AGING AND GEROPROTECTIVE TECHNOLOGIES

p62: Intersection of Antioxidant Defense and Autophagy Pathways

G. A. Shilovsky[a, b, *, **]

[a] *Biological Faculty, Moscow State University, Moscow, 119991 Russia*
[b] *Kharkevich Institute of Information Transmission Problems, Russian Academy of Sciences, Moscow, 127051 Russia*
*e-mail: gregory_sh@list.ru
**e-mail: grgerontol@gmail.com

Abstract—Numerous regulatory cascades link the cell response to oxidative stress and the mechanisms that maintain homeostasis and cell viability. The review summarizes the molecular mechanisms of interaction of the autophagy protein p62 with cell defense systems, primarily through the NRF2/KEAP1/ARE pathway. Understanding the cross-regulation of antioxidant defense and autophagy pathways contributes to the search for promising molecular targets to prevent and treat age-related diseases.

INTRODUCTION

In mammals, the Kelch-like ECH-associated protein 1 (KEAP1[1])/NFE2 (nuclear factor, erythroid derived 2)-related factor 2 (NRF2)/antioxidant response element (ARE) pathway and autophagy are main intracellular systems that protect the cell from oxidative stress and maintain homeostasis [1–3]. The transcription factor (TF) NRF2 was initially identified as a main redox homeostasis regulator that controls expression of certain genes involved in alleviating oxidative and electrophilic stresses. However, a far broader range of roles is played by NRF2 in regulating many processes involved in the cell stress response. NRF2 was shown to regulate expression of the genes that control ferroptosis, which is an iron and lipid peroxidation-dependent form of cell death [2]. An increasing number of studies are now focusing not only on the classic NRF2 role (induction of genes coding for antioxidant defense and detoxification proteins), but also on the NRF2 roles in other cell processes, including inflammation [4], the regulation of circadian biorhythms [5], and cell death in normal conditions and in conditions of aging-associated disorders [6, 7]. The function of endothelial cells is affected by NRF2 via multiple mechanisms, and advantages and drawbacks of NRF2 activation in the endothelium of the cardiovascular system were studied in normal and pathological conditions [8]. The NRF2 role in atherosclerosis is still incompletely understood; i.e., both protective effects and proatherogenic activity

were reported for NRF2 from different studies (for a review, see [8]). Beneficial effects of NRF2 activation are that oxidative stress and inflammatory activation of the endothelium are reduced, the normal function of mitochondria is restored, and NO bioavailability is increased by preventing eNOS uncoupling. Negative effects are also known for NRF2. For example, NRF2 increases expression of the *NOX4* gene for NADPH oxidase, which is responsible for generation of reactive oxygen species (ROS). A dual role in carcinogenesis is played by NRF2. On the one hand, NRF2 is involved in the mechanisms that protect normal cells from mutagenesis and malignant transformation. On the other hand, the survival of cancer cells is facilitated by the same mechanisms after their development. The angiogenesis-stimulating properties of NRF2 promote vascularization of tumors and thus further contribute to tumor progression [8]. The functions of proteins that regulate autophagy and the KEAP1/NRF2/ARE signaling cascade are considered comprehensively in this review.

SIGNALING PATHWAYS INDUCING NRF2 ACTIVITY

Several levels are known for NRF2 regulation. The TF NRF2 ensures cell adaptation to oxidants and electrophiles mostly because stress induces modification of the cysteine thiol groups in KEAP1, which acts as a NRF2 repressor and interact with Cullin-3 RING (CRL) ubiquitin ligase to form the CRL−KEAP1 complex. Cysteine modification in KEAP1 blocks CRL−KEAP1 activity, and newly synthesized NRF2

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[1] All genes and proteins are designated as accepted for human cells, if not otherwise specified.

consequently accumulates in the nucleus de novo and induces expression of its target genes.

A main mechanism that stabilizes NRF2 in the cell is based on the accumulation of proteins that distort the association between KEAP1 and NRF2 by competing with NRF2 for binding sites on KEAP1. The set includes p62 (a protein important for autophagy), Hrd1 (an adapter protein), p21, PALB2, PGAM5, WTX, and the IκB kinase subunit β (IKKβ) (a regulator of the nuclear factor κB (NF-κB) pathway). The E(S)T/L/NGE conserved motif is found in each of the proteins [9]. KEAP1 was detected in mitochondria and found to interact with PGAM5 there [10, 11]. KEAP1 is crucial for maintaining mitochondrial homeostasis. For example, p62 recruits KEAP1 into mitochondria and acts together with RBX1 to mediate mitochondrial ubiquitination, thus preventing the formation of dysfunctional megamitochondria and alleviating alcohol-related liver disease [12]. The β-transducin repeat-containing protein (β-TrCP), which is a component of the SKP1−Cullin-1−F-box ubiquitin ligase complex (SCF−β-TrCP), also possesses NRF2-inhibiting activity. However, generation of a phosphodegron in NRF2 by glycogen synthase kinase 3 (GSK3) is inhibited by stimuli that activate protein kinase B (PKB)/AKT. In particular, phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin complex 2 (mTORC2) are capable of increasing PKB/AKT activity. This property explains why genes regulated via antioxidant response elements (AREs) are induced by growth factors and nutrients [13].

