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Review

An insight into the role of autophagy in cell responses in the aging and neurodegenerative brain

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Summary. Oxidative stress, inflammation and the aggregation of oxidized, misfolded or aberrant proteins in the brain induces deregulations in programmed cell death: apoptosis and autophagy. Apoptosis is one of processes implicated in aging and neurodegenerative pathologies, and for the last decade, has been one of the most studied processes due to its essential role, not only in aging, but also in many neurodegenerative diseases, including Parkinson's, Alzheimer's and Huntington's. However, autophagy being the major intracellular pathway for the degradation and recycling of long-live proteins and organelles is widely involved in the pathogenesis or prevention of many age-related diseases, including neurodegenerative conditions. Recently, autophagy activation has been considered as part of the cellular responses to elevated oxidative stress, eliminating unwanted, damaged and oxidative structures; thus favouring, in this way, the key anti-aging mechanism associated with the caloric restriction. Longevity factors, such as sirtuins, and redox-sensitive transcriptional factors, such as NF-κB and p53, can also regulate basal autophagy in cells, with a direct impact on longevity and the development of inflammation and neurodegeneration. Here, we reviewed the critical changes of autophagy in the aging and neurodegenerative brain and the role of key regulators of autophagy, which are directly related to oxidative stress, inflammation and longevity pathways.

Key-words: Neurodegeneration, Autophagy, Sirtuins, NF-κB, p53

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Introduction to oxidative stress and inflammation in the aging brain

Aging is defined as a complex, irreversible and multifactorial process that leads to changes over time, affecting multiple biological functions, with a gradual deterioration in the adaptability of the organisms to environmental changes and stressful conditions. These changes are detected at all levels, molecular, cellular, tissular levels and organismal (Yu and Chung, 2006), leading to functional systemic disorders related to the aging process and a higher risk of succumbing to age-related pathologies, such as neurodegenerative disease, diabetes, autoimmune and inflammatory diseases and cancer. Initially, aging was proposed as the major risk factor in most neurodegenerative disorders (Floyd and Hensley, 2002). The incidence of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) increases significantly with age (Wilson et al., 2007). Given that the ratio of elderly people is increasing, it is crucial that research uncovers the mechanisms associated with senescence and implicated in the transition from benign aging to degenerative disease to prevent the development of the age-related pathologies and in particular, the cognitive decline associated with aging. In the central nervous system, the neuroendocrine changes observed during aging appear to be more related to disorders of the relationship between neural and hormonal signals, rather than alterations of specific structures (Ferrari and Magri, 2008; Ferrari et al., 2008).

However, in a review of aging, it is essential discuss the previously well-known processes underlying the aging phenomenon, such as oxidative stress and its subsequent inflammation. Oxidative stress is the main causal factor of aging and the development of various diseases, including age-related sporadic degenerative

diseases (e.g., AD, atherosclerosis and diabetes) (Dubinina and Pustygina, 2007). In fact, the enhancement of oxidative stress resistance is considered to be the mechanism underlying the extended longevity of genetic variants of non-mammalian and mammalian organisms (Agarwal and Sohal, 1996; Holzenberger et al., 2003; Madsen et al., 2004; Ayyadevara et al., 2005, 2008). The free radical theory of aging proposes a slow and progressive generation of reactive oxygen species (ROS), an unavoidable consequence of life in an aerobic environment, resulting in the accumulation of defective cellular components (Harman, 1956, 1992). Oxidative stress can be defined within the context of a subtle changed redox status (Yoon et al., 2002). In this regard, the age-related oxidative stress in mammalian cells is generated by a redox deregulation (Humphries et al., 2006) as a consequence of prominent enzymatic defects, leading to an increased production of free radicals, including ROS, reactive nitrogen species (RNS) and other oxidant agents, together with an important decrease in antioxidant levels and impairment of the repair of oxidative damages. Hence, aging occurs as the result of accumulative and unrepaired damage in the cellular constituents, best exemplified by products of lipid peroxidation, protein oxidation and toxic aggregates, such as lipofuscin, toxic proteins (α-synuclein, phosphorylated Tau), the glycoxidation of macromolecules and oxidative modifications in nuclear and mitochondrial DNA (Stadtman, 1992; Beckman and Ames, 1998; Sohal, 2002) (Fig. 1). Oxidatively altered structures and functions are detected and accumulated at all levels along the aging phenomenon (Yu and Chung, 2006). An increase in protein carbonyl levels has been demonstrated for various brain regions including the hippocampus (Siqueira et al., 2005), a key area of brain implicated in learning and memory functions. The effects of aging on energy production or changes in ROS production could be particularly detrimental in non-proliferating neuronal tissues. In fact, damage by ROS is more exacerbated in the brain, because it is highly vulnerable to free radical damage due to its higher oxygen utilization, high concentrations of polyunsaturated fatty acids and transition metals, such as iron, and low concentration of cytosolic antioxidants (Reiter, 1995).

Inflammation is another important factor that affects the normal brain and, in particular, the aging of the brain. The age-related chronic inflammatory state creates an activated immune response that includes the acute phase protein response, cytokines (interferon and interleukins), macrophages, lymphocytes, and other immune system cells. Nitric oxide (NO) and nitrite levels (NO•) accurately reflect the nitrosative stress status that is caused by inflammation. The increase of nitrite levels is particularly relevant because it is well documented that NO• and its toxic metabolite, peroxynitrite, can inhibit components of the mitochondrial respiratory chain, leading to a cellular energy deficiency and, eventually, to cell death (Cassina et al., 2000; Brown, 2001). Within the brain, neurons, in contrast to astrocytes, appear particularly vulnerable to the effects of nitrosative stress. Mammalian

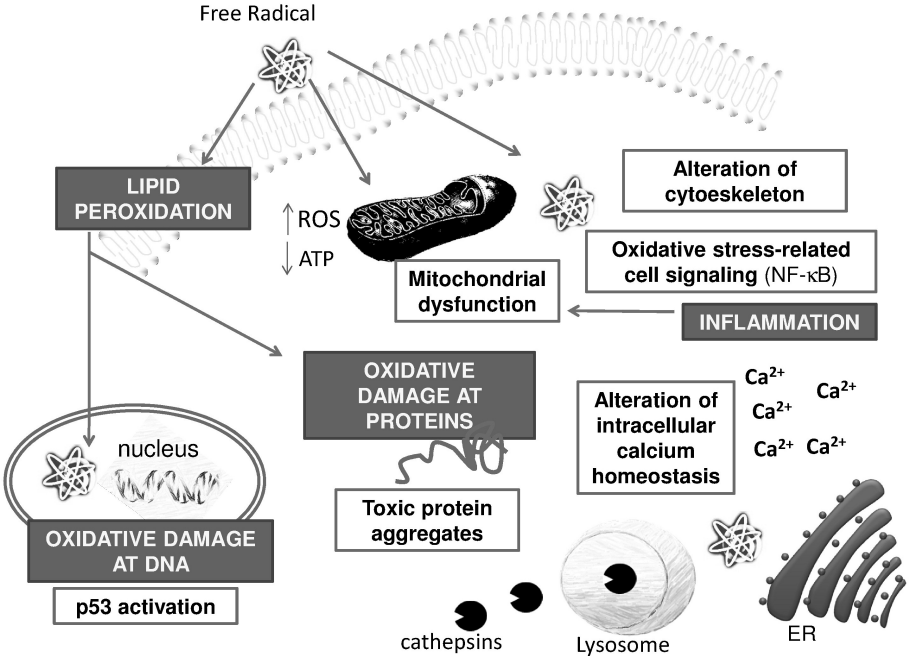

Fig 1. Oxidative damages associated with aging and neurodegeneration. The increase of reactive oxygen species (ROS) during aging in the brain leads to significant damage to molecules that are key for cell survival. The oxidative modifications of lipids (lipid peroxidation) from the cellular membrane lead to changes in cell membrane fluidity and can also favor oxidative modifications of proteins, leading to the formation of toxic protein aggregates inside cells and the alteration of several enzymatic activities. The oxidative modifications of nuclear DNA can favor mutations. Other important oxidative alterations that can compromise cell survival include alterations of the cytoskeleton, by the oxidation of structural and microtubule-associated proteins that stabilize the cytoskeleton. Transcription factors can be activated under oxidative stress, such as p53 and NF-κB, the latter promotes the expression of several pro-inflammatory genes. In addition, the alteration of several organelles, such as mitochondria, results in the generation of less cellular ATP and the production of even more ROS, further contributing to oxidative damage. The dysfunction of the endoplasmic reticulum (ER) alters calcium homeostasis and multiple calcium-dependent signaling pathways. The oxidative modifications of lysosomal membranes release proteolytic enzymes (such as cathepsins) to the cytosol, which can be pro-apoptotic signals.

inflammation in the aging brain is also associated with the activation of the NF-κB transcription factor system (Caballero et al., 2008) and the chronic activation of NF-κB signaling has the capacity to induce the senescent phenotype associated with aging (Salminen and Kaarniranta, 2009a). The NF-κB system is an ancient host defense system concerned with immune responses and different external and internal dangers, such as oxidative and genotoxic stress. In addition to being the master regulator of inflammatory responses, NF-κB signaling can also regulate several homeostatic responses through its anti-apoptotic effects (Michiels et al., 2002) and antioxidant functions; NF-κB can increase the expression of antioxidant enzymes in responses to elevated oxidative stress (Tomas-Zapico and Coto-Montes, 2005). Therefore, an increased rate of free radical generation, inflammation and the inefficiency of the reparative/recycling mechanisms are factors that primarily contribute to the age-related deterioration during the aging brain, what implies that an antioxidant treatment can be highly beneficial against these processes (Gutierrez-Cuesta et al., 2007; Caballero et al., 2008, 2009; Garcia et al., 2010).

Autophagy, oxidative stress and neurodegeneration

In postmitotic cells, such as neurons, which cannot become senescent because they are already terminally differentiated, autophagy (self-eating) is a major homeostatic mechanism to cope with stress. The damaged organelles, long-lived or aberrant proteins and superfluous or aged portions of the cytoplasm are eliminated by the autophagy-lysosomal system that does not compromise cellular functions and tissue homeostasis. The best characterized form of autophagy, macroautophagy (mainly referenced in this review), involves the rearrangement of sub-cellular membranes to sequester parts of cytoplasm and organelles in double-membrane vesicles, called autophagosomes, for delivery to lysosomes where the sequestered cargo is degraded and recycled within autophagolysosomes (Cuervo et al., 2005; Klionsky, 2005; Cuervo, 2008). This sequestration process is controlled by the mammalian target of rapamycin (mTOR) kinase pathway, the major negative regulator of macroautophagy, which is regulated by insulin via the phosphoinositol 3 kinase/serine-threonine protein kinase (PI3K/AKT) pathway and by specific amino acids via AMP kinases (Petiot et al., 2000). Upstream of mTOR, macroautophagy can be inhibited by the insulin/IGF-1 (insulin-like growth factor-1) receptor pathway (Levine and Kroemer, 2008). In contrast, microautophagy sequesters the cytosolic materials through direct invagination of the lysosome membrane in a constitutive mechanism. Lastly, chaperone-mediated autophagy (CMA) is responsible for the selective lysosomal degradation of cytosolic proteins with a particular pentapeptide motif (KERFQ), after targeting them with a cytosolic chaperone complex and by their selective translocation after binding to the lysosome-membrane associated protein type 2a (Lamp2a) (Cuervo et al., 2005).

The primary roles of autophagy are the baseline turnover of intracellular proteins and organelles, the production of amino acids in nutrient emergency, and the regression of retired tissues (Bergamini et al., 2007). But, in recent works, autophagy has started to be considered as a cytoprotective response during stress conditions (Cuervo, 2004; Moore, 2008) to remove toxic or altered components and unwanted or unnecessary organelles (mitochondrias, peroxisomes, etc...), recycling the components for reuse (Kim and Klionsky, 2000). These actions are a quality control mechanism for organelles, particularly important for neuron survival, since these might, otherwise, can lead to cell death by apoptosis (Erlich et al., 2006; Li et al., 2006; Cao and Klionsky, 2007). In this way, ROS induce cytoprotection since they are essentials to stimulate autophagy by boosting the activity of autophagic protein 4 (ATG4) (Scherz-Shouval et al., 2007). During intracellular stress, including the aggregation of misfolded proteins (Qin et al., 2003), the accumulation of altered organelles (Klionsky and Ohsumi, 1999; Klionsky and Emr, 2000) and during starvation and hypoxia conditions (Yen and Klionsky, 2008), the degradation by basal autophagy is increased to allow cell survival. Recently, the different types of macroautophagy have been characterized by the stimuli that mediate their activation or by the molecular mechanisms involved in the activation and execution of autophagy; basal in-bulk macroautophagy and starvation-induced autophagy are at the extremes of this scale, whereas quality-control autophagy and autophagy induced by protein aggregates, organelle stress or patho¬gen invasion are located in the middle levels of this classification (Wong and Cuervo, 2010) along with the essential properties of the cellular stress responses. Moreover, in non-physiological situations, autophagic cell death, known as type II non-apoptotic programmed cell death, which has been also reported in neurons (Larsen and Sulzer, 2002), shows a negative feedback on apoptosis; autophagy can lead to cell death when apoptosis is inhibited (Shimizu et al., 2004) and consequently, if autophagy is inhibited under nutrient starvation conditions, cell death by apoptosis is accelerated (Maiuri et al., 2007).

It is well-known that a decline of autophagic degradation in older tissues (Cuervo and Dice, 1998, 2000) impairs the cellular housekeeping process of aberrant and dysfunctional molecules, organelles and protein aggregates. Defective autophagy has been extensively linked to aging and the development of age-related neurodegeneration (review in Wong and Cuervo, 2010). At first sight, macroautophagy is altered during aging as a consequence of impaired autophagosomes formation or maduration to autophagolysosomes (Terman, 1995). In the brain of mice prone to accelerated senescence, control quality by autophagy is severely altered contributing to the accumulation of toxic protein aggregates that are already observed at early ages

(Caballero et al., 2008, 2009). In addition, it is well-known that defects in autophagic activity and the loss of the basal autophagy level causes neurodegeneration (Hara et al., 2006; Komatsu et al., 2006) such as occurs in AD and Huntington's diseases (HD) (Levine and Kroemer, 2008). Reduced autophagy induction, enhanced in the repression of autophagy, altered cargo recognition, inefficient autophagosome/lysosome fusion or inefficient degradation of the autophagic cargo in lysosomes are all potential defects that could influence the malfunctioning of macroautophagy in different neurodegenerative disorders (Wong and Cuervo, 2010). Indeed, Pickford et al. (2008) reported that cellular levels of autophagy-related protein beclin1 were often correlated with autophagic activity, and that the heterozygous deletion of beclin-1 leads to neurodegeneration (Pickford et al., 2008). Therefore, the elimination of basal neuronal autophagy is sufficient to cause neurodegeneration in the absence of other insults (Hara et al., 2006; Komatsu et al., 2006). Thus, it seems that increased autophagic activity might help to clear aggregates of toxic proteins (such as mutant α-synuclein and Huntingtin), which are associated with pathologies such as Parkinson's and Huntington's disease (Lee and Gao, 2008). However, autophagy functions may not always be beneficial (Hashimoto et al., 2009). For instance, Yu et al. (2005) demonstrated that induced neuronal macroautophagy in the presenilin (PS)/Aß precursor protein (APP)-mouse model of ß-amyloidosis was impaired causing the profuse accumulation of autophagic vacuoles (AVs) in dystrophic dendrites due to an impaired maturation of AVs to lysosomes (Yu et al., 2005). An extensive basal activation of autophagy, rather than the characteristic decline occurred during normal aging, could contribute to the systemic degeneration and premature aging observed in progeroid mouse models (Mariño et al., 2008). Therefore, the dual role of autophagy, in cytoprotection and cell death as well as its impact on longevity is one of the most fascinating features of this process, which clearly has a direct impact on age-related development of neurodegeneration (Table 1).

Autophagy and longevity: role of key regulators of cellular stress responses

The accumulation of cellular damage is the major hallmark of the aged cell; oxidized, misfolded, cross-linked or aggregated macromolecules and damaged organelles cannot function properly and can actively compromise cellular functions. However, the overall rate at which damage is accumulated is influenced by conserved longevity pathways and redox-sensitive transcriptional factors, which have key roles in cell responses to stress conditions. Autophagy activity is essential for life-span extension and cytoprotective responses during cellular stress because it can eliminate unwanted or damaged intracellular materials; this activity is, therefore, regulated by longevity proteins and redox-sensitive factors, thus making autophagy a central regulatory mechanism for aging (Salminen and Kaarniranta, 2009b). Thereby, we review the regulatory features of sirtuins, p53 proteins and the NF-κB system in autophagy activity with special emphasis on their impact in the aging brain or under neurodegeneration.

Autophagy and NF-κB activation

The NF-κB/Rel DNA-binding complexes contain the Rel family components, RelA/p65, c-Rel, and RelB, as well as the NF-κB components p50 (p105) and p52 (p100). The inhibitory IκB components α, ß, γ, ε and Bcl-3, the IKK kinases complex proteins IKKα and IKKß, and the regulatory NEMO protein can trigger NF-κB activation. The NF-κB complexes are normally located in the cytoplasm because they are bound to the inhibitory IκB proteins. Multiple stressors, such as oxidative stress, DNA damage and death receptor activation, induces the phosphorylation of the IκB proteins that are subsequently ubiquitinated and degraded via the proteasome. After their release from the IκB proteins, NF-κB complexes can translocate to nuclei and activate the transcription of a number of specific target genes, especially those of inflammatory genes that are up-regulated during aging (Haddad, 2002; Salminen and Kaarniranta, 2009a). NF-κB signaling is the master regulator of inflammatory and immune responses (Qing et al., 2006) and plays a key role in the cellular responses to oxidative stress (Michiels et al., 2002) by its antioxidant and anti-apoptotic functions (Tomas-Zapico and Coto-Montes, 2005). Remarkably, the NF-κB system is key in aging regulation since a reduced longevity could be due to the constitutive activation of NF-κB factor by ROS, which can lead to cancer, inflammation and others diseases related to aging (Libert et al., 2006). For this reason, the DNA-binding activity of the NF-κB complex is significantly increased in several rat and mouse tissues during aging (Salminen and Kaarniranta, 2009a). Moreover, NF-κB has been considered as a new therapeutic target against inflammatory damages associated with neuro-degenerative diseases (Camandola and Mattson, 2007). Inflammation is a potent inhibitor of autophagy (Salminen and Kaarniranta, 2009b), and remarkably, the activation of NF-κB system can suppress autophagy functions, thus contributing to neurodegeneration (Caballero et al., 2008, 2009). Other studies have also reported the reciprocal inhibition between autophagy and NF-κB activation (Djavaheri-Mergny et al., 2007; Zhu et al., 2011), therefore, NF-κB signaling might be considered as a potent inhibitor of autophagocytosis (Lee et al., 2007; Dan and Baldwin, 2008; Salminen and Kaarniranta, 2009b). Similarly, autophagy negatively regulates NF-κB through the autophagocytosis-mediated degradation of the NF-κB-inducing kinase (NIK) and IKK kinases (Qing et al., 2006, 2007). Notably, IKK can also promote the autophagic pathway in an NF-κB - independent manner (Criollo et al., 2010; Comb et al.,

2011). All these observations suggest that, the interaction between oxidative stress-induced NF-κB activation and autophagy activity is important in the regulation of cellular responses in the aged brain. Aging-related chronic inflammation by NF-κB activation can contribute to neurodegeneration by two ways; the defective/altered autophagy in neurons (Caballero et al., 2008, 2009) and cell death and inflammatory damages due to astrocytes activation (Hwang et al., 2010). Thus, it is reasonable that signaling via longevity factors, such as FoxOs and sirtuins, can inhibit the NF-κB system and simultaneously protect against chronic inflammation duration the aging process (Salminen et al., 2008) to improve longevity.

Sirtuins and autophagy

Lifespan extension seems to depend on the efficient maintenance of autophagic degradation (Hars et al., 2007; Jia and Levine, 2007; Cavallini et al., 2008; Vellai et al., 2009). Therefore, there is an increased interest in studying the longevity signaling pathways that can regulate autophagy. Considering that acetylation is an important post-translational modification, which regulates autophagosome formation (Lee et al., 2008), activity of sirtuins becomes more interesting for understanding the aging process. Sirtuins are NAD^+-dependent histone/protein deacetylases that are homologous to the yeast protein Sir2 (silent information regulator 2) (Sinclair et al., 1998). The mammalian sirtuins (SIRT1-SIRT7) have important functions in the regulation of metabolism, growth and differentiation, inflammation, cellular survival and aging (review in Salminen and Kaarniranta, 2009c). Oxidative stress, mitochondrial dysfunction, inflammation and defective autophagy are hallmarks of the aging process, and therefore, it is reasonable to think that the regulation of sirtuins in these processes is essential for longevity control. Moreover, sirtuins play a role in mitochondrial ROS production (Nakagawa and Guarente, 2011) and can also mediate peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α) effects to regulate

Table 1. An insight into the impact of changes in autophagy on neurodegeneration and longevity.

Positive or Negative effects of Autophagy in Neurodegeneration/Longevity	References
Life span-extending effect of the p53 orthologue CEP-1 mutation by increasing baseline autophagy in C.elegans	Tavernarakis et al. 2008
Promoting levels of autophagy in the nervous system enhances longevity and oxidant resistance in adult Drosophila melanogaster.	Simonsen et al., 2008
Autophagy is required for lifespan extension in various long-lived mutant organisms	Cuervo, 2008; Reviewed in Vellai et al., 2009
Autophagy is required for dietary restriction-mediated life span extension in C.elegans	Jia and Levine, 2007
Caloric restriction and resveratrol prolong longevity via the Sirt-1 dependent induction of autophagy	Morselli et al., 2010
Impairment of the ubiquitin-proteasome system or the autophagy-lysosome pathway predispose individuals to neurodegenerative disorders such as Parkinson's disease	Matsuda and Tanaka, 2010
Autophagy may also function to restrict lifespan in C.elegans	Hashimoto et al., 2009
Cytoprotective function of autophagy-lysosome pathway by disruption of the synthesis, transport, folding or glycosylation of ER-targeted in Drosophila	Arsham and Neufeld, 2009
Defective autophagy has been linked to age-related neurodegeneration development	Cao et al., 2006; Komatsu et al., 2006; Hara et al., 2006; Pickford et al., 2008
ß-amyloid production by accumulated autophagy vacuoles in dystrophic dendrites of the presenilin (PS)/A, precursor protein (APP) mice model	Yu et al., 2005
Autophagy activity helps to clear aggregated-prone proteins from the cytosol	Williams et al., 2006
Autophagy alterations in the brain of senescence accelerated mouse prone 8 (SAMP8)	Caballero et al., 2009; Ma et al., 2011
Increased autophagy clearance toxic proteins associated with pathologies such Parkinson's and Huntington's disease	Ferrucci et al., 2008; Lee and Gao, 2008
Autophagy has anti-aging effects being beneficial toward retardation of aging and prevention of age-related disease in humans	Bergamini et al., 2007
Autophagy induction in the systemic metabolic response associated with premature aging	Mariño et al., 2008
TOR-mediated autophagy suppresses cell death in Drosophila model of Huntington's disease	Wang et al., 2009a
Loss of PINK1 or Parkin results in failure of mitophagy and may contribute to the pathogenesis of Parkinson's disease	Geisler et al., 2010
Contribution of the autophagy-lysosomal genes deficits to Alzheimer and Parkinson diseases and potential involvement in tuberous sclerosis, neuronal ceroid-lipofuscinoses, sepsis and neoplasms	Jegga et al., 2011

mitochondrial biogenesis and the supply of new mitochondrias (Aquilano et al., 2010; Kong et al., 2010). Remarkably, SIRT1 is induced by calorie restriction increasing organism longevity in yeast, worms, flies and mammals (Guarente and Picard, 2005; Vellai et al., 2009); SIRT1 can be directly associated with the sirtuins-dependent induction of autophagy (Morselli et al., 2010) for the clearance of old and damaged organelles. In this regard, SIRT1 activity can regulate autophagocytosis by the direct deacetylation of autophagic proteins, such as ATG5, ATG7 and ATG8, thus activating the basal level of recycling autophagy activity (Lee et al., 2008). Likewise, SIRT1 activity can inhibit NF-κB-mediated transcription by the deacetylation of the RelA/p65 subunit of the NF-κB complex, protecting against age-related inflammation (Salminen et al., 2008) and hence also favoring autophagy functions. However, it should be noted that the activation of sirtuins, per se, induces the autophagy required for the lifespan-prolonging effects of caloric restriction and pharmacological Sirtuin-1 activators (Morselli et al., 2010). Sirtuins regulate not only several physiologic conditions (embryogenesis, glucose metabolism, apoptosis, autophagy, chromatin integrity, and transcriptional state) but also pathologic (diabetes, cancer, cardiovascular disorders, and neurodegeneration) conditions. Driven by all these considerations, sirtuins have been considered as novel therapeutic targets to treat age-associated diseases (Lavu et al., 2008). Under neurodegenerative conditions, SIRT1 appears to protect against certain forms of neuronal degeneration (Kim et al., 2007). In fact, SIRT1 activation by the natural phytocompound resveratrol, proved beneficial for reducing amyloid-beta protein accumulation in both *in vitro* and *in vivo* models of AD (Albani et al., 2009). Resveratrol and caloric restriction also induced neuroprotective actions by SIRT1 activation in Parkinson's disease, Huntington's disease and epilepsy (Qin et al., 2006; Albani et al., 2010). In this regard, several neurodegenerative conditions and other age-related pathologies can be benefit from the induction of basal autophagy though an increase of sirtuins activity (Lee et al., 2008). Remarkably, SIRT1 expression decreases with age in the senescent and neurodegenerative brain (Gutierrez-Cuesta et al., 2008), and autophagy is altered (Caballero et al., 2009; Wong and Cuervo, 2010). Therefore, the decreased SIRT1 expression in the aging brain might have two important consequences: to have a negative and direct effect on autophagy or to indirectly favor age-related inflammation through NF-κB activation, which also interferes in autophagy. Sirtuins likely play a key role in brain susceptibility to neurodegeneration during aging through its well-established effect on the regulation of autophagy in physiological and pathological conditions.

