Review

Oxidation as an important factor of protein damage: Implications for Maillard reaction

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Protein oxidation, the process caused especially by reactive oxygen and nitrogen species, is thought to play a major role in various oxidative processes within cells and is implicated in the development of many human diseases. This review provides a brief overview of the protein oxidation with the emphasis on the types of oxidation (oxidation of protein backbone and amino acid residues side chains, site-specific metal-catalysed protein oxidation), oxidation-dependent generation of protein hydroperoxides, carbonyl derivatives and protein–protein cross-linkages. Non-enzymatic glycoxidation (also known as Maillard reaction) as an important factor of protein damage, consequences of oxidative protein impairment and related diseases as well as means of monitoring and assessment of protein modifications are discussed.

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1. Introduction

Proteins are the most abundant and functionally diverse biological macromolecules in living organisms. Most of them spontaneously fold to a unique three-dimensional 'native' conformation, which is a prerequisite for their proper function (e.g. transport, enzymatic activity). This conformation can be changed or disturbed by various processes, such as non-covalent or covalent modifications (Bousova *et al.* 2011; Trnkova *et al.* 2011), denaturation or peptide bond cleavage, often resulting in various catastrophic consequences for organisms (Herges *et al.* 2002).

One of the most deleterious factors leading to the serious damage of proteins is oxidation, which is very often related to oxidative stress. The oxidative stress represents an imbalance between the excessive production of reactive oxygen and nitrogen species (RONS) and their elimination by protective antioxidant systems (Halliwell and Gutteridge 2007). RONS, coming from various exogenous (e.g. environmental factors) and endogenous (e.g. normal metabolic processes, glycoxidation reactions) systems (Finkel and Holbrook 2000; Kelly 2004; Schröder and Krutmann 2005), react promptly with various biologically important biomolecules, including proteins and enzymes, in the reactions often catalysed by the transition metals (e.g. Cu, Fe) (Avery 2011). Under certain circumstances, they are required for the proper physiological functions of some systems (e.g. cell signalling, immune defense, gene expression) (Forman *et al.* 2004; Halliwell and Gutteridge 2007; Forman 2010; Finkel 2011). In contrast, if RONS are produced in large quantities, they can become harmful with the potential to damage or even kill the organism (Droge 2002; Pan *et al.* 2009). The oxidative stress has been implicated in the pathogenesis of many human age-related disorders and diseases (Elahi *et al.* 2009; Gella and Durany 2009; Pan *et al.* 2009; Ferguson 2010; Jomova *et al.* 2010; Klaunig *et al.* 2010; Whaley-Connell *et al.* 2011) and also plays an important role in the physiological process of aging (Stadtman 2004; Romano *et al.* 2010).

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To fight an excessive production of RONS, the organism has developed protective systems and mechanisms against their toxic effects. These protective mechanisms include the systems preventing RONS formation or trapping transition metal ions by chelating agents, scavengers and trappers of RONS (i.e. high and low molecular weight antioxidants), and the repair systems (Halliwell and Gutteridge 2007; Durackova 2010). In last two decades, great attention has been focused on dietary plant flavonoids as effective antioxidants. However, under certain circumstances these compounds can act as pro-oxidants and thus participate in tissue impairments and consequently in the development of various diseases (Prochazkova *et al.* 2011).

Detailed information regarding the protein oxidation can be found in several excellent reviews (Stadtman and Levine 2003; Stadtman 2006; Rees *et al.* 2008; Cadet and Di Mascio 2009; Bachi *et al.* 2013) and in the most authoritative summary of this area up to the year 2012 (Davies 2012). The aim of this review is to provide brief overview of protein oxidation focused on the oxidation, including non-enzymatic glycoxidation, as an important factor of protein damage.

2. Protein oxidation

Oxidative damage to proteins may be important *in vivo* both in its own right (affecting the function of enzymes, receptors, transport proteins etc. and perhaps generating new antigens that can provoke immune response) and because it can contribute to the secondary damage to other biomolecules (e.g. inactivation of DNA repair enzymes and loss of fidelity of DNA polymerases in replicating DNA) (Halliwell 2001). Chemical reactions resulting from RONS attack to proteins are complex since there are 20 amino acid residues in their molecules and each of them can give rise to multiple products upon oxidation (Davies and Dean 1997). The RONS can cause oxidation of the protein backbone resulting in the protein fragmentation, oxidation of amino acid residue side chains, and formation of protein–protein cross-linkages (Miller and Shaklai 1994; Shacter 2000; Avery 2011). Moreover, radical-mediated attack on proteins can generate amino acid radicals reacting with O_2 to give peroxyl radicals and then protein peroxides, which can decompose in a number of ways, promoted by transition metal ions or heat (Cadet and Di Mascio 2009; Davies and Dean 1997). The oxidatively modified proteins are not mostly repaired and must be removed from the organism by proteolytic degradation. Decrease in the efficiency of proteolysis causes their accumulation in the cellular content, which can lead to disruption of the cellular functions either by loss of catalytic and structural integrity or by interruption of regulatory pathways (Shacter 2000; Avery 2011). The amount of oxidatively modified proteins in cells reflects the balance between prooxidant and antioxidant activities of the organism and is dictated by prevailing environmental, genetic and dietary factors.

