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Nitric oxide mediated redox regulation of protein homeostasis

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ABSTRACT

Nitric oxide is a versatile diffusible signaling molecule, whose biosynthesis by three NO synthases (NOS) is tightly regulated at transcriptional and posttranslational levels, availability of co-factors, and calcium binding. Above normal levels of NO have beneficial protective effects for example in the cardiovascular system, but also contribute to the pathophysiology in the context of inflammatory diseases, and to aging and neurodegeneration in the nervous system. The effect specificity relies on the functional and spatial specificity of the NOS isoenzymes, and on the duality of two major signaling mechanisms (i) activation of soluble guanylycylase (sGC)-dependent cGMP production and (ii) direct S-nitrosylation of redox sensitive cysteines of susceptible proteins. The present review summarizes the functional implications of S-nitrosylation in the context of proteostasis, and focuses on two NO target proteins, heat shock cognate of 70 kDa (Hsc70/HSPA8) and the ubiquitin 2 ligase (UBE2D), because both are modified on functionally critical cysteines and are key regulators of chaperone mediated and assisted autophagy and proteasomal protein degradation. SNO modifications of these candidates are associated with protein accumulations and adoption of a senescent phenotype of neuronal cells suggesting that S-nitrosylations of protein homeostatic machineries contribute to aging phenomena.

1. Introduction

1.1. Nitric oxide generation and functions

NO is a versatile, multi-functional diffusible signaling molecule, which is produced by three isoforms of nitric oxide synthases. Neuronal NOS1 and endothelial NOS3 are constitutive with on demand upregulation, and inducible NOS2 is absent in most unstimulated tissues, except for example gut epithelia [1], but is strongly upregulated in response to pro-inflammatory stimuli.

NO is produced from arginine in a reduction-oxidation cycle of a heme iron within the catalytic site of NOS dimers [2,3], which act in cooperation with the coenzyme, tetrahydrobiopterin (BH4) [4], NADPH, flavin-mononucleotide (FMN) [5] and zinc. Binding of calmodulin (CAM) confers calcium sensitivity [6]. Further fine-tuning of activity, expression or positioning is mediated by phosphorylation, sumoylation [7], 3' UTR AU rich elements determining transcript stability [8], binding to caveolin [9] plus protein shuttling (NOS3), postsynaptic density (PSD) domain anchoring (NOS1) [10,11], coenzyme availability (BH4) and transcriptional regulation e.g. via hypoxia inducible factor (HIF1alpha), p38 MAP kinase or nuclear factor kappa B (NFκB).

Hydrogen peroxide (H_2O_2) is a byproduct of NO synthesis, and its production predominates if the stoichiometric balance of NOS and BH4 is disrupted [12–14], mostly originating from unequal upregulations of NOS and GTP cyclohydrolase, GCH1. The latter is the key enzyme of BH4 de novo synthesis, whose regulation of expression and activity is as complex as that of the NOSs.

1.2. NO-cGMP-PKG pathway

In the cardiovascular system, NO is best characterized for its vasodilating properties, which arise from activation of soluble guanylylcyclase (sGC), subsequent production of cyclic GMP (cGMP) and activation of cGMP dependent protein kinase, PKG1, [15] leading to smooth muscle relaxation via regulation of intracellular calcium stores [16] and actin-myosin dynamics. PKG1 is also directly activated through H_2O_2-mediated oxidation and dimerization via a disulfide bond [17,18], thereby maintaining PKG1 activity in absence of NO. The dimer has higher activity than the monomer. In the nervous system, the respective NOS1-NO-cGMP-PKG1 pathway is active at the synapse of NOS1 positive postsynaptic neurons, and contributes to NO-dependent forms of long-term-potentiation [19,20], which is a synaptic up-scaling of electrical activity upon N-Methyl-D-aspartate (NMDA) receptor mediated activation. In this, NOS1 is activated by calcium entry through the NMDA receptor, requiring binding of calmodulin. NO is released from the postsynaptic neuron, activates sGC of the presynaptic neuron, and then cGMP activates presynaptic PKG1, resulting in an increase of synaptic vesicle release. NO-dependent LTP is interpreted as a form of memory [21] but increases the risk of glutamate excitotoxicity [22].

1.3. Direct S-nitrosylation

To avoid such overshoot, NO has the ability to modulate the NMDA-receptor directly via posttranslational redox modification [23], because, in addition to the second messenger-mediated effects, NO directly modifies protein functions and interactions via S-nitrosylation of redox sensitive cysteines [24,25]. About 3000 different targets have been identified and are summarized in the "dbSNO" database of protein S-nitrosylations (http://dbSNO.mbc.nctu.edu.tw). Some of the most prominent SNO targets include the NMDA receptor, calmodulin, NOS themselves [23,26,27], GAPDH, GOSPEL [28,29], caspase 3 [30] and protein disulfide isomerases (PDI) [31], which are all involved in the maintenance of neuronal integrity [26]. Depending on the site of the respective cysteine, the SNO modification may affect enzyme activity, protein-to-protein binding, membrane-anchoring, transport, protein-folding and stability, and aggregation propensity. It is of note that S-nitrosylations are reversible physiologic posttranslational non-enzymatic modifications [32], and the functional outcome depends on the site, time and redox context, and quantitative

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aspects. Despite its diffusible nature, NO mediated SNOing events primarily occur in direct vicinity of target and source. Consequently, experiments performed with NO-donors do not necessarily replicate the in vivo situation imposed by NOS upregulations, which for all NOSs occur mainly in the context of disease.

Hence, irrespective of its protective functions in the cardiovascular system and of NO-mediated "memory" mechanisms in the brain, it is well known that upregulations of NOS1 occur in the aging brain and are associated with a cognitive decline and with neurodegenerative diseases [33–36]. The results of these studies suggest that permanent NOS-upregulations interfere with mitochondrial and protein quality control mechanisms [37–40], whose fading functions during live contribute to aging and occurrence of neurodegenerative diseases [41]. Permanently elevated levels of NO likely promote aging and reduce neuronal longevity. Indeed, protein S-nitrosylations precipitate protein misfolding [31,42], contribute to the toxicity of beta amyloid protein or mutant Huntingtin [33,35,36,43] and lead to disruptions of protein homeostasis [24,26,44–46]. The latter is a hallmark of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Neuronal NOS upregulations were also observed in models of axonal injury leading to an increase of SNO modified proteins, particularly proteins involved in mitochondrial functions and maintenance of protein homeostasis [47–49]. To further understand SNO modifications in the context of aging, we have recently studied the impact of SNO-PTMs on proteostasis in SH-SY5Y neuroblastoma cells [50], which have been extensively used as a model in neurodegeneration research [51]. These experiments revealed two major NO-dependent paths to protein allostasis, namely SNOing of critical cysteines of ubiquitin 2 ligases and the heat shock protein, HSC70/HSPA8, one affecting the catalytic site (Cys85 of UBE2D, similar 86 and 87 of UBE2L, 2N), the other the ATP-binding domain (Cys17 of HSC70). HSC70 is a key regulator of chaperone-mediated autophagy (CMA), protein folding and shuttling, and clathrin uncoating, all depending on ATP binding to its nucleotide-binding region (NBR) [52].

Because of the relevance of these targets, the present review focuses on the functions of NO for protein degradation via ubiquitination-dependent proteasomal lysis and HSC70 dependent autophagy and the interconnections of both pathways. In particular, the review summarizes the implications of SNOing of these targets for proteostasis in the context of aging and neurodegenerative disease.

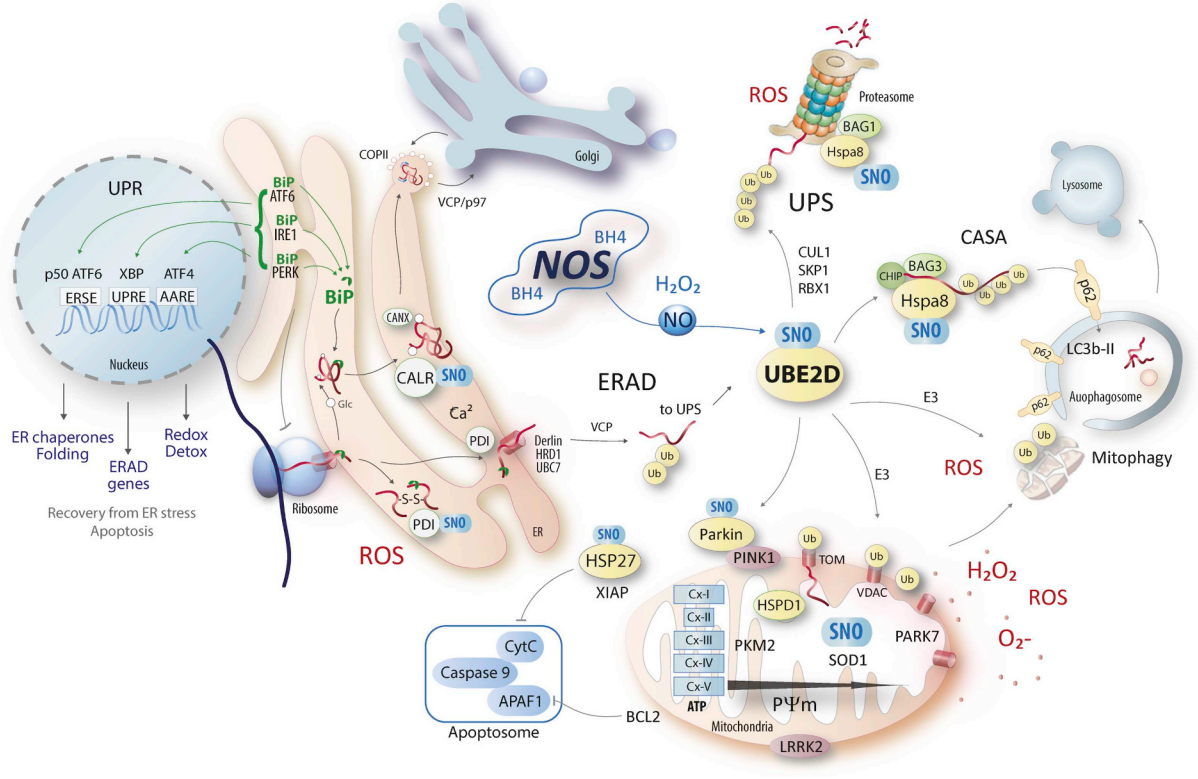
1.4. SNO modifications and protein diposal machineries

Inefficient disposal of protein waste is a major feature of neurodegenerative diseases [42,53,54] and may also contribute to detrimental long-lasting neuronal adaptations after axonal injury [49]. In addition, previous studies revealed that redox stresses imposed by "too much" nitric oxide increase the occurrence of aggregate prone proteins particularly in the context of neurodegenerative diseases [42,55–57].

Protein degradation machineries can be direct targets of NO-evoked modifications, or these machineries are overwhelmed or clogged with high loads of oxidized substrate proteins. The proteasome does not readily digest oxidized proteins [31,44,58,59], particularly not if they are in the form of oxidized protein aggregates [60,61]. The latter are normally not present in unstressed cells because endogenous quality control systems maintain protein homeostasis by coordinating protein synthesis and degradation [62,63]. Likewise, SNO modifications are normally well balanced and constitute subtle transient regulations of protein functions [64], but prolonged cellular stresses such as starvation, radiation, hypoxia or overwhelming ROS generation increase the SNO and aggregate burden [65,66]. The consequences are detrimental particularly for neurons [67], which do not renew and cannot make use of some alternative clearance mechanisms owing to their restricted brain environment. For example, even if they expel toxic lysosomal content by using the lysosomal exosome pathway [68], the expelled material is not readily cleared from the brain but taken up by surrounding microglia, which are better apt to digest the material than neurons but still transform to pro-inflammatory phagocytes that release pro-inflammatory mediators. This is a major hurdle in the clearance of beta amyloid protein [69]. It is therefore not surprising that the SNO-modifications of the proteostasis network, which occurred in NOS1-positive SY-SH5Y cells was associated with a switch towards a senescent phenotype [50], strongly suggesting and supporting the idea that permanent increases of SNO modifications are associated with pro-aging phenomena. It is of note that SNO-modifications were also prominent in metabolic proteins involved in carbohydrate energy utilization [50] suggesting that two NO-evoked sequential challenges cooperate, one imposing starvation that normally increases protein degradation, and the second imposing a failure of efficient protein degradation. Hence, the latter precludes efficient adaptation to the former.

Eucaryotic cells utilize two major mechanistically distinct, complementary systems for protein degradation, the 26S proteasome, which recognizes substrate proteins labeled with ubiquitin, and the autophagolysosome [70–74]. The concerted actions ensure a specific and tightly regulated degradation process, which is highly sensitive to oxidative stress [75–80]. Oxidized proteins are prone to form large aggregates due to covalent cross-linking or high surface hydrophobicity, and unless repaired or removed, these oxidized proteins are toxic [65,81–84]. Clearance by the proteasome requires that proteins enter one by one, hence requiring a resolution if they are aggregated [61,65,80]. "Too much" nitric oxide may interfere with the efficiency of proteasomal degradation depending on the redox environment and the capacity of redoxins. A negative effect may arise from SNO modifications and further oxidation of ubiquitin ligases, of proteasomal subunits or the substrates [31,42,85–87]. The implications and targets of SNOing are summarized in Figs. 1 and 2.

Illustrations of direct protein S-nitrosylation in protein folding and degradation pathways



Text box to figure 1. SNOing in UPS and UPR

nNOS: Neuronal nitric oxide synthase (NOS1) is localized at sites of high protein turn-over in the cytoplasm, the perinuclear region, in the endoplasmic reticulum and the pre- and postsynaptic densities. Calmodulin confers calcium sensitivity to the NOS dimer, which catalyzes the oxidoreduction of L-arginine → NO + H2O + citrulline in the presence of the cofactor tetrahydrobiopterin (BH4) and NADPH. NO signals through two major pathways (i) activation of soluble guanylylcyclase and subsequently, cGMP dependent protein kinase and (ii) direct S-nitrosylation of target proteins, the latter depending on the redox environment. SNO-modification of chaperones and ubiquitin ligases may interfere with protein quality control, folding and degradation. SNO targets are marked with "SNO".

De-novo protein folding: Newly synthesized nascent polypeptides are transferred from the ribosome into the lumen of the endoplasmic reticulum via the translocon complex and are then tagged with the chaperone BIP/GRP78, which maintains proteins in a state competent for posttranslational modifications, folding and oligomerization. Once glycosylated, proteins are folded with the calcium dependent lectin chaperones, calreticulin and calnexin, which are subject of SNO modifications. If proteins are misfolded, binding to calreticulin or calnexin prevents them from being exported from the ER to the Golgi, which allows for a correction of glycosylation errors and re-folding. If this fails, BIP will guide the terminally misfolded protein to ER associated degradation (ERAD).

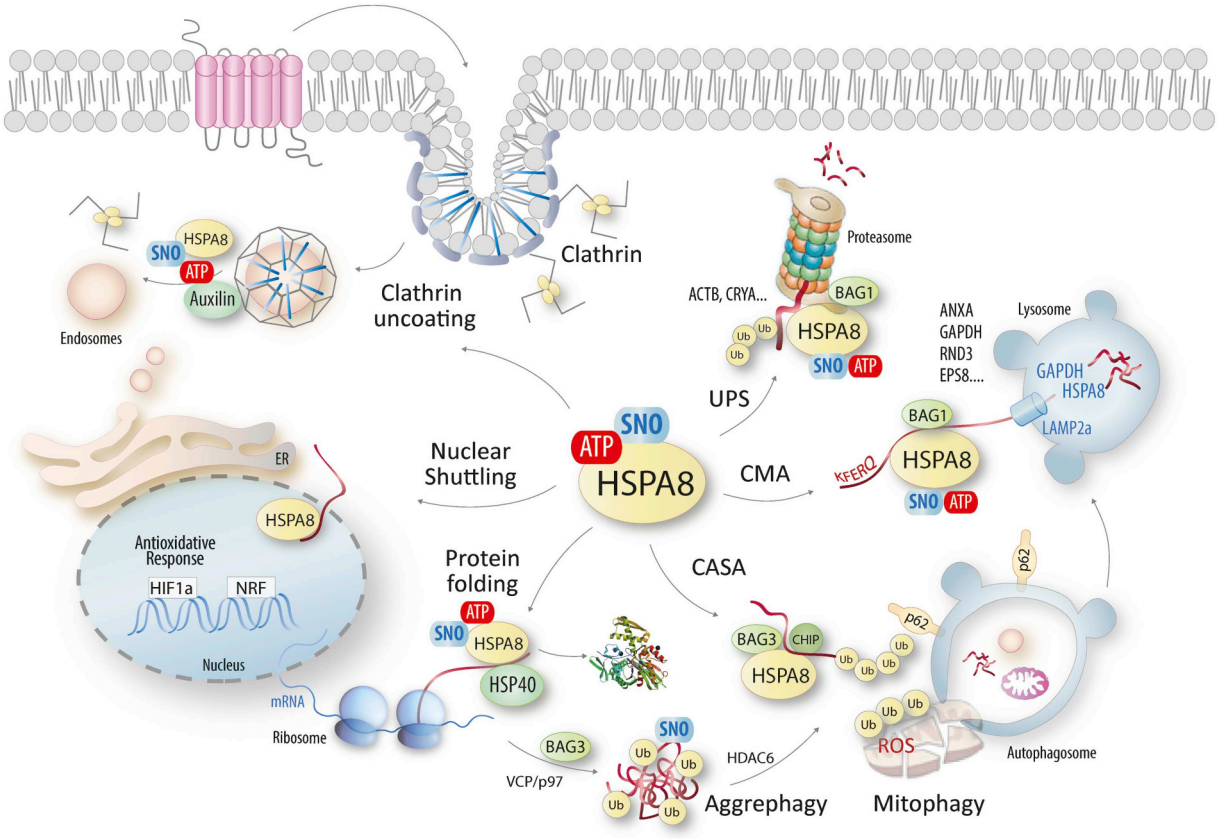
ERAD: In ERAD, the ER degradation enhancer, EDEM governs the retro-translocation of the malfolded protein back into the cytosol in transient complexes with protein disulfide isomerases (PDI) and BIP. The retro-transport is mediated by the ATPase valosin containing protein VCP/p97. At the membrane or in the cytoplasm the protein enters ubiquitin-ligase complexes, which tag the protein with multiple ubiquitin molecules to prepare the degradation via the ubiquitin proteasome system, UPS. The cytoplasmic ubiquitin ligase complex consists of the E2 ligase UBE2D1/UBCH5, and E3 ligases including PARKIN (PARK2), or the SCF complex consisting in SKP1, Cullins and RBX1. The ubiquitin conjugation requires a trans-thioesterification that occurs at the SNO-targeted cysteine of the catalytic site of the UBE2D enzymes.

Protein disulfide isomerases: Protein disulfide isomerases (PDIs) are thioredoxin-like enzymes that catalyze in their oxidized form the formation of disulfide bonds between cysteine residues within proteins. The PDI is subsequently reduced by ERO1. The reduced PDI catalyzes the reduction of mis-paired thiol residues in a client protein, acting as an isomerase. This results in a disulfide exchange and rearrangement of disulfide bonds. The functioning of PDIs is highly sensitive to alterations of the redox environment and their enzymatic activity is modified by S-nitrosylation.

Unfolded Protein Response (UPR): If the folding machinery cannot meet the requirements for example due to enhanced translation or chaperone malfunctions, BIP initiates the Unfolded Protein Response (UPR), triggered by ER-membrane UPR sensors PERK, ATF6 and IRE1. They are normally kept inactive by BIP, which is attached to their luminal side. If more BIP is needed to bind unfolded proteins, it dissociates from these UPR sensor sites to meet the requirement, allowing the UPR sensors to become active. The initial UPR has two key functions, first to stop translation and cell cycle progression and second to upregulate proteins, which are needed for re-folding and ERAD. If the stress continues, the UPR may turn into apoptosis mediated by CHOP, which bypasses the PERK evoked translational block and downregulates mitochondrial anti-apoptotic factors.

Chaperone mediated and chaperone assisted autophagy: Aggregate prone, defective and oxidized proteins are hard to digest by the proteasome. Therefore, neurons and other cells utilize the autophagolysosome to target proteins for degradation. In contrast to unspecific macroautophagy, chaperones and ubiquitin can confer selectivity to autophagic protein degradation by two processes: chaperone mediated autophagy (CMA) and chaperone assisted autophagy (CASA), both governed by HSC70/HSPA8, which is a major target of S-nitrosylation (details in Fig. 2).

Mitophagy: PARKIN is subject to S-nitrosylation and is crucial for mitophagy of damaged mitochondria in the context of Parkinson's disease. It is recruited to the mitochondria by binding to PINK1. PARKIN ubiquitinates outer mitochondrial membrane proteins including VDACs, TOM proteins and mitofusins, thereby labeling the mitochondrium for autophagy-receptor guided engulfment and mitophagy. S-nitrosylation of mitochondrial proteins including DJ-1/PARK7, LRRK2, SOD1 and PKM2 may cause oxidative stress and energy deficits, and S-nitrosylation of the mitochondrial HSP60/HSPD1 may interfere with the folding of mitochondrially imported proteins, hence eliciting a mitochondrial unfolded protein response, called MUPR (list of gene names and functions in Suppl. Table 2).



Text box to figure 2. SNOing of HSPA8/HSC70 and functional implications

HSPA8 is a member of the Hsp70 family of chaperones. It is composed of an N-terminal ATP-binding domain (NBD), a C-terminal substrate-binding domain (SBD), and an unstructured region at the very end of the C-terminus. The nucleotide binding domain (NBD) consists of four subdomains split into two lobes, which form a central ATP/ADP binding pocket. The NBD carries a critical cysteine at position Cys17 (human), is essential for ATP/ADP binding and primary target of redox modification. The unstructured region at the very end of the C-terminal is believed to be the docking site for co-chaperones and contains two SNO-targeted cysteines, Cys574, Cys603, with unknown functions. The co-chaperones include J-domain Hsp40 chaperones, nucleotide exchange factors such as BAG1, 2, 3 and the tetratricopeptide (TPR) domain chaperones such as STUB1/CHIP.

HSPA8 mediated protein folding: The folding of newly synthesized proteins in the cell requires the cooperative functions of molecular chaperone machineries. These molecules recognize and bind to nascent polypeptide chains and partially folded proteins, preventing their aggregation and misfolding. The chaperones most involved are the 40-kDa heat shock proteins (HSP40, DNAJ family), 60-kDa heat shock proteins (HSP60, HSPD1), and 70-kDa heat shock proteins (HSP70, HSPA8, DNAK family). For the latter two, the binding of ATP triggers a critical conformational change leading to the release of the bound substrate protein. The major role of the HSP70/HSP40 chaperone system is to minimize aggregation of newly synthesized proteins.

HSPA8 mediated protein shutting to and from organelles: HSPA8 carries a 20 amino acid nuclear localization signal, which resides within the variable C-terminal domain. A short mutant, HSC54, lacking amino acids 464-616, remains in the cytosol. In addition to translocate itself, HSAPA8 serves as a shuttle protein for nuclear import or export of client proteins including transcription factors and viral proteins. It promotes the export of nuclear import receptors.

HSPA8 mediated clathrin vesicle coating and uncoating in cooperation with auxilin: Clathrin-coated vesicles transport selected integral membrane proteins from the cell surface and the trans-Golgi network to the endosomal system. Before fusing with their target, the vesicles must be stripped of the coats, which is mediated by the coat protein auxilin/DNAJC6 in cooperation with HSPA8. Auxilin is an Hsp40 family protein that catalytically supports the uncoating. It binds with high affinity to assembled clathrin lattices and in the presence of ATP, it recruits HSPA8 to the complex allowing for the clathrin disassembly, which is an ATP hydrolysis-driven process.

HSPA8 dependent chaperone mediated and chaperone assisted autophagy: Aggregate prone or defective proteins may evade proteasomal degradation and are targeted to degradation via the autophagolysosome. In macroautophagy, cytosolic content is engulfed randomly by the growing phagophore, hence unspecific, but chaperones and ubiquitin can confer selectivity to autophagic protein degradation by two processes: chaperone mediated autophagy (CMA) and chaperone assisted autophagy (CASA), both governed by HSC70/HSPA8, which is a major target of S-nitrosylation.

In chaperone mediated autophagy HSC70/HSPA8 selects client soluble cytosolic proteins destined for degradation, brings them directly to the lysosome where they are transferred across the lysosomal membrane upon binding to the multidimeric LAMP2a receptor, which is aided from inside by HSP90 and lysosomal HSPA8. The process requires the recognition of a KFERQ-like pentapeptide motif in the client protein by HSC70/HSPA8 and the help of the co-chaperone BAG1. CMA is strongly activated in response to oxidative and nitrosative stress and nutrient deficiency. The shuttle process requires ATP binding to HSPA8. Hence, S-nitrosylation of Cys17 may interfere with its functions.

In chaperone assisted autophagy (CASA), HSC70/HSPA8 acts in concert with the cochaperones BAG3 and the chaperone-dependent E3 ligase STUB1/CHIP to ubiquitinate the substrate protein. Once labeled with ubiquitin the substrate is recognized by autophagy cargo receptors, like SQSTM1/p62, which bind both the cargo and LC3b-II on the inner sheath of the autophagosome and drags the protein into the autophagosome. Proteolysis is finally carried out within the lysosome after fusion of the autophagosome with the lysosome.

Aggrephagy: Both CMA and CASA require the dissolution of protein aggregates to target single proteins one by one for degradation. If aggregates are beyond dissolution BAG3 can also aid in a dynein-mediated and VCP/p97 dependent transport of protein aggregates along microtubules to the aggresome, whose content is then degraded by aggrephagy. This process depends on ubiquitination of the aggregate by an E3 ligase such as PARKIN and the delivery of the ubiquitinated aggregate to HDAC6. The latter helps to transport the aggregate along microtubules to the aggresome, which is finally recognized by p62 for autophagy. S-nitrosylated proteins or aggregates might be “indigestible” by this route and S-nitrosylation of PARKIN may impair its functions (list of gene names and functions in Suppl. Table 2).

While the proteasome is overburdened with oxidized proteins or aggregates, autophagy offers an alternative resource to remove oxidized proteins or aggregates in total. Specific autophagy pathways are also utilized to remove damaged organelles, pathogens, engulfed bulk material and long lived cytosolic proteins, all requiring specific forms of autophagy for example micro- and macroautophagy, xenophagy, mitophagy, pexophagy, lysophagy, aggrephagy, chaperone-assisted and chaperone-mediated autophagy [88,89]. It is not clear if specific forms of autophagy are more or less prone to SNO-dependent protein modifications [90,91], because pro-autophagy stimuli such as inhibition of mTOR or inhibition of the proteasome will stimulate more than one of the autophagy routes. Using prediction algorithms, we have identified several proteins of the human autophagy network [92] as putative SNO targets (Suppl. Table 1). However experimentally, SNOing was not prominent in proteins of the classical autophagy assembly machinery but rather occurred upstream and in the chaperone network [50]. In line with this result, it has been described that macroautophagy is disrupted by SNO-modifications of upstream signaling molecules such as c-Jun N-terminal kinase (JNK1), and of the initiating enzymes [93]. In addition, SNOing was found to impair selective ubiquitin-dependent removal via the autophagosome by masking recognition sites for cargo adapter proteins like sequestosome 1 (SQSTM1/p62) [94,95]. SQSTM1 accumulates itself if autophagy is impaired, which results in secondary deficits of proteasomal degradation [96–98], and importantly, inactive proteasomes or defective lysosomes are also targeted for degradation via autophagy, the latter process called lysophagy [99], which requires ubiquitination of specific lysosomal membrane proteins [100].

1.5. SNO modifications of HSPA8

A further link between the key degradation pathways is the very versatile HSC70/HSPA8, which has three SNO-susceptible cysteines, one within the N-terminal ATP-binding region (Cys17) whose SNOing increases upon starvation or mTOR inhibition [50], and the other two in the unstructured very end of the substrate binding C-terminus, Cys574 and Cys603 (human HSC70), whose functions are unknown. It is believed that the terminal unstructured region is the site of interactions of HSPA8 with its cochaperones, BAG1, 2, or 3 [52]. HSC70/HSPA8 promotes proteasomal degradation of some proteins such as beta actin, alpha-crystalline and GAPDH. The experimental data suggest that it helps the respective E3 ligase to bind ubiquitin to the substrate likely by unfolding and exposing the binding sites [101]. As a chaperone, HSC70/HSPA8 catalyzes protein folding and unfolding, but is also involved in clathrin uncoating [102], the latter contributing to multiple transport and sorting mechanisms such as clathrin-dependent endocytosis and organelle import-export shuttling [52,103,104] (Fig. 2). Clathrin-coated vesicles transport selected integral membrane proteins from the cell surface and the trans-Golgi network to the endosomal system. Before fusing with their target, the vesicles must be stripped of the coats, which is mediated by the coat protein auxilin/DNAJC6 in cooperation with HSPA8 [105,106]. Auxilin binds with high affinity to assembled clathrin lattices and in the presence of ATP, it recruits HSPA8 to the complex allowing for the disassembly. It is of note that this process is important for the maintenance of NOTCH signaling [107,108], which is a key regulator of neuro- and angiogenesis and cell differentiation [109–111], and auxilin/DNAJC6 mutations have been linked to juvenile Parkinson's disease [112]. HSPA8 also assists in ubiquitin dependent selective autophagy [113] called chaperone assisted autophagy, CASA, and it is the key carrier protein in chaperone-mediated autophagy (CMA), in which substrate proteins are recognized via a KFERQ-like motif, and are then transferred to the lysosomal receptor, LAMP2A.

All of these functions require ATP-binding to the nucleotide binding domain (NBD) of HSPA8, and upon replacement of Cys17 with lysine, HSPA8 lost 95% of its protein folding activity in vitro [114] suggesting that SNOing of Cys17 is functionally relevant for the maintenance of protein homeostasis.

2. SNO modification of the chaperone HSC70/HSPA8

S-nitrosylation and reversible oxidation of Cys17 of HSC70/HSPA8 appears to be a key event in SNO-mediated regulation of protein homeostasis, which is accompanied by SNO-modifications of co-chaperones (e.g. BAG1 and BAG3, STUB1/CHIP, ST13, DNAJC12, CDC37) and further heat shock proteins including HSPB1, HSPD1 and HSP90s [50]. The modification is very likely to affect multiple functions of HSPA8 because the target cysteine is localized within the nucleotide-binding region. HSPA8-dependent mechanisms all require ATP binding. Its functions include protein-folding, clathrin uncoating, UPS mediated degradation of specific proteins, assistance in ubiquitin-dependent selective autophagy, and chaperone-mediated autophagy. The structure of HSPA8 is highly flexible and only partly known. It is not predictable by in silico methods if redox modifications of HSPA8's Cys17 or one of the other SNO-sensitive sites, Cys574 or Cys603, affect its phosphorylation [115], the ability to bind ATP/ADP, or the substrate [52]. Cys17 is localized within the first lobe in subdomain Ia of the nucleotide binding domain (NBD), which flexibly forms a pocket with the second lobe enabling the ATP/ADP cycling [116]. A Cys17 to lysine mutant (C17K) of HSC70/HSPA8 retained less than 5% of ATPase activity [114], strongly suggesting that ATP hydrolysis and hence functions of this protein including its carrier services will be affected by redox modifications of this site. Cys574 or Cys603 are localized C-terminal of the substrate binding site, which ranges from 394-509 amino acids. Both cysteines are localized within the alpha-helical lid subdomain and unstructured tail of HSC70 (AA 541-646), which interacts with the tetratricopeptide repeat domain (TPR) of the E3 ligase, STUP1/CHIP [117]. The two work in concert with the

cochaperone, BAG3 to ubiquitinate misfolded proteins and transfer the cargo proteins to the autophagosome [118]. The process is referred to as chaperone assisted autophagy [119]. The first evidence for this mechanism was obtained in a study showing that HSPA8 plus the small HSPB8 associate with the cargo protein filamin, assisted by the cochaperone BAG3, allowing the transfer of ubiquitin via STUB1/CHIP. Instead of being targeted for proteasomal degradation, the ubiquitinated filamin was then attached to the autophagy cargo adapter, SQSTM1/p62 (sequestosome 1) and finally degraded via autophagy. Ubiquitin-dependent selective autophagy [120] of specific protein also included the autophagy cargo receptor p62/SQSTM1 itself [121,122] and subunits of inactive 26S proteasomes [74].

If re-folding fails, and if in addition CASA or other intracellular degradation mechanisms are overburdened, misfolded proteins are deposited in juxtanuclear aggresomes, and interestingly, the same triple of HSC70-BAG3-CHIP promotes aggresome formation under these conditions [123]. Presently, it is speculation that redox modification of one or more of the partners impacts on the triage decision of protein folding, degradation and aggregation.

In addition to chaperone assisted autophagy, HSC70 is well known as the key regulator of chaperone mediated autophagy (CMA) [113,124,125]. This degradation process does not require the classical autophagosome assembly machinery but is a direct path to the lysosome for specific proteins. CMA is activated in response to prolonged starvation [126,127], exposure to toxic compounds, or oxidative and nitrosative stress [77,124,125,128,129], and a decline of CMA efficiency has been linked with aging processes [130]. For CMA, HSC70 binds long-lived cytosolic substrate proteins, which are recognized via a KFERQ-like recognition sequence. While about 30% of cytosolic proteins are carriers of such a sequence, only specific candidates expose it to HSPA8. Once HSPA8 has caught its target, it transfers the substrate protein into the lysosome via the LAMP2a receptor. The monomeric LAMP2a dimerizes upon binding of the client protein and drags the protein into the lysosomal lumen [131–133], a process that requires the help of a lysosomal luminal variant of HSPA8 [134] and of HSP90. The SNOing of HSPA8 likely interferes with the binding and transfer process [50]. A number of typical CMA-targets [28,29,135–137] including aldolase A, annexin A2 and -6, transcription intermediary factor 1-beta (TRIM28), elongation factor 2, Rho-related GTP-binding protein (RND3), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and DNA-dependent protein kinase (PRKDC) all accumulated in NOS1 positive SY-5YSH cells upon exposure to starvation [50]. On the cytosolic site, this lysosomal import via LAMP2a requires that HSPA8 associates with its cochaperones HSP90, BAG1, HSP40, ST13, and STIP1/HOP, out of which HSP90, ST13 and BAG1 are further SNO targets [50]. Hence, all of these processes require an 'assembly of macromolecular complexes', which is likely affected by SNO modifications of one or more of the interacting partners, and CMA appears to be particularly vulnerable to changes of redox homeostasis.

The redox modification of HSPA8 links autophagy with ubiquitin-proteasome system (UPS) and the unfolded protein response (UPR) caused by ER stress [138] (i) via its protein folding properties, and (ii) via the transport and transfer processes [139–142]. It is of note that ubiquitination of p62 involves UBE2D3 [143], suggesting that selective ubiquitin dependent autophagy is particularly prone to redox-mediated regulations, in addition to CMA. Some experimental evidence suggest that S-nitrosylation and phosphorylation of HSC70 are reciprocal posttranslational modifications, which may regulate both chaperone mediated or assisted autophagy processes. Phosphorylation of HSC70 regulates the shuttling of HSC70 between nucleus and cytoplasm [115] and impacts on its properties to shuttle other proteins between cytoplasm and nucleus [115]. The shuttle properties were demonstrated for calmodulin-dependent nuclear import of the sex-determining factor SRY [144], nuclear export of viral ribonucleoproteins [145] and for the export of nuclear import receptors [146], the latter presumably leading to a broad modulation of nuclear transport processes. The shuttle properties require ATP binding and are likely sensitive to redox modification of Cys17, whereas the recognition of the nuclear localization signal of HSPA8 resides in its variable C-terminus carrying the redox-sensitive cysteines 574 and 603 (human HSPA8).

3. SNO modification of ubiquitin ligases

S-nitrosylation events appear to affect protein folding and stress responses produced by unfolded proteins. SNO modification also occur in proteins involved in ubiquitination, in particular the E2 ligases UBE2D3 at its catalytic site (Cys85) and other E2 ligases including 2K, 2L (Cys86) and 2N (Cys87), the ubiquitin modifier UBA1 and the ubiquitin hydrolases UCHL1 (Cys152) through UCHL5 [50], all suggesting that S-nitrosylation of ubiquitination networks maintain protein homeostasis and protein quality.