The p53 and autophagy

Considered the "guardian of the genome" and main tumor suppressor, the p53 transcriptional factor responds to a wide variety of stress signals, including DNA damage, hypoxia, heat/cold shock, nutrition starvation and oncogene activation, to maintain genomic stability by limiting the error frequency of cell growth and division. The p53-mediated cellular responses, such as cell cycle arrest, DNA repair and apoptosis, depend on cell type, environmental context and degree of stress (Feng, 2010). The relationship between p53 and aging appears to be complex. The p53 functions decline with aging, increasing tumor incidence in older organs (Feng et al., 2007). Remarkably, there is functional antagonism between p53 and NF-κB signaling; the aging-associated decline in p53 efficiency favors the NF-κB-mediated senescence and inflammation (Salminen and Kaarniranta, 2011). It is well-known that aberrant or non-regulated p53 activity could also accelerate aging (Serrano and Blasco, 2007). Indeed, mice models showing over-expressing of p53 and increased p53 activity present shortened life-spans (Tyner et al., 2002; Maier et al., 2004). However, mouse models with controlled, constitutive p53 activity are resistant to cancer and display a normal life span and aging (Garcia-Cao et al., 2002, 2006). In short, inappropriate p53 activity promotes aging, whereas the normal and robustly regulated p53 response provides protection from the aging process (Vigneron and Vousden, 2010). Furthermore, p53 can regulate aging by autophagy (Tavernarakis et al., 2008). Recently, it has been suggested a regulation of senescence by p53 due to its ability to promote or inhibit oxidative stress and autophagy according its level of acetylation, which will have contrary effects on longevity and aging (Vigneron and Vousden, 2010). In this regard, it is important to note that nuclear p53 can induce autophagy through its transcriptional effects, while cytoplasmic p53 acts as a master repressor of autophagy (Tasdemir et al., 2008; Green and Kroemer, 2009). Thus, loss of cytoplasmic p53 can induce autophagy in humans, mice and nematode cells (Tasdemir et al., 2008), and this effect has been linked to longevity in nematodes (Tavernarakis et al., 2008). The mechanism through which p53 can activate autophagy includes the down-regulation of IGF-1/AKT-1/mTOR pathways and the up-regulation of the transcription of autophagy proteins, such as the damage-regulated autophagy modulator (DRAM) and Sestrin2 (Green and Kroemer, 2009; Feng, 2010). However, as with aging, inappropriate p53 activity can contribute to neurodegeneration by inducing apoptotic and/or autophagic cell death (Wang et al., 2008, 2009b; Pehar et al., 2010). Interestingly, p53 was the first discovered non-histone target of SIRT1 (Luo et al., 2001). The deacetylation of p53 by SIRT1 leads to the inactivation of p53-mediated transcription (Vaziri et al., 2001; Luo et al., 2001), which is important in neuronal survival (Hasegawa and Yoshikawa, 2008). In fact, SIRT1 can regulate both types of known p53-mediated apoptotic pathways, transcriptional dependent and independent mechanisms (Yi and Luo, 2010) and, even, block the nuclear translocation of p53 induced by oxidative stress via deacetylation (Han et al., 2008). As a potent tumor

suppressor, SIRT1 can negatively regulate various tumor suppressors, including p53, ß-catenin and survivin (Yi and Luo, 2010) and SIRT1 interactions with p53 can also regulate both autophagic degradation and lifespan extension (Salminen and Kaarniranta, 2009c). Therefore, considering these observations, the regulation of p53 responses could favor autophagy and neuronal survival during the aging brain with an important positive impact on longevity and against neurodegeneration.