KEAP1−NRF2−ARE SYSTEM AND AUTOPHAGY

Apart from oxidative (electrophilic) stress, distorted protein turnover activates the NRF2 system [14]. The KEAP1−NRF2−ARE signaling pathway is redox sensitive and functionally interacts with the autophagy system [14, 15]. The multifunctional cytoplasmic protein p62 (also known as sequestosome 1 (SQSTM1)) plays an important role in the autophagy-related regulation of NRF2 [16]. A higher p62 concentration is necessary for p62-mediated NRF2 induction, making it more likely that p62 competitively displaces NRF2 from its complex with KEAP1. This mechanism probably works in the case of long-term NRF2 activation because NRF2 upregulates p62 expression by binding to the ARE-containing promoter of *SQSTM1*, which codes for p62. Thus, p62 is a product of a NRF2 target gene; i.e., there is a positive feedback loop in expression of the two proteins. An accumulation of p62 facilitates NRF2 activation, and activated NRF2 acts to further increase the p62 level [15]. An increasing p62 pool sequesters KEAP1, thereby stabilizing NRF2 and maintaining its activity [15]. KEAP1 is degraded via p62-dependent autophagy [17], which is preceded and facilitated by KEAP1

ubiquitination [18]. The KEAP1 potential to repress NRF2 is reduced by p62 via mechanistic mammalian target of rapamycin complex 1 (mTORC1). Thus, the PI3K/AKT activation cascade and mTORC1 are involved in the p62−NRF2 axis in mammals. NRF2 positively regulates mTOR expression [19]. The p62 protein interacts with the molecules that interact with mTOR and form the mTORC1 complex [20]. mTORC1 promotes transmission of cell growth signals, and its mutations were identified in several human cancers [21].

Cytoprotective activity of NRF2 is not restricted to its classic target genes because products of other ARE-containing genes also possess anti-inflammatory activity [22] and are involved in proteasomal degradation of oxidized proteins [23].

Distortion of autophagy in the liver hinders p62 turnover and causes severe damage to the organ. The process is accompanied by the formation of inclusion bodies, which contain p62, KEAP1, and ubiquitinated proteins, and leads to higher expression of NRF2 target genes [14]. NRF2 elimination can compensate for liver injury in this model. Therefore, constitutive activation of NRF2 in conditions of defective selective autophagy is harmful to the functional integrity of hepatocytes. The NRF2/ARE system is additionally involved in transmitting signals for hepatocyte death, including death via ferroptosis [24].

STRUCTURE AND MECHANISM OF ACTION OF p62 (SQSTM1)

The p62 protein has six conserved domains, which interact with proteins involved in various signaling cascades (Fig. 1). The domains include a Phox and Bem1p (PB1) domain, a ZZ-type zinc finger (ZZ) domain, a TRAF6-binding (TB) domain, a ATG8/LC3 interaction region (LIR), a KEAP1 interaction region (KIR), and a ubiquitin-associated (UBA) domain. The N-terminal PB1 domain of p62 forms oligomers and dimers with other proteins, including atypical protein kinase C (aPKC) and extracellular signal-regulated protein kinase (ERK). The ZZ domain has a zinc finger structure, which allows p62 to act as a TF and to bind to DNA. Utilizing its TB domain, p62 binds with TNF-α receptor-associated factor 6 (TRAF6) and activates NF-κB, thus modulating the inflammatory process. The C-terminal domains LIR, KIR, and UBA serve to bind KEAP1 and ubiquitinated proteins and to stimulate their degradation via autophagy. KIR is structurally similar to the ETGE sequence of NRF2, and p62 is consequently capable of interacting with KEAP1 to disrupt its association with NRF2 and to induce its subsequent ubiquitination. In addition, the interaction of p62 with KEAP1 leads to KEAP1 degradation via the autophagy pathway [26].
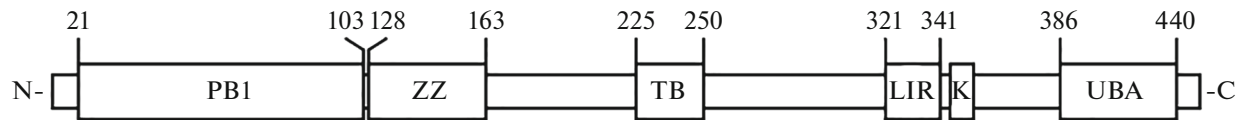
Fig. 1. Structural organization of p62. The domain structure of human p62 (440 aa): residues 21−103, the PB1 domain with the Phox and Bem1p motifs; 128−163, the ZZ zinc finger domain; 225−250, the TRAF6-binding (TB) domain; 321−341, the LC3 interaction region (LIR); 346−359, the KEAP1 interaction region (K); and 386−440, the ubiquitin-binding domain (UBA).

