Review

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Oxidised protein metabolism: recent insights

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Abstract: The 'oxygen paradox' arises from the fact that oxygen, the molecule that aerobic life depends on, threatens its very existence. An oxygen-rich environment provided life on Earth with more efficient bioenergetics and, with it, the challenge of having to deal with a host of oxygen-derived reactive species capable of damaging proteins and other crucial cellular components. In this minireview, we explore recent insights into the metabolism of proteins that have been reversibly or irreversibly damaged by oxygen-derived species. We discuss recent data on the important roles played by the proteasomal and lysosomal systems in the proteolytic degradation of oxidatively damaged proteins and the effects of oxidative damage on the function of the proteolytic pathways themselves. Mitochondria are central to oxygen utilisation in the cell, and their ability to handle oxygen-derived radicals is an important and still emerging area of research. Current knowledge of the proteolytic machinery in the mitochondria, including the ATP-dependent AAA+ proteases and mitochondrial-derived vesicles, is also highlighted in the review. Significant progress is still being made in regard to understanding the mechanisms underlying the detection and degradation of oxidised proteins and how proteolytic pathways interact with each other. Finally, we highlight a few unanswered questions such as the possibility of oxidised amino acids released from oxidised proteins by proteolysis being re-utilised in protein synthesis thus establishing a vicious cycle of oxidation in cells.

Keywords: mitochondria; oxidative damage; oxidised protein metabolism; proteaphagy; proteolysis; reactive oxygen species.

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Introduction: survival in an oxygen-rich environment

Life on Earth is thought to have originated and evolved in an anoxic environment. A major change occurred with the so-called Great Oxygenation Event driven by the ability of oxyphotobacteria (ancestors of cyanobacteria) to produce substantial amounts of oxygen (O_2) as a byproduct of oxygenic photosynthesis (Fischer et al., 2016). The oxygen-rich environment provided life with new bioenergetic opportunities but also with the challenge of coping with oxidative stress (Fischer et al., 2016). Consequently, all living organisms, including anaerobes, have evolved a diverse range of mechanisms for preventing oxidative damage to biomolecules and for dealing with any oxidant damaged material generated. In the case of proteins, oxidative damage is a double-edged sword because, in addition to damage to many important functional molecules, there can also be damage to the systems which facilitate their removal.

In this minireview, we discuss recent developments that have extended early observations that showed that oxidised proteins can be selectively removed from mammalian cells by cysteine proteases (lysosomes) (Kurz et al., 2008) and the multicatalytic protease (proteasome) (Rivett and Levine, 1987; Stadtman et al., 1988; Grune et al., 1996, 1997). Recent studies have provided a better understanding of how these proteolytic pathways are regulated and the extent to which the proteolytic machinery itself is susceptible to oxidative damage. We discuss important advances in our understanding of the role that dysfunctional mitochondria play in protein oxidation and the endogenous mechanisms that limit damage to this organelle and to the cell. The unfolded protein response in the endoplasmic reticulum is now known to play a key role in the regulation of oxidised protein levels and the latest advances in this field will also be discussed. We focus on recent insights into the cellular handling of oxidatively damaged proteins rather than the role that protein oxidation can play in cell signalling.

Types of modification to proteins

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are inevitable by-products of cellular

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metabolism and are important mediators of biological functions via redox signalling (Jung et al., 2014). Unregulated oxidative modifications caused by ROS and RNS can result in reversible or irreversible damage to proteins, with specific modifications leading to each endpoint (Figure 1) (Jung et al., 2014). Irreversible oxidative modifications can either cause global protein damage or target specific amino acid residues. For example, when cysteine residues are exposed to oxidative stress, ROS cause the reversible loss of thiol (–SH)– groups and the formation of sulfenic acids (Poole, 2015). In another reversible reaction, methionine can be oxidised to methionine sulfoxide when oxygen binds to the its sulphur molecule (Schöneich, 2005). Arginine, glutamine, isoleucine, leucine, lysine, proline and valine side chains are the most susceptible to oxidative protein modifications in the form of carbonylation (Jung et al., 2014) and the resulting carbonyls can be used as markers of global protein oxidation (Augustyniak et al., 2015). Approaches commonly used to detect or quantify protein carbonyls in biological samples have been comprehensively reviewed by Augustyniak et al. (2015). The products of oxidative modification to the aromatic amino acid residues in proteins are also widely used as biomarkers of oxidative damage in ageing, inflammation and a range of disease processes involving oxidative stress (Dalle-Donne et al., 2006; Whiteman and Spencer, 2008; Bechtold et al., 2009; Frijhoff et al., 2015). Oxidative modification to the aromatic amino acids produce an array of products depending on the oxidant involved. The short-lived hydroxyl radical will generate products such as 3,4-dihydroxyphenylalanine (DOPA) and meta-tyrosine locally from oxidation of tyrosine and phenylalanine residues in proteins respectively (Stadtman and Levine, 2003). In addition to radical oxidants, two electron oxidants such as hypochlorous acid (HOCl) and peroxynitrous acid (ONOOH) also generate characteristic products on tyrosine side chains such as 3-nitrotyrosine (Radi, 2013) and 3-chlorotyrosine (Ogata, 2007) respectively (Feeney and Schoneich, 2012). While these two electron oxidants react with aromatic amino acids, methionine and cysteine residues are the preferred targets in proteins (Feeney and Schoneich, 2012).

Tryptophan side chains are also known to generate a number of characteristic products on oxidation. The major products of photo-oxidation of tryptophan are kynurenine and *N*-formylkynurenine (Pattison et al., 2012). Other types of modifications can result in irreversibly modified proteins. For example, reducing sugars react non-enzymatically with amino groups in proteins, generating products that can undergo further glycation and molecular rearrangement resulting in the generation of advanced glycation end products (AGEs) (Morgan et al., 2002). In addition, the degradation products of lipid peroxides such as 4-hydroxynonenal can form covalent adducts with the side chains of nucleophilic amino acids (Kaur et al., 1997). The extent of modification to proteins is important since there is a correlation between increased oxidative modification, decreased accessibility to the degradation machinery, and increasing aggregate formation (Jung et al., 2014). This bi-phasic pattern of protein degradation was clearly demonstrated using a novel *in vitro* model system in which DOPA-containing proteins were biosynthetically

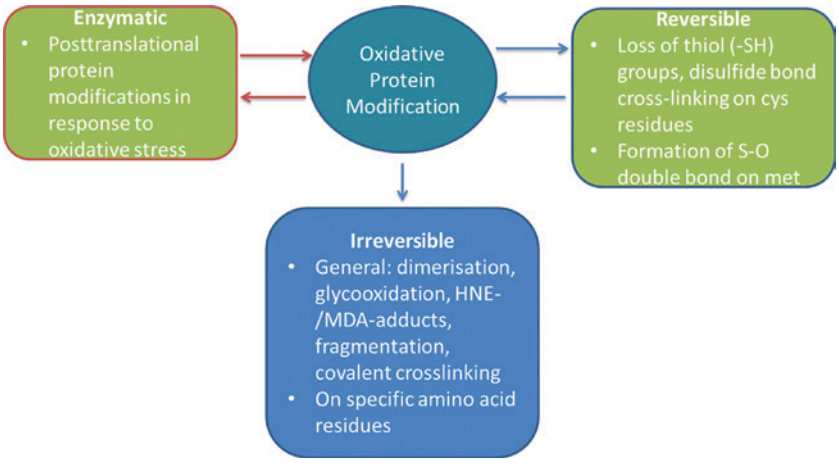

Figure 1: Overview of oxidative modifications to proteins.
This Figure depicts reversible (green) and irreversible (blue) oxidative protein modifications. Enzymatic posttranslational protein modifications that occur in response to oxidative stress are reversible, functional modifications that do not cause cellular damage (red arrows). Conversely, reversible modifications due to the loss of sulfhydryl (-SH) groups and irreversible oxidative modifications are not functional and induce cellular stress (blue arrows).

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generated in cells from incorporation of L-DOPA into proteins in place of L-tyrosine (Rodgers et al., 2002). In this 'oxidant-free' model, proteins containing lower levels of DOPA were degraded faster than native proteins but with increasing levels of DOPA in the polypeptide chain, proteins became more aggregate prone and protease-resistant (Rodgers et al., 2002; Dunlop et al., 2008). The metabolism of oxidised proteins is also reliant upon the cellular location of the modified protein. Multiple proteolytic pathways exist in different cellular compartments to metabolise the diversity of oxidised proteins that can be generated in the cell and prevent or limit their deleterious effects (Figure 2). Oxidised proteins in the extracellular matrix can either be degraded *in situ* or endocytosed and degraded within the cell (Nowotny and Grune, 2014).

Reversible protein oxidation

Repair of reversible oxidative modifications to proteins is mediated by enzymatic reduction regardless of the cellular location of the modified protein (Höhn et al., 2013). Sulfenic acids and disulfides formed by the oxidation of cysteine thiols can be reduced by the thioltransferases thioredoxin and glutaredoxin (Poole, 2015). Further cysteine oxidation results in an irreversible modification, the formation of sulfinic and sulfonic acids. However, there is one exception and the enzyme sulfiredoxin exclusively reduces sulfinic acid in peroxiredoxins in an ATP-consuming reaction (Jeong et al., 2012).

Similarly, the reduction of methionine sulfoxide (MetSO), formed by the oxidation of methionine, is catalysed by methionine sulfoxide reductases (MSRs) (Tarrago et al., 2012). Within the past 5 years, our knowledge of MSRs has expanded significantly. It was discovered that the two classes of MSR enzymes, MsrA and MsrB, act on the S and R stereoisoforms of MetSO respectively (Devarie-Baez et al., 2016). In addition, MSRs preferentially protect cells from protein unfolding due to oxidative damage in the yeast *Saccharomyces cerevisiae* (Tarrago et al., 2012) and the MsrB enzyme SelR reverses actin oxidation in the cytoskeleton of *Drosophila* (Hung et al., 2013). Recently, the ubiquitous nature of enzymatic reduction was highlighted with the discovery of the first mitochondrial MSR substrate, the adenine nucleotide exchange factor Mge1 that acts as an oxidative sensor during mitochondrial protein import. Upon oxidation Mge1 is reduced by MsrB (Marada et al., 2013; Allu et al., 2015).

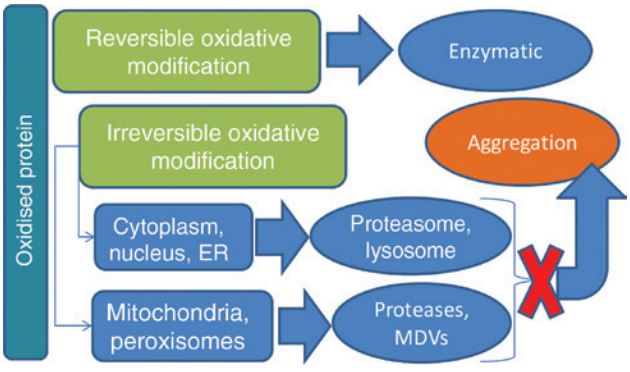

Figure 2: Pathways of oxidised protein removal.
The Figure depicts the mechanisms of metabolism for the two types of oxidative protein modifications. Reversible modifications are reversed by enzymes such as thioltransferases and methionine sulfoxide reductases. Conversely, proteins with irreversible oxidative damage must be removed by proteolysis. Those that occur in the cytoplasm, nucleus or endoplasmic reticulum (ER) are degraded either by the proteasomal and lysosomal systems. Peroxisomes and mitochondria rely on organelle specific proteases to maintain proteostasis and mitochondria also utilise mitochondrial-derived vesicles (MDVs) to transport oxidised cargo to the lysosome. Where these mechanisms are unsuccessful, aggregation of oxidised proteins occurs.

Irreversible protein oxidation

In the case of non-repairable oxidative modification to proteins, removal by proteolysis is required to maintain cellular protein homeostasis (proteostasis). While all proteins are at risk of oxidant attack, proteins in the cytosol, nucleus, endoplasmic reticulum and mitochondria are the primary targets of oxidative modification (Baraibar and Friguet, 2013). Therefore, it is important to understand the proteolytic systems in each subcellular location responsible for degrading irreversibly oxidised proteins.

Oxidised protein removal from the cytoplasm, nucleus and endoplasmic reticulum

The proteasomal and lysosomal degradation pathways are utilised to remove proteins from the cytoplasm, nucleus and endoplasmic reticulum (ER). As the focus of this mini-review is on recent insights, these proteolytic pathways will only be briefly reviewed and more detailed reviews can be found elsewhere (Pickering and Davies, 2012; Settembre et al., 2013; Chondrogianni et al., 2014; Raynes et al., 2016). Natively folded proteins can be efficiently

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degraded by the ATP-and ubiquitin-dependent 26S proteasome, a system comprising a 20S core and a regulatory 19S particle bound to either side of the core (Chondrogianni et al., 2014). The ATP- and ubiquitin-independent 20S proteasomal system is considered the main degradation pathway for oxidatively damaged proteins as unlike native proteins, oxidised proteins are not ubiquinated (Kästle et al., 2012). An increase in ubiquinated proteins following oxidative stress has been linked to a faster turnover of some key proteins required by cells to handle the oxidised proteins (Kästle et al., 2012).

The 20S proteasome is a cylindrical shaped protein complex, made up of four rings, containing seven subunits each (Jung and Grune, 2013). The first and fourth rings contain α subunits, while the second and third contain β subunits. Thus, the proteasome has the ring structure α, β, β, and α (Jung and Grune, 2013). Substrate binding is mediated by the two outermost α rings and main proteolytic chamber is between the two β rings (Pickering and Davies, 2012; Jung and Grune, 2013). Recently, it was found that the molecular chaperone heat shock protein 70 (Hsp70) is induced following protein oxidation and forms a substrate with the oxidised protein that promotes the removal of oxidised proteins by the 20S proteasome (Reeg and Grune, 2015; Reeg et al., 2016). However, the 20S system is limited by its requirement for protein unfolding and exposed hydrophobic surface structures to stick to the α binding domain (Pickering and Davies, 2012). As a result, only mildly oxidised proteins can be degraded by the proteasome. The proteasome can also be inhibited by highly oxidised, covalently cross-linked protein aggregates (Sitte et al., 2000). Lipofuscin, a protein aggregate and hallmark of ageing, is made up of an oxidised and cross-linked core with surface hydrophobic oligopeptides that allow the α domain of the 20S proteasome to bind (Sitte et al., 2000). Despite this binding, degradation is inhibited due steric hindrance caused by the cross-linked core and the multiple unsuccessful attempts reduce the overall proteolytic capacity of the proteasome (Hohn et al., 2011). The vulnerabilities and limitations of the proteasome highlight the necessity of multiple proteolytic pathways.

One such alternative route of protein degradation is the lysosomal pathway. Lysosomes are cytoplasmic membrane bound organelles containing acidic hydrolases, including proteases, nucleases and lipases (Settembre et al., 2013). Lysosomal proteases are able to degrade more highly oxidised proteins than the proteasome (Hohn et al., 2011; Kang et al., 2011). In addition, autophagy is also responsible for the removal of a wider range of cellular subunits including lipids, DNA, RNA, extracellular material and entire organelles (Höhn et al., 2013). The method by which these subunits are delivered to the lysosome gives rise to the three major types of autophagy; macroautophagy, microautophagy and chaperone-mediated autophagy. For a detailed review of these pathways and their molecular components please see (Höhn et al., 2013; Navarro-Yepes et al., 2014). Of these cellular digestive mechanisms, macroautophagy is the best characterised and is utilised to selectively degrade organelles such as mitochondria (mitophagy), peroxisomes (pexophagy) and ribosomes (ribophagy) (Hubbard et al., 2012). Decreases in lysosomal proteolysis that occur naturally during ageing have been associated with the accumulation of oxidised proteins and lipofuscin (Lynch and Bi, 2003).

Though the two systems are able to operate independently, there is some interplay between them. Proteasomal inhibition results in the upregulation of autophagy (Chondrogianni et al., 2014). At present, research into the complementary actions of the two systems has focused on the 26S proteasome (Liebl and Hoppe, 2016). However, a specific understanding of how the 20S proteasome and lysosome interact when degrading oxidised proteins has not been developed.

The stability of the lysosomal membrane is a key factor in determining cell survival (Johansson et al., 2010). Lipid peroxidation from ROS can destabilise the lysosomal membrane resulting in proton leakage and an increase in lysosomal pH (Johansson et al., 2010). Oxidised proteins can also cause lysosomal membrane permeabilisation, increase lysosomal pH, and trigger a cascade of pro-apoptotic events (Dunlop et al., 2011). A very important study recently identified Apolipoprotein D (ApoD), an extracellular lipid-binding lipoprotein, as having a lysosomal membrane stabilising function (Pascua-Maestro et al., 2017). ApoD can reduce radical-propagating lipid hydroperoxides (Bhatia et al., 2012) and was shown to be endocytosed and to inhibit lysosomal lipid peroxidation *in vitro* (Pascua-Maestro et al., 2017). The authors suggested that ApoD could play an important role in the brain by protecting neurones against oxidative damage and could have important implications in neurodegenerative disorders (Pascua-Maestro et al., 2017).

ER-specific proteolysis

The precise degradation pathway of oxidised proteins in the ER has not yet been elicited but since oxidised proteins can be generated in the ER, the unique ER-specific mechanism to maintain proteostasis, termed ER-associated degradation (ERAD) is likely to be relevant to oxidised proteins.

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As the organelle responsible for cellular protein folding and disulfide bond formation, the ER is a highly oxidising environment (Perri et al., 2016). The formation of disulfide bonds in the ER leads to the production of oxidants, inherently linking the ER and oxidative stress (Chakravarthi et al., 2006; Baker et al., 2008; Hudson and Pagliassotti, 2015). Oxidative stress and its corresponding oxidative protein modifications fall under the umbrella term ER stress which can also be caused by mutations, nutrient deprivation or viral infection among other things (Pluquet et al., 2015).

The lumen of the ER is an oxidative environment, critical for formation of disulfide bonds and proper folding of proteins (Perri et al., 2016). A certain amount of basal protein misfolding occurs in the ER which is generally corrected by retrograde transport of misfolded proteins into the cytosol for proteasome-dependent degradation (Xu et al., 2005). Disturbances in the normal functions of the ER can increase the amount of unfolded proteins, triggering the unfolded protein response (UPR). Unfolded or misfolded proteins resulting from ER stress are handled by a unique ER-specific mechanism termed ER-associated degradation (ERAD) (Pluquet et al., 2015). The precise degradation pathway of oxidised proteins in the ER has not yet been elicited but they could also be handled by ERAD. While ERAD is able to transport proteins to the cytosol for proteasomal or lysosomal degradation, the unfolded protein response (UPR) is the main quality control system in the ER. The UPR restores ER proteostasis using three transmembrane proteins: protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α) and activating transcription factor-6 (ATF6). Together these three arms of the UPR activate transcription factors encoding quality control proteins to reduce protein synthesis and upregulate degradation machinery such as the antioxidant pathway Nrf2 (Hudson and Pagliassotti, 2015; Pluquet et al., 2015). Future research into oxidised protein metabolism by the UPR may focus on the effect of specific oxidised proteins on each transmembrane protein. For example, a recent study of ER stress caused by advanced oxidation protein products (AOPPs) in human proximal tubular cells (HK-2) cells, a chronic kidney disease model, found that the ATF6 pathway of UPR helped reduce AOPP-induced hypertrophy and epithelial to mesenchymal transition (Tang et al., 2015).

Removal of oxidised proteins from the mitochondria

The mitochondrial electron transport chain produces ROS as a by-product of respiration (Zorov et al., 2014). Consequently, mitochondrial proteins, especially those in the protein-rich inner membrane, are primary targets for oxidative damage and mitochondria require well-developed primary and secondary defences (Gerdes et al., 2012; Hamon et al., 2015). Since the mitochondria do not contain proteasomes, ATP-dependent AAA+ proteases are responsible for maintaining mitochondrial proteostasis (Bayot et al., 2010; Gerdes et al., 2012). AAA+ proteases are part of a superfamily of hexameric proteins containing a conserved P-loop ATPase Walker motif and a metalloprotease domain with a HExxH motif for proteolysis (Gerdes et al., 2012). The Lon and Clp protease families located in the mitochondrial matrix are responsible for the bulk of oxidised protein removal (Lionaki and Tavernarakis, 2013; Hamon et al., 2015). Like the 20S proteasome, the Lon protease selectively degrades mildly oxidised hydrophobic substrates and is unable to degrade aggregated severely oxidised substrates (Baker et al., 2011). Lon knockdown in yeast and human HeLa cells led to an increase in mitochondrial ROS and the accumulation of carbonylated proteins (Bayot et al., 2014). In a mouse model of pressure overload heart failure, where ATP-dependent proteolytic activity is reduced due to the oxidation of AAA+ proteases, impairment of the Lon homologue LONP1 also led to an increase in the production of ROS and carbonylated proteins in the mitochondria (Hoshino et al., 2014). This suggests a vicious cycle where protease dysfunction is associated with the increased oxidative stress and accumulation of oxidatively damaged proteins that occur in heart failure (Wang and Robbins, 2006). In another unfortunate knock-on effect, a decrease in yeast Lon homologue Pim1-mediated proteolysis caused by ageing resulted in elevated levels of oxidised and aggregated protein in the cytosol, leading to proteasome inhibition (Erjavec et al., 2013).

A novel degradation pathway for more extensively oxidised proteins in the mitochondria has emerged more recently. This selective removal of proteins is mediated by small mitochondrial-derived vesicles (MDVs) that transport their cargo to the lysosome (Soubannier et al., 2012a). When first observed in 2008, MDVs were shown to form independently of dynamin-mediated mitochondrial fission and autophagy (Neuspiel et al., 2008). The absence of the requirement for GTPase dynamin Drp1 protein suggested a more complex mechanism for MDV formation and recent literature contributed greatly to our understanding of MDVs. One of the most important findings has been that MDVs are produced upon exposure to mitochondrial stressors such as oxidative stress and are highly selective for oxidised proteins (Soubannier et al., 2012b). It has been suggested that conformational changes caused by oxidation allow protein targets to be identified

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for incorporation into MDVs. Soubannier et al. observed that subunits of Complexes II, III, and IV are differentially incorporated into the vesicles, whereas proteins of complex I and ATP synthase are excluded (Soubannier et al., 2012b). The reasoning behind this additional selectivity is still not understood, although size differences and stress-specific protein removal have been suggested (Hammerling and Gustafsson, 2014). The discovery that MDV formation requires the presence PINK1 and Parkin has been another important recent development (McLelland et al., 2014). Both proteins are also involved in traditional mitophagy; however, the pathway used in MDV formation is independent of this as it occurs in the absence of the autophagy-related genes ATG5, Rab9 and Beclin (Soubannier et al., 2012a; McLelland et al., 2014). Unlike mitophagy, which is preceded by global cellular depolarisation and kinetically slower, MDVs are generated at an early stage of ROS production (McLelland et al., 2014). This may indicate that MDVs allow damaged oxidised proteins to be removed before the entire organelle is compromised (Ni et al., 2015). Cadete et al. have identified MDVs in cultured cardioblasts following treatment with antimycin-A and H_2O_2 and visualised MDVs *in vivo* in mice using transmission electron microscopy, electron tomography and immunogold staining (Cadete et al., 2015). The presence of MDVs in cardiac tissues may suggest that they are utilised in cell types that are highly dependent on a healthy mitochondrial network to meet energy demands and where the removal of larger, unspecific portions of mitochondria would be an unsuitable method of metabolising oxidised proteins (Roberts et al., 2016). Though the exact mechanisms of MDV biogenesis and how oxidised cargo are transported to the lysosome for degradation are still unknown, a major breakthrough has been made by the McClelland lab with the identification of the SNARE protein syntaxin-17 in MDVs (McLelland et al., 2016). SNARE proteins mediate membrane fusion events and are utilised by MDVs to fuse with lysosomes (McLelland et al., 2016). With this development and further studies the exact mechanisms by which MDVs remove oxidised mitochondrial components may be elucidated.

Removal of oxidised proteins from peroxisomes

Peroxisomes are vital cellular organelles that perform a variety of metabolic reactions using enzyme (Antonenkov et al., 2010). Primarily, they are responsible for the metabolism of substrates including long chain fatty acids by an oxidative reaction that produces H_2O_2 (Antonenkov et al., 2010). Peroxisome quality control is an area that has recently come under investigation as redox imbalance during the cellular metabolism of hydrogen peroxide (H_2O_2) can make the organelle a major producer of ROS and hence the generation of oxidised proteins (Antonenkov et al., 2010). Although morphologically similar to lysosomes, quality control in peroxisomes more closely resembles that of mitochondria. Peroxisomes contain a specific Lon isoform known as peroxisomal Lon peptidase (LONP2) that is involved in the maintenance of proteostasis (Bartoszewska et al., 2012; Nordgren and Fransen, 2014). PLN is a homologue of peroxisomal Lon and in *Penicillium chrysogenum* digests unfolded protein substrates such as oxidatively damaged catalase-peroxidase. PLN deletion strain peroxisomes contained protein aggregates, including catalase-peroxidase aggregates (Bartoszewska et al., 2012). Without H_2O_2 pre-treatment to induce oxidative damage, catalase-peroxidase was resistant to proteolysis by Lon while following exposure to low concentrations significant catalase degradation was observed. Therefore, oxidatively misfolded catalase-peroxidase is a good substrate for peroxisome-specific Lon, but not its native counterpart (Bartoszewska et al., 2012; Pomatto et al., 2016).

Oxidised extracellular matrix proteins

Extracellular matrix (ECM) proteins such as collagen and elastin as well as ECM glycoproteins and proteoglycans are also subject to oxidative modifications from oxidants generated on the plasma membrane or extracellularly (Kennett et al., 2011; Chuang et al., 2014). There is evidence that the extracellular compartment in many biological tissues is poorly equipped with antioxidants compared to the intracellular domain and this, coupled with a high number of long-lived proteins, can result in the accumulation of oxidised proteins within the ECM (Kennett et al., 2011; Chuang et al., 2014). Much of the more recent work in this area has been performed in the context of ageing and often specifically in relation to skin ageing. For example, in skin biopsies from mice, levels of AGEs increased with age but protein carbonylation was unchanged (Nowotny and Grune, 2014). Collagen is the most abundant protein in ECM of the skin and has low turnover rates so might be more susceptible to oxidative damage (Nowotny and Grune, 2014). *In vitro* studies showed that while collagenase was able to degrade oxidised and AGE-modified collagen more efficiently than native collagen, once

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collagen became heavily cross-linked it was resistant to proteolytic degradation (Nowotny and Grune, 2014). Photoaged skin is also characterised by the deposition of abnormal elastin and changes to glycosaminoglycan (GAG) structure (Kammeyer and Luiten, 2015). Damage to elastin can occur directly due to a combination of UV- or ROS-induced changes (Kammeyer and Luiten, 2015). Oxidative damage to skin can also result in increased activity of elastases and collagenases due to activation of macrophages, neutrophils and fibroblasts resulting in a faster turnover of these ECM proteins (Kammeyer and Luiten, 2015). ECM oxidation can have a profound effect on cell behaviour and can influence factors such as adhesion, proliferation and can stimulate the release of a range of proteolytic enzymes (Kennett et al., 2011). Repetitive irradiation with UVB resulted in loss of the GAG hyaluronic acid (HA) from murine dermis (Dai et al., 2007). This was found to be due in part to downregulation of HA synthetase enzymes (Dai et al., 2007). The turnover of extracellular proteins was directly examined in an *in vitro* culture system utilising rat primary microglial cells (Stolzing et al., 2002). The activated microglial cells were able to endocytose and degrade oxidised extracellular proteins (laminin and myelin basic protein) utilising mainly lysosomal proteases however based on inhibitor studies around 25% of the degradation was attributable to the proteasome (Stolzing et al., 2002). Again, the efficiency of degradation of oxidised proteins decreased when proteins became more highly oxidised and able to form cross-links (Stolzing et al., 2002).

Damage to proteolytic pathways in ageing and disease

As discussed earlier, highly oxidised protein-containing aggregates such as lipofuscin can inhibit the activity of the proteasome, a phenomenon that occurs during the ageing process (Höhn et al., 2013). Aggregated, oxidised proteins are recognised as a hallmark of ageing (Höhn et al., 2013). Recently deficiencies in the ability of the 20S proteasome to respond to oxidative stress have been observed in aged *Caenorhabitis elegans* due to a defect in the Nrf2 homolog SKN-1 (Raynes et al., 2017). An emerging area of research is the autophagic degradation of damaged proteasomes and the material they contain, dubbed proteaphagy (Hoeller and Dikic, 2016). This occurs in response to non-degradable oxidatively damaged proteins that are often linked to pathological conditions such as neurodegenerative disease and stroke (Dasuri et al., 2013). While proteasomal inhibition and oxidative stress have been identified as precursors to proteaphagy, at present, studies into the degradation of the 20S proteasome are limited. The mechanism of proteophagy is still not fully understood but it has been suggested that in the case of the 26S proteasome ubiquitination of the entire proteasome is involved (Khaminets et al., 2016). This complementary relationship between the two primary degradative systems was confirmed when disabled *Arabidopsis* proteasomes were selectively ubiquinitated and removed via autophagy (Marshall et al., 2015). It has also been shown that when the proteasome undergoes ubiquitination, it is subunit- and site-specific and mediated by the autophagy scavenger protein complex nucleoporin p62 (p62) (Cohen-Kaplan et al., 2016). Furthermore, the proteasome subunit RPN10 acts as a specific receptor for 26S degradation (Marshall et al., 2015; Wen and Klionsky, 2016). Future research will expand our knowledge of the conditions responsible for the onset of this phenomenon and the mechanisms involved. At present, research into the cross-talk between the proteasomal and autophagic systems has not explored the 20S proteasome. More research into the specific removal of the 20S proteasome when its proteolytic capacity is compromised is required. Furthermore, an understanding of the overall proteaphagic mechanisms that take place in response to oxidised proteins will give new insights into their metabolism.

Ageing, cancer, metabolic syndromes, cellular senescence and chronic oxidative stress conditions have also been associated with a decrease in mitochondrial protease activity (Ngo et al., 2013; Quiros et al., 2015). One of the most significant findings of the last 5 years in research into the Lon protease has been that this human stress protein cannot be induced in senescent cells and Lon dysregulation is accompanied by an increase in the amount of oxidised carbonyl-containing proteins (Ngo et al., 2011). As discussed previously deletion of Pim1 in yeast led directly to accelerated ageing and proteasome inhibition, measured by a decline in proteasome peptidase activity (Erjavec et al., 2013). Conversely, an additional link between these systems has been found in ischemic mouse cardiac mitochondria and proteasomes where mitochondrial oxidative damage following reperfusion injury caused an increase in proteasome substrate specificity for damaged mitochondrial proteins (Lau et al., 2012). The mechanisms behind these differing effects of oxidised protein aggregates on proteolytic systems and the overall importance of these responses are still not understood and whether these effects are purely pathological or serve a cellular function have not yet been clarified. Erjavec et al. suggests that proteolytic machinery between organelles may be

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more connected than our current understanding allows and that proteasome inhibition caused by a decline in an AAA+ protease may act as a signal for autophagic degradation of deficient mitochondria (Erjavec et al., 2013).

Conclusions

Oxidised proteins are an inevitable by-product of cellular metabolism which continually generates reactive species. The cellular location of the damaged proteins and the extent of oxidation determine firstly if the modification can be reversed, and if not, which proteolytic systems facilitate their degradation and removal. While in most cases the defence systems can successfully recognise and degrade oxidised proteins and restore proteostasis, their removal can be inefficient in ageing and in certain pathological conditions.

The inability of cells to remove damaged proteins from the ER for a prolonged period of time triggers an apoptotic cell death pathway (Hiramatsu et al., 2015; Song et al., 2017). A similar observation was made *in vitro* when cells were exposed to high levels of oxidised amino acids to generate oxidised proteins (Dunlop et al., 2008) suggesting that oxidised proteins can also trigger apoptotic cell death in a similar way. In the case of highly oxidised proteins, additional strategies may be required for their degradation. This often involves interplay and communication between different proteolytic pathways. This interplay and the mechanisms utilised to degrade oxidatively damaged organelles themselves are an important and emerging area of research that will further our overall understanding of the metabolism of oxidised proteins and the roles they play in ageing and various disease states.

Generally, complete proteolysis releases the constituent amino acids from proteins for use in the synthesis of new proteins. The fate of the oxidised amino acids released from proteolysis of oxidised proteins is unclear. In some cases oxidised amino acids that are close structural analogues of the parent 'protein' or canonical amino acid and can be mistakenly incorporated into proteins by protein synthesis (Rodgers and Dean, 2000; Rodgers et al., 2002; Rodgers and Shiozawa, 2008; Dunlop et al., 2009). We suggest that this could create a vicious cycle where chemical oxidation of proteins *in vivo* generates oxidised amino acid residues that are subsequently released by proteolysis and utilised in the synthesis of new proteins. The cycle could terminate when the oxidised amino acid is present in a cross-linked protein aggregate that cannot be degraded by the proteolytic machinery of the cell.

References

Allu, P.K., Marada, A., Boggula, Y., Karri, S., Krishnamoorthy, T., and Sepuri, N.B. (2015). Methionine sulfoxide reductase 2 reversibly regulates Mge1, a cochaperone of mitochondrial Hsp70, during oxidative stress. Mol. Biol. Cell *26*, 406–419.

Antonenkov, V., Grunau, S., Ohlmeier, S., and Hiltunen, J.K. (2010). Peroxisomes are oxidative organelles. Antioxid. Redox. Sig. *13*, 525–537.

Augustyniak, E., Adam, A., Wojdyla, K., Rogowska-Wrzesinska, A., Willetts, R., Korkmaz, A., Atalay, M., Weber, D., Grune, T., Borsa, C., et al. (2015). Validation of protein carbonyl measurement: a multi-centre study. Redox Biol. *4*, 149–157.

Baker, K.M., Chakravarthi, S., Langton, K.P., Sheppard, A.M., Lu, H., and Bulleid, N.J. (2008). Low reduction potential of Ero1α regulatory disulphides ensures tight control of substrate oxidation. EMBO J. *27*, 2988.

Baker, M.J., Tatsuta, T., and Langer, T. (2011). Quality control of mitochondrial proteostasis. Cold Spring Harb Perspect Biol. *3*, a007559.

Baraibar, M.A. and Friguet, B. (2013). Oxidative proteome modifications target specific cellular pathways during oxidative stress, cellular senescence and aging. Exp Geront. *48*, 620–625.

Bartoszewska, M., Williams, C., Kikhney, A., Opaliński, Ł., van Roermund, C.W.T., de Boer, R., Veenhuis, M., and van der Klei, I.J. (2012). Peroxisomal proteostasis involves a Lon family protein that functions as protease and chaperone. J. Biol. Chem. *287*, 27380–27395.

Bayot, A., Gareil, M., Rogowska-Wrzesinska, A., Roepstorff, P., Friguet, B., and Bulteau, A.L. (2010). Identification of novel oxidized protein substrates and physiological partners of the mitochondrial ATP-dependent Lon-like protease Pim1. J. Biol. Chem. *285*, 11445–11457.

Bayot, A., Gareil, M., Chavatte, L., Hamon, M.-P., L'Hermitte-Stead, C., Beaumatin, F., Priault, M., Rustin, P., Lombès, A., Friguet, B., et al. (2014). Effect of Lon protease knockdown on mitochondrial function in HeLa cells. Biochimie. *100*, 38–47.

Bechtold, U., Rabbani, N., Mullineaux, P.M., and Thornalley, P.J. (2009). Quantitative measurement of specific biomarkers for protein oxidation, nitration and glycation in *Arabidopsis* leaves. Plant J. *59*, 661–671.

Bhatia, S., Knoch, B., Wong, J., Kim, W.S., Else, P.L., Oakley, A.J., and Garner, B. (2012). Selective reduction of hydroperoxyeicosatetraenoic acids to their hydroxy derivatives by apolipoprotein D: implications for lipid antioxidant activity and Alzheimer's disease. Biochem J. *442*, 713–721.

Cadete, V.J., Deschênes, S., Cuillerier, A., Brisebois, F., Sugiura, A., Picard, M., McBride, H., and Burelle, Y. (2015). Increased cardiac mitochondrial-derived vesicle formation in response to acute stress and doxorubicin-induced cardiotoxicity. Can. J. Cardiol. *31*, S64–S65.

Chakravarthi, S., Jessop Ce Fau-Bulleid, N.J., and Bulleid, N.J. (2006). The role of glutathione in disulphide bond formation and endoplasmic-reticulum-generated oxidative stress. EMBO J. *7*, 271–275.

Chondrogianni, N., Petropoulos, I., Grimm, S., Georgila, K., Catalgol, B., Friguet, B., Grune, T., and Gonos, E.S. (2014). Protein damage, repair and proteolysis. Mol. Aspects Med. *35*, 1–71.

Unauthenticated
Download Date | 6/13/18 8:18 AM

Chuang, C.Y., Degendorfer, G., and Davies, M.J. (2014). Oxidation and modification of extracellular matrix and its role in disease. Free Radic. Res. *48*, 970–989.

Cohen-Kaplan, V., Livneh, I., Avni, N., Fabre, B., Ziv, T., and Tae Kwon, Y. (2016). p62- and ibuquitin-dependent stress-induced autophagy of the mammalian 26S proteasome. Proc. Natl. Acad. Sci. USA *113*, 201615455.

Dai, G., Freudenberger, T., Zipper, P., Melchior, A., Grether-Beck, S., Rabausch, B., de Groot, J., Twarock, S., Hanenberg, H., Homey, B., et al. (2007). Chronic ultraviolet B irradiation causes loss of hyaluronic acid from mouse dermis because of down-regulation of hyaluronic acid synthases. Am. J. Pathol. *171*, 1451–1461.

Dalle-Donne, I., Rossi, R., Colombo, R., Giustarini, D., and Milzani, A. (2006). Biomarkers of oxidative damage in human disease. Clin. Chem. *54*, 601–623.

Dasuri, K., Zhang, L., and Keller, J.N. (2013). Oxidative stress, neurodegeneration, and the balance of protein degradation and protein synthesis. Free Radic. Biol. Med. *62*, 170–185.

Devarie-Baez, N.O., Silva Lopez, E.I., and Furdui, C.M. (2016). Biological chemistry and functionality of protein sulfenic acids and related thiol modifications. Free Radic. Res. *50*, 172–194.

Dunlop, R.A., Brunk, U.T., and Rodgers, K.J. (2009). Oxidized proteins: mechanisms of removal and consequences of accumulation. IUBMB Life *61*, 522–527.

Dunlop, R.A., Brunk, U.T., and Rodgers, K.J. (2011). Proteins containing oxidized amino acids induce apoptosis in human monocytes. Biochem. J. *435*, 207–216.

Dunlop, R.A., Dean, R.T., and Rodgers, K.J. (2008). The impact of specific oxidized amino acids on protein turnover in J774 cells. Biochem. J. *410*, 131–140.

Erjavec, N., Bayot, A., Gareil, M., Camougrand, N., Nystrom, T., Friguet, B., and Bulteau, A.-L. (2013). Deletion of the mitochondrial Pim1/Lon protease in yeast results in accelerated aging and impairment of the proteasome. Free Radic. Biol. Med *56*, 9–16.

Feeney, M.B. and Schoneich, C. (2012). Tyrosine modifications in aging. Antioxid. Redox Signal. *17*, 1571–1579.

Fischer, W.W., Hemp, J., and Valentine, J.S. (2016). How did life survive Earth's great oxygenation? Curr Opin Chem Biol *31*, 166–178.

Frijhoff, J., Winyard, P.G., Zarkovic, N., Davies, S.S., Stocker, R., Cheng, D., Knight, A.R., Taylor, E.L., Oettrich, J., Ruskovska, T., et al. (2015). Clinical relevance of biomarkers of oxidative stress. Antioxid. Redox Signal. *23*, 1144–1170.

Gerdes, F., Tatsuta, T., and Langer, T. (2012). Mitochondrial AAA proteases – towards a molecular understanding of membrane-bound proteolytic machines. Biochim. Biophys. Acta. *1823*, 49–55.

Grune, T., Reinheckel, T., and Davies, K.J. (1997). Degradation of oxidized proteins in mammalian cells. FASEB J *11*, 526–534.

Grune, T., Reinheckel, T., and Davies, K.J.A. (1996). Degradation of oxidized proteins in K562 human hematopoietic cells by proteasome. J. Biol. Chem. *271*, 15504–15509.

Hammerling, B.C. and Gustafsson, Å.B. (2014). Mitochondrial quality control in the myocardium: cooperation between protein degradation and mitophagy. J. Mol. Cell Cardiol. *75*, 122–130.

Hamon, M.-P., Bulteau, A.-L., and Friguet, B. (2015). Mitochondrial proteases and protein quality control in ageing and longevity. Ageing Res. Rev. *23*, Part A, 56–66.

Hiramatsu, N., Chiang, W.C., Kurt, T.D., Sigurdson, C.J., and Lin, J.H. (2015). Multiple mechanisms of unfolded protein response-induced cell death. Am. J. Pathol. *185*, 1800–1808.

Hoeller, D. and Dikic, I. (2016). How the proteasome is degraded. Proc. Natl. Acad. Sci. USA *113*, 13266–13268.

Hohn, A., Jung, T., Grimm, S., Catalgol, B., Weber, D., and Grune, T. (2011). Lipofuscin inhibits the proteasome by binding to surface motifs. Free Radic. Biol. Med. *50*, 585–591.

Höhn, A., König, J., and Grune, T. (2013). Protein oxidation in aging and the removal of oxidized proteins. J Proteomics *92*, 132–159.

Hoshino, A., Okawa, Y., Ariyoshi, M., Kaimoto, S., Uchihashi, M., Fukai, K., Iwai-Kanai, E., and Matoba, S. (2014). Oxidative post-translational modifications develop LONP1 dysfunction in pressure overload heart failure. Circ. Heart Fail *7*, 500–509.

Hubbard, V.M., Valdor, R., Macian, F., and Cuervo, A.M. (2012). Selective autophagy in the maintenance of cellular homeostasis in aging organisms. Biogerontology *13*, 21–35.

Hudson, W.M. and Pagliassotti, M.J. (2015). Oxidative stress and the unfolded protein response in the liver. In: Oxidative Stress in Applied Basic Research and Clinical Practice, E. Albano and M. Parola, eds. (Switzerland: Springer), pp. 113–122.

Hung, R.J., Spaeth, C.S., Yesilyurt, H.G., and Terman, J.R. (2013). SelR reverses Mical-mediated oxidation of actin to regulate F-actin dynamics. Nat. Cell Biol. *15*, 1445–1454.

Jeong, W., Bae, S.H., Toledano, M.B., and Rhee, S.G. (2012). Role of sulfiredoxin as a regulator of peroxiredoxin function and regulation of its expression. Free Radic. Biol. Med. *53*, 447–456.

Johansson, A.C., Appelqvist, H., Nilsson, C., Kagedal, K., Roberg, K., and Ollinger, K. (2010). Regulation of apoptosis-associated lysosomal membrane permeabilization. Apoptosis *15*, 527–540.

Jung, T. and Grune, T. (2013). The proteasome and the degradation of oxidized proteins: part I – structure of proteasomes. Redox Biol. *1*, 178–182.

Jung, T., Höhn, A., and Grune, T. (2014). The proteasome and the degradation of oxidized proteins: part II – protein oxidation and proteasomal degradation. Redox Biol. *2*, 99–104.

Kammeyer, A. and Luiten, R.M. (2015). Oxidation events and skin aging. Ageing Res. Rev. *21*, 16–29.

Kang, H.T., Lee, K.B., Kim, S.Y., Choi, H.R., and Park, S.C. (2011). Autophagy impairment induces premature senescence in primary human fibroblasts. PLoS One *6*, e23367.

Kästle, M., Reeg, S., Rogowska-Wrzesinska, A., and Grune, T. (2012). Chaperones, but not oxidized proteins, are ubiquitinated after oxidative stress. Free Radic. Biol. Med. *53*, 1468–1477.

Kaur, K., Salomon, R.G., O'Neil, J., and Hoff, H.F. (1997). (Carboxyalkyl)pyrroles in human plasma and oxidized low-density lipoproteins. Chem. Res. Toxicol. *10*, 1387–1396.

Kennett, E.C., Chuang, C.Y., Degendorfer, G., Whitelock, J.M., and Davies, M.J. (2011). Mechanisms and consequences of oxidative damage to extracellular matrix. Biochem. Soc. Trans. *39*, 1279.

Khaminets, A., Behl, C., and Dikic, I. (2016). Ubiquitin-dependent and independent signals in selective autophagy. Trends Cell Biol. *26*, 6–16.

Kurz, T., Terman, A., Gustafsson, B., and Brunk, U.T. (2008). Lysosomes and oxidative stress in aging and apoptosis. Biochim. Biophys. Acta. *1780*, 1291–1303.

Lau, E., Wang, D., Zhang, J., Yu, H., Lam, M.P., Liang, X., Zong, N., Kim, T.Y., and Ping, P. (2012). Substrate- and isoform-specific proteome stability in normal and stressed cardiac mitochondria. Circ. Res. *110*, 1174–1178.

Unauthenticated
Download Date | 6/13/18 8:18 AM

Liebl, M.P. and Hoppe, T. (2016). It's all about talking – two-way communication between proteasomal and lysosomal degradation pathways via ubiquitin. Am. J. Physiol. Cell Physiol. *311*, C166–C178.

Lionaki, E. and Tavernarakis, N. (2013). Oxidative stress and mitochondrial protein quality control in aging. J. Proteomics *92*, 181–194.

Lynch, G. and Bi, X. (2003). Lysosomes and brain aging in mammals. Neurochem. Res. *28*, 1725–1734.

Marada, A., Allu, P.K., Murari, A., PullaReddy, B., Tammineni, P., Thiriveedi, V.R., Danduprolu, J., and Sepuri, N.B. (2013). Mge1, a nucleotide exchange factor of Hsp70, acts as an oxidative sensor to regulate mitochondrial Hsp70 function. Mol. Biol. Cell *24*, 692–703.

Marshall, R.S., Li, F., Gemperline, D.C., Book, A.J., and Vierstra, R.D. (2015). Autophagic degradation of the 26S proteasome is mediated by the dual ATG8/ubiquitin receptor RPN10 in *Arabidopsis*. Mol. Cell *58*, 1053–1066.

McLelland, G.-L., Lee, S.A., McBride, H.M., and Fon, E.A. (2016). Syntaxin-17 delivers PINK1/parkin-dependent mitochondrial vesicles to the endolysosomal system. J. Biol. Chem. *214*, 275–291.

McLelland, G.L., Soubannier, V., Chen, C.X., McBride, H.M., and Fon, E.A. (2014). Parkin and PINK1 function in a vesicular trafficking pathway regulating mitochondrial quality control. EMBO J. *33*, 282–295.

Morgan, P.E., Dean, R.T., and Davies, M.J. (2002). Inactivation of cellular enzymes by carbonyls and protein-bound glycation/glycoxidation products. Arch. Biochem. Biophys. *403*, 259–269.

Navarro-Yepes, J., Burns, M., Anandhan, A., Khalimonchuk, O., del Razo, L.M., Quintanilla-Vega, B., Pappa, A., Panayiotidis, M.I., and Franco, R. (2014). Oxidative stress, redox signaling, and autophagy: cell death versus survival. Antioxid. Redox Signal. *21*, 66–85.

Neuspiel, M., Schauss, A.C., Braschi, E., Zunino, R., Rippstein, P., Rachubinski, R.A., Andrade-Navarro, M.A., and McBride, H.M. (2008). Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. Curr Biol *18*, 102–108.

Ngo, J.K., Pomatto, L.C., Bota, D.A., Koop, A.L., and Davies, K.J. (2011). Impairment of lon-induced protection against the accumulation of oxidized proteins in senescent wi-38 fibroblasts. J. Gerontol. A Biol. Sci. Med. Sci. *66*, 1178–1185.

Ngo, J.K., Pomatto, L.C., and Davies, K.J. (2013). Upregulation of the mitochondrial Lon Protease allows adaptation to acute oxidative stress but dysregulation is associated with chronic stress, disease, and aging. Redox Biol. *1*, 258–264.

Ni, H.-M., Williams, J.A., and Ding, W.-X. (2015). Mitochondrial dynamics and mitochondrial quality control. Redox Biol. *4*, 6–13.

Nordgren, M. and Fransen, M. (2014). Peroxisomal metabolism and oxidative stress. Biochim. *98*, 56–62.

Nowotny, K. and Grune, T. (2014). Degradation of oxidized and glycoxidized collagen: role of collagen cross-linking. Arch. Biochem. Biophys. *542*, 56–64.

Ogata, N. (2007). Denaturation of protein by chlorine dioxide: oxidative modification of tryptophan and tyrosine residues. Biochem. *46*, 4898–4911.

Pascua-Maestro, R., Diez-Hermano, S., Lillo, C., Ganfornina, M.D., and Sanchez, D. (2017). Protecting cells by protecting their vulnerable lysosomes: identification of a new mechanism for preserving lysosomal functional integrity upon oxidative stress. PLoS Genet. *13*, e1006603.

Pattison, D.I., Rahmanto, A.S., and Davies, M.J. (2012). Photo-oxidation of proteins. Photochem. Photobiol. Sci. *11*, 38–53.

Perri, E.R., Thomas, C.J., Parakh, S., Spencer, D.M., and Atkin, J.D. (2016). The unfolded protein response and the role of protein disulfide isomerase in neurodegeneration. Front Cell Dev. Biol. *8*, 80.

Pickering, A.M. and Davies, K.J.A. (2012). Degradation of damaged proteins: the main function of the 20S proteasome. Prog. Mol. Biol. Transl. Sci. *109*, 227–248.

Pluquet, O., Pourtier, A., and Abbadie, C. (2015). The unfolded protein response and cellular senescence. A review in the theme: cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. Am. J. Physiol. Cell Physiol. *308*, C415.

Pomatto, L.C.D., Raynes, R., and Davies, K.J.A. (2016). The peroxisomal Lon protease LonP2 in aging and disease: functions and comparisons with mitochondrial Lon protease LonP1. Biol. Rev. Camb. Philos. Soc. *92*, 739–753.

Poole, L.B. (2015). The basics of thiols and cysteines in redox biology and chemistry. Free Radic. Biol. Med. *80*, 148–157.

Quiros, P.M., Langer, T., and Lopez-Otin, C. (2015). New roles for mitochondrial proteases in health, ageing and disease. Nat. Rev. Mol. Cell Biol. *16*, 345–359.

Radi, R. (2013). Protein tyrosine nitration: biochemical mechanisms and structural basis of functional effects. Acc. Chem. Res. *46*, 550–559.

Raynes, R., Pomatto, L.C.D., and Davies, K.J.A. (2016). Degradation of oxidized proteins by the proteasome: distinguishing between the 20S, 26S, and immunoproteasome proteolytic pathways. Mol. Aspects Med. *50*, 41–55.

Raynes, R., Juarez, C., Pomatto, L.C., Sieburth, D., and Davies, K.J. (2017). Aging and SKN-1-dependent loss of 20S proteasome adaptation to oxidative stress in *C. elegans*. J. Gerontol. A Biol. Sci. Med. Sci. *72*, 143–151.

Reeg, S. and Grune, T. (2015). PP32 – Hsp70 promotes the proteolysis of oxidatively damaged proteins. Free Radic. Biol. Med. *86*, (Suppl. 1), S30.

Reeg, S., Jung, T., Castro, J.P., Davies, K.J.A., Henze, A., and Grune, T. (2016). The molecular chaperone Hsp70 promotes the proteolytic removal of oxidatively damaged proteins by the proteasome. Free Radic. Biol. Med. *99*, 153–166.

Rivett, A.J. and Levine, R.L. (1987). Enhanced proteolytic susceptibility of oxidized proteins. Biochem. Soc. Trans. *15*, 816–818.

Roberts, R.F., Tang, M.Y., Fon, E.A., and Durcan, T.M. (2016). Defending the mitochondria: the pathways of mitophagy and mitochondrial-derived vesicles. Int J Biochem Cell Biol. *79*, 427–436.

Rodgers, K.J. and Dean, R.T. (2000). Metabolism of protein-bound DOPA in mammals. Int. J. Biochem. Cell Biol. *32*, 945–955.

Rodgers, K.J. and Shiozawa, N. (2008). Misincorporation of amino acid analogues into proteins by biosynthesis. Int. J. Biochem. Cell Biol. *40*, 1452–1466.

Rodgers, K.J., Wang, H., Fu, S., and Dean, R.T. (2002). Biosynthetic incorporation of oxidized amino acids into proteins and their cellular proteolysis. Free Radic. Biol. Med. *32*, 766–775.

Unauthenticated
Download Date | 6/13/18 8:18 AM

Schöneich, C. (2005). Methionine oxidation by reactive oxygen species: reaction mechanisms and relevance to Alzheimer's disease. Biochim. Biophys. Acta. *1703*, 111–119.

Settembre, C., Fraldi, A., Medina, D.L., and Ballabio, A. (2013). Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat. Rev. Mol. Cell Biol. *14*, 283–296.

Sitte, N., Huber, M., Grune, T., Ladhoff, A., Doecke, W.D., Von Zglinicki, T., and Davies, K.J. (2000). Proteasome inhibition by lipofuscin/ceroid during postmiotic aging of fibroblasts. FASEB J. *14*, 1490–1498.

Song, S., Tan, J., Miao, Y., Li, M., and Zhang, Q. (2017). Crosstalk of autophagy and apoptosis: involvement of the dual role of autophagy under ER stress. J. Cell Physiol. *9999*, 1–8.

Soubannier, V., McLelland, G.-L., Zunino, R., Braschi, E., Rippstein, P., Fon, E.A., and McBride, H.M. (2012a). A Vesicular transport pathway shuttles cargo from mitochondria to lysosomes. Curr. Biol. *22*, 135–141.

Soubannier, V., Rippstein, P., Kaufman, B.A., Shoubridge, E.A., and McBride, H.M. (2012b). Reconstitution of mitochondria derived vesicle formation demonstrates selective enrichment of oxidized cargo. PLoS One *7*, e52830.

Stadtman, E.R. and Levine, R.L. (2003). Free radical-mediated oxidation of free amino acids and amino acid residues in proteins. Amino Acids *25*, 207–218.

Stadtman, E.R., Oliver, C.N., Levine, R.L., Fucci, L., and Rivett, A.J. (1988). Implication of protein oxidation in protein turnover, aging, and oxygen toxicity. Basic Life Sci. *49*, 331–339.

Stolzing, A., Wengner, A., and Grune, T. (2002). Degradation of oxidized extracellular proteins by microglia. Arch. Biochem. Biophys. *400*, 171–179.

Tang, X., Liang, X., Li, M., Guo, T., Duan, N., Wang, Y., Rong, G., Yang, L., Zhang, S., and Zhang, J. (2015). ATF6 pathway of unfolded protein response mediates advanced oxidation protein product-induced hypertrophy and epithelial-to-mesenchymal transition in HK-2 cells. Mol. Cell Biochem. *407*, 197–207.

Tarrago, L., Kaya, A., Weerapana, E., Marino, S.M., and Gladyshev, V.N. (2012). Methionine sulfoxide reductases preferentially reduce unfolded oxidized proteins and protect cells from oxidative protein unfolding. J. Biol. Chem. *287*, 24448–24459.

Wang, X. and Robbins, J. (2006). Heart failure and protein quality control. Circ. Res. *99*, 1315–1328.

Wen, X. and Klionsky, D.J. (2016). The proteasome subunit RPN10 functions as a specific receptor for degradation of the 26S proteasome by macroautophagy in *Arabidopsis*. Autophagy *12*, 905–906.

Whiteman, M. and Spencer, J.P.E. (2008). Loss of 3-chlorotyrosine by inflammatory oxidants: Implications for the use of 3-chlorotyrosine as a bio-marker *in vivo*. Biochem. Biophys. Res. Commun. *371*, 50–53.

Xu, C., Bailly-Maitre, B., and Reed, J.C. (2005). Endoplasmic reticulum stress: cell life and death decisions. J. Clin. Invest. *115*, 2656–2664.

Zorov, D.B., Juhaszova, M., and Sollott, S.J. (2014). Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol. Rev. *94*, 909.

Unauthenticated
Download Date | 6/13/18 8:18 AM