2.1 *Oxidation of protein backbone*

Reactive oxygen species (ROS) can directly attack protein polypeptide backbone. Reaction of protein with hydroxyl radical (•OH), which can be formed by ionizing radiation or by transition metals-catalysed decomposition of hydrogen peroxide, leads to the abstraction of a hydrogen atom from the protein polypeptide backbone to form a carbon-centered radical (~NHC•RCO~), which can either react with another carbon-centered protein derivative to form a –C–C– cross-linked protein derivative, or yield a peroxyl radical (~NHCOO•RCO~) under aerobic conditions. The peroxyl radical can further abstract a hydrogen atom from another amino acid residue in the same or another protein molecule to form another carbon-centered radical derivative, or can be gradually converted to an alkyl peroxide derivative (~NHCOOHRCO~), an alkoxyl radical (~NHCO•RCO~), or a hydroxyl derivative (~NHCOHRCO~) in the presence of protonated form of superoxide (HO_2•) or transition metal ions (Dean *et al.* 1997; Hawkins and Davies 2001). However, HO_2•-mediated protein oxidation seems irrelevant for biological systems due to its low pKa. The alkoxyl radical can also undergo a peptide bond splitting either through the α-amidation or diamide pathways, both involving β-scission cleavage mechanism (Cadet and Di Mascio 2009). Protein hydroperoxides may be important propagating species in the protein oxidation as they can initiate further oxidation via both radical and non-radical reactions (Hampton *et al.* 2002; Morgan *et al.* 2002). Protein bond cleavage can occur also by hydroxyl radical-initiated attack of the glutamic acid and proline residues of proteins (Stadtman 2004). Figure 1 depicts the scheme of protein backbone oxidation. The protein fragmentation is connected with the loss of its enzymatic, signal or transport function (Stadtman and Levine 2000).

2.2 *Oxidation of amino acid residue side chains*

The side chains of amino acid residues in proteins are also susceptible to the oxidation by reactive oxygen species resulting often ingeneration of irreversibly oxidatively modified proteins (table 1), which must be removed from the organism by proteolytic degradation.

The sulphur-containing amino acid residues (i.e. cysteine and methionine) are the most sensitive residues to the oxidation by almost all kinds of ROS. In contrast to other ROS-mediated oxidations, their oxidation is mostly reversible process. The oxidation of cysteinethiol groups of proteins leads mainly to the production of disulphide derivatives, i.e. intra-molecular (R1-S-S-R1) and inter-molecular disulphides

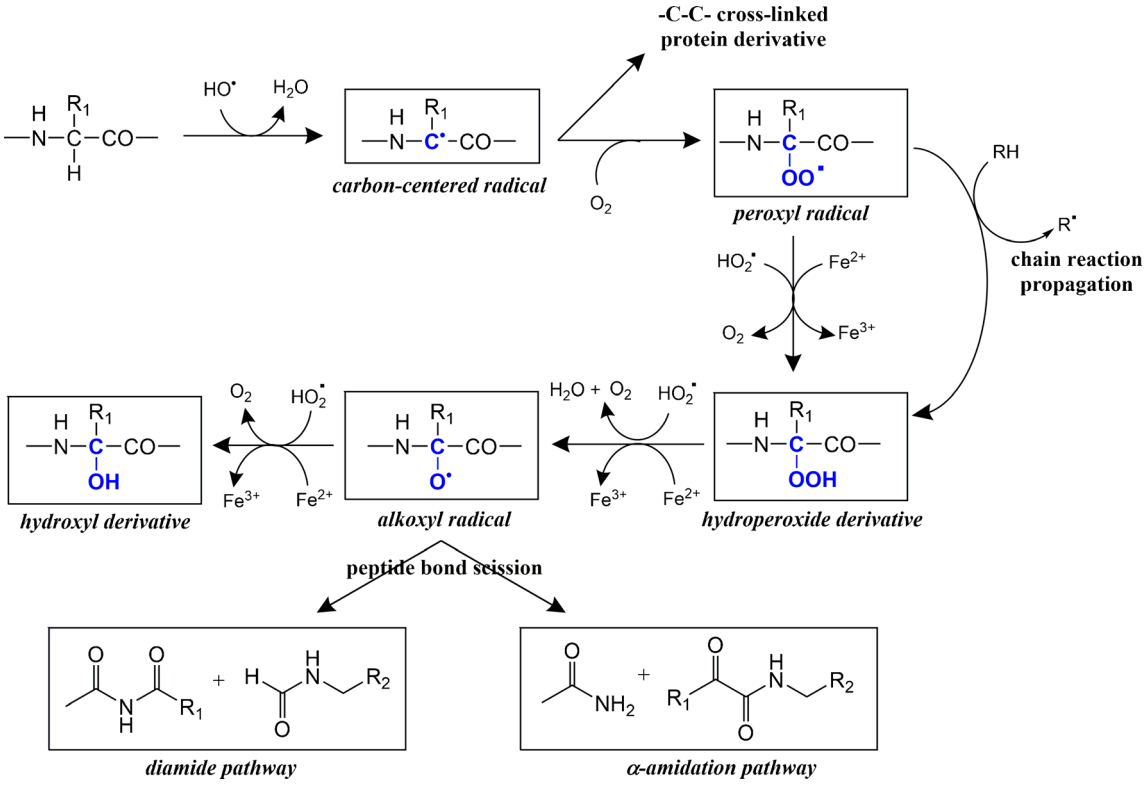

Figure 1. Scheme of protein backbone oxidation.

(R1-S-S-R2) or mixed disulphides with oxidized form of glutathione (R1-S-S-G), which can be regenerated by disulphide exchange reactions of the glutathione system catalysed by thiol-transferases or thioredoxin (Stadtman 2004; Biswas *et al.* 2006). In addition, cysteine residues can be also converted into nitroso adducts (RS-NO) or oxy

Table 1. Oxidative modifications of amino acid residues side chains

Amino acid residue	Product
Arg	Glutamic semialdehyde (carbonyls), AGEs[a]
Cys	Sulphenic acid, sulphinic acid, sulphonic acid, disulphides, nitroso-Cys
Glu	Oxalic acid, pyruvate adducts, hydroperoxides
His	2-Oxohistine, 4-hydroxy-Glu, hydroperoxides
Ile	Hydroperoxides
Leu	3-Hydroxy-Leu, 4-hydroxy-Leu, 5-hydroxy-Leu, hydroperoxides
Lys	α-Aminoadipicsemialdehyde (carbonyls), AGEs[a], hydroperoxides
Met	Met-sulphoxide, Met-sulphone
Phe	2-, 3-, and 4-Hydroxy-Phe, DOPA[b]
Pro	Glutamic semialdehyde (carbonyls), 2-pyrrolidone (carbonyls), 4- and 5-hydroxy-Pro, pyroglutamic acid, hydroperoxides
Thr	2-Amino-3-ketobutyric acid (carbonyls)
Trp	2-, 4-, 5-, 6-, and 7-Hydroxy-Trp, *N*-formylkynurenin, kynurenin, 3-hydroxykinurenin, 6-nitro-Trp, bi-Trp[c], hydroperoxides
Tyr	DOPA[b], bi-Tyr, 3-chloro-Tyr, 3,5-dichloro-Tyr, 3-nitro-Tyr, hydroperoxides
Val	Hydroperoxides

[a] Advanced glycation end products, [b] 2,3-dihydroxyphenylalanine,[c] tryptophan dimmers.

acids (sulphenic acid, RSOH; sulphinic acid, RSO_2H; or sulphonic acid, RSO_3H) (Biswas *et al.* 2006; Turell *et al.* 2009). Methionine residues in proteins are oxidized to methionine sulphoxide (Met-SO), which can be converted back to methionine residues by methionine sulphoxide reductases (Vogt 1995; Stadtman *et al.* 2005).

Aromatic and heterocyclic amino acid residues are also prime targets for the oxidation by various ROS. Tryptophan residues are readily oxidized to kynurenine or formylkynurenine, to various hydroxyl derivatives (Kikugawa *et al.* 1994; Stadtman 2004) and tryptophan dimers (Silva *et al.* 1994; Vaz *et al.* 2009; Arenas *et al.* 2013), or they can be nitrated by peroxynitrite to 6-nitrotryptophan (Ducrocq *et al.* 1999; Ferrer-Sueta and Radi 2009). Phenylalanine and tyrosine residues yield a number of hydroxyl derivatives (Maskos *et al.* 1992), while histidine residues are converted mainly to 2-oxohistidine and in some cases also to asparagine and aspartic acid (Uchida and Kawakishi 1993). Tyrosine residues can be also converted to tyrosyl radicals that can interact with one another to form dityrosine inter- or intra-protein cross-linked derivatives (Huggins *et al.* 1993; Miller and Shaklai 1994). Tyrosine residue can be also chlorinated by hypochlorous acid (HOCl) to 3-chlorotyrosine derivative (Stadtman and Levine 2000) or nitrate by peroxynitrite to 3-nitrotyrosine (Alvarez and Radi 2003; Ferrer-Sueta and Radi 2009).

Other amino acid residues such as those of leucine and valine are converted into hydroxyl derivatives. Lysine and both arginine and proline residues are oxidized into amidoadