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Reactive oxygen and nitrogen species (ROS and RNS, respectively) are part of any aerobic lifestyle/metabolism: low (i.e., subtoxic) concentrations of selected ROS and RNS are continuously produced inside and outside the cell by a number of pathways, either accidentally or purposefully. In all eukaryotic cells, the mitochondrial electronic transport chain is the main endogenous source during cellular respiration. Activated phagocytes also release significant amounts of various ROS and RNS by NADPH oxidase, myeloperoxidase, and nitric oxide synthase activity while attacking microorganisms or damaged host cells. Other biologically significant sources of ROS and/or RNS include ionizing radiation, cytochrome p450 activity, the enzymatic system of hypoxanthine/xanthine oxidase, especially in ischemia/reperfusion, metal catalyzed reactions, osmotic stress, and chemotherapeutic drugs (Halliwell & Gutteridge, 2007; Jomova et al., 2010).

Due to their high chemical reactivity, ROS and RNS can modify and oxidize various biological molecules, often altering their biological function, such as unsaturated lipids, carbohydrates, nucleic acids, but mostly, because of their high abundance, proteins. These oxidized (and often damaged) cellular molecules can cause toxicity as such and/or may degrade to form further toxic products, such as reactive carbonyl species (RCS) generated by peroxidation of polyunsaturated fatty acids (PUFAs). For example, highly reactive a,b-unsaturated aldehydes/hydroxyl-alkenals such as 4-hydroxy-2-nonenal and 4-hydroxy-2-hexenal derive from the degradation of peroxidized n—6 and n—3 PUFAs (Catalá, 2009; ; Fritz & Petersen, 2011; Fritz & Petersen, 2013). RCS can, in turn, react with the nucleophilic sites of proteins, binding to the sulfhydryl group of cysteine, the e-amino group of lysine or the imidazole group of histidine residues to form Michael or Schiff base protein adducts, known as advanced

oxidation, may thus be an early cellular response to mild oxidative stress and may also play an important role in redox signaling pathways (Dalle-Donne et al., 2007, 2009; DÕAutreaux & Toledano, 2007; Brandes, Schmitt, & Jakob, 2009; Rudolph & Freeman, 2009; Zhang et al., 2011; Higdon

As discussed above, there is much evidence that protein thiol oxidation occurs not only as a consequence of oxidative/nitrosative stress conditions, but this modification plays a crucial role in redox signaling pathways in the healthy cell. Amongst the different post-translational oxidative modifications that can occur at the cysteine thiol group, cysteine sulfenic acid (CySOH) is a key player in redox regulation of protein functions under both physiological and oxidative stress conditions and can mediate the transduction of the intracellular signal, hydrogen peroxide, acting as a second messenger, into a biological response (Poole & Nelson, 2008; Haskew-Laytona et al., 2010; Roos & Messens, 2011). However, relatively few molecular details of how this oxidant acts to regulate protein function are currently understood. Furdui and Poole (2013) describe in detail primarily classical and emerging chemical tools and approaches that can be applied to study protein sulfenylation in biological systems, also providing some of the biologically meaningful data that have been collected using such approaches, including demonstration of CySOH formation in IQGAP, a VEGF receptor binding scaffold protein involved in ROS-dependent endothelial cell migration and post-ischemic angiogenesis. *S*-Nitrosylation of proteins as well, that is, the addition of an NO group to a Cys thiol to form an *S*-nitrosoprotein, plays a regulatory role, mediating many of nitric oxide actions and participating in both physiological and pathophysiological processes (Murphy et al., 2012; Piantadosi, 2012; Maron, Tang, & Loscalzo, 2013; Nakamura et al., 2013). In this special issue, Pérez-Sánchez, López-Pedrera, & Rodríguez-Ariza (2013) exhaustively present up-to-date advances in proteomic methods that are providing researchers with improved tools for exploring protein *S*-nitrosylation. In addition, they also review some recent studies of the

products involve some form of carbonylation, even though different structures are associated with carbonyl groups, with the most reactive and common of these being in the form of lipid peroxidation-derived aldehydes. Carbonyl groups may be introduced within the protein primary structure at different sites and

Butterfield DA, Kanski J. 2001. Brain protein oxidation in age-related neurodegenerative disorders that are associated with aggregated proteins. Mech Ageing Dev 122:945—962.

Butterfield DA, Stadtman ER. 1997. Protein oxidation processes in aging brain. Adv Cell Aging Gerontol 2:161—191.

Butterfield DA, Reed T, Sultana R. 2011. Roles of 3-nitrotyrosine- and 4-hydroxynonenal-modified brain proteins in the progression and pathogenesis of Alzheimer's disease. Free Radic Res 45:59—72.

