



Cysteines as Redox Molecular Switches and Targets of Disease

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Thiol groups can undergo numerous modifications, making cysteine a unique molecular switch. Cysteine plays structural and regulatory roles as part of proteins or glutathione, contributing to maintain redox homeostasis and regulate signaling within and amongst cells. Not surprisingly therefore, cysteines are associated with many hereditary and acquired diseases. Mutations in the primary protein sequence (gain or loss of a cysteine) are most frequent in membrane and secretory proteins, correlating with the key roles of disulfide bonds. On the contrary, in the cytosol and nucleus, aberrant post-translational oxidative modifications of thiol groups, reflecting redox changes in the surrounding environment, are a more frequent cause of dysregulation of protein function. This essay highlights the regulatory functions performed by protein cysteine residues and provides a framework for understanding how mutation and/or (in)activation of this key amino acid can cause disease.

Keywords: cellular redoxstasis, cysteine mutation, signaling pathways, disulfide bonding, protein misfolding

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INTRODUCTION

Amino acids are much more than mere building blocks of proteins: their different chemical properties dictate the catalytic activity of enzymes, protein half-life and a plethora of different post-translational modifications that govern protein function. This essay concentrates on the role of cysteine, a thiol containing amino acid that can participate in a variety of chemical reactions such as post-translational oxidative modifications. Many of them are reversible at physiological conditions, thereby allowing cysteine to act as a powerful molecular switch, akin to protein phosphorylation-dephosphorylation cycles. Hence, cysteine modifications are not limited to the well-known structural role of disulfide bonds in proteins synthesized in the endoplasmic reticulum (ER), but participate in fundamental intra- and inter-cellular signaling pathways. The downside of the pleiotropic reactivity of cysteines resides in their high susceptibility to undesired activation/inactivation in conditions of redox disequilibrium (either oxidative or reductive stress).

Abbreviations: AATD, Alpha-1-antitrypsin deficiency; BiP, Immunoglobulin heavy chain-binding protein; CFTR, Cystic fibrosis transmembrane conductance regulator; CXCR4, C-X-C chemokine receptor type 4; ER, Endoplasmic reticulum; ERAD, ER associated degradation; Ero1, Endoplasmic reticulum oxidoreductin 1; Gpx, Glutathione peroxidase; GR, Glutathione reductase; Grx, Glutaredoxin; GSH/GSSG, Reduced/oxidized glutathione; HMGB1, High mobility group protein B1; KEAP1, Kelch-like ECH-associated protein 1; MD2, Lymphocyte antigen 96; Nrf2, Nuclear factor erythroid 2-related factor 2; PDI, Protein disulfide isomerase; Prx, Peroxiredoxin; PTEN, Phosphatase and tensin homolog; QSOX, Quiescin sulfhydryl oxidase; RAGE/ARGE, Advanced glycosylation end product-specific receptor; ROS, Reactive oxygen species; SOD1, Superoxide Dismutase 1; TLR4, Toll-like receptor 4; TNF, Tumor necrosis factor; TNFR, TNF receptors; Trx, Thioredoxin; TrxR, Thioredoxin reductase; VcOR, Vitamin K epoxide reductase.

In many genetic diseases and cancer, mutations can either directly target a cysteine or affect residues that contribute to maintain optimal cysteine pKa, accessibility and/or reactivity.

Here we briefly discuss redoxstasis in cell compartments and provide examples of disease—associated modifications/mutations of key cysteine residues.