Oxidation of cysteine Cys85 in UBE2D impairs its function i.e. transfer of ubiquitin to the E3 ligase [50], because it is the cysteine within the catalytic site. Small molecular inhibitors of UBE2D work by forming a covalent adduct with its active cysteine, hence blocking the ubiquitin transfer [147]. Protein ubiquitination is a multistep process orchestrated by the concerted action of three enzymes. The reaction starts with an ubiquitin-activating enzyme (E1), which forms a thioester bond between the activated C-terminus of ubiquitin and a cysteine residue of the E1, from which the E2 ligase catches the activated ubiquitin and shuttles it to the E3 ligase [148]. The E3 ligase finally transfers the ubiquitin to the lysine residues of the substrate. Hence, SNO-modification of this critical cysteine of the catalytic E2 site presumably interferes with the conjugation of ubiquitin [149]. The idea is supported by NO-donor evoked inhibition of UBE2D3 in vitro activity [50]. UBE2D isoenzymes all share the Cys85 and interact with various Ring finger or U-box E3 ligases, including SIAH1 [150], which promotes ubiquitination and aggregation of alpha synuclein, and STUB1/CHIP [151], which acts in concert with HSPA8 in chaperone mediated autophagy. Hence, SNO-modification of Cys85 may alter the efficiency of protein ubiquitination and degradation through both the proteasomal and CMA pathways. Further, concerted SNOing of HSC70/HSPA8 and UBE2D may particularly interfere with HSC70 assisted selective autophagy, for which neuronal nitric oxide synthase itself likely is a target [152]. The functions of UBE2D are summarized in Fig. 1.

4. SNO modification of the proteasome

A number of studies show that oxidative modifications of proteasome subunits interfere with protein degradation via the proteasome and are associated with aging [80]. The functions of nitric oxide are less well studied, but it was shown that S-nitrosylations modulate the levels of a number of proteins that are normally kept under control by proteasomal degradation including hypoxia inducible factor, HIF1alpha [153], tumor suppressor p53, iron response proteins, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and Iκb/NFκB. Mostly, these effects occurred by SNOing of the substrate protein, a regulatory partner or the ubiquitin E3 ligase and not so much so by SNOing of the proteasome itself. One study describes that the NO-donor S-nitroso N-acetylpenicillamine (SNAP) inhibits the activation of the 26S proteasome by reducing the expression of the 11S proteasome activator PA28, possibly mediated by SNOing of PA28 [154]. SNAP exposure resulted in S-nitrosylation of the 20S core proteasome unit and resulted in a reduction of 26S proteasome activity, possibly one mechanism, by which NO regulates the cell cycle and response to hypoxia. In our studies, endogenous NO produced by transgenic NOS1 in SH-SY5Y cells resulted in a similar reduction of proteasome activity, which further decreased upon rapamycin evoked "starvation" [50]. Hence, the proteasome is a direct NO-target, but effects on ubiquitination appear to be more robust.

4.1. SNO modifications of chaperones impacting on protein folding and ER transfer

S-nitrosylations also occur in further chaperones including heat shock proteins (HSPD1, HSPB1), peptidyl-prolyl cis-trans isomerases (PPIA) and calreticulin (CALR), and reticulon that modifies the activity of protein disulfide isomerases [155]. Calreticulin is a major chaperone in the lumen of the endoplasmic reticulum and its primary function is the folding of glycosylated proteins. Under stress, it is exposed at the cell surface or is secreted from dying cells to activate immune responses [156]. Calreticulin appears to be constitutively S-nitrosylated [50]. Under stress like starvation, this SNO-modification appears to be lost and enables a cleavage of the flexible C-terminus that bears the ER retention signal [157]. So freed from its normal location, it enhances cell stress and apoptosis [158].

4.2. PDIs

S-nitrosylation of protein disulfide isomerases (PDI) was shown to link protein misfolding to neuronal death [31,159,160]. PDIs are upregulated during neuronal stresses [160], and facilitate protein maturation and transport of unfolded secretory proteins. This adaptation helps to survive the injury. S-nitrosylation of PDI negatively affects its catalytic chaperone and thiol-disulfide oxidoreductase functions, leading to accumulation of misfolded proteins and induction of autophagy and cell death. In addition to ER-PDIs, secreted PDI or PDI exposed at the cell surface maintain the reduced state of extracellular proteins. Particularly, cell surface PDI may enable the transfer of NO from extracellular SNOs to intracellular thiols in order to transfer NO bioactivity from the extracellular environment into the cytosol [161]. In addition, cell surface PDI maintains the sheddase ADAM17 in an inactive closed state. Upon redox modulation of the environment, and consequent PDI inactivation, ADAM17 adopts an active conformation, which is accompanied by changes in disulfide bonds in the ADAM17 ectodomain [162]. ADAM17 cleaves diverse cell-surface receptors and adhesion molecules, including the p75 neurotrophin receptor (p75NTR) [163], amyloid precursor protein and NOTCH [164,165], which are relevant candidate proteins in the context of aging and neurodegeneration versus neurogenesis.

4.3. P53 and HIF1alpha

Proteasomal degradation of p53 is mediated by its ubiquitination through the sequential actions of the E2 ligase UBE2D3 and the E3-ligase human homologue of mouse double-minute-2 (HDM2), whose functions are disrupted by S-nitrosylation of single, critical cysteines either within UBE2D3 and/or within HDM2 [166]. Hence, p53 stability is subject to a sequential regulation via S-nitrosylation.

The NO-dependent transcriptional activity of hypoxia-inducible factor 1 alpha (HIF1α) is mediated, in part, by S-nitrosylation of a single cysteine residue within HIF1α, which facilitates binding of the transactivator, cyclic-AMP-responsive-element-binding protein (p300/CBP) [167]. In addition, an NO-dependent modification prevented binding of hydroxylated HIF1α to the E3 ubiquitin ligase, von Hippel Lindau protein (VHL) that ligates ubiquitin to HIF1α and thereby primes HIF1α to

degradation [168]. Hence, SNOing of HIF1α prevents its ubiquitination-dependent routing to the proteasome. Possibly, as a rescue, HIF1α may undergo chaperone-mediated autophagy [169], which likely equally takes SNO-modified and unmodified HIF1α.

These examples emphasize the importance of nitric oxide mediated redox modifications during stressful situations imposed e.g. by starvation, hypoxia, inflammation or just the normal decline of organelle functions during life.