Autophagy in animal models of accelerated aging

SAMP8 mice are non-genetically modified mice that show a shortened life-span with important learning and memory deficits (Miyamoto et al., 1986, 1992; Miyamoto, 1997), which are also well-known age-related signs and symptoms of human aging. Interestingly, for the actual aging research, the SAMP8 mouse appears to be an excellent model for studying the mechanism of age-related cognitive dysfunction and neurodegeneration (Alvarez-Garcia et al., 2006; Caballero et al., 2008, 2009; Zhang et al., 2009), displaying degenerative changes caused by the impairment of oxidative metabolism (Zhang et al., 2009), resembling those observed in brain affected with AD (Diez-Vives et al., 2009). Indeed, oxidative-stress related alterations in SAMP8 mice are observed at early ages not only in the brain, but also in various key organs, such as the liver and spleen (Alvarez-Garcia et al., 2006; Lardone et al., 2006; Caballero et al., 2008, 2009). In addition, increased levels of protein carbonyl and several neurodegenerative markers, such as phosphorylated Tau in the neurofibrillary tangles, α synuclein (Alvarez-Garcia et al., 2006; Caballero et al., 2008) and ß-amyloid aggregates (Morley, 2002; Gutierrez-Cuesta et al., 2008), are described in the SAMP8 brain. The toxic protein aggregates from the aged brain of SAMP8 mice were also associated with deficits in specific lysosomal and cytosolic proteolytic activities (Caballero et al., 2009), although without an important neuronal loss by apoptosis (Takeuchi et al., 2000). Neurotransmission in the SAMP8 brain is also altered by a decrease in levels of NMDA (N-methyl-d-aspartic acid) (Tomobe and Nomura, 2009), MT-1 (high-affinity G-protein-coupled melatonin receptor) and ROR-α (Retinoic acid receptor-related orphan receptor alpha) receptors (Caballero et al., 2008) together with an early loss in adenosine receptors (Castillo et al., 2009). Inflammatory processes were driven by the strong activation of NF-κB in the SAMP8 brain (Caballero et al., 2008; Gutierrez-Cuesta et al., 2008). It is remarkable that, although our previous research did not show the activation of autophagy in the brain of 5 and 10-month-old SAMP8 mice (Caballero et al., 2009), more recent work have described autophagic markers in the 7-month-old SAMP8 brain, especially in the cortex and hippocampus, which decrease at 12-months of age, displaying autophagic vacuoles accumulation in the axons and cytoplasm in both areas, similar to late-onset AD (Ma et al., 2011). Therefore, it must be emphasized that the age-related autophagy alterations in the brains of SAMP8 mice can be associated with their susceptibility to age-related neurodegeneration and early cognitive decline.

Thus, taken together, there are several factors that might impair autophagy in the SAMP8 brain. Higher oxidative stress-induced NF-κB signaling in the SAMP8 brain (Caballero et al., 2008) would lead to age-related pro-inflammation (Rodriguez et al., 2007), and both factors are well-known autophagy suppressors (Salminen and Kaarniranta, 2009a,b). Notably, p53 was also increased with age in the SAMP8 brain (Caballero et al., 2009), but without a higher activation by acetylation (Gutierrez-Cuesta et al., 2008). Thus, the alteration of both the p53 and NF-κB responses might be also a key factor in regulating autophagy levels. Remarkably, SIRT1 expression decreased with age in the SAMP8 brain (Gutierrez-Cuesta et al., 2008). Therefore, the loss of this longevity factor, which plays a key role in autophagy induction (Lee et al., 2008), together with an increased inflammatory process and proteolytic deficiencies, might play a role in autophagy impairments in SAMP8. Moreover, the SAMP8 brain is also a useful model for glucose hypometabolism, which is also observed in the aged brain and with dementias (Kurokawa et al., 1996; Ohta et al., 1996). A diminished glucose metabolisms has been shown to induce the hyperphosphorylation of Tau (Planel et al., 2004) and increased production of the ß-amyloid peptide (Gabuzda et al., 1994) and both markers are also observed in the SAMP8 brain (Gutierrez-Cuesta et al., 2008; Caballero et al., 2009). More recent studies have revealed that these mice have low glucose levels in serum as compared with their control SAMR1 mice (Jiang et al., 2008). The energy production (ATP) in the central nervous system is based almost exclusively upon the oxidation of glucose, and in that way, diminished energy production in the brain down-stream impairs ATP-dependent processes, such as synaptic functions, ubiquitin-proteasome system degradation and, therefore, also autophagy degradation. Likewise, there is an increased glucose transport to the brain by increased GLUT3 expression in zones, such as the cortex, of the SAMP8 brain (Sato et al., 1994). Glucose, considered a pro-aging factor, could activate the insulin receptor signaling pathway (Kassi and Papavassiliou, 2008), leading to the subsequent activation of the mTOR complex, which inhibits several steps in autophagosome formation (Kamada et al., 2000). In this way, the increased glucose transport to the SAMP8 brain, together with a decreased glucose metabolism, could also negatively affect autophagy in these mice. Taken together, these results suggest that there are several longevity factors and oxidative/nitrosative stress-related signaling pathways that can disrupt cellular responses to increase the susceptibility of the SAMP8 brain to early neurodegenerative changes.

