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Toxicant-mediated redox control of proteostasis in neurodegeneration

Stefanos Aivazidis[1], Colin C. Anderson[1] and James R. Roede

Abstract

Disruption in redox signaling and control of cellular processes has emerged as a key player in many pathologies, including neurodegeneration. As protein aggregations are a common hallmark of several neuronal pathologies, a firm understanding of the interplay among redox signaling, oxidative and free radical stress, and proteinopathies is required to sort out the complex mechanisms in these diseases. Fortunately, models of toxicant-induced neurodegeneration can be used to evaluate and report mechanistic alterations in the proteostasis network (PN). The epidemiological links between environmental toxicants and neurological disease give further credence in characterizing the toxicant-mediated PN disruptions observed in these conditions. Reviewed here are examples of mechanistic interaction between oxidative or free radical stress and PN alterations. Additionally, investigations into toxicant-mediated PN disruptions, specifically focusing on environmental metals and pesticides, are discussed. Finally, we emphasize the need to distinguish whether the presence of protein aggregations are contributory to phenotypes related to neurodegeneration or if they are a byproduct of PN deficiencies.

Addresses

Department of Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA

Corresponding author: Roede, James R (james.roede@ucdenver.edu)

[1] Authors contributed equally to this manuscript.

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Introduction

Preservation of a healthy proteome is crucial for cellular and organismal physiology, which is why organisms have developed a sophisticated system responsible for protein quality control called the proteostasis network (PN). The major goals of the PN are proper protein synthesis, correct protein folding into functional structures, and degradation of misfolded and damaged peptides [1–3]. Dysfunction within the PN has the ability to propagate protein misfolding and aggregate formation. Interestingly, PN collapse is associated with the molecular events involved in the pathology of several disorders, such as diabetes [4–10] and aging [2,11–13], and is a major feature of neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) (Table 1).

Similar to protein aggregation, cellular redox imbalance and free radical damage are also hallmarks of neurodegeneration [14–19]. Several environmental toxicants are associated with neurodegeneration, with converging mechanisms including mitochondrial dysfunction, reactive oxygen species (ROS) production, and disruptions in compartmental redox signaling and control [19–24]. Of great importance to this review, protein folding, autophagy, and proteasomal activity can all be modulated through thiol redox signaling and control mechanisms [25–31]. These observations highlight the significance of the interplay between the proteome and redox homeostasis.

Although redox regulation of the PN is an emerging topic that has not been fully explored, recent studies have yielded significant information. The cell displays several examples of PN tuning or disruption through redox reactions [25,29,31–34]. This review aims to evaluate mechanisms participating in the cross talk between these networks of pathways, as well as the relationship between PN disruption and redox imbalance from a toxicological perspective.

Redox regulation of the proteostasis network

The proteostasis network

Preserving proper production, function, and integrity of the cellular proteome is absolutely necessary for cell survival because proteins participate in nearly every cellular process [35]. For this reason, organisms have developed a highly dynamic set of pathways called the PN, which promotes vigilant protein quality control and

Table 1 Neurodegenerative diseases and genes associated with proteostasis collapse.

Disease	Protein aggregate	Responsible protein	Disease genes	References
Alzheimer's disease	Aβ Plaques	Aβ peptide	APP	[91,187–189]
Alzheimer's disease-tauopathies	Neurofibrillary tangles	Tau	MAPT	[190]
Parkinson's disease	Lewy bodies	α-synuclein	SNCA	[132,191]
Huntington's disease	Polyglutamine inclusion bodies	Huntingtin	HTT	[90,192,193]
ALS	Superoxide dismutase 1 aggregate	Superoxide dismutase 1	SOD1	[194,195]
ALS	Stress granules	TDP-43/FUS	TARDBP/FUS	[196]
Creutzfeldt–Jakob disease-Prion diseases	Prion aggregates	PrP^{SC}	PRNP	[197,198]

ALS, amyotrophic lateral sclerosis.

