the acetylation-dependent role of PARP-1 as transcriptional coactivator does not require ADP-ribosylation (Messner et al., 2009).

Several studies have demonstrated that an increase in the potency of the PARP-1 enzyme can extend the lifespan (Muiras, 2003; Burkle et al., 2005). It seems that efficient DNA repair is required to maintain DNA integrity during aging. However, excessive or sustained insults to DNA integrity, e.g. in progeroid syndromes and UV-B radiation, can trigger the NF-κB system either through the NEMO shuttle or the PARP-1-mediated coactivation.

4.1.3. Innate immunity: PAMPs and DAMPs

A large body of research has demonstrated that the aging process is associated with the pro-inflammatory changes (e.g. Franceschi et al., 2000, 2007; Sarkar and Fisher, 2006; Salminen et al., 2008a; De Magalhaes et al., 2009). During aging, adaptive immunity clearly declines which is called immunosenescence (Larbi et al., 2007). On the contrary, the innate immunity seems to be activated inducing a chronic inflammatory phenotype (Sarkar and Fisher, 2006; Franceschi et al., 2007; Salminen et al., 2008a; De Magalhaes et al., 2009). There are clear tissue-specific differences in the level of inflammatory changes. Franceschi et al. (2000) have called this inflammatory profile "inflamm-aging". This immune status can probably provoke and aggravate age-related degenerative diseases, e.g. atherosclerosis and neurodegenerative diseases.

Innate immunity is an ancient host defence system in multicellular organisms (Danilova, 2006). The innate immunity system recognizes a plethora of invading pathogen structures, called PAMPs (pathogen-associated molecular patterns), but also DAMPs which are danger-associated endogenous molecular patterns (Medzhitov and Janeway, 2000; Bianchi, 2007). PAMPs and DAMPs are recognized by a variety of PRRs (pattern recognition receptors) which are linked mainly to the NF-κB signaling pathway. Interestingly, organisms can utilize the same PRRs to defend themselves against pathogenic and endogenous insults, i.e. PRRs are multiligand receptors. Thus PRRs can recognize different DAMPs accumulating during aging, e.g. debris of apoptotic and necrotic cells, fragments of extracellular matrix, and abnormal molecular modifications. This is an important characteristic since the accumulation of waste products during aging can be recognized by PRRs which trigger NF-κB-driven responses (Section 6).

TLRs (toll-like receptors) represent an evolutionarily conserved PRR system (Medzhitov and Janeway, 2000; Kaisho and Akira, 2006; Trinchieri and Sher, 2007). The major pathway of TLR signaling is linked via IKKβ to the NF-κB system (Kaisho and Akira, 2006). Many studies have demonstrated that the hyaluronan fragments from the extracellular matrix can act for danger signals that stimulate TLR2 and TLR4 receptors in several cell types (Taylor et al., 2004; Scheibner et al., 2006; Noble and Jiang, 2006). Some other extracellular matrix degradation products, e.g. biglycan, fibronectin fragments and tenascin C, can also activate TLR2 and TLR4 (Schaefer et al., 2005; Miyake, 2007; Midwood et al., 2009). TLRs can also recognize different alarmins which are endogenous, secreted molecules that provide signals about tissue and cell damage (Bianchi, 2007). HMGB1 (high mobility group box 1), S100, HSP60, HSP70 and defensins, are typical alarmin-type of DAMPs released from injured cells (Bianchi, 2007; Miyake, 2007). In particular, the role of HMGB1 is interesting since Welle et al. (2003) observed that aging increased the expression of HMGB1 in muscles. The expression of HMGB1 was also noted to be augmented in astrocytes during aging (Enokido et al., 2008). HMGB1 can activate TLR2, TLR4 and RAGE (receptor for advanced glycation endproducts) receptors and stimulate downstream signaling, mostly via NF-κB pathway (Lotze and Tracey, 2005). HMGB1 can also directly interact with the NF-κB complex and increase the transactivation efficiency of NF-κB complex (Agresti et al., 2003). HMGB1 seems to be a versatile amplifier of NF-κB signaling during cellular stress and it can promote the activation of innate immunity defence (Hreggvidsdottir et al., 2009). In general, TLRs have a crucial role in the recognition of cellular danger and may well play a crucial role in the pathogenesis of several diseases (Chen et al., 2007b).

Maillard reaction is a well-known non-enzymatic glycosylation mechanism of long-lived macromolecules (Lee and Cerami, 1992;

Brownlee, 1995). Proteins, lipids and DNA can be the target of Maillard reactions. Protein glycation products have been called AGEs (advanced glycation end products) and because oxygen radicals are involved in the reaction, it is also called glycoxidation. Oxidative stress and hyperglycemia can clearly enhance the formation of AGEs. Molecular AGEing is strongly increased during ageing (Brownlee, 1995; Baynes, 2001). AGEing is a harmful molecular modification which, for instance, can activate innate immunity defence. RAGE receptors are multiligand PRRs which can recognize a variety of targets, e.g. modified proteins particularly those of AGEs, aggregated proteins containing β-sheet fibrils, and alarmins HMGB1 and S100/calgranulin (Bierhaus et al., 2005). RAGE receptors are linked to the NF-κB signaling pathway although some other pathways can also support the induction of inflammatory responses via RAGE (Schmidt et al., 2001). Interestingly, there is a positive feedback in RAGE/NF-κB signaling since NF-κB can transactivate the expression of the RAGE gene, i.e. RAGE ligands can potentiate the expression of RAGE receptors. This system provides an effective but also, if necessary, sustained response to the accumulation of toxic AGEs.

Several studies have demonstrated that the contents of different types of AGEs increase in tissues during aging (Brownlee, 1995; Baynes, 2001; Aronson, 2003; Ramasamy et al., 2005). The AGEing process is also increased in diabetes, atherosclerosis, neurodegeneration and several inflammatory diseases. In particular, the glycation of collagen and elastin could have detrimental effects during aging, e.g. in vascular pathology (Ramasamy et al., 2005; Robert et al., 2008). Considering that RAGE activates NF-κB signaling, it seems that the AGEing reaction can have a crucial role in the maintenance of anti-apoptotic and pro-inflammatory phenotype during aging.

4.1.4. TNF superfamily

Activation of innate immunity during aging (see above) generates a group of inflammatory products of which cytokines are mostly observed to be at the elevated level during aging (e.g. Bruunsgaard et al., 2001; Krabbe et al., 2004; Johnson, 2006; De Magalhaes et al., 2009). Several cytokines can activate the NF-κB signaling pathway and in this way propagate and aggravate the inflammatory changes. IL-6 (interleukin-6) and TNF-α (tumor necrosis factor-α) are clearly upregulated with aging but their exact role in the aging process has been difficult to establish since they have complex, cell-type specific functions (Huang et al., 2005; Maggio et al., 2006). For instance, TNF-α can regulate adaptive immunity and be involved in the generation of immunosenescence (Gupta and Gollapudi, 2005; Huang et al., 2005; Larbi et al., 2008).

The TNF superfamily is a large cluster of immune regulators containing some subfamilies, e.g. death domain proteins (Bodmer et al., 2002). TNF receptors act through transducer proteins to activate a complex network of signaling pathways of which NF-κB, JNK, and caspase pathways are the most important. The signaling properties have been extensively reviewed (Aggarwal, 2003; Dempsey et al., 2003). The members of TNF family have a vital role in the regulation of immune system but in addition, they can integrate the effects of the peripheral tissues, e.g. in cell death (Locksley et al., 2001). The role of TNF superfamily in the regulation of the aging process is largely unknown but there are great expectations that understanding may lead to therapeutic advances. Members of TNF family regulate several properties which also appear in the aging process. One such process is tissue atrophy, in particular those involved in age-related muscle atrophy, i.e. sarcopenia (Argiles et al., 2005), and the cachexia often encountered in cancer and inflammatory diseases (Delano and Moldawer, 2006).

It was discovered over 20 years ago that TNF-α has a fundamental role in the process of tissue atrophy, in particular in muscle tissues (Beutler and Cerami, 1988). The major pathway of TNF-α signaling is mediated via the activation of NF-κB system, both in cachexia and sarcopenia (Cai et al., 2004; Kandarian and Jackman, 2006). In addition, other signaling pathways are also involved in muscle atrophy and furthermore, it seems that there are differences between cachexia and sarcopenia, e.g. in endocrine regulation (Thomas, 2007). In muscle atrophy, the NF-κB signaling induces the expression of the muscle-specific E3 ubiquitin ligase, MuRF1 (muscle RING finger 1) which is linked to proteasomal protein degradation (Cai et al., 2004; Cao et al., 2005). The FoxO factor, regulated by insulin signaling (see Section 4.2.2), activates the expression of atrogin-1, which is another E3 ligase capable of enhancing muscle protein degradation via proteasomes (Sandri et al., 2004). Recent studies have demonstrated that the NF-κB system can be an important target for the prevention of skeletal muscle loss during cachexia and sarcopenia (Li et al., 2008; Mourkioti and Rosenthal, 2008).

Several other members of the TNF family have been linked to the NF-κB-dependent catabolic processes. TWEAK (TNF-related weak inducer of apoptosis) is a multifunctional cytokine which can regulate e.g. inflammatory responses, apoptosis, and osteoclastogenesis (Winkles, 2008). Dogra et al. (2007) observed that TWEAK can enhance NF-κB-dependent muscle atrophy and its chronic administration clearly reduced the body weight. The RANK (receptor activator of NF-κB) member of TNF family has a key role in the osteoporosis (Clowes et al., 2005). T cells secrete RANKL (RANK ligand) which can activate osteoclasts and in that way induce bone resorption. In addition to TNF-α (Gupta and Gollapudi, 2005; Huang et al., 2005), FasL (Fas ligand) and TRAIL (TNF-related apoptosis-inducing ligand) have functions which could enhance the age-related senescence of immune system (Hsu et al., 2005; Falschlehner et al., 2007). It seems that several of the TNF-related cytokines, e.g. BAFF (B cell activating factor), TWEAK, RANKL and TRAIL, activate NF-κB signaling via the alternative, NIK-dependent pathway (Dejardin, 2006). The function of the TNF superfamily has been extensively studied in cancer and immune biology but in the future, it will be important to reveal the role of TNF-related inflammatory mediators in the catabolic aging process.

4.1.5. Insulin/IGF signaling

The diapause state of *C. elegans*, so-called dauer larva, is the most widely studied lifespan extension model. The genetic background of this arrested stage of development has been revealed and extensively reviewed (Burnell et al., 2005; Braeckman and Vanfleteren, 2007). The DAF-2 (dauer formation-2) pathway has been confirmed to be the main regulator of the dauer phenotype. The non-functional mutations of the genes of DAF-2 pathway, e.g. DAF-2, AGE-1 and PDK-1, can strikingly extend the lifespan of *C. elegans*. The DAF-2 pathway is analogous to the insulin/IGF-1 pathway in mammals. Interestingly, the deficiencies in the mammalian insulin/IGF pathway can evoke the appearance of a dwarfish phenotype which is associated with extended lifespan, at least in rodents (Bartke and Brown-Borg, 2004; Brown-Borg, 2009). This phenomenon has been called the insulin/IGF paradox in aging research.

The insulin/IGF paradox proposes that excessive insulin/IGF signaling during the older age could enhance the aging process. It is well known that suppressing the insulin/IGF pathway triggers FOXO signaling which supports the appearance of long-lived phenotype (see Section 4.2.2). Several studies have demonstrated that insulin/IGF signaling can stimulate the NF-κB system via the activation of IKKα/β complex. This signaling can enhance inflammatory responses (Che et al., 2002; Iwasaki et al., 2009; Martins et al., 2009) and support resistance to apoptosis (Bertrand et al., 1998, 1999; Mitsiades et al., 2002). The longevity-related signaling of insulin/IGF-1 receptors (or DAF-2 in *C. elegans*) is

mediated via the PI-3K/AKT pathway. The activation of PI-3K/AKT kinases inhibits the FOXO longevity factor (see Section 4.2.2) but triggers the IKK/NF-κB signaling. Madrid et al. (2001) demonstrated that AKT kinase can activate IKKβ and p38 kinases which phosphorylate the Ser 529 and 536 residues in the transactivation domain of the p65 component. These changes clearly potentiated the transactivation efficiency of NF-κB complex. Tanaka et al. (2005) revealed that the activation of PDK1, an upstream AKT kinase, can also activate IKKβ kinase and subsequently trigger the NF-κB signaling. Furthermore, Dan et al. (2008) showed that AKT kinase can stimulate the IKKα kinase via the formation of complex between IKKα and mTOR kinases which enhances the DNA-binding and transactivation of the NF-κB complex. Gustin et al. (2006) demonstrated that AKT kinase can activate IKKα and subsequently trigger the processing of p100 to the active p52 component. All these studies clearly emphasize the fact that activation of insulin/IGF-1 axis can trigger the NF-κB signaling.

Given that impairing the signaling of insulin/IGF-1 pathway can activate the FOXO-dependent lifespan extension, this implies that the NF-κB signaling could be driving the aging process via the insulin/IGF axis. In particular, this is plausible since FOXO factors can inhibit the NF-κB signaling (see Section 4.2.2).

4.1.6. Protein modifications: acetylation and O-glycosylation

Several post-translational modifications of the core components of NF-κB signaling pathway can trigger the activation of the pathway but also regulate the transcriptional efficiency of NF-κB system (Perkins, 2006). Phosphorylation and ubiquitination are the major regulatory modifications in the activation step but the extent of acetylation, O-glycosylation, and sumoylation of the core proteins can control the efficiency of the NF-κB-dependent transcription (Chen and Greene, 2003; Perkins, 2006; Mabb and Miyamoto, 2007; Calao et al., 2008). With respect to aging, acetylation and O-glycosylation seem to be important modifications enhancing the NF-κB signaling during stress. For instance, it is commonly observed that inflammatory responses can be potentiated through the increased acetylation of NF-κB components (e.g. Ito et al., 2007). It is also recognized that augmented protein acetylation can trigger cellular senescence (Place et al., 2005; Furukawa et al., 2007). Furthermore, SIRT1 longevity factor can deacetylate p65 and in that way repress the NF-κB signaling, along with extending the lifespan (see Section 4.2.1). Chang and Min (2002) have reviewed the role of histone deacetylases in the regulation of lifespan.

The Greene Laboratory has studied extensively the significance of protein acetylation in the regulation of transcriptional activity of NF-κB complexes (Chen and Greene, 2003). The NF-κB complexes can recruit antagonistic coregulators: (i) histone acetyltransferases (HATs) which can acetylate p65 and p50 factors and in that way potentiate transcriptional efficiency, on the other hand, (ii) histone deacetylases (HDACs) can deacetylate these components and repress transcription (Chen and Greene, 2003; Calao et al., 2008). CBP (CREB-binding protein), p300 and PCAF (p300/CBP-associated factor) are the typical HATs in the coactivation of NF-κB signaling whereas SIRT1 and HDAC-3 are the corepressors for NF-κB signaling. Protein acetylation of Rel/NF-κB components can repress the binding of inhibitory IκBα protein, enhance the DNA-binding of complexes, and potentiate the transcriptional activity of NF-κB system. However, the role of protein acetylation in the enhancement of organismal aging process needs to be explored.

There is evidence to indicate that during aging, glucose tolerance declines involving increased insulin resistance with hyperglycemic disorders (e.g. Preuss, 1997; Suji and Sivakami, 2004). Kassi and Papavassiliou (2008) proposed that glucose could be a pro-aging factor. Chronic hyperglycemia can induce glucotoxicity through the formation of AGEs (Baynes, 2001, see Section 4.1.3) or via the production of O-linked N-acetylglucosamine (O-GlcNAc)-modified proteins (Issad and Kuo, 2008). Fulop et al. (2008) have observed that the levels of O-glycosylated proteins are clearly increased during aging in rat heart, aorta, brain and skeletal muscle. Recently, Kawauchi et al. (2009) observed that increased glucose concentration could enhance glycolysis and subsequently promote O-glycosylation of IKKβ protein which clearly enhanced the activity of IKKβ. O-GlcNAc modification on the Ser733 blocks the inactivation site of the IKKβ kinase. It seems that enhanced glycolysis can stimulate NF-κB signaling through the sustained activation of IKKβ. Yang et al. (2008) demonstrated that O-glycosylation could also target p65 protein and potentiate the transactivation efficiency of NF-κB factors. O-GlcNAc modification in p65 protein is able to repress the binding of inhibitory IκBα protein to p65 protein. Several studies have demonstrated that p53 can inhibit aerobic glycolysis (e.g. Bensaad and Vousden, 2007) and subsequently suppress the activation of IKKβ/NF-κB signaling (see Section 4.2.3).

In conclusion, it seems that the well-known pro-aging factors and insults can either directly or indirectly promote the NF-κB signaling. Given that the inflammation and the activation of NF-κB system are associated with several age-related diseases, e.g. atherosclerosis, arthritis, diabetes and neurological degeneration (Kumar et al., 2004), it is plausible that the aging process can expose the organism to several inflammatory and degenerative diseases.

4.2. Longevity factors inhibit NF-κB signaling

4.2.1. Sirtuins SIRT1 and SIRT6

Sinclair and Guarente (1997) were the first who demonstrated that the aging of budding yeast is caused by the recombination in rDNA locus and at that time extrachromosomal rDNA circles are cleaved and subsequently accumulate in the old mother yeast. Kaeberlein et al. (1999) observed that Sir2 (silent information regulator 2) can suppress the recombination and extend yeast longevity. Later studies revealed that Sir2 is an NAD^+-dependent histone deacetylase (Imai et al., 2000). The Sir2 types of enzymes are evolutionary conserved proteins and they form the class III histone deacetylases, called Sirtuins (Michan and Sinclair, 2007). In humans, there are seven Sirtuins, from SIRT1 to SIRT7. Sirtuins are longevity factors in several species, also in mammals, although the aging of mammals is not caused by the recombination in the rDNA locus (Guarente and Kenyon, 2000). In mammals, Sirtuins are involved in several cellular functions, e.g. metabolic regulation and maintenance of cell survival, and they are linked to the aging process and some age-related diseases, such as atherosclerosis and neurodegenerative diseases (Guarente, 2006; Longo and Kennedy, 2006; Michan and Sinclair, 2007).

Mammalian Sirtuins can deacetylate several transcription factors, in addition to histones, and in that way regulate gene expression. Yeung et al. (2004) demonstrated that SIRT1 can interact with the p65/RelA protein and specifically cleave the acetyl group from the lysine-310 of p65 protein. This acetyl group is known to enhance greatly the transactivation efficiency of the NF-κB complex. The experiments of Yeung et al. (2004) revealed that SIRT1 was a potent intracellular inhibitor of NF-κB signaling (Fig. 1). Recently, Kwon et al. (2008) observed that the HIV-1 Tat protein could bind to the SIRT1 protein and in that way inhibited the SIRT1-mediated deacetylation of p65 protein. The sustained acetylation of p65 protein potentiates the function of NF-κB system e.g. involving the hyperactivation of T cells and the depletion of CD4+ T cells (Kwon et al., 2008). Sirt1 can bind to TLE1 (transducin-like enhancer of split-1), a non-DNA binding co-repressor, and Ghosh et al. (2007) demonstrated that both SIRT1 and TLE1 were required for the inhibition of NF-κB activity.

SIRT1 seems to be a potent inhibitor of NF-κB signaling also *in vivo* conditions. There are a large variety of different activators of SIRT1 which can subsequently inhibit NF-κB and affect lifespan regulation. Diet contains a plethora of sirtuin-activating compounds (STACs) (Allard et al., 2009). For instance, several plant polyphenols can activate SIRT1 *in vitro*, e.g. resveratrol, quercetin, fisetin, and piceatannol. In general, these plant STACs have anti-inflammatory and anti-cancer properties which may be linked to the inhibition of NF-κB signaling. However, several other plant non-STACs, e.g. terpenoids, have similar effects (Salminen et al., 2008b) which indicate that the SIRT1 activation, if any, could be indirect. Resveratrol, a phytostilbene, is the most widely studied STAC and several studies have indicated that the effects of resveratrol mimic those induced by caloric restriction which also activates SIRT1 (Wood et al., 2004; Barger et al., 2008b; Allard et al., 2009). Caloric restriction can generally extend the lifespan (see Section 5) but also resveratrol can prevent the appearance of aging parameters, even in mice (Barger et al., 2008b). However, the target of STACs in cells could be some of the upstream kinases which activate SIRT1, such as AMPK (AMP kinase) (Dasgupta and Milbrandt, 2007). AMPK is a sensor of energy status and a key regulator of cellular metabolism. Fulco and Sartorelli (2008) have reviewed the role of AMPK-SIRT1 axis in the control of organismal physiology and pathophysiology. We propose that some of the effects of that axis are mediated via the inhibition of IKK/NF-κB signaling.

SIRT6 is another mammalian Sirtuin protein which is associated with the regulation of aging process (Lombard et al., 2008). Mostoslavsky et al. (2006) established a SIRT6 knockout mouse which displayed a dramatic aging-like phenotype with several age-related degenerative processes. Kawahara et al. (2009) demonstrated that SIRT6 could interact with p65 protein and recruited to the promoters of NF-κB-dependent genes where it deacetylated the lysine 9 of histone H3. This repressed the transactivation capacity of NF-κB complexes and in that way attenuated the NF-κB-dependent responses. In SIRT6-deficient cells, the transactivation efficiency of NF-κB complexes was clearly increased, inducing cellular senescence. Kawahara et al. (2009) observed that the NF-κB-driven gene expression profiles were potentiated in SIRT6 knockout mice. Their study highlights the role of NF-κB signaling in the premature type of organismal aging (Fig. 1).

4.2.2. FoxOs/PTEN

Studies on the *C. elegans* dauer larva model have revealed that impairing the DAF-2/insulin pathway can clearly extend the lifespan of worms (see Section 4.1.5). The most important protein responsible for the evoked longevity is DAF-16 which is analogous to mammalian FOXO proteins (Guarente and Kenyon, 2000; Coffer and Burgering, 2004; Barthel et al., 2005; Braeckman and Vanfleteren, 2007). DAF-16 protein is normally located in cytoplasm but the inhibition or functional deficiences of DAF-2 pathway can trigger the translocation of DAF-16 to the nucleus where it induces a gene expression pattern of cell survival genes linked to lifespan extension (Greer and Brunet, 2005; Mukhopadhyay et al., 2006). The regulation mode of the FOXO family, consisting of FOXO1, FOXO3a, FOXO4 and FOXO6, has been well conserved during evolution. The DAF-2 pathway can be inhibited by DAF-18, a protein phosphatase analogous to mammalian PTEN, the overexpression of which can also extend lifespan of *C. elegans* (Mihaylova et al., 1999). In general, DAF-2 and FOXO transcription factors enhance the stress resistance by modifying cellular metabolism, proliferation and host defence systems (Coffer and Burgering, 2004; Barthel et al., 2005; Greer and Brunet, 2005).

FOXO and NF-κB factors can undergo several interactions (Peng, 2005; Salminen et al., 2008c). Lin et al. (2004) demonstrated that FOXO3a deficiency in mice induced a spontaneous lymphoproliferation and evoked inflammatory responses in several tissues. Autoinflammation correlated with the presence of hyperactivated helper T cells. Their studies revealed that FOXO3a could inhibit NF-κB signaling and in that way FOXO3a deficiency could trigger the sustained overactivity of NF-κB signaling and induce autoinflammatory responses in mice (Fig. 1). Lin et al. (2004) also observed that the expression levels of IκBβ and IκBε, inhibitory proteins of NF-κB complexes, were clearly reduced in the T cells of FOXO3a deficient mice. It seems that FOXO3a does not directly upregulate the expression of IκB proteins but via the FOXJ1 expression (Lin et al., 2004; Peng, 2005). Another possibility is to act via κB-Ras1 protein (IκB-interacting Ras-like protein-1) which can suppress NF-κB activation by inhibiting IκB degradation (Chen et al., 2004). Lee et al. (2008) observed that FOXO3a could clearly induce the expression of κB-Ras1 protein in HUVEC cells. Interestingly, Spencer et al. (1997) demonstrated that the activation level of NF-κB system was constitutively upregulated with aging in the major lymphoid tissues and cells.

There is a clear antagonism between FOXO factors and IKK/NF-κB signaling e.g. with respect to oxidative stress: FOXO proteins have been reported to induce an antioxidative response whereas oxidative stress triggers NF-κB signaling (Schreck et al., 1992; Greer and Brunet, 2005). Furthermore, IKKα and IKKβ can phosphorylate FOXO3a protein and induce its ubiquitination and subsequent degradation (Hu and Hung, 2005). It seems that FOXO proteins are important repressors of the NF-κB system, deciding the cellular fate in the choice between cancerous growth and senescence.

PTEN is a potent upstream inhibitor of insulin/IGF-1/PI-3K/AKT pathway and in that way can regulate the function of FOXO proteins (Datta et al., 1999). PTEN can also control the signaling through IKK/NF-κB pathway since the PI-3K/AKT signaling activates IKKα/β and subsequently the NF-κB system (Madrid et al., 2001; Mayo et al., 2002). This means that the repression of PTEN activates IKK/NF-κB signaling whereas stimulation triggers the FOXO activation but inhibits NF-κB system (see Section 4.1.5). This is one example of the antagonism between the FOXO and NF-κB pathways. However, PI-3K/AKT signaling targets IKKα/β kinases which does not necessarily lead to the activation of NF-κB signaling since these kinases can undergo several other interactions (Perkins, 2007). Moreover, it has been reported that the activation of NF-κB can inhibit the expression of PTEN (Vasudevan et al., 2004) which may still potentiate NF-κB signaling. PTEN is an important PI-3K-AKT regulator in the cytosol but recent studies have established that PTEN can be translocated to nuclei where it is capable of regulating chromosome stability, DNA repair and cell-cycle arrest (Planchon et al., 2007) which are all important characteristics in the maintenance of genomic integrity during aging (Vijg, 2008).

4.2.3. p53

The p53 tumour suppressor protein has an important role both in cancer and aging process although its function in the organismal aging needs to be clarified (Campisi, 2005; Papazoglu and Mills, 2007). The p53 protein is involved in the complex network of signaling pathways and it can affect the integrity of several functions, e.g. genome stability, DNA repair, and mitochondrial metabolism (Chumakov, 2007; Olovnikov et al., 2009). It also participates in the regulation of cellular senescence and apoptotic cell death. Recent studies have emphasized its crucial role in the energy metabolism, in particular in the balancing of mitochondrial respiration and glycolysis (Bensaad and Vousden, 2007; Ma et al., 2007; Olovnikov et al., 2009). Several studies have indicated that the metabolic rate is an important parameter in the regulation of maximum lifespan, i.e. a higher metabolic rate translates into a shorter lifespan (Hulbert et al., 2007).

Currently, there are several conflicting observations on the role of p53 in the aging process. Tyner et al. (2002) generated a p53 mutant mouse which overexpressed a truncated p53 protein. These mice displayed a premature aging phenotype with several age-related disorders. Moore et al. (2007) demonstrated that the truncated p53 could interact with the wild-type p53 protein and in that way increase the stability and protein level of the wild-type protein, consistent with a hyperactive p53 state. Recently, Mendrysa et al. (2006) generated a transgenic mouse which expressed a reduced level of Mdm2, an inhibitor of p53, and in that way the p53-dependent expression was increased. Unexpectedly, these mice were cancer resistant but did not exhibit premature aging. Another model, the so-called Super p53, carrying extra copies of the p53 gene displayed cancer resistance but showed no indication of premature aging. In contrast, Matheu et al. (2007) generated a mouse model with transgenic alleles of p53 and Arf, an activator of p53 expression. These mice showed a slight increase in the p53 protein level and were able to resist cancer. Surprisingly, these mice displayed a reduced level of age-related oxidative damage and exhibited a clear delay in the aging process (Matheu et al., 2007). It seems that the effects induced by the modulation of p53 expression are largely context dependent. Recently, several studies have demonstrated that the cytoplasmic location of p53 can clearly repress autophagic degradation in cells (Green and Kroemer, 2009). It is known that autophagic cleansing declines during aging (Salminen and Kaarniranta, 2009). Studies on the modulation of p53 expression levels highlight the importance of verifying the localization of p53 protein in cells.

Feng et al. (2007) observed that the functional activity of p53 clearly declined with aging in mice. In particular, the transcriptional activity of p53 decreased and the response of p53 to several stress signals was significantly suppressed in several mouse tissues. This study seems to explain why the cancer incidence is increased in elderly people. The decrease in the functional activity of p53 during aging seems to fit together with the energy metabolic changes observed during aging, i.e. decrease in mitochondrial respiration and increased glycolysis. There are several observations demonstrating that p53 can enhance mitochondrial respiration. For instance, p53 can induce the expression of SCO_2, a major regulator of the function of cytochrome c oxidase complex (Bensaad and Vousden, 2007). Furthermore, p53 was reported to inhibit aerobic glycolysis by inducing the expression of TIGAR protein (Bensaad et al., 2006) and activating the pentose phosphate pathway (Olovnikov et al., 2009).

Recently, Kawauchi et al. (2008) demonstrated that p53 protein can regulate the IKK/NF-κB pathway via glucose metabolism. Loss of p53 protein activated the NF-κB signaling and significantly increased the rate of aerobic glycolysis. Their data also indicated that p53 can prevent the activation of IKK/NF-κB pathway by suppressing glycolysis. Recently, they confirmed that the increased glycolysis could promote the O-glycosylation of IKKβ and in that way clearly potentiated the activity of IKKβ and subsequently NF-κB signaling (Kawauchi et al., 2009). On the other hand, Yang et al. (2009) have elucidated that the inhibition of IKKβ was able to increase the stability and expression of p53 protein and subsequently evoked cell cycle arrest via p21 expression. Several other studies have also revealed the crosstalk between p53 and NF-κB (Tergaonkar and Perkins, 2007). In conclusion, it seems that p53, a tumor suppressor and plausible longevity gene, inhibits NF-κB signaling by suppressing the GlcNAc modification of IKK kinases (see Section 4.1) induced by enhanced aerobic glycolysis.

4.2.4. Heat shock proteins (HSPs)

An increased stress resistance is a hallmark of all long-lived mutants, e.g. those of *C. elegans*, *Drosophila* or even mice (Johnson et al., 2000; Munoz, 2003; Murakami, 2006; Vermeulen and Loeschcke, 2007). Molecular chaperones, in particular those of HSPs, have been shown to improve the stress resistance properties that subsequently increase longevity (Soti and Csermely, 2000; Hsu et al., 2003; Munoz, 2003; Morley and Morimoto, 2004; Murakami, 2006). It is well known that HSP responses clearly decline during aging although the effect seems to be tissue-specific, at least in mammals. The mammalian HSP system involves the families of HSP90, HSP70, HSP60, HSP40, and small HSPs (Jolly and Morimoto, 2000). In cellular stress, HSPs can prevent protein denaturation and aggregation and assist in protein refolding process after stress. The heat shock response is activated by the trimerization of HSF1 (heat shock factor 1) which binds to the heat-shock element in the promoters of HSP genes and subsequently initiates the transcription. Several studies have demonstrated that the overexpression of HSF1 and distinct HSPs can increase the lifespan in *C. elegans* (e.g. Yokoyama et al., 2002; Hsu et al., 2003; Morley and Morimoto, 2004). On the other hand, the knockdown of HSF1 and HSPs can trigger a premature aging process. However, the cellular stress resistance induced by HSPs involves a complex system of co-chaperones and protein modifications in mammals (Shamovsky and Gershon, 2004; Voellmy and Boellmann, 2007). For instance, Westerheide et al. (2009) recently demonstrated that SIRT1 could deacetylate human HSF1 protein and in that way could prolong the DNA-binding of HSF1 and potentiate the transcription of HSP genes to subsequently increase the protein levels of HSPs. This would be predicted to improve the protein quality control and prevent age-related proteotoxic responses.

Several studies have indicated that the cellular stress involving the elevation of cellular HSP levels can suppress the NF-κB-mediated inflammatory responses (Demeester et al., 2001; Malhotra and Wong, 2002; Chen et al., 2007a). We have recently reviewed this topic (Salminen et al., 2008d). Agou et al. (2002) and Ran et al. (2004) have demonstrated that HSP70 can bind to the NEMO regulatory unit (IKKγ) of IKK complex and disturb the oligomerization of NEMO proteins and in that way impair the formation of active IKK complex. Weiss et al. (2007) observed that the presence of HSP70 in the IKK complex can prevent the phosphorylation and proteasomal degradation of IκBα protein and consequently the NF-κB signaling. They also demonstrated that the enhanced expression of HSP70 could protect against sepsis-induced acute respiratory distress syndrome in rats. It seems that also HSP27, a small HSP protein, can bind to the IKK complex and inhibit its capacity to activate NF-κB signaling (Park et al., 2003). Furthermore, Chen et al. (2006) demonstrated that HSP70 could bind to the TRAF6 protein (tumor necrosis factor receptor-associated factor 6) and inhibit the NF-κB signaling induced by LPS exposure. It does seem that HSP27 and HSP70 have a crucial role in the maintenance of cellular stress resistance and the prevention against inflammatory insults.

Several studies have indicated that HSP90 can also regulate the function of the IKK complex and NF-κB signaling (Broemer et al., 2004; Pittet et al., 2005; Hinz et al., 2007). HSP90 protein is a molecular chaperone which can bind several client proteins and in that way regulate the function of many signal transduction pathways. Chen et al. (2002) demonstrated that the HSP90 protein, together with its co-chaperone Cdc37, could bind to and stabilize the IKK complex which is necessary for the activation of NF-κB signaling. However, cellular stress can induce the dissociation of the HSP90/Cdc37 chaperones from the IKK complex, inactivating the complex and downstream the NF-κB signaling (Pittet et al., 2005). The mechanism of the stress-induced dissociation of the IKK complex is not defined in detail. Moreover, HSP90 chaperone can bind to the Monarch-1/NLRP12 (nucleotide-binding domain, leucine-rich repeat) protein which bears both a structural and functional homology to the plant R proteins (stress-resistance proteins) (Nimchuk et al., 2003). HSP90 protein is an important stabilizer

of the Monarch-1 protein which can induce the proteasomal degradation of NIK and in that way suppress the non-canonical NF-κB signaling (Arthur et al., 2007; Lich et al., 2007). The specific inhibition of HSP90, e.g. by geldanamycin, was reported to trigger the proteasomal degradation of Monarch-1 and subsequently induced the p52-dependent immune response in monocytes. Interestingly, HSP90 and R proteins have a critical role in disease resistance and senescence in plants (Nimchuk et al., 2003).

In conclusion, it seems that several HSP proteins are powerful inhibitors of the NF-κB signaling, both canonical and non-canonical pathways, and in that way can suppress the NF-κB-driven aging processes and extend the lifespan (Fig. 1).

4.2.5. Others: Klotho, INGs

A number of other longevity genes has been identified in human genetic studies (e.g. Bonafe and Olivieri, 2009; Bostock et al., 2009) but the molecular mechanisms linking them to the aging process need to be clarified. Furthermore, several ongoing genetic studies will undoubtedly disclose new candidate genes but it will be some time before their functionality and molecular association to the aging process are fully understood. Klotho is one of the longevity genes established in mouse studies (Kuro-o et al., 1997). The Klotho mouse with a non-functional *klotho* gene displays a short-lived phenotype resembling the mouse aging process including several age-related diseases. Klotho can be viewed as an aging suppressor gene since the overexpression of Klotho can extend the lifespan of mice (Kurosu et al., 2005). Klotho has also been associated with human aging in genetic association studies (Arking et al., 2002). Recent studies have established that the Klotho proteins are important cofactors in the FGF signaling, in particular mediated by FGF19, FGF21, and FGF23 (Kuro-o, 2008; Kurosu and Kuro-o, 2009). These factors comprise the endocrine FGF19 subfamily which controls several tissue-specific physiological processes, e.g. lipolysis in adipocytes and inhibition of vitamin D metabolism in kidney. The signaling pathways which are regulated by Klotho via the endocrine FGF19 family of proteins have not been characterized thoroughly although there are some findings of its link with p53/p21 signaling, insulin/IGF-1 signaling and Wnt signaling (Wang and Sun, 2009).

Klotho protein can repress insulin/IGF-1 signaling and induce insulin resistance (Kurosu et al., 2005). The suppression of the insulin/IGF-1/PI-3K/AKT pathway activates FOX factors and induces protection against oxidative stress (Yamamoto et al., 2005). The inhibition of PI-3K/AKT signaling blocks also the IKK/NF-κB signaling pathway (see Section 4.2.2). Recently, Maekawa et al. (2009) demonstrated that the Klotho protein could inhibit the TNF-α-induced activation of NF-κB signaling and subsequently reduce the inflammatory reaction in endothelial cells. Currently, it is not known whether or not the mechanism is related to the inhibition of the insulin/IGF-1 pathway.

The ING (inhibitor of growth) family of tumor suppressors has interesting characteristics with respect to aging and senescence (Campos et al., 2004; Russell et al., 2006; Coles and Jones, 2008). The five members of INGs regulate several biological activities, e.g. cell growth, DNA repair, apoptosis, and senescence, via the interaction of major transcription factors. For instance, several ING factors can regulate the signaling of p53 and NF-κB pathways either directly by interacting with these factors or by indirectly modulating the signaling networks. Furthermore, they are co-factors of HATs (histone acetyltransferases) and HDACs (histone deacetylases) and in that way affect the gene transcription and DNA stability. ING1 can bind to p53 protein and enhance its apoptotic capacity. The mechanism of ING-dependent activation of p53 is still elusive. Defects in INGs have been identified in different types of human cancers (Coles and Jones, 2008). Recently, Soliman et al. (2008) demonstrated that the ING1a variant enhances replicative senescence whereas ING1b augments apoptosis. The role of replicative senescence in organismal aging is a topic being debated in aging research today. However, it does seem that ING proteins are important co-regulators of p53, e.g. in the age-related metabolic regulation (see Section 4.2.3).

Nozell et al. (2008) demonstrated that ING4 protein could bind to NF-κB proteins but it did not prevent the activation of the complex in cytosol, its nuclear translocation or its DNA-binding but instead, ING4 repressed the transactivation of NF-κB-dependent genes by inhibiting the phosphorylation of p65 protein and the acetylation of histones, in particular in promoters containing H3-Me3K4 residues. For instance, the down-regulation of ING4 could stimulate the transcription of NF-κB, increase the expression of IL8 and COX2, and enhance the angiogenesis and tumor growth in brain (Garkavtsev et al., 2004). ING4 was also reported to bind to p53 protein and potentiate the p53-dependent transcription (Shiseki et al., 2003). It seems that ING4 protein has the critical characteristics for the tumor suppressor type of a longevity factor which would function as a repressor of NF-κB signaling.

4.2.6. Hormetic phytochemicals

There are a plethora of plant-derived, folk medicinal compounds and extracts which have been claimed to have anti-aging efficiency (Ness et al., 1999; Trichopoulou, 2004). However, only a few of traditional remedies has been subjected to a clinical trial. Recently, many promising compounds have been identified and they are now being scrutinized (Zhu et al., 2004; Corson and Crews, 2007). Polyphenols, e.g. flavonoids and terpenoids, are the major ingredients present in fruits, vegetables, and different spices. Traditionally, they have been used to alleviate the symptoms of inflammatory diseases and cancer but it seems that they can also protect against age-related degeneration (e.g. Rossi et al., 2008; Weaver et al., 2008). Interestingly, many of these polyphenols are inhibitors of NF-κB signaling (Bremner and Heinrich, 2002; Nam, 2006; Salminen et al., 2008b) (Fig. 1). Several polyphenols are potent antioxidants and in that way can inhibit ROS production and NF-κB activation (see Section 4.1.1). Some of them can also more directly inhibit IKK/NF-κB signaling, e.g. many terpenoids (Salminen et al., 2008b).

Many phytochemicals are plant toxins, e.g. terpenoids, which plants synthesize to combat insect attack. With low-dose exposures, they can trigger a cellular stress response and subsequently induce adaptive stress resistance, also called hormesis (Mattson and Cheng, 2006; Mattson, 2008a,b). Stress resistance involves several molecular adaptations, e.g. via the activation of AMP kinase and subsequently alterations in cell survival genes including Sirtuins, FoxOs and p53, i.e. the longevity genes discussed above (Jones et al., 2005; Greer et al., 2007a,b; Fulco and Sartorelli, 2008). There are several review articles examining the role of hormesis in aging (e.g. Gems and Partridge, 2008; Rattan, 2008). We propose that the anti-inflammatory and anticancer responses induced by phytochemicals are caused by the phytohormetic stress resistance involving the suppression of NF-κB signaling.

Resveratrol, a stilbene phytochemical, has recently received considerably attention as a SIRT1 activator (Howitz et al., 2003). Resveratrol has several targets in cells, e.g. AMP kinase and NF-κB signaling, and it has been claimed to exert therapeutic effects in several diseases, in particular inflammatory diseases and cancer (Cucciolla et al., 2007; Shakibaei et al., 2009). Many studies have revealed that resveratrol inhibits the NF-κB-dependent signaling but the suppression seems to be indirect, probably via the activation of survival genes. Furthermore, a number of studies have demonstrated that resveratrol can extend the lifespan in organisms ranging from yeast to mice (Howitz et al., 2003; Barger

et al., 2008b). In conclusion, it seems that hormetic phytochemicals may be able to modulate the activity of cell survival mechanisms involving the regulation of longevity factors.

5. Caloric restriction, longevity factors and NF-κB signaling

Caloric restriction (CR) is the most potent way to extend lifespan in mammals, especially in rodents (e.g. Weindruch, 1996; Bishop and Guarente, 2007). Recently, it was reported that CR can increase the expression of SIRT1 as well as the concentration of SIRT1 activator, NAD+, implying that SIRT1 could be one of the longevity factors in CR (Bordone and Guarente, 2005). Bordone et al. (2007) observed that the phenotype of SIRT1 overexpressing mice resembled that induced by CR. Barger et al. (2008a) demonstrated that short-term resveratrol treatment and long-term caloric restriction induced similar changes in gene expression profiles in mouse heart. These observations indicate that SIRT1 has an important functional role during CR. There is also evidence that CR can affect the age-related changes in p53-mediated transcriptional profile (Edwards et al., 2007). Furthermore, several studies have indicated that FOXO factors are involved in the CR-mediated lifespan extension in *C. elegans*, *Drosophila* and mice (Greer et al., 2007a,b; Wang et al., 2007; Giannakou et al., 2008). These results support the general observation that caloric restriction increases the stress resistance which subsequently can prevent age-related diseases (Sinclair, 2005; Mattson, 2008a,b).

Activation of innate immunity during aging most likely enhances the aging process as well as age-related inflammatory and degenerative diseases (Franceschi et al., 2000; Salminen et al., 2008a). Clinical studies have demonstrated that caloric restriction can attenuate the system-wide inflammatory processes (Holloszy and Fontana, 2007; Morgan et al., 2007). Microarray studies support the clinical observations since CR can prevent the age-related pro-inflammatory changes in gene expression profiles (Weindruch et al., 2001). There is recent evidence indicating that CR can also decrease the activation of IKK/NF-κB signaling pathway (Jung et al., 2009). In conclusion, it seems that CR causes a stress response in the body and longevity factors can induce the stress resistance including the inhibition of NF-κB signaling and in that way can prevent age-related inflammatory and degenerative changes.

6. NF-κB signaling as a survival factor

The NF-κB system is a pleiotropic regulator which has opposite effects, both beneficial and detrimental responses. The main function is the maintaining of host defence including e.g. innate immunity reactions and protection against apoptosis. NF-κB signaling triggers the first line defence against environmental attacks as well as tissue injuries. It provides a powerful protection against tissue damage which can generate apoptotic cell death (Karin and Lin, 2002; Dutta et al., 2006). NF-κB system transactivates several survival genes, e.g. those of IAPs (inhibitor of apoptosis) and Gadd45β, inhibitor of JNK signaling (see Section 4.1.1). In particular, NF-κB signaling can antagonize the ROS-mediated activation of JNK and subsequently apoptotic and necrotic cell damage triggered by JNK activation (Papa et al., 2006). In addition, NF-κB system can activate the expression of HIF-1α (hypoxia-inducible factor-1α) (Van Uden et al., 2008). HIF-1α is a potent inducer of the expression of glycolytic enzymes and glucose transporters (Marin-Hernandez et al., 2009) which enhance glycolytic energy production and in that way can improve survival of tissues in different pathological conditions, e.g. in hypoxia. HIF-1α can also stimulate autophagocytosis by the induction of BNIP3 and BNIP3L expression (Bellot et al., 2009). Autophagic degradation is important survival mechanism, e.g. in starvation.

One characteristic aspect of the NF-κB system is the observation that the activation mechanisms and responses are specific for different cell types. Moreover, NF-κB signaling seems to have a dual role in many diseases, i.e. either promoting or preventing the disease process. In the neurons, NF-κB signaling can protect against apoptotic insults, e.g. those of excitotoxic and oxidative conditions, and increase synaptic plasticity (Mattson et al., 2000; Mattson and Meffert, 2006; O'Mahony et al., 2006). Interestingly, the NF-κB signaling induced by TNFα and ceramide can also confer the resistance for neurons against oxidative stress (Mattson et al., 1997). Several later studies have confirmed that pro-inflammatory cytokine TNFα can have neuroprotective effects (Figiel, 2008). This may be caused by the inhibition of the JNK signaling pathway via the NF-κB signaling (see above, Papa et al., 2006). Recently, Sarnico et al. (2009) demonstrated that the susceptibility of neurons to ischemia is dependent on the NF-κB complexes activated. c-Rel/p50 dimers reduce the vulnerability to ischemic damage whereas RelA/p50 dimers are pro-apoptotic in neurons. The RelA-containing complexes induce the transcription of pro-apoptotic *Bim* and *Noxa* genes while the c-Rel-containing dimers promote the expression of anti-apoptotic *Bcl-xL* gene (Sarnico et al., 2009). In the brain, the responses of neurons and glial cells to the activation of NF-κB signaling seem to be opposite, i.e. the activation of NF-κB system promotes the survival of neurons whereas in glial cells it triggers pathological responses (Camandola and Mattson, 2007).

Generally, it seems that the transient NF-κB signaling has beneficial effects but excessive and/or prolonged activation leads to deleterious effects. There are several negative autoregulatory feedback loops which regulate the termination of NF-κB response (Renner and Schmitz, 2008). The termination programs controlling the timing and extent of NF-κB signaling are potent regulators of aging and age-related degenerative diseases but currently they are incompletely known. Renner and Schmitz (2008) have listed several proteins which affect the feedback inhibition of NF-κB signaling. The induction of IκB protein expression is the well-known mechanism but NF-κB activation can also induce the transcription of deubiquitinating enzymes, e.g. A20 and Cezanne, which inhibit the activation of NF-κB complexes (Enesa et al., 2008; Coornaert et al., 2009). NF-κB signaling stimulates the expression of Twist-1 and -2 which repress the cytokine expression via the interaction with RelA (Sosic et al., 2003). Active NF-κB complexes can also recruit COMMD (COMM domain containing) proteins which enhance the ubiquitination and degradation of NF-κB components (Maine and Burstein, 2007). Furthermore, the activation of NF-κB signaling can induce the expression of dominant-negative signal transducers, e.g. IRAK (IL-1-receptor-associated kinase) variants (Renner and Schmitz, 2008). In future, it is important to understand better the negative feedback loops of NF-κB signaling which can regulate the balance between the beneficial and detrimental effects of NF-κB signaling.

7. Conclusions: is aging an entropic host defence catastrophe?

There is increasing evidence demonstrating that the NF-κB signaling system is activated during aging (see Section 3). This is plausible since nearly all insults enhancing the aging process are well-known activators of NF-κB, e.g. oxidative stress, DNA damage, UVB light, and activation of innate immunity (see Section 4.1). The NF-κB system is the lynchpin of host defence receiving the input signaling from the danger recognition receptors and subsequently organizing the transcriptional output response against the acute threat. However, one can view the aging process as a slowly progressing degenerative process and in that way could evoke a

chronic, sustained activation of NF-κB system. When one considers the properties of NF-κB system, it seems that its activation is not a consequence of degeneration but rather an enhancer of the process, probably spurring on the aging process. The key question remains how does NF-κB signaling implement this degenerative process?

The NF-κB system is a powerful guardian against apoptosis, activating the expression of several apoptotic inhibitors, e.g. Bcl-L, c-IAP1, c-IAP2 and XIAP (Karin and Lin, 2002; Dutta et al., 2006). Furthermore, NF-κB signaling can also repress the function of JNK, a key protein in apoptotic signaling (see Section 4.1.1). However, increased resistance to apoptosis has many undesirable effects, (i) it can induce cancer in mitotic cells and (ii) in non-mitotic cells, it can prevent the cleansing of damaged cells and natural renewal of cells in several tissues, a process which can lead to the cellular senescence. Senescent cells demonstrate an increase in resistance to apoptosis in vitro (Wang, 1997). Several observations indicate that apoptosis declines during aging and the repression of apoptotic renewal of tissues encourages the accumulation of functionally deficient cells (Zhang and Herman, 2002; Warner, 2007).

It seems that autophagic uptake also declines during aging (Cuervo, 2008; Salminen and Kaarniranta, 2009). Deficient housekeeping leads to the accumulation of waste products and non-functional organelles, e.g. damaged mitochondria. This increases the cellular entropy and is support for the "garbage-can hypothesis". It is clear that the increased resistance to apoptosis and the decline in autophagic cleansing can lead to a vicious cycle, since both processes increase the pressure to allocate more resources to the host defence involving the activation of NF-κB system.

Increased oxidative stress and genotoxic stress can create a vicious cycle in the host defence system resulting in cellular senescence. Interestingly, senescent cells can secrete molecules that have deleterious effects on their neighbors (Campisi, 2005). Rodier et al. (2009) demonstrated that persistent DNA damage in senescent cells can trigger the secretion of inflammatory cytokines, i.e. it activates the innate immunity defence. There is a vast literature demonstrating that innate immunity defence becomes activated during aging (see Section 4.1.3). The mechanism is still largely a matter of debate but it does seem to be associated with DNA damage and cellular senescence may be the outcome since DNA damage is a potent inducer of the NF-κB system (see Section 4.1.2). A chronic inflammatory response has several harmful effects in tissues e.g. it increases oxidative stress and lipid peroxidation as well as evokes the secretion of metalloproteinases which can cause cell matrix degeneration. Furthermore, inflammation can generate the secretion of the TNF family members which can trigger tissue-specific age-related degenerative processes.

Considering that the NF-κB system can enhance the entropic aging process in many different ways, it is not surprising that longevity factors can suppress the NF-κB signaling (see Section 4.2). Currently, the emerging evidence indicates that certain longevity factors, e.g. Sirtuins, FoxOs and HSPs, are able to regulate the aging process also in mammals. The characteristics of most longevity factors demonstrate that they are stress resistance and survival factors (see Section 4.2). It seems that longevity factors are potent inhibitors of NF-κB signaling and can suppress the catastrophic consequences of NF-κB-driven entropic aging process.

Acknowledgement

The authors thank Dr. Ewen MacDonald for checking the language of the manuscript.

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