CYSTEINES REACTIVITY AND REDOX HOMEOSTASIS

Redox reactions involve the gain (reduction) or loss (oxidation) of electrons in the reacting compounds. From its reduced form (SH), the sulfur atom of a cysteine residue can undergo a wide-range of oxidative modifications (**Figure 1**). Reactivity is greatly enhanced for cysteines whose thiol side chain is in the thiolate form, i.e., deprotonated at physiological pH (S^-), and is influenced by structural factors (Ferrer-Sueta et al., 2011). Disulfide bonds stabilize the tertiary and/or quaternary structures of many proteins. They also serve as regulatory functional switches, a prototype being the activation of the bacterial transcription factor OxyR in response to oxidative stress (Zheng et al., 1998; Jo et al., 2015). Progressive cysteine oxidation by H_2O_2 leads to cysteine sulfenylation (SOH), sulfinylation (SO_2H) and sulfonylation (SO_3H). Among these, oxidation to SO_3H is regarded as irreversible. S-sulfydration (also called persulfidation) can occur after reactions between derivatives of hydrogen sulfide (H_2S) and thiols (Mishanina et al., 2015). Reactive nitrogen species (RNS) like nitric oxide (NO) react with some cysteines causing S-nitrosylation/nitrosation (Evangelista et al., 2013). Cysteines can also undergo lipid modifications including palmitoylation and prenylation or bind metals such as Zn, Fe and Cu. This latter property is crucial for formation of zinc fingers and iron-sulfur clusters (Oteiza, 2012; Rouault, 2015). Owing to their nucleophilic properties, thiolate groups also participate in non-redox reactions as in the catalytic groups of cysteine-proteases and ubiquitin ligases. For a detailed discussion on cysteine reactivity, its chemotypes and the methods for their detection, we refer to excellent reviews (Nagy, 2013; Paulsen and Carroll, 2013; Go et al., 2015).

Cysteine thiols are key players in conditions of oxidative stress. Most non-protein antioxidants as well as antioxidant enzymes are thiol based. Glutathione (GSH, γ -L-Glutamyl-L-cysteinylglycine) acts as a redox buffer and a cofactor of many enzymes including glutathione peroxidases (Gpx) that scavenge peroxides generating oxidized glutathione (GSSG). In humans, there are eight Gpxs, localized in different compartments (Brigelius-Flohé and Maiorino, 2013; **Figure 2**). Other key peroxide scavengers are peroxiredoxins (Prx; Perkins et al., 2015). Of the six human Prxs, two are localized in mitochondria and one in the ER. Thioredoxins (Trx) and glutaredoxins (Grx) reduce oxidized protein thiols. Oxidized Trx and Grx are reduced by Trx reductases (TrxR) and GSH, respectively (Holmgren, 1979; Mustacich and Powis, 2000; Fernandes and Holmgren, 2004). Glutathione reductase (GR) is also a key player for redox homeostasis, replenishing the GSH pool at the expense of GSSG.

It is important to stress that both GR and TrxR rely on the NADPH/NADP system for their activity, thus establishing a link between the nicotinamide and thiol redox systems (Jones and Sies, 2015). Another important player is sulfiredoxin-1, an ATP-dependent enzyme capable of reducing sulfinylated proteins (Biteau et al., 2003; Mishra et al., 2015).

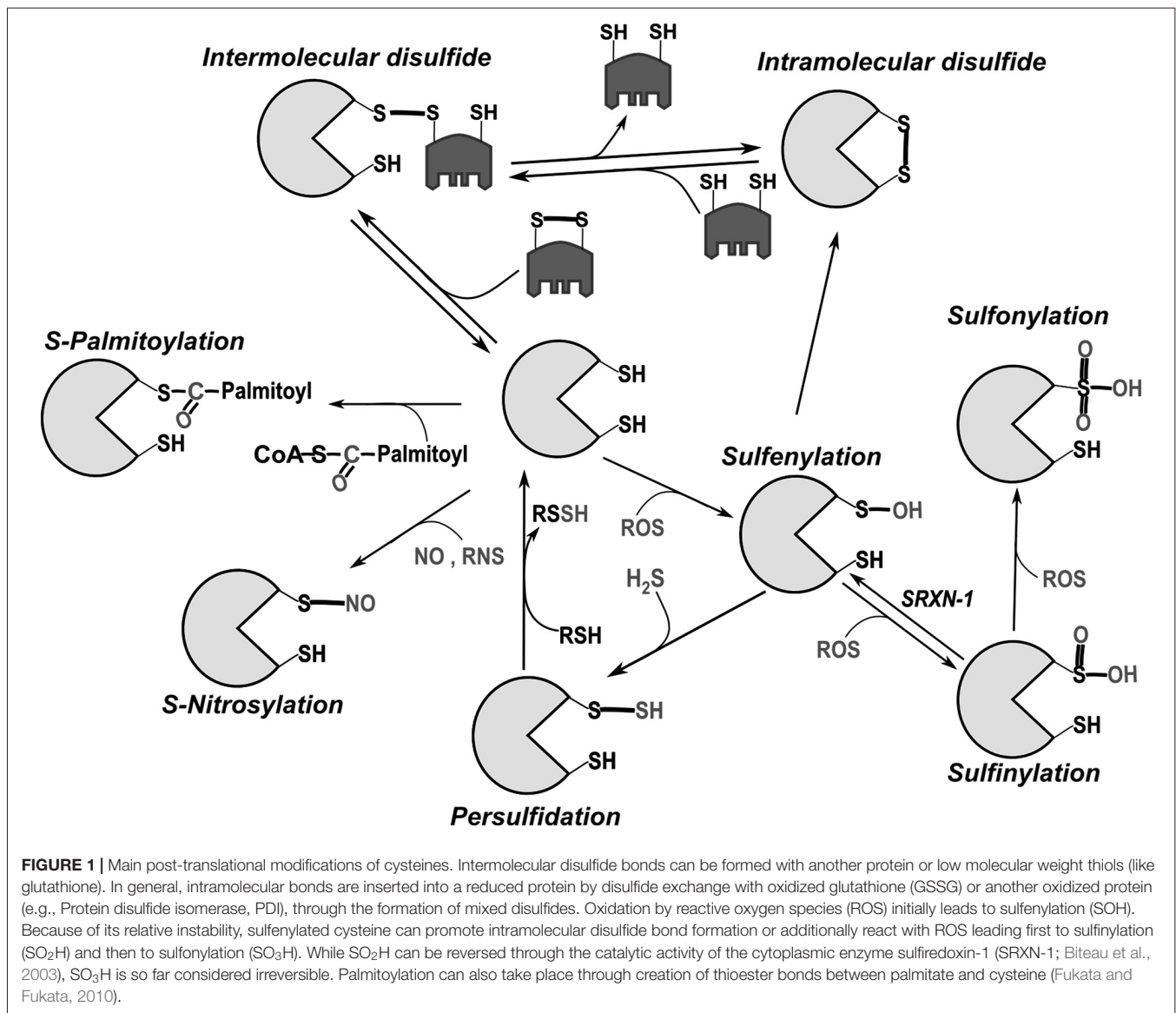
REDOX COMPARTMENTALIZATION

The organelles of eukaryotic cells can differ dramatically with respect to the redox poise of their various redox couples (**Figure 2**). The chemistry of primordial cells evolved in an oxygen-free atmosphere, and cytosolic and mitochondrial cysteines tend to remain in the reduced states (Go et al., 2015). Incidentally, this is why most cell-free protocols that recapitulate nuclear or cytoplasmic reactions include the addition of DTT or other reductants to work efficiently. *In vivo*, the establishment of stable disulfide bonds in these compartments is extremely unfavorable because of the combined reducing power of GSH, Grxs and Trxs.

However, there are places where disulfide bonds need to be inserted into selected proteins. For example, the Mia40/Erv1 relay allows formation of disulfide bonds in proteins and their import into the inter-membrane mitochondrial space, where the low Grx pool kinetically favor this process (Mesecke et al., 2005; Kojer et al., 2015; Erdogan and Riemer, 2017).

The redox couples present in organelles of the exocytic pathway display redox poises similar to the extracellular space. In the ER, nascent membrane and secretory proteins form disulfide bonds, preparing for their adult life in the oxidizing extracellular environments. Thus, oxidative power is needed in the ER, but redox conditions must be tightly controlled to allow isomerization or reduction of non-native disulfides. The occurrence of opposite reactions is guaranteed by protein relays capable of selectively inserting or removing disulfides (Fassio and Sitia, 2002; Hagiwara and Nagata, 2012). Oxidative folding is catalyzed by enzymes of the protein disulfide isomerase (PDI) superfamily, which receive oxidative power from oxidases like endoplasmic reticulum oxidoreductin 1 (Ero1) and quiescin sulphydryl oxidase (QSOX; Bulleid and Ellgaard, 2011; Hudson et al., 2015). The human genome encodes for numerous PDI-like enzymes whose activity largely depends on the number of Trx-like domains and the redox potential of their CXXC motifs (Hatahet and Ruddock, 2009; Okumura et al., 2015). Depending on the surrounding redox and ionic conditions, oxidoreductases may oxidize, isomerize or reduce disulfides. In this wide range of activities, ERdj5 is most suited for reducing disulfides (Dong et al., 2008; Ushioda et al., 2008). TrxR and import of cytosolic GSH have been proposed as reducing powers to prevent ER hyperoxidation (Molteni et al., 2004; Appenzeller-Herzog, 2011; Poet et al., 2017).

Disulfide interactions with PDI-like enzymes provide key quality control of the secretome, preventing the release of immature proteins. For instance, ERp44, captures proteins with exposed thiols and redox-active enzymes lacking suitable ER localization signals (e.g., Ero1, Prx4, Sumf1), retrieving



them to the ER (Vavassori et al., 2013; Anelli et al., 2015).

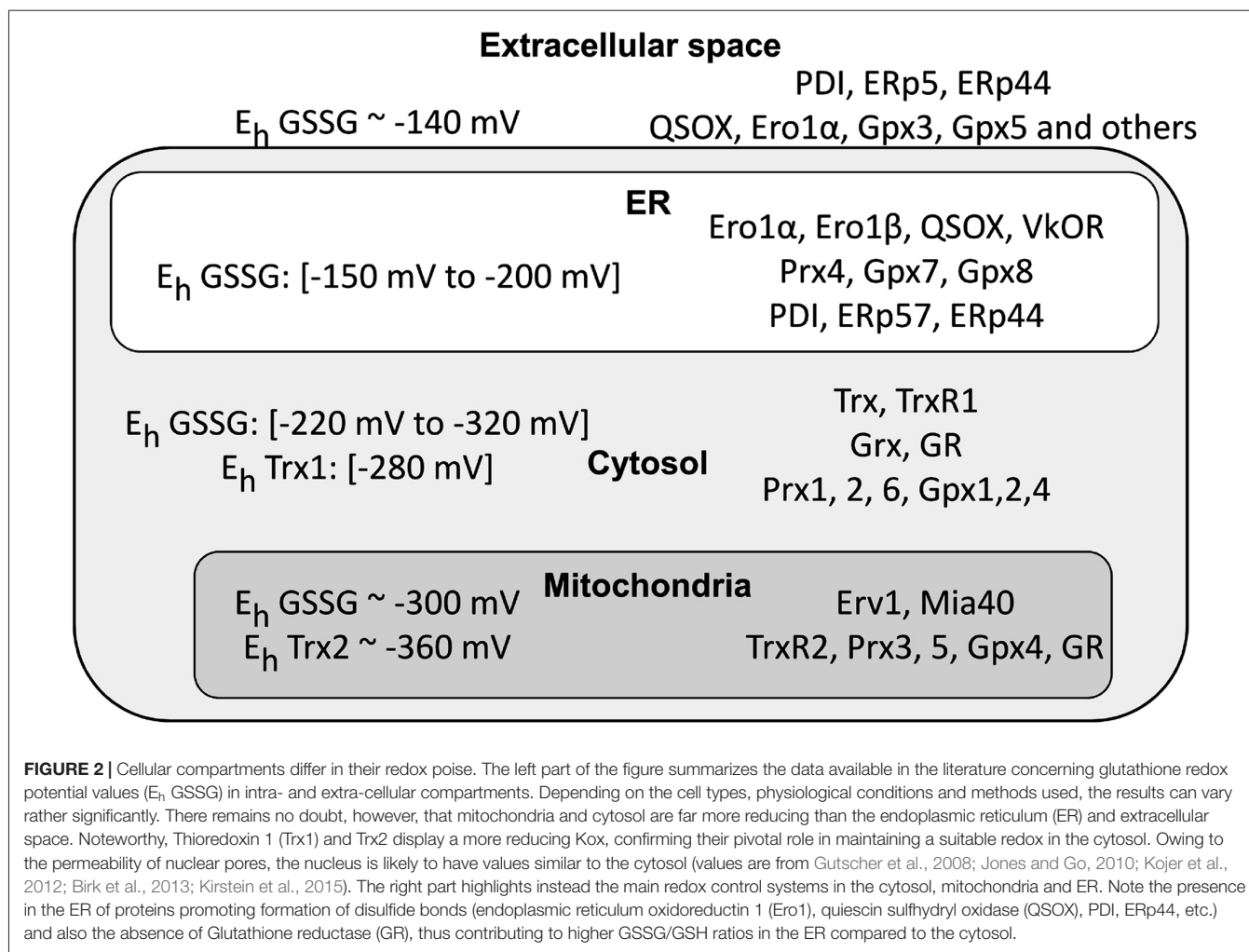
CYSTEINES AS REDOX MOLECULAR SWITCHES

Mechanisms ensuring tight redoxstasis control are present in the three cellular compartments where protein folding takes place (cytosol, ER and mitochondria) and they are intimately linked to protein quality control (Anelli et al., 2015). However, cells additionally exploit cysteine reactivity for purposes other than oxidative protein folding, namely as switches regulating signaling and adaptive responses.

A prototypic example is provided by the Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor whose nuclear translocation is prevented by interactions with Kelch-like ECH-associating protein 1 (Keap1). Upon oxidation,

Keap1 dissociates from Nrf2, which can reach the nucleus and promote transcription of antioxidant response genes (Dinkova-Kostova et al., 2002). Recently, unexpected links between Nrf2, redox and ER stress emerged. Ire1 is a transmembrane protein that initiates the unfolded protein response upon accumulation of misfolded proteins in the ER lumen. Upon oxidative stress, Ire1 is sulfenylated and activates the Nrf2 pathway, abandoning its canonical ER stress sensing function (Hourihan et al., 2016). Thus, a subtle cysteine modification can shift the pathway to which a signal transducer is affiliated.

Redox modifications also play key roles in regulating protein tyrosine phosphorylation. Cysteine oxidative modifications such as SOH, disulfide formation and S-nitrosylation inhibit phosphatase and tensin homolog (PTEN) and other protein tyrosine phosphatases by interfering for example with their cysteine-dependent catalytic activity (Numajiri et al., 2011; Corcoran and Cotter, 2013; Pulido, 2015). As an example



of physiological importance, abolishing this rheostat circuit dampens B lymphocyte activation and antibody production (Bertolotti et al., 2016). Moreover, a growing body of evidence supports the redox regulation of several tyrosine kinases, as described for c-Src (Giannoni and Chiarugi, 2014) and Janus kinase 2 (JAK2; Smith et al., 2012).

High mobility group protein B1 (HMGB1) is a DNA-binding nuclear protein that can be released by stressed cells. In the extracellular space, HMGB1 mediates inflammation or tissue repair, according to its redox state. If fully reduced, it binds to Advanced glycation end product-specific receptor (RAGE) and C-X-C chemokine receptor type 4 (CXCR4) and activates cell migration and autophagy. Upon formation of an intramolecular disulfide bond, HMGB1 binds Toll-like receptor 4 (TLR4)/MD-2 receptors complex and stimulates cytokine secretion. Sulphonylation then inactivates HMGB1, highlighting how a protein switches function depending on its cysteine redox state (Fiuza et al., 2003; Venereau et al., 2012; Vénéreau et al., 2015). Oxidation of a conserved cysteine residue also modulate the permeability of aquaporin 8 by reversibly inhibiting the transport of H_2O_2 and H_2O across the membrane of stressed cells (Medraño-Fernandez et al., 2016).

Another example of redox-based functional re-targeting aimed to prevent protein aggregation is the induction of holdase activity in the ER chaperone Immunoglobulin heavy chain-binding protein (BiP) by cysteine oxidation (Wei et al., 2012; Wang et al., 2014). Similarly, Prx sulphonylation promotes formation of homo-oligomers endowed with chaperone activity (Jang et al., 2004; Hanzén et al., 2016).

Thus, cysteine modifications are key in many intra- and inter-cellular signaling and adaptive pathways. The sub-compartmental organization of redoxstasis, based on spatially constrained protein relays (Woo et al., 2010), and the low diffusibility of small redox active compounds such as H_2O_2 (Bienert and Chaumont, 2014) can explain how redox-dependent signals can propagate in the presence of powerful antioxidant systems.

CYSTEINES AND DISEASES

Secretory Proteins

Owing to the importance of structural and regulatory disulfide bonds in membrane and secretory proteins, mutations in

luminal cysteines generally have dramatic consequences. Hence, acquisition or loss of a cysteine often causes retention of the mutated protein in the ER by thiol-mediated mechanisms (Anelli et al., 2015), with consequent loss or gain of function. The difficulty in forming the proper array of disulfide bonds in the cysteine-rich domains of many membrane receptors can lead to ER retention and degradation (loss of function), but also gain of function by interchain disulfide bonding that chronically activates signal transduction. An astonishing example comes from type 2A multiple endocrine neoplasia (MEN2A). This severe condition is often due to mutations in the cysteine-rich luminal portion of a tyrosine kinase receptor, RET, with strong genotype-phenotype correlations. The oncogenic hit is the formation of ligand-independent, covalent homodimers that constitutively deliver growth signals (Asai et al., 1995; Mulligan, 2014). RET malfunction can also lead to congenital abnormalities characterized by failure of neuroblast migration and defective maturation of the enteric nervous system (Hirschsprung disease), a condition that in some families coexisted with MEN2A (Takahashi et al., 1999; Frank-Raue et al., 2011).

Many genetic diseases are caused by gain or loss of a cysteine in secretory or membrane proteins. Aberrant thiol-mediated interactions via unpaired cysteines can directly provoke ER retention and aggregation besides misfolding. In Pelizaeus-Merzbacher disease, a myelination defect, a subgroup of mutations affecting the extracellular loop of the PLP/DM20 protein impair formation of intramolecular disulfide bridges and cause abnormal protein cross-links, ER retention and oligodendrocyte death (Dhaunchak et al., 2011). Similar mechanisms have been demonstrated in some forms of autism (Comoletti et al., 2004), color blindness (Patel et al., 2005) and von Willebrand disease (Wang et al., 2012).

Mutations of uromodulin, causing medullary cystic kidney disease/familial juvenile hyperuricemic nephropathy most often affect one of the 48 conserved cysteine residues (Rampoldi et al., 2003; Scolari et al., 2015). Cysteine mutations and aberrant disulfide bonding underlie the pathogenesis of CD40 deficiency (Lanzi et al., 2010), TNFR1-associated periodic fever syndrome (Lobito et al., 2006) and MiDY insulin-deficient diabetes (Liu et al., 2010). Mutations causing conformational alterations of alpha-1-antitrypsin make its only cysteine more prone to form aberrant disulfide bonds in the ER, thus facilitating the intracellular retention and polymerization of alpha-1-antitrypsin in Alpha-1-antitrypsin deficiency (AATD; Ronzoni et al., 2016).

Marinesco-Sjogren is a syndrome causing ataxia, intellectual disability and muscle weakness. This rare disease is caused by mutations in Sil1, a cofactor of BiP (Anttonen et al., 2005; Krieger et al., 2013). In yeast recovering from stress, Sil1 reduces oxidized Kar2, the paralog of human BiP, restoring its normal foldase activity (Siegenthaler et al., 2017). It remains to be seen whether and how mutations in Marinesco-Sjogren patients also impact the reductase function of Sil1.

Cytosolic and Nuclear Proteins

In cytosolic proteins, cysteines can be direct targets of mutations, but more frequently they are dysregulated or inactivated by oxidative stress or other environmental conditions. Both

mechanisms have been shown in Parkinson's disease (PD). Parkin (PARK2) is an E3 ubiquitin ligase whose dysfunction causes accumulation of protein aggregates, endangering dopaminergic neurons (Charan and LaVoie, 2015). Parkin is highly expressed in the brain and frequently mutated in autosomal recessive juvenile PD (Biskup et al., 2008). These mutations often affect cysteines, causing loss of function and decreased stability of the enzyme (Wang et al., 2005; Seirafi et al., 2015). Parkin can also be inactivated by S-nitrosylation or sulphonylation (Chung et al., 2004; Meng et al., 2011). Recent studies describe interesting interplays between parkin oxidative modifications, its role in mitochondrial quality control and PD onset (Zhang et al., 2016). In dopaminergic neurodegenerative disorders, a key pathogenetic event is also the inactivation of tyrosine hydroxylase, a rate-limiting enzyme in dopamine and norepinephrine biosynthesis, by oxidative injury (Di Giovanni et al., 2012).

Mutations of the antioxidant superoxide dismutase gene (SOD1) are linked to about one fifth of the cases of familial amyotrophic lateral sclerosis, a degenerative disorder of motor neurons. Wild type SOD1 is a covalent disulfide-linked homodimer localized in part in the mitochondrial intermembrane space. Pathogenic SOD1 mutants form high molecular weight oligomers, inducing mitochondrial dysfunctions (Ferri et al., 2006; Magrané et al., 2009). Noteworthy, intermolecular disulfide cross-links and glutathionylation enhance mutant SOD1 aggregation (Cozzolino et al., 2008; Redler et al., 2011; McAlary et al., 2013), cysteine 111 being a key residue (Valle and Carri, 2017).

In addition, Alzheimer's disease (AD) is associated with thiol modifications, in particular S-nitrosylation. NO is produced in the brain by neuronal NO synthase (nNOS) and serves as a key second messenger for instance, regulating neuronal plasticity and survival (Nakamura and Lipton, 2016; Chong et al., 2017). However, aberrant S-nitrosylation of proteins such as PDI and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) can occur in AD (Uehara et al., 2006; Zhao et al., 2015). S-nitrosylation of GAPDH enhances its binding to the ubiquitin ligase Siah1. GAPDH/Siah1 complexes accumulate in the nucleus triggering neuronal apoptosis via excessive protein degradation and trans-nitrosylation signaling cascades (Hara et al., 2005; Sen and Snyder, 2011; Nakamura and Lipton, 2013).

Numerous examples of "gain of cysteine" mutations are found in cancer, p53, KRAS and other oncogenes being preferred targets. The acquired cysteines cause decreased stability or impaired DNA binding of the tumor suppressor p53, while KRAS oncogenes are constitutively activated. Noteworthy, such acquired cysteines are potential targets for antitumor treatments (Visscher et al., 2016).

CONCLUDING REMARKS

The multiple chemical reactions of cysteines and their reversibility in physiological conditions make them ideal tuneable devices for regulating protein function. Indeed, evolution has increasingly exploited the regulatory potential

of cysteine chemistry as atmospheric oxygen became more abundant and complex multicellular organisms evolved. The frequency and conservation of this amino acid is indeed higher in mammals (>2% of the proteome) than in prokaryotes (0.5%). The examples provided in this essay reveal the pathophysiological relevance of cysteine redox modifications in the different compartments of human cells. Disulfide bonds prevail in the exocytic and endocytic compartments, organelles which are in direct contact with the oxidizing extracellular environment. These covalent bonds increase protein stability, facilitate quality control (Medraño-Fernandez et al., 2014) and underlie the functional regulation of many secreted proteins. A wider range of modifications acts in the cytosol and mitochondria, whose chemistry reflects their origin in an oxygen free atmosphere. Cysteine residues in these compartments are largely found in the reduced thiol/thiolate state, which permits regulation of protein function and activity by way of a wide-range of oxidative post-translational modifications. The redox gradients that form within and amongst cells hence provide ample opportunities to regulate signaling, transcription and other key biological processes. The price we pay is the many diseases caused by cysteine mutations or oxidative deregulation. Novel reagents (Chen et al., 2013; Kim et al., 2015; Bilan and Belousov, 2016; Wagener et al., 2016) are being

developed to better understand cysteine modifications and their links with disease, ultimately offering ample practical exploitations (Nakamura and Lipton, 2016; Wani and Murray, 2017).

AUTHOR CONTRIBUTIONS

AF, EDY and RS discussed the concepts and pitfalls, and wrote the manuscript.

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