favors proteome homeostasis [13,36]. The PN is primarily composed of molecular pathways that regulate translation, folding, and degradation of proteins [2]. Several other secondary but essential molecular circuitries, such as the unfolded protein response (UPR) [37], participate in the PN and provide its necessary dynamic nature and its ability to respond during stresses. Protein synthesis requires precise translation by the ribosome [38], while molecular chaperones aid in cotranslational folding [35]. Accurate control of unstable folding intermediates and misfolded proteins is necessary for a healthy proteome and is also regulated by chaperones systems [1]. Degradation of misfolded or defective individual peptides happens through proteasomal degradation [39], while autophagy is responsible for bulk protein and aggregate clearance [40]. This section of the review aims to provide an overview of the PN and present examples of redox regulation of PN components.

Radical and nonradical damage to proteins

In the cellular milieu, the proteome is constantly under an overwhelming quantity of stresses [41], and oxidative stress is a well-characterized example of a condition which can facilitate protein damage [42–44]. Oxidative stress is a process characterized by disruption of cellular redox homeostasis and production of radical and nonradical (NR) molecules [45]. Free radical species (e.g. superoxide, hydroxyl radical) occur naturally in the cell as metabolic by-products [46]. ROS and reactive nitrogen species (RNS) can attack the protein backbone to inhibit function and promote fragmentation of the polypeptide chain, which can result in protein unfolding [42,47,48]. Amino acid residues, such as histidine, leucine, and methionine and aromatic amino acids such as phenylalanine, tyrosine, and tryptophan, can undergo oxidative modifications that can lead to protein cross-linking and aggregation [49]. Perhaps the most vital signaling disruption due to oxidative stress is within the cysteine-based thiol redox proteome [50,51]. These critical residues are involved in redox-regulated control of several cellular functions [52,53], and their oxidation/reduction states are regulated through activity of glutathione (GSH) and thioredoxin (Trx) systems. NR oxidant molecules (e.g. peroxides, aldehydes, epoxides) are also produced in the cell and have the ability to oxidize thiols independently of free radical presence [54]. Oxidation and modification of critical thiol entities can produce cellular redox imbalance to disrupt thiol redox signaling. Pathological conditions, such as neurodegenerative diseases (AD, PD, Huntington's Disease (HD), ALS), are characterized by increased generation of free radicals and NRs [55,56]. Also, general oxidative injury can induce lipid peroxidation and reactive aldehyde production, which can also promote protein damage through adduct formation and favor protein misfolding [57–59].

Oxidative damage to components of the PN, such as chaperones, is of great importance to this review. Proper protein folding is regulated by molecular chaperones [1,13,36], and their function is an important cell defense to prevent aggregation and abrogate pathogenesis. Direct oxidation or adduct formation of sensitive chaperone thiols can result in inhibition of chaperone function and diminish cellular protein quality control [60–62]. Ethanol toxicity is a great example of how oxidative damage to members of the chaperone family can impede protein folding [63,64]. Also, incubation of PC12 neuronal cells with the highly reactive peroxynitrite can promote tyrosine nitration of the chaperone heat shock protein 90 (HSP90) and promote motor neuron death [65]. Another important component of chaperone function is sufficient levels of adenosine triphosphate (ATP) [66] as many chaperones use ATP hydrolysis to facilitate folding [35]. Therefore, energy deficits as a result of xenobiotic-mediated mitochondrial dysfunction can also affect protein folding.

Redox control of proteasomal degradation

Protein degradation is a cornerstone of protein quality control because removal of misfolded proteins prone to aggregation is critical to prevent disease pathogenesis [67–69]. To remove damaged and misfolded proteins, the cell uses the ubiquitin-proteasome system (for review: [70,71]). Briefly, misfolded or damaged proteins are labeled with ubiquitin by E1, E2, and E3 ubiquitin ligase enzymes [72], which 'flags' these misfolded proteins for

degradation through the proteasome [39]. The proteasome is a unique protein complex consisting of two regulatory subunits (19S) and one catalytic subunit (20S). As ubiquitin-tagged proteins are introduced to the proteasome complex, ubiquitin is removed from tagged peptides by the regulatory subunits and then single polypeptides enter the 20S core where they are processed and cleaved by proteolytic subunits. In the presence of mild oxidative stress, the activity of the proteasome is increased because it is responsible for removal of proteins suffering from oxidative damage [43,44]. Increased intensity of redox imbalance can induce separation of the proteasomal subunits (20S and 19S), switching the mode of proteolytic degradation from Ub dependent (ATP dependent) to Ub independent (ATP independent), resulting in degradation of oxidized proteins [73]. Once again, the importance of energy balance and ATP production in PN preservation is highlighted. However, oxidative stress after major oxidative insults can result in inhibition of proteasomal activity. As reviewed extensively by Pajares et al. [25], proteasomal subunits can be modified by post-translational modifications (PTMs) (S-glutathionylation, carbonylation and HNE adduction) that are closely related to redox imbalance as they form as byproducts of oxidative damage [30,74–76]. S-nitrosylation and S-glutathionylation can also modify critical thiols in ubiquitin-related enzymes responsible for protein ubiquitination, resulting in damaged proteins escaping protein quality mechanisms and disruption of cellular physiology [77,78]. The proteasome is also responsible for regulation and degradation of several transcription factors (e.g. Nrf2, NF-kB), which are extensively redox regulated. This is an important point as decreased proteolytic activity disturbs the regulatory capacity of these critical transcription factors, potentially leading to system dysregulation and promotion of pathology [79–81]. Finally, oxidative modification of the 26s proteasome is a common observation in aging [70,82] and other neurological disorders [83–86]; therefore, from a toxicological perspective, the involvement of redox regulation of the proteasome can be of great mechanistic importance.

Redox signaling in autophagy

Autophagy is an essential molecular pathway involved in major cellular processes [87–91], such as immune function, aggregate clearance, and energy metabolism. There are three different forms of autophagy: (1) chaperone-mediated autophagy, in which the heat shock cognate (Hsc70) chaperone shuttles individual misfolded peptides to the lysosome, where they are degraded (reviewed here [92]); (2) microautophagy, in which the lysosomal membrane forms invaginations that sequester cytosolic material for degradation (reviewed here [93]); and (3) macroautophagy (hereby referred as autophagy), which is the bulk protein degradation pathway of the cell [40]. The process of autophagy is mainly regulated by the mammalian target of Rapamycin (mTOR) complex, a central regulator of cell metabolism that functions as a sensor for cellular nutrient and energy levels [11,94]. At basal conditions, mTOR is activated by several metabolic signals and inhibits autophagy. Under stresses such as amino acid depletion or protein aggregate formation, mTOR is inhibited and autophagy is activated. During autophagy, cytosolic material, for example, protein aggregates, organelles, and lipids, is engulfed by a double-membrane vesicle called the autophagosome and is transported to the lysosome to undergo degradation (for review: [28,89,95]). Autophagy is vital for preserving cellular physiology, and its importance is highlighted by the fact that autophagic clearance of mitochondria (mitophagy) is the only known procedure that promotes mitochondrial turnover [28]. Additionally, dysfunction of autophagy is a common observation in neurodegenerative diseases [96], and impaired autophagic clearance promotes protein aggregation of pathological proteins (Table 1). Also, autophagy is involved in the removal of oxidized macromolecules [33,97–99], and dysfunctional autophagy can result in ROS/RNS production [100–102]. The interplay between autophagy and thiol redox signaling has not been investigated thoroughly but it has been reported that ROS and RNS can induce autophagy by inhibiting mTOR [103–105]. For example, a validated redox switch critical for autophagosome formation includes oxidation of an important Cys residue near the catalytic site of Atg4 family members [29]. Atg4 proteins possess cysteine protease activity that aids in lipidation of LC3-I and delipidation of LC3-II [106]. Oxidation or mutation of Cys [81] inhibits Atg4 activity, blocks autophagosome formation, and restricts the cell from using autophagy. Another convergence point of autophagy and thiol redox signaling involves the p62-Nrf2-Keap1 axis. The autophagy receptor p62 binds ubiquitinated molecules to form the autophagosome cargo [107], and reports show that p62 can modulate antioxidant responses by binding Keap1 [108–111], which is a major regulator of antioxidant defense [79,112–114]. Dysfunctional p62 clearance results in p62 accumulation, possibly leading to increased Keap1 sequestration and subsequent Nrf2 overactivation, which is associated with cancer pathology [115–117]. These few examples indicate that exploration of mechanisms governing cross talk between autophagy and thiol redox signaling can be of great interest and can be used in toxicology to decipher xenobiotic-mediated mechanisms of pathogenesis.

Endoplasmic reticulum stress and disulfide bond formation

The endoplasmic reticulum (ER) serves as a hub for nascent peptide folding because to-be-secreted proteins enter the ER cotranslationally to fold into their proper three-dimensional form [118]. Disturbance of ER physiology can inhibit protein folding, propagate aggregation, and activate the UPR [119,120]. This event results in activation of three ER-transmembrane proteins (IRE-1a, PERK, and ATF6a) that inhibit translation and

transcriptionally activate protein degradation pathways as a defense mechanism. UPR also induces expression of folding facilitators, for example, chaperones, to help the cell cope with the increased load of misfolded proteins [121]. Toxicologically, the inability of the cell to defend against prolonged ER stress can eventually result in cell death [122]. Many xenobiotics that exert toxicity through ER stress have been identified [123–125], and examples of thiol redox regulation of the UPR are common [32,105,126,127]. This is because a major process in protein folding is the disulfide bond formation that takes place solely in the ER [128]. Additionally, the formation of intermolecular or intramolecular disulfide bonds between cysteine residues is important for protein stability [62]. Protein disulfide isomerase (PDI) oxidoreductases work as a disulfide donor by promoting cysteine oxidation of candidate peptides [123,129]. PDI is also responsible for disulfide bond isomerization in proteins, a rather important process regarding protein folding, and its disruption can instigate misfolding. Owing to the importance of structural disulfide bonds, reducing factors such as dithiothreitol can cause ER stress through breaking disulfide bonds and modulation of protein folding [124,130]. Also, post-translational modifications of cysteines in the active site of PDI can inhibit its function [123,131] and might be involved in neurodegeneration because PDI levels are increased in brains of patients suffering from neurological disorders [128,132–134]. In general, UPR dysfunction or overactivation is involved in several neurodegenerative disorders, and exploration of ER stress induction through several toxicants can provide valuable information regarding development of pathology.

Toxicants that impact the PN via redox interactions

With the emergence of PN disruption as a hallmark for multiple pathologies, characterization of toxicants, from either epidemiological studies or research models, has led to better understanding of disease mechanisms. Table 2 represents a snapshot of toxicants that impact the PN and a brief description of pathways/protein targets that are disrupted. It should become apparent that common themes exist between toxicants and across the classic modes of PN dysfunction, such as the profound effect of environmental toxicants (heavy metals and pesticides) on all defined categories. Also, it is important to note that there are many converging mechanisms and cross talk (signaling and ROS) among defined PN disruptions. For the focus of this review, we will discuss metals and pesticides and their impact on the redox control of the PN as it relates to neurotoxicology.

A review by Farina et al. [135] does well to describe the vital role of metals in biochemical reactions, as well as the implications of environmental exposure to certain

Table 2 Toxicants known to disrupt cellular proteostasis and mechanisms impacted.

PN pathology	Toxicant	Mechanism	References
ER stress	Acetaminophen	ATF6, CHOP, Caspase-12	[199–202]
	HIV drugs (i.e. Efavirenz, Lopinavir)	CHOP, GRP78, eIF2α, XBP1S, ATF4	[203–206]
	Type II diabetes drugs (i.e. troglitazone, ciglitazone)	ERK, PPARγ, eIF2α, MAPK	[207,208]
	Ethanol	ATF4, CHOP, GRP78	[209–212]
	Environmental toxicants (acrolein)	eIF2α, ATF3/4, CHOP	[167]
	Chemical toxicants (iodoacetamide, TBHP, and menadione)	Caspase-12, GRP94, GRP78	[213,214]
	Metals (Cd, Cu, Fe, Zn, As, and Mn)	CHOP, GADD34, ATF4	[160,215]
	Pesticides (i.e. deltamethrin, PQ, MB)	CHOP, Caspase-12, GRP78	[162,216–219]
Protein misfolding and chaperones	Pesticides (rotenone, PQ, MB, and chlorpyrifos)	BiP, PDI, CHOP, ATF4, HSPs	[84,168–170,174,175,220]
	Metals (Cd)	HSPs, metalloproteins	[156,171]
Proteasome inhibition	PD-related pesticides (rotenone, PQ, and MB)	Mitochondrial dysfunction, 20S inhibition	[85,174,181,221]
	Metals (Cu and Pb)	Selenium inactivation, 20S inhibition	[179,180,222–224]
	Pesticides (i.e. TPT)	Direct inhibition of proteasome	[225]
Autophagy	Pesticides (rotenone, PQ, MB, and chlorpyrifos)	Acetylated α-tubulin, Atg7/12, MAPK, Parkin	[174,184,186]
	Metals (Cd, Mn, Cu, and Pb)	mTOR/p70S6K, ERK, GSK-3β	[157,182,183,226,227]
	Rapamycin, 3-MA, and chloroquine	mTOR, PI3K, Ca^{++}, lysosome pH	[228–230]
ROS generation	PD-related pesticides (rotenone, PQ, and MB)	Mitochondrial dysfunction, redox signaling	[151,231]
	Formaldehyde	SOD1	[232]
	Metals (Cd, Hg, and As)	Trx, GSH, NOX, Fenton reaction, mitochondrial dysfunction	[135,136,145,156,233–237]

metals associated with oxidative stress and neurodegeneration. Mechanisms of toxicity including Fenton chemistry, selenium inactivation, direct oxidation of cellular components (lipids, DNA, and proteins), and vital metal replacement impact all aspects of the PN, with redox disruption as a key player in neurodegeneration [136,137]. Specifically, several metals, such as Cadmium (Cd), Copper (Cu), Manganese (Mn), Arsenic (Ar), Mercury (Hg), and Lead (Pb), have been shown to impact the PN at multiple points or compartments (i.e. mitochondria/cytosol) [136,137].

Although evaluation of pesticide safety has led to regulation and control of human exposure, understanding of the toxicological impacts of chronic exposure to low levels of these compounds is still widely unknown. A recent review by Sabarwal et al. [138] describes pesticide exposure and the many toxic outcomes including cancer, neurodegenerative diseases (i.e. PD and AD), respiratory and reproductive disorders, and endocrine disruptions. Similar to metals, certain pesticides, such as rotenone, paraquat (PQ), and maneb (MB), have been found to be related to PN disruption in neurodegeneration, through either epidemiological studies or mechanistic research, such as those related to PD [139–141].

ROS generation and cellular antioxidant defense

As previously mentioned, oxidative and free radical damage of proteins has a widespread impact on the PN and the cellular defenses designed to maintain both protein function and redox state of the proteome. Mechanisms of toxicity throughout the PN disruptions listed in the following section may be independent or resultant of toxicant-induced ROS generation. For example, Cu and iron (Fe) can undergo Fenton chemistry to directly produce hydroxyl radicals from hydrogen peroxide resulting in oxidative damage to lipids, DNA, and proteins [142]. While Cd does not participate in Fenton reactions, it does substitute itself in membrane and cytosolic metalloproteins (i.e. ferritin), leading to a higher abundance of unbound Cu and Fe to impart oxidative stress [142–144]. Cd exposure does cause ROS generation directly through other ROS species; however, there are several ROS-independent mechanisms that contribute to overall oxidative and free radical damage and PN disruption. Additionally, exposure to Cd results in cysteine oxidation and Trx oxidation and significantly impacts the mitochondrial compartment far more than the cytoplasmic compartment [20,145]. Another metal of particular interest is Mn and its relation to neurodegeneration involving ROS generation via increased mitochondrial respiration [146]. It has been proposed that Mn^{2+} exposure disrupts Ca^{2+} dynamics and directly impacts the electron transport chain of the mitochondria [146–148]. Mn is also the metal component of the dithiocarbamate pesticide MB with similar associations to neurodegeneration through similar but not identical pathways [139]. Regarding MB, it has been shown to directly inhibit complex III of the electron transport chain and impact mitochondrial membrane dynamics [149,150]. However, direct ROS production has not been consistently observed with MB exposure, which may be explained by Nrf2 activation and increase in cellular GSH [151]. In contrast, PQ, used in a co-exposure model of PD with MB, causes ROS production without activation of the Nrf2 response, contributing to the complex interplay of oxidative mechanisms seen in PD [151]. For the remainder of this review, we will present both ROS-mediated and ROS-independent mechanisms of PN disruption.