Finally, the Zmpste24-deficient mouse is a reliable model of human Hutchinson-Gilford progeria, a type of

accelerated aging in which autophagy plays an important role. These progeroid mice, display defects in nuclear architecture because Zmpste24 (also called FACE-1) is a metalloproteinase involved in the maturation of laminin A and is an essential component of the nuclear envelope. These nuclear envelope abnormalities are associated with premature aging and progeroids syndromes in both mice and humans (Mariño et al., 2008). Surprisingly, these prematurely-aged mouse models exhibit an extensive basal activation of autophagic degradation instead of the characteristic decline in this process that occurs during normal aging. Therefore, the increase in autophagy in Zmpste24-deficient mice was linked to severe metabolic alterations in glucose and lipid metabolism, which lead to elevated liver kinase B1 and the up-regulation of the AMP-activated protein kinase pathway, which ends with mTOR inhibition (Mariño et al., 2008). The authors noted that these metabolic changes, including lower insulin and glucose levels in blood, respectively, resemble those occurring under calorie restriction or in other situations reported to prolong life-span. In this regard, they have described a novel and paradoxical role for autophagic cellular degradative pathways during pathological aging processes (Mariño et al., 2008; Mariño et al., 2010). Remarkably, the chronic activation of autophagy can have a negative effect on cell death (Maiuri et al., 2007). Hence, the progressive muscle and cardiac deterioration in Zmpste24-deficient mice is related with uncontrolled autophagy activity (Mariño et al., 2008). In addition, the Zmpste24-deficiency mice show a stress signaling pathway associated with a strong hyperactivation of the tumor suppressor p53 (Varela et al., 2005), reflecting the key role of a deregulated p53 responses in premature aging, which might be also linked to autophagy impairment. Although, there is not relevant information about the changes on NF-κB signaling or longevity factor expression in these progeroid mice, it should be noted that defective NF-κB transcriptional activity has been previously shown in laminin A/C-deficient cells (Lammerding et al., 2004). Therefore, further alterations in cellular stress responses and longevity pathways might be involved in the up-regulation of autophagy in progeroid mice.

Concluding remarks

Aging and autophagy are two processes that are clearly dependent on increased ROS production, which maintain a narrow, though inverse, relationship. It seems that when people age, their autophagic capability becomes reduced. This review shows that molecules, such as sirtuins, p53 and NF-κB that are reported by many articles to be key players in longevity, also have an important role in autophagic regulation. The functions of these molecules in both processes are conflicting and, sometimes, confusing. Some reports show that, while sirtuins and nuclear p53 induce autophagy, NF-κB abolishes it (Fig. 2).

The relationship between aging and autophagy has yet to be elucidated. Although some advances have been made, results seem contradictory, and while certain aging animal models show that autophagy decreases with aging, progeria models present uncontrolled

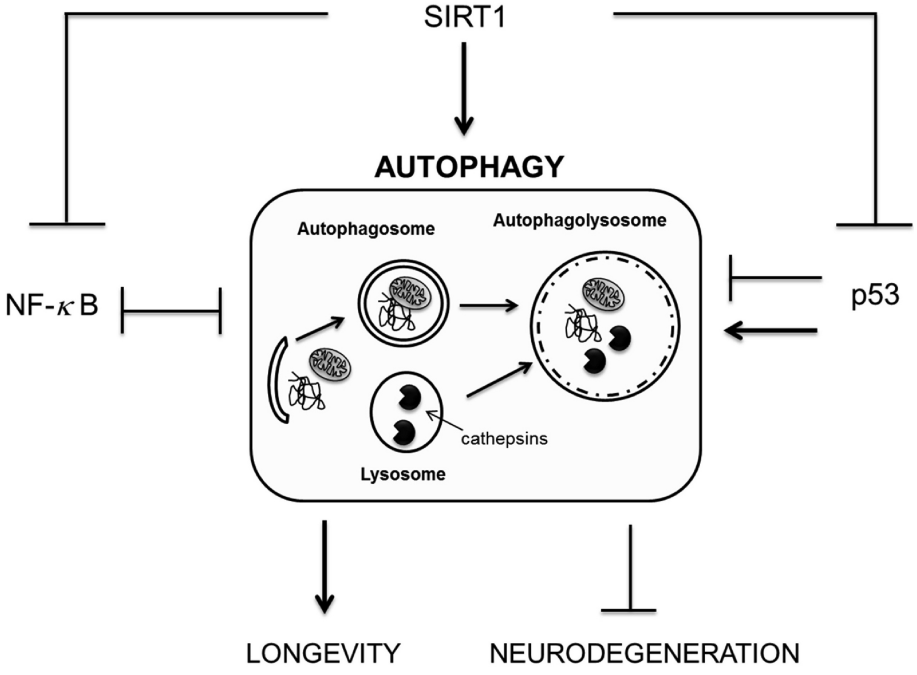

Fig.2. Influence of NF-κB, p53 and sirtuins on autophagy activity. The positive effect of autophagy on longevity can also be associated with its well-known negative regulation of neurodegenerative damages. Longevity factors, such as sirtuins 1 (SIRT1), can positively affect longevity by the direct activation of autophagy, which directly impact against neuro-degenerative levels. Likewise, there is a negative regulation of autophagy by oxidative stress-related transcriptional factors, such as NF-κB signaling and p53 activity. In fact, autophagy can be blocked by NF-κB-mediated inflammation and levels of autophagic activity can be modified according to the level of p53 acetylation.

autophagy increases.

Although this connection has huge research potential, further experiments are required to gain a better understanding for the complex interactions that exits among longevity, neurodegeneration and autophagy.

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