5. SNOing in aging and Parkinson's disease

Upregulations of NOS1 in the aging brain have been suggested to contribute to aging processes of neurons although endothelial NOS3 upregulations in the vascular system are protective owing to the vasodilating functions of NO, which also apply to the neurovascular system in the prevention of stroke. Nevertheless, neurons overexpressing NOS1 appear to be vulnerable to stress imposed by failing protein quality control or disposal machineries [19,27,31,37,42,128,170–172]. Such proteostatic stress occurs during normal, but particularly pathological aging [173]. Indeed, experiments with neuronal NOS1 positive SH-SY5Y cells revealed that the constitutive NOS1 expression imposes a phenotypic switch to a proliferation senescent phenotype [50], which has been previously described in these cells upon interfering with CMA or oxidative targeting of the proteasome [113,174,175]. Hence, NOS1-positive SH-SY5Y cells are a valuable novel cellular model in aging research [176]. Because of NO's versatile functions it is not possible to pin down the pro-aging phenomena to a single target but the combined SNOing of HSC70 and UBE2D are key events in this cellular model. If this applies to human neurons in the context of neurological diseases cannot be answered on the basis of current knowledge, but reprogramming technologies suggest that further insight is within technical reach.

Several of the proteins, which were S-nitrosylated upon "starvation" stress in NOS1-positive SH-SY5Y cells [50] are experimentally or genetically linked to the pathogenesis of Parkinson's disease including UBA1 (E1-ligase), UBE2D, the E3 ligase PARKIN/PARK2, UCHL1 [177], voltage dependent anion channels (VDACs) [178], dopamine beta hydroxylase (DBH) and the parkinsonism associated deglycase, PARK7/DJ-1 [179]. For example, the redox status of distinct cysteines of PARK7 determines its structure and dimerization properties [180]. Specifically, the substitution of the critical cysteine, Cys46, with alanine diminished its dimerization, which is a fundamental feature of this protein, suggesting that SNOing impacts on its functions [180]. SNOing of PARK7 at Cys106 is required for PARK7-mediated transnitrosylation, i.e. the transfer of the SNO from one protein to the other. Through this mechanism PARK7 transfers SNO to the phosphatase, PTEN, resulting in a reduction of its phosphatase activity and improvement of cell survival [181]. Importantly, SNO-PTEN levels were reduced in the brain of patients with sporadic PD [181]. These examples provide some mechanistic insight into the putative neuroprotective versus detrimental effects of SNOing processes in the context of PD. Dysfunctional SNOing or high oxidation like sulfoxidation of critical cysteine thiols could thus contribute to neurodegenerative disorders like PD.

Hence, the pathophysiology of PD likely involves SNO-evoked protein dysfunctions, which contribute to mitochondrial damage, defective mitophagy, and enhanced formation or defective removal of protein aggregates, finally resulting in a destruction of dopaminergic, sensory and autonomic neurons. The pathology of Parkinson's disease combines complex environmental factors [182] such as exhaustive exercise [183] with mitochondrial oxidative damage and pathological protein aggregates of alpha-synuclein, the latter caused both by abnormal ubiquitination [150,184] and deficient chaperone mediated autophagy [53,185]. Specifically, HSPA8 plays a critical role for removal of alpha-synuclein [186]. A number of further studies addresses the functional implications of the HSC70-dependent transport and degradation pathways in PD. In particular, PD-associated genetic variants of LRRK2 succumbed to enhanced HSC70-dependent degradation [187], whereas mutant UCHL1 inhibited CMA by blocking access to LAMP2A [188]. Interestingly, drosophila mutants expressing human LAMP2A presented with accelerated autophagic flux protecting aging flies against stress and locomotor decline, a result which was replicated in a PD-model with flies carrying a human synuclein mutation [189]. Further direct evidence for HSC70's pathology in PD comes from HSC70-5/mortalin deficient drosophila [190]. These flies had reduced ATP levels, abnormal wing posture, shortened life span, reduced spontaneous locomotor and climbing ability and loss of synaptic mitochondria [190], hence, replicating key features of PD. Although the impact of SNO-modifications of HSC70 was not studied, one may assume that redox modification of the critical cysteine of the ATP binding region imposes subtle but relevant changes of the functionality of HSC70.

Damaged mitochondria may spill mitochondrial DNA into the cytoplasm, particularly if they cannot be effectively removed via mitophagy. The latter essentially depends on ubiquitination via UBE2N, 2L and 2D enzymes [191], which all transfer ubiquitin to the E3 ligase, PARKIN [192], a process that depends on binding and transfer of ubiquitin to and from the redox-sensitive critical cysteine within the catalytic site [50]. In addition, S-nitrosylation of PARKIN/PARK2 compromises the transfer of ubiquitin to PINK1, which targets defective mitochondria to mitophagy [193] via p62/SQSTM1 interactions [194]. Cytosolic mitochondrial DNA (mtDNA) activates the "mitochondrial innate immune" system [183,195,196], which is progressively deregulated in PINK1 deficient mouse models of Parkinson's diseases [197,198]. When mitochondrial integrity is compromised and mtDNA released into the cytosol, mitochondrial damage-associated molecular patterns engage a signaling cascade leading to interferon-dependent gene transcription and inflammation, promoting the pathology in a growing number of diseases [196]. In addition, S-nitrosylation of mitochondrial chaperones such as HSP60 may trigger the mitochondrial unfolded protein response (MUPR) [199,200]. Hence, Parkinson's disease may be a prototypical disease, in which S-nitrosylation contributes to the deterioration of neuronal functions and temporary NOS1 inhibition might provide potential therapeutic benefit as suggested by experimental studies in mouse models of Parkinson's disease [201] and in MPTP evoked Parkinson's disease in baboons [202]. Further support comes from genetic studies, which found significant associations of PD with polymorphisms of NOS1 and NOS2 [203] and with GTP cyclohydrolase 1, the key enzyme providing the cofactor, tetrahydrobiopterin [204–206]. However, presently there is no direct evidence or proof for a SNO-mediated pathology in human PD, which is basically due to the transient nature of the modifications.

6. Summary

Nitric oxide mediated protein S-nitrosylations affect proteins involved in key mechanisms of proteostasis including protein folding, transport and degradation and mitochondrial integrity. Enhanced SNOing of ER-associated and mitochondrial chaperones, of the versatile HSC70/HSPA8 and of the ubiquitin ligase UBE2D, the latter two at crucial cysteines, results in protein accumulation and slowing of cell proliferation and renewal. As a consequence of NO overload in combination with reversible and irreversible protein oxidations imposes a switch towards an aged, proliferation-senescent phenotype, suggesting that upregulation of NOS1 in the aging brain are functionally relevant in the context of healthy versus pathological aging, particularly in the context of Parkinson's disease.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cellsig.2018.10.019.

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