Another impact of environmental exposures involves the thiol-containing proteins involved in the cellular antioxidant response. Cd, Hg, and As have been shown to significantly impact of the redox states of Trx proteins without impacting the GSH/GSSG redox status [145]. The disruption of the Trx pathway can have a significant impact on the resolution of oxidative damage to proteins not only through the thiol redox proteome but also through aberrant signaling and control of many cellular functions, such as mitochondrial function, ATP production, and apoptosis [20,152,153]. As these metals do not undergo Fenton-type chemistry, this impact is proposed to be directly on free thiols, leading to apoptosis pathway induction and/or accumulation of damaged proteins. Furthermore, similar observations are observed in pesticide exposures that mimic neurodegenerative pathology [151]. MB and PQ have been shown to differentially carbonylate proteins within the cortex and striatum of mice [154]. While the direct reactivity of MB to protein thiols has been reported, the association between oxidation of thiols and neurodegenerative endpoints such as protein aggregation, ATP depletion, and mitochondrial function is still being investigated [19,20,155].

ER stress

Metal-induced ER stress is characterized by ROS generation, oxidation of protein thiols, oxidative damage, and the substitution of catalytic metals in enzymes (i.e. Cu/Zn SOD) [156]. Manganese (Mn), an essential nutrient and trace element, has also been shown to induce activation of ER stress–related proteins, such as CHOP and eIF2α, as a result of oxidative damage to proteins and induction of the UPR [136]. Furthermore, Mn has been linked to neurodegeneration via Mn-induced apoptosis of dopaminergic neurons in PD and manganism via ER stress and disrupted autophagy [157]. One such mechanism includes the abundance and activity of MnSOD, which has been shown to be altered by exogenous Mn exposure [158,159]. In addition, Zn has also shown induction of ER stress in hypothalamic neurons, with enhancement of toxicity with co-exposure to Cu [160]. Lead (Pb), a metal that is

widely accepted to negatively impact IQ in children, has also been reported to cause ER stress, leading to protein aggregation [161].

In regards to pesticide-induced ER stress, a recent study published by Hossain et al. reports the detrimental impact of deltamethrin, a pyrethroid pesticide, on SK-N-AS human neuroblastoma cells through induction of apoptosis via the UPR pathway [162]. Their investigation lead to a description of deltamethrin mechanism involving calpain activation leading to CHOP/GADD153 induction and caspase-12 cleavage with following caspase cascade. Although pyrethroid compounds have been shown to induce ROS and oxidative damage, the unique calpain apoptosis pathway activated with deltamethrin presents the possibility of a non−ROS-mediated ER stress mechanism [163]. Combined with epidemiological links of pyrethroid exposure to neurodegeneration, similar induction of calpain-mediated apoptosis via caspase-12 has been observed in neurodegenerative pathologies such as AD, ALS, and PD [164,165]. There are also reported associations between PQ and ER stress outcomes; however, determination of direct interaction or indirect oxidative damage to proteins has yet to be made [125]. MB has also been shown to induce the ER stress pathways, potentially due to its ability to modify critical protein thiols [19,86,166]. Furthermore, the environmental pollutant acrolein found in cigarette smoke has also shown induction of ER pathways as a result of damaged and misfolded proteins via oxidative adducts [167].

Chaperones

As previously mentioned, molecular chaperones, such as the family of HSPs, are vital for not only the proper folding of native proteins but also the UPR maintenance of misfolded and damaged proteins, leading to recycling or disposal via chaperone-mediated autophagy. Induction of HSPs is not only a marker of pathological ER stress but can be independently inhibited or altered by toxicant exposure as reported by several investigations [168−170]. Specifically, HSP70 and HSP40 have been observed to play a key role in PD pathology. While metals have been highly studied because of their association with proteinopathies of the brain, their direct effect on molecular chaperones are still widely unknown. Cd has been reported to induce protein aggregation through multiple mechanisms, one being direct binding and inhibition of unfoldases (DnaK, DnaJ, Hsp70, Hsp60, and Hsp104) and ATP-driven proteases (Lon and ClpAB) [171]. Furthermore, silencing of Hsp70 ameliorated Cd-mediated apoptosis in SN56 neuroblastoma cell culture, possibly due to the modification of an allosteric redox switch on Hsp70 [172,173]. With alterations in molecular chaperones presenting in multiple neurodegenerative diseases, it is no surprise that pesticides have shown similar alterations in HSP abundance and activity [168]. For instance, co-exposure of MB and PQ causes increased abundance of Hsp70 and Hsp90 in mice [174]. Investigations of other pesticides and human HSP modulation are rare, but chlorpyrifos and esfenvalerat have been shown to induce HSP expression in salmon [175]. Combination of toxicant-mediated alterations in native protein folding and UPR described previously and disruptions in proper protein degradation and exocytosis creates this complex network of PN deficiencies observed in neurodegeneration.

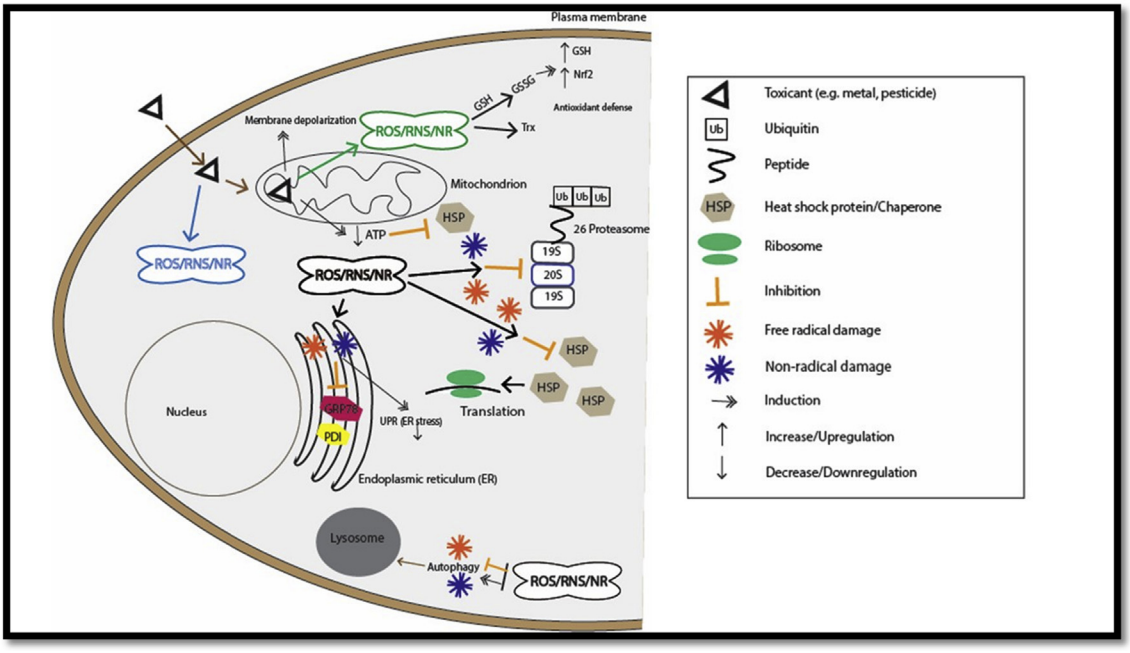
It is important to note here the impact of oxidative stress and redox modifications on the signaling transduction pathways associated with heat shock factor 1, the transcriptional regulator of chaperone expression and heat shock response HSR. Heat shock factor 1 is heavily regulated through phosphorylation via protein kinase and phosphatase activity, enzymes shown to be modulated by ROS presence [176−178]. Increased cellular ROS can potentially dampen the HSR, allowing yet another indirect impact of general ROS on PN maintenance.

Proteasome and autophagy

Proper function of the ubiquitin-proteasome pathway and removal of defective proteins are imperative to cellular defense against protein aggregation and maintenance of the proteome. Cu has been reported to directly inhibit proteasome activity and induce apoptosis in jurkat T cells and human breast cancer cells [179]. In addition, As, Cd, and Pb showed inhibition of proteasomal activity in blood samples of a case−control investigation [180]. Similarly, the PD-related pesticides rotenone and PQ also show direct inhibition of the catalytic 20S subunit of the proteasome [125,181]. However, direct mechanistic links between thiol oxidation and proteasome inhibition by environmental toxicants have yet to be reported.

Metal-mediated alterations in autophagy have been highly reviewed in neurodegenerative diseases such as PD, AD, and HD [182,183]. For instance, Mn exposure in rats revealed dysfunctional lysosomes and quenched signaling for autophagy induction through mTOR/p70S6K pathway [157,183]. PQ and rotenone also have the ability to directly impact the autophagy machinery through alterations of chaperones involved in transport to the lysosome, mTOR signaling, and fusion of the lysosome with the autophagosome [174,184]. Furthermore, PQ has been shown to disrupt ubiquitin-dependent autophagy by reducing ubiquitin abundance with no reduction in mRNA [185]. Chlorpyrifos has also been reported to enhance LC3-II expression in a dose-dependent manner, with associations to mitochondrial dysfunction and apoptosis [186]. Again, a direct mechanistic link to protein thiol oxidation and toxicant-induced deficiencies in autophagy has yet to be made within neurotoxicology.

Figure 1



Schematic overview of the possible PN disruptions through toxicant-mediated oxidative adduction, free radical damage, and nonradical modifications. Briefly, toxicants can impact the PN via direct mechanisms, such as redox cycling and direct oxidation of critical proteins involved in proteasomal degradation, autophagy, and heat shock protein chaperones. In addition, the PN can be negatively impacted by toxicant exposure via toxicant-mediated mitochondrial dysfunction, which can impair ATP production and exacerbate ROS production. PN, proteostasis network; ATP, adenosine triphosphate.

Toxicological impact of redox stress and PN dysfunction on neurodegeneration: separating disrupted signaling and protein aggregation

Two main pathways describe the major impacts of thiol redox homeostasis disruption on protein aggregation. First, alterations in protein thiols vital for the resolution and maintenance of oxidative damage to proteins will sensitize cells to ER stress and will exacerbate deficiencies in proper autophagy. Because of this, toxicants impacting these redox sensitive systems should display altered protein degradation and aggregation, as seen in rotenone-mediated alteration of α-synuclein metabolism [181]. However, it is vital to separate the impact of environmental exposures on redox signaling and the end result of protein aggregation as many interventions target protein aggregations to alleviate pathology. The detrimental effect of protein aggregation on neuronal functions, such as synaptic transmission and autophagy, cannot be discounted but may also represent a byproduct of upstream disruptions in PN control.

As mechanistic evaluation of toxicant models of neurodegeneration uncovers more pathways altered in disease, focus must be made on the wide range of PN disruptions that can occur through modifications of the redox proteome via oxidative and free radical stress (Figure 1). Research performed with this focus will have the potential to find therapeutics that target protein aggregation in the earliest phases of its neurodegenerative phenotype and stop errant protein agglomerations whether as the cause or byproduct of pathology.

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Conflict of interest

Nothing declared.

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