The LIR domain is responsible for the role of p62 in autophagy signaling and directly interacts with the autophagy marker microtubule-associated protein 1A/1B-light chain 3 (LC3) [27]. LIR binds with ATG8/LC3 [25], which occurs on autophagosome membranes. Cargoes recruited by p62 are consequently included in autophagosomes. Oxidative stress sensitivity was reported for p62 and assumed to facilitate the activation of autophagy [28].

In addition, p62 harbors binding sites for many other functionally important proteins, including ubiquitin, KEAP1, etc. This allows p62 to compete with NRF2 for KEAP1 binding and to activate the NRF2 pathway [14, 26]. The C-terminal UBA domain of p62 binds with ubiquitin to recruit polyubiquitinated protein. A receptor role of p62 was observed in many forms of selective autophagy [29]. Two types of autophagy are possible to recognize: microautophagy and macroautophagy. The former is chaperone-mediated autophagy (CMA), is triggered via active involvement of the HSC70 chaperone, and targets certain proteins to the lysosome for degradation. HSC70 targets the protein intended for degradation to the LAMP-2A receptor on the lysosome surface. In macroautophagy, a membrane structure known as the autophagosome forms to engulf the cell material that needs to be degraded. ATG family proteins play a main role in the process, and one of them, ATG8/LC3, provides a marker of the start of autophagy [30].

Nonselective autophagy occurs in cells exposed to nutrient deficiency. Selective autophagy works to selectively eliminate particular organelles to regulate their number in this situation. Mitophagy is a particular case of selective mitochondrial autophagy [31]. Mitophagy depends on PTEN-induced kinase 1 (PINK1). PINK1 contains a mitochondrial targeting sequence (MTS). In the absence of mitochondrial damage, PINK1 penetrates through the outer (via the TOM complex) and inner (via the TIM complex) membranes into mitochondria. PINK1 is partly cleaved on the inner membrane to produce the pre-senelins-associated rhomboid-like protein (PARL). This PINK1 form is cleaved by mitochondrial matrix proteases [32]. In damaged mitochondria, the inner membrane is depolarized and TIM-mediated protein import is consequently altered. PINK1 consequently fails to reach the mitochondrial matrix and to undergo its normal cleavage, but accumulates on the outer mitochondrial membrane. This activates cytosolic E3 ubiquitin ligase PARKIN, which ubiquitinates proteins on the outer mitochondrial membrane and thus triggers mitophagy (Fig. 2). PARKIN promotes K63-associated polyubiquitination of mitochondrial substrates and recruits ubiquitin- and LC3-binding p62 to mitochondria [33].

A complex that includes RIP kinase, aPKC, TRAF6, and K63 ubiquitin ligase plays a crucial role in IKKβ phosphorylation, which is important for activation of the NF-κB TF [34]. A higher p62 level was found to correlate with a higher production of interleukin 1β (IL-1β). It was found that p62 binds with c-Jun N-terminal kinase (JNK) and ERK and thereby increases the activation of NF-κB and, consequently, IL-1β expression. In addition, caspase-1 activation in inflammasomes, which is necessary for IL-1β proteolytic processing, is promoted by p62 accumulation [35].

The p62 protein acts as an adaptor molecule that directly interacts with ubiquitinated molecules on the autophagosome. Elimination of p62 completely blocks damaged mitochondrial clearance [36]. Thus, activation of the PINK1/PARKIN/p62 axis (Fig. 2) plays an important role in selective elimination of damaged mitochondria and, therefore, mitochondrial quality control. It should be noted that a PINK1/PARKIN-independent pathway is also possible for p62-mediated ubiquitination and mitophagy [37].

Two ubiquitin-like protein conjugation systems are known to be necessary for autophagosome biogenesis: ATG12-ATG5-ATG16 and ATG8. Augophagy, which is essentially nonselective, was assumed to be selective in part. Selective autophagy substrates include damaged mitochondria; intracellular pathogens; and even a subset of cytosolic proteins recognized by ubiquitin-binding autophagy adaptors, such as p62, NBR1, NDP52, TAX1BP1, and Optineurin. The adaptor proteins selectively recognize the autophagic cargoes and mediate their delivery into autophagosomes by binding with small ubiquitin-like modifiers of the ATG8/LC3 family [38, 39]. Among the proteins, p62 is the best characterized as a protein that mediates autophagic clearance of polyubiquitinated cargoes, such as aggregated proteins [40].

Neighbor of BRCA1 gene 1 (NBR1) is another adaptor employed in selective autophagy. NBR1 utilizes its PB1 domain to interact with p62 and its UBA and LIR domains to play a role in recruiting and autophagosomal degradation of ubiquitinated proteins
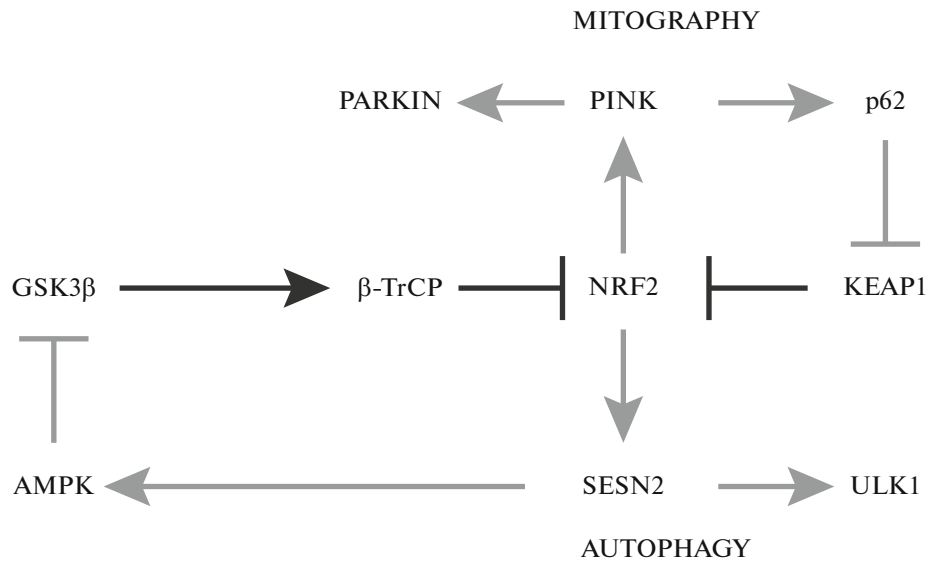
MITOGRAPHY

Fig. 2. NRF2 regulation pathways in mitophagy and autophagy. The simplified scheme consists of two regulatory loops. One includes p62, KEAP1, and NRF2. The other includes 5'-AMP-activated protein kinase (AMPK), sestrin 2 (SESN2), and UNC-51-like autophagy activating kinase 1 (ULK1). Sharp arrows indicate direct stimulatory effects, including catalysis; blunt arrows indicate inhibitory or suppressor effects on NRF2 activity or expression.

[25]. Optineurin and NDP52 were described as xenophagy receptors, which involve autophagy machinery in eliminating ubiquitinated intracellular pathogens [41]. Both of these adaptors play a role in protein aggregate clearance [42, 43] and are necessary for the regulation of NF-κB signal transmission [44]. While all of the above receptors mediate degradation of ubiquitinated proteins, more specific adaptors are known to mediate elimination of damaged or excess mitochondria (e.g., yeast Atg32 and mammalian NIX) or peroxisomes (e.g., yeast Atg30 and Atg36). The adaptors recognize their particular binding partners on the surface of their target organelles and utilize their LIR domains to deliver their cargoes to a maturing autophagosome [33]. Phylogenetic and interaction network analyses showed that the function of the ATG proteins is conserved even in plants of the genus *Arabidopsis* and the barrelclover *Medicago truncatula* [45]. In plants, a functional hybrid homolog of p62 and NBR1 (NBR1 in *Arabidopsis* and Joka2 in *Nicotiana*) plays an important role in utilization of polyubiquitinated proteins accumulated in abiotic stress [46, 47].

ROLE OF p62 IN AUTOPHAGOSOME FORMATION

A direct interaction between p62 and ubiquitin is known to be rather weak, and the formation of polyubiquitinated aggregates consequently starts with p62 auto-oligomerization via the PB1 domain [29]. An initial simple hypothesis assumed that protein aggregates intended for degradation are delivered by attaching a polyubiquitin side chain to the cargo and anchoring ATG8/LC3 on the phagophore surface with the

help of p62. The situation was found to be more intricate in recent studies. Both UBA domain−ubiquitin and LIR−ATG8 interactions are weak.

Homodimerization of the UBA domain is partly responsible for its low affinity for ubiquitin, mutually excluding ubiquitin binding [48]. Affinity increases when the UBA domain is phosphorylated at S403 of by casein kinase 2 (CK2) and TANK-binding kinase 1 (TBK1) [49]. Inhibition of S403 phosphorylation in p62 facilitates the formation of perinuclear aggresomes of ubiquitinated proteins, providing an important mechanism of cell defense against proteasomal dysfunction. Phosphorylation of T269/S272 in p62 inhibits S403 phosphorylation, thus increasing the formation of ubiquitinated protein aggresomes and protecting the cell from proteotoxic crisis [49].

The LIR motif of p62 has the sequence DDDWTHL and binds with LC3B in a micromolar concentration range [40]. Oligomerization mediated by the PB1 domain allows p62 to tightly and selectively bind the cargo, including misfolded proteins accumulating ubiquitin [50]. A similar effect was observed for the LIR−LC3B interaction, i.e., PB1-mediated oligomerization leads to a binding with LC3 clustered on the membrane with very high affinity, such that a dissociation rate is almost zero [50]. This tight interaction enables p62 to bend the membrane around the cargo; the property is preserved in yeast Atg19 [50]. In fact, aggregates containing p62 and ubiquitinated proteins provide an initial scaffold for autophagosome biogenesis, possibly acting via a binding of several ATG proteins [29, 51]. Moreover, phagophores were reported to form predominantly in p62 aggregates neighboring

lysosomes in *Drosophila melanogaster* cells, the location being similar to that of the phagophore assembly site (PAS) near a vacuole or a lysosome in yeast *Saccharomyces cerevisiae* cells [52]. In addition, p62 interacts with mTORC1 [53]. The latter binds to lysosomes, promoting the cell growth and inhibiting autophagy via phosphorylation of ATG1 (ULK1/2) [54, 55]. Then ATG8/LC3 is recruited to the nascent phagophore and interacts with p62 and other proteins to produce a p62-containing aggregate engulfed by the double membrane [56]. Deubiquitinase Leon/USP5 also interacts with ATG1/ULK1, thereby negatively regulating the autophagy process [57].

ROLE OF p62 IN REGULATION OF AUTOPHAGY

As early as 2011, Duran et al. [19] reported that activation of the mTORC1 complex promotes its translocation onto the lysosome surface and concluded that a decrease in p62 or mTORC1 inactivation may stimulate autophagy. However, Zhou et al. [46] showed that p62 releases the ATG6 homolog Beclin1 by breaking its association with BCL-2 in HEK293 and HeLa cells and thus positively regulates the induction of autophagy. In addition, p62 interacts with histone deacetylase 6 (HDAC6) and regulates its activity. HDAC6 acts to modify the F-actin network, which is involved in selective autophagy [58].

A silencing of *SQSTM1*, which codes for p62, in carcinoma cells caused the formation of abnormal autophagosomes and eventually led to autophagic cell death [59]. Thus, the role of p62 in autophagy induction is intricate and probably depends on particular conditions. The p62 protein can shuttle between the nucleus and the cytoplasm and export the ubiquitinated substrates from the nucleus into the cytosol, where autophagy proceeds most intensely [60].

Numerous cell organelles, such as nucleoli, P granules, stress granules, and PML bodies, are sufficiently stable. Many of these membraneless organelles are thought to form via phase separation and condensation of high-molecular-weight compounds (proteins, RNA, and DNA) to produce large aggregates [61–63]. In addition to the organelles, temporary cell condensates (puncta) also form via phase separation [64]. Biomolecules contained in condensates differ in mobility, conferring different physical properties on the condensates. Condensates that form via liquid–liquid phase separation are characterized by a high mobility of macromolecules concentrated within them [61, 62]. While exact molecular mechanisms underlying liquid–liquid phase separation are still poorly understood, low-affinity multivalent interactions of macromolecules seems to be responsible for the phenomenon [61]. The presence of unstructured regions promotes liquid–liquid phase separation [65]. It is of interest that filamentous oligomers of p62 and ubiquitin possess these properties. On the one hand,

the UBA domain of p62 interacts with ubiquitin with micromolar affinity and is connected with the other part of p62 by an extended unstructured region. On the other hand, ubiquitin chains harbor many interaction sites for p62 [66].

LEVELS OF p62 REGULATION

The p62 regulation occurs at transcriptional and posttranscriptional levels. Transcription of the *SQSTM1* is regulated by the TFs NF-κB, AP-1, and farnesoid X receptor (FXR) [67]. In addition, *SQSTM1* is a NRF2 target. ARE is contained in region −1306...−1295 of *SQSTM1*, thus forming a positive feedback loop [15]. Ubiquitination of KEAP1 strengthens its interaction with p62, although Sestrins make the greatest contribution to the process [68, 69]. The promoter of the *SESN2* gene, which codes for Sestrin 2 (SESN2) contains ARE, which enhances the activating effect of SESN2 on the KEAP1/NRF2/ARE system via positive feedback [68] (Fig. 2). SESN2 is capable of forming complexes with p62 and KEAP1 and inhibiting mTORC1 to activate autophagy. To facilitate mitophagy as a special form of autophagy, SESN2 inhibits mTORC1 or utilizes other mechanisms, such as interactions with the p62 autophagic receptor and RBX1 E3 ubiquitin ligase RBX1 [70, 71].

The mechanism whereby Sestrins activate autophagy and mitophagy includes mTORC1 inhibition and ULK1 activation, which help to reduce the ROS level and to eliminate dysfunctional mitochondria. ULK1 phosphorylates SESN2 to induce mitophagy, and phosphorylated SESN2 activates ULK1 to further stimulate autophagy via positive feedback (Fig. 2).

Sestrins increase the insulin sensitivity by blocking the mTORC1 and ribosomal protein S6 kinase B1 (p70S6K1) pathway, which is responsible for degradation of insulin receptor substrate 1 (IRS1). IRS1 is necessary for signal transmission from the insulin receptor to PI3K and subsequent activation of kinases PDK1 and mTORC2 and AKT phosphorylation. An increase in SESN2 expression stimulates AMPK activation and mTORC1 inhibition, thus maintaining high AKT activity and facilitating suppression of gluconeogenesis and a decrease in blood sugar [72]. In addition, Sestrins reduce lipid accumulation and endoplasmic reticulum stress by inhibiting mTORC1 via activation of AMPK and binding of GATOR2 (GAP activity towards Rags 2) [69, 73]. In addition to their role in the general regulation of autophagy, SESN2 controls specific cleavage of proteins in lysosomes. AMPK was shown to activate NRF2 by inhibiting glycogen synthase kinase 3 β (GSK3β) [74]. Convergence of the AMPK and NRF2 pathways is of importance, for instance, for the anti-inflammatory effect of berberine on lipopolysaccharide-stimulated macrophages and mice exposed to endotoxin shock [75]. AMPK activation leads to metabolic reprogram-

ming to more intense catabolism and less intense anabolism by phosphorylating the key factors in many biosynthetic pathways and, in particular, mTOR [76, 77]. The well-known tumor suppressor serine/threonine kinase 11 (STK11, or liver kinase B1 (LKB1)) also acts as an AMPK activator [78−80]. Experiments with tissue-specific *Lkb1* knockouts in mice showed that Lkb1 acts as a main mediator of adaptive AMPK activation in energy stress in most tissues. The finding gave grounds to conclude that a connection exists between the regulation of energy metabolism and tumor suppression [78, 79].

SESN2 plays an important role in regulating mitophagy in inflammation and sepsis. For example, SESN2 controls the recognition and delivery of damaged mitochondrial fragments into autophagosomes by interacting with p62, which acts as a transporter of autophagosome substrates [81]. Interacting with KEAP1, p62, and RBX1, Sestrins cause degradation of KEAP1 and subsequent activation of NRF2 [70]. SESN2 binds with NRF2 not only to regulate its stability, but also to maintain its transcriptional activity in the nucleus [82]. SESN2 decreases NOX4 expression and thereby performs the antioxidant function in certain cells, for example, in renal glomeruli [83].

As mentioned above, the E(S)T/L/NGE and ^{349}STGE^{352} motifs of p62 are similar, in particular, to the KEAP1-binding motif ^{79}ETGE^{82} of NRF2. Therefore, p62 is capable of competing with NRF2 for KEAP1 binding. When autophagy is distorted, the p62 level increases to cause KEAP1 degradation and thus to stabilize NRF2 [14]. KEAP1 interacts with p62 when the STGE motif is phosphorylated in p62. Its phosphorylation is performed by mTORC1 [84] or TGF-β-activated kinase 1 (TAK1) [85, 86]. The negative charge of the motif increases upon serine phosphorylation, thus allowing the motif to interact with positively charged residues of the Kelch domain of KEAP1. KEAP1 affinity for KIR of p62 is slightly lower than for DLGex (NRF2 region M17−Q51, which is important for the interaction with KEAP1) and substantially lower than for the ETGE motif of NRF2 [14]. The structural similarity of the KEAP1-binding sequences of p62 and NRF2 consequently plays no role in the classic activation of the NRF2/KEAP1/ARE system by electrophilic compounds. As already mentioned, an increase in p62 concentration is necessary for the p62-mediated induction of NRF2 expression because a higher p62 concentration makes it more likely that p62 competitively displaces the NRF2 DLGex motif from its complex with KEAP1. This mechanism probably works only in the case of long-term NRF2 activation, when NRF2 increases p62 expression by binding to the promoter of the p62 gene. As a result, abundant p62 molecules sequester KEAP1 to stabilize NRF2 and to maintain its activity [15]. Phosphorylation of S349 in human p62 (S351 in mouse p62) significantly increases p62 affinity for KEAP1 to a level that is higher than KEAP1 affinity for the ETGE motif of NRF2 and certainly for DLGex [84]. The modification is possible when p62 is preliminarily phosphorylated at S403 by TBK1 and forms aggregates with other p62 molecules and ubiquitinated targets. The resulting aggregates provide targets for autophagy and, on the other hand, act as sites of KEAP1 sequestration, which leads to NRF2/ARE induction [84]. KEAP1 facilitates autophagic clearance of ubiquitin aggregates by interacting with p62 and LC3. In response to selective autophagy, KEAP1 is transferred into inclusion bodies upon its iteraction with p62 [15]. KEAP1 colocalizes with p62, and their colocalization promotes KEAP1 degradation [87]. The p62−KEAP1 interaction becomes tighter when p62 is involved in phase separation (and appears as inclusions (puncta)) that is controlled by cytoplasmic death-associated protein 6 (DAXX) [88]. Mutations that affect KIR of p62 and abolish the p62 interaction with KEAP1 are found in various pathologies, such as amyotrophic lateral sclerosis [89].

In addition, KEAP1 interacts with the autophagy regulator ATG5 [90]. Direct interactions of KEAP1 were observed with the proteasome subunits PSMD2 and PSMD4 and segregase Vcp/p97 [9], which negatively regulates the NRF2 stability [91]. Several KEAP1 mutations collectively known as ANCHOR (additionally NRF2-complexed hypomorph) were found to strongly affect the association with NRF2, to stabilize the tertiary structure of KEAP1, and to induce the formation of p62-dependent phase-separated spherical clusters. A cluster contains a KEAP1-positive core, which is surrounded by unmodified and phosphorylated p62, polyubiquitin, and NRF2. The studies made it possible to better understand the molecular mechanisms that sustain the regulation and subcellular localization of KEAP1 and the effects of mutations on the KEAP1 conformational cycle and transcription of NRF2 target genes [9].

Arginylation of the N end in proteins is another mechanism that regulates autophagy with the involvement of p62 [92]. In addition to generating substrates that carry the N-degron and are targeted for proteolysis, N-terminal arginylation can trigger selective microautophagy by activating autophagic N-recognin and p62 [93, 94]. Zhang et al. [95] and Cha-Molstad et al. [96] showed that the N-terminal arginine (N-degron) of a protein binds with the ZZ domain of p62 and thus facilitates the elimination of the protein. In addition, arginyl-tRNA transferase 1 (ATE1) and p62 were found to cluster together with their cargoes. It is possible to assume that ATE1 clustering and assembly of p62 bodies provide a mechanism whereby ATE1 sustains arginylation and subsequent autophagic utilization of accumulating substrates [97]. In the case of lipophagy, p62 bound with N-terminal Arg undergoes autopolymerization and recruits LC3$^+$ phagophores to the site of lysosomal

degradation of lipid granules. Mice with a liver-specific *Ate1* knockout develop severe nonalcoholic fatty liver disease when fed a high-fat diet. Small-molecule p62 agonists were found to facilitate lipophagy and to exert a therapeutic effect in obesity and hepatic steatosis in wild-type mice, but not in mice knocked out in the p62 gene (*Sqstm1*) [98].

The ubiquitous expressed transcript (UXT) was shown to facilitate p62-mediated selective autophagy [99, 100]. UXT binds to protein aggregates and the PB1 domain of p62 to form oligomers and thus to increase the p62 clustering. This ensures a more efficient p62 targeting to protein aggregates and facilitates the formation of p62 bodies and their elimination via autophagy [99, 101]. UXT-V2 (a truncated UXT isoform that is 157 aa in size, while UXT-V1 has additional 12 aa on the N end) specifically interacts with stimulator of interferon response cGAMP interactor 1 (STING1), which is a main adaptor protein of the cyclic GMP-AMP synthase (cGAS)/STING1 signaling pathway [101]. However, excess or long-term STING1 activation is associated with autoinflammatory and autoimmune disorders. Preventing excess STING1 activation is therefore of importance for maintaining immune homeostasis. STING1 undergoes selective autophagic degradation upon its interaction with p62 [100]. Yoon et al. [99] showed that ectopic expression of human *UXT* in a *Xenopus* model delays motor neuron degeneration induced by a mutant form of superoxide dismutase 1 (SOD1) and that specific disruption of the UXT−p62 interaction inhibits UXT-mediated protection. The findings make it possible to assume that UXT functions as an adaptor of p62-dependent autophagy [99]. The UXT-V2 isoform of UXT acts as a transcriptional cofactor and interacts with p65, which is a component of the NF-κB transcriptional enhanceosome, which is responsible for the development of inflammation. A decrease in endogenous UXT-V2 increases apoptosis induced by TNF-α [101, 102].

Compounds that increase the p62 level, such as rapamycin [103] and trehalose [104], were evaluated in phase II and phase III clinical studies as potential drugs to treat diabetes mellitus, systemic lupus erythematosus, and autosomal dominant polycystic kidney disease. Therapeutic fasting increases AMPK activity and inhibits mTORC1. The effects presumably decrease S351 phosphorylation in the STGE motif of p62 and minimize autophagosome-mediated degradation of KEAP1. A high-carbohydrate diet resumed after fasting increases KEAP1 degradation via a combined effect of p62 and SESN1/SESN2, leading to the induction of NRF2 target genes [70].

CONCLUSIONS

Autophagy is responsible for degradation of intracellular proteins and damaged organelles in stress induced by endogenous or exogenous factors (oxidative, hypoxic, and endoplasmic reticulum stresses) and in starvation due to nutrient and growth factor deficiencies [105−107]. Oxidative stress is not only a cause of mitochondrial dysfunction, but also a consequence of alterations in mitochondrial quality control. An imbalance arises when mitochondrial biogenesis and mitophagy are dysregulated [108]. Suppression of mitochondrial biogenesis and activation of mitophagy lead to energy deficiency. To the contrary, when mitophagy is inhibited and mitochondrial biogenesis activated, many damaged mitochondria accumulate in the cell. These mitochondria produce ROS to high levels, but fail to meet the energy demand because their respiratory chain is nonfunctional [109]. NTF2 can rescue the cell in this case, forming the regulatory loops to play its role in mitochondrial biogenesis. For example, NRF2 increases expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), which is a main regulator of mitochondrial biogenesis, and nuclear respiratory factor 1 (NRF1), which regulates transcription of mitochondrial DNA. In turn, PGC-1α inactivates GSK3β through p38 [110], thus blocking one of the NRF2 inactivation pathways (see Fig. 2). Blockage of another NRF2 inactivation pathway involves interactions with p62, which interacts with the NRF2 inhibitor KEAP1. The NRF2-dependent regulation of mitophagy is not restricted to the above mechanisms. The TF NRF2 regulates expression of PINK1, which plays a key role in inducing mitophagy. It is of importance for cell viability that NRF2 activation does not shift the balance toward mitophagy or mitochondrial biogenesis, but maintains the dynamic balance that ensures mitochondrial stability [111, 112].

Acting individually or together, the p62 and NRF2 signaling pathways are tightly associated with cell viability [113, 114]. On the one hand, the pathways act to prevent tissue degeneration, including age-related degeneration [115, 116]. Given that ubiquitin plays a central role in elimination of misfolded and aggregated protein molecules, Ma et al. [117] considered p62 as a promising target for modulation of proteasomal pathways. A silencing or inactivation of the p62 gene (*Sqstm1*) in mice caused Alzheimer's-like signs (working memory impairment) and led to hyperphosphorylation of the tau protein, the formation of neurofibrillary tangles, and neurodegeneration [118]. Similar observations were made in a rat model of Alzheimer's disease induced by injecting the β-amyloid precursor protein (APP) into the hippocampus; i.e., lower p62 expression in the brain was reduced in model rats [119]. An increase in P62 expression decreased the β-amyloid level and improved cognitive functions in APP/PS1 mice (a model of Alzheimer's disease) [1, 120].

On the other hand, studies with animal models showed that activation of the p62−KEAP1−NRF2 axis can induce cancer and, in particular, hepatocellular carcinoma by increasing the UDP-glucuronate and

glutathione production [121, 122]. Several mechanisms were considered for p62- and NRF2-induced carcinogenesis in hepatocellular carcinoma. One mechanism is based on mutations of the *NFE2L2* (NRF2) and *KEAP1* genes [123]. Another mechanism is that chronic inflammation [4, 124] causes constitutive activation of NRF2 and stable overexpression of p62 [125]. Certain pathological conditions are accompanied by an accumulation of aberrant p62 and a possible decrease in autophagy. The set includes alcoholic or nonalcoholic steatohepatitis, Wilson−Konovalov disease, and primary biliary cholangitis [126−129]. Because accumulating p62 interacts with KEAP1 to cause NRF2 accumulation, cytoprotective target genes of NRF2 must be expressed to higher levels in these pathological conditions.

In addition to a p62 accumulation, high-level expression of NRF2 target genes is characteristic of cancer cells [130]. Because the viability of cells (including transformed cells) increases with upregulation of NRF2 target genes, poor prognosis seems logical to expect for patients with p62-positive cancers. It is of interest that p62 phosphorylation mediated by the mTORC1 complex increases p62 affinity for KEAP1 in cancer cells; i.e., p62 sequesters the NRF2 inhibitor. Thus, mTORC1 activity further enhances the stabilization of NRF2 and transcription of its target genes [84]. The p62−NRF2 regulatory loop is already considered to provide a promising target for pharmacological interventions [131, 132], in particular, when designing drugs to suppress the aging-related neurodegenerative processes that lead to Parkinson disease, Alzheimer's disease, and other pathological conditions.

ABBREVIATIONS AND NOTATION

ROS	reactive oxygen species
TF	transcription factor
AKT	protein kinase B
AMPK	5'-AMP-activated protein kinase
AP1	activating protein 1
aPKC	atypical protein kinase C
ARE	antioxidant response element
ATE1	arginyl-tRNA transferase 1
ERK1/2	extracellular signal-regulated protein kinase 1/2
FXR	farnesoid X receptor
GSK3β	glycogen synthase kinase 3β
IKKβ	IκB kinase subunit β
JAK/STAT	Janus kinase/signal transducer and activator of transcription
JNK	c-Jun N-terminal kinase (MAPK family)
KEAP1	Kelch-like ECH-associated protein 1
KIR	Keap-interacting region
LC3	microtubule-associated protein 1A/1B light chain 3
LIR	LC3-interacting region
MAPK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
mTORC1/2	mammalian target of rapamycin complex 1/2
Neh	NRF2-ECH homology (ECH is a chicken NRF2 analog)
NES	nuclear export signal
NFE	nuclear factor, erythroid derived;
NF-κB	nuclear factor κB;
NLS	nuclear localization signal;
NRF2	NFE2-related factor 2;
p38 MAPK	p38 mitogen activated protein kinase
p62/SQSTM1	ubiquitin-binding p62/sequestosome 1
PB1	Phox and Bem1
PGAM5	phosphoglycerate mutase family, member 5
PI3K	phosphatidylinositol 3-kinase
PKC	protein kinase C
PPARγ	peroxisome proliferator-activated receptor γ
PTEN	phosphatase and tensin homolog deleted on chromosome 10
RBX1	RING-box protein 1
SESN	sestrin
TAK1	TGF-β-activated kinase 1
TBK1	TANK-binding kinase 1
TRAF6	TNFα receptor-associated factor 6
βTrCP	β-transducin repeat-containing protein
UBA	ubiquitin associated (domain)
ULK	UNK-51-like autophagy activating kinase
UXT	ubiquitous expressed transcript

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

As author of this work, I declare that I have no conflicts of interest.

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