Butterfield DA, Perluigi M, Reed T, Muharib T, Hughes CP, Robinson RA, Sultana R. 2012. Redox proteomics in selected neurodegenerative disorders: From its infancy to future applications. Antioxid Redox Signal 17:1610—1655.

Butterfield DA, Gu L, Di Domenico F, Robinson RAS. 2013. Mass spectrometry and redox proteomics: Applications in disease. Mass Spectrom Rev 33: DOI: 10.1002/mas.21374

Cabiscol E, Tamarit J, Ros J. 2013. Protein carbonylation: Proteomics, specificity and relevance to aging. Mass Spectrom Rev 33:21—48.

Calabrese V, Mancuso C, Calvani M, Rizzarelli E, Butterfield DA, Giuffrida Stella AM. 2007. Nitric oxide in the nervous system: Neuroprotection vs. neurotoxicity. Nat Rev Neurosci 8:766—775.

Castro JP, Ott C, Jung T, Grune T, Almeida H. 2012. Carbonylation of the cytoskeletal protein actin leads to aggregate formation. Free Radic Biol Med 53:916—925.

Castro JP, Jung T, Grune T, Almeida H. 2013. Actin carbonylation: From cell dysfunction to organism disorder. J Proteomics pii: S1874-3919(13) 00241-8, doi: 10.1016/j.jprot.2013.05.006

Catalá A. 2009. Lipid peroxidation of membrane phospholipids generates hydroxy-alkenals and oxidized phospholipids active in physiological and/or pathological conditions. Chem Phys Lipids 157:1—11.

Charles R, Jayawardhana T, Eaton P. 2013. Gel-based methods in redox proteomics. Biochim Biophys Acta pii: S0304-4165(13)00149-9, doi: 10.1016/j.bbagen.2013.04.021

Codreanu SG, Zhang B, Sobecki SM, Billheimer DD, Liebler DC. 2009. Global analysis of protein damage by the lipid electrophile 4-hydroxy-2-nonenal. Mol Cell Proteomics 8:670—680.

Colombo G, Clerici M, Giustarini D, Rossi R, Milzani A, Dalle-Donne I. 2012a. Redox albuminomics: Oxidized albumin in human diseases. Antioxid Redox Signal 17:1515—1527.

Colombo G, Dalle-Donne I, Orioli M, Giustarini D, Rossi R, Clerici M, Regazzoni L, Aldini G, Milzani A, Butterfield DA, Gagliano N. 2012b. Oxidative damage in human gingival fibroblasts exposed to cigarette smoke. Free Radic Biol Med 52:1584—1596.

Colombo G, Clerici M, Giustarini D, Portinaro NM, Aldini G, Rossi R, Milzani A, Dalle-Donne I. 2013. Pathophysiology of tobacco smoke exposure: Recent insights from comparative and redox proteomics. Mass Spectrom Rev 33: DOI: 10.1002/mas.21392

Colzani M, Aldini G, Carini M. 2013. Mass spectrometric approaches for the identification and quantification of reactive carbonyl species protein adducts. J Proteomics pii: S1874-3919(13)00177-2.

D'Autreaux B, Toledano MB. 2007. ROS as signalling molecules: Mechanisms that generate specificity in ROS homeostasis. Nat Rev Mol Cell Biol 8:813—824.

Dalle-Donne I, Rossi R, Giustarini D, Gagliano N, Lusini L, Milzani A, Di Simplicio P, Colombo R. 2001. Actin carbonylation: From a simple marker of protein oxidation to relevant signs of severe functional impairment. Free Radic Biol Med 31:1075—1083.

Dalle-Donne I, Giustarini D, Colombo R, Rossi R, Milzani A. 2003. Protein carbonylation in human diseases. Trends Mol Med 9:169—176.

Dalle-Donne I, Scaloni A, Giustarini D, Cavarra E, Tell G, Lungarella G, Colombo R, Rossi R, Milzani A. 2005. Proteins as biomarkers of oxidative/nitrosative stress in diseases: The contribution of redox proteomics. Mass Spectrom Rev 24:55—99.

Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A. 2006a. Biomarkers of oxidative damage in human disease. Clin Chem 42:601—623.

Dalle-Donne I, Aldini G, Carini M, Colombo R, Rossi R, Milzani A. 2006b. Protein carbonylation, cellular dysfunction, and disease progression. J Cell Mol Med 10:389—406.

Dalle-Donne I, Scaloni A, Butterfield DA. 2006c. Redox proteomics: From protein modifications to cellular dysfunction and disease. Hoboken: John Wiley & Sons, Inc. 944p.

Dalle-Donne I, Rossi R, Giustarini D, Colombo R, Milzani A. 2007. S-Glutathionylation in protein redox regulation. Free Radic Biol Med 43:883—898.

Dalle-Donne I, Rossi R, Colombo G, Giustarini D, Milzani A. 2009. Protein S-glutathionylation: A regulatory device from bacteria to humans. Trends Biochem Sci 34:85—96.

Dewaele M, Martinet W, Rubio N, Verfaillie T, de Witte PA, Piette J, Agostinis P. 2011. Autophagy pathways activated in response to PDT contribute to cell resistance against ROS damage. J Cell Mol Med 15:1402—1414.

Di Domenico F, Sultana R, Ferree A, Smith K, Barone E, Perluigi M, Coccia R, Pierce W, Cai J, Mancuso C, Squillace R, Weingele M, Dalle-Donne I, Wolozin B, Butterfield DA. 2012. Redox proteomics analyses of the influence of co-expression of wild type or mutated LRRK2 and tau on *C. elegans* protein expression and oxidative modification: Relevance to Parkinson disease. Antioxid Redox Signal 17:1490—1506.

Erickson JR, Joiner ML, Guan X, Kutschke W, Yang J, Oddis CV, Bartlett RK, Lowe JS, O'Donnell SE, Aykin-Burns N, Zimmerman MC, Zimmerman K, Ham AJ, Weiss RM, Spitz DR, Shea MA, Colbran RJ, Mohler PJ, Anderson ME. 2008. A dynamic pathway for calcium-independent activation of CaMKII by methionine oxidation. Cell 133:462—474.

Fedorova M, Bollineni RC, Hoffmann R. 2013. Protein carbonylation as a major hallmark of oxidative damage: Update of analytical strategies. Mass Spectrom Rev 33: DOI: 10.1002/mas.21381

Feeney MB, Schoneich C. 2012. Tyrosine modifications in aging. Antioxid Redox Signal 17:1571—1579.

Forman HJ, Maiorino M, Ursini F. 2010. Signaling functions of reactive oxygen species. Biochemistry 49:835—842.

Fritz KS, Petersen DR. 2011. Exploring the biology of lipid peroxidation-derived protein carbonylation. Chem Res Toxicol 24:1411—1419.

Fritz KS, Petersen DR. 2013. An overview of the chemistry and biology of reactive aldehydes. Free Radic Biol Med 59:85—91.

Furdui CM, Poole LB. 2013. Chemical approaches to detect and analyze protein sulfenic acids. Mass Spectrom Rev 33: DOI: 10.1002/mas.21384

Ghesquière B, Gevaert K. 2013. Proteomics methods to study methionine oxidation. Mass Spectrom Rev 33: DOI: 10.1002/mas.21386

Grimm S, Hoehn A, Davies KJ, Grune T. 2011. Protein oxidative modifications in the ageing brain: Consequence for the onset of neurodegenerative disease. Free Radic Res 45:73—88.

Halliwell B. 2011. Free radicals and antioxidants—Quo vadis? Trends Pharmacol Sci 32:125—130.

Halliwell B, Gutteridge J. 2007. Free radicals in biology and medicine.

Jomova K, Vondrakova D, Lawson M, Valko M. 2010. Metals, oxidative stress and neurodegenerative disorders. Mol Cell Biochem 345:91—104.

Jung T, Grune T. 2008. The proteasome and its role in the degradation of oxidized proteins. IUBMB Life 60:743—752.

Kaushik S, Cuervo AM. 2006. Autophagy as a cell-repair mechanism: Activation of chaperone-mediated autophagy during oxidative stress. Mol Aspects Med 27:444—454.

Keeney JT, Swomley AM, Förster S, Harris JL, Sultana R, Butterfield DA. 2013. Apolipoprotein A-I: Insights from redox proteomics for its role in neurodegeneration. Proteomics Clin Appl 7:109—122.

Kiffin R, Christian C, Knecht E, Cuervo AM. 2004. Activation of chaperone-mediated autophagy during oxidative stress. Mol Biol Cell 15:4829—4840.

Kim G, Weiss SJ, Levine RL. 2013. Methionine oxidation and reduction in proteins. Biochim Biophys Acta pii: S0304-4165(13)00193-1, doi: 10.1016/j.bbagen.2013.04.038

Kumar V, Kleffmann T, Hampton MB, Cannell MB, Winterbourn CC. 2013. Redox proteomics of thiol proteins in mouse heart during ischemia/reperfusion using ICAT reagents and mass spectrometry. Free Radic Biol Med 58:109—117.

Levine RL. 2002. Carbonyl modified proteins in cellular regulation, aging, and disease. Free Radic Biol Med 32:790—796.

Levine RL, Stadtman ER. 2001. Oxidative modification of proteins during aging. Exp Gerontol 36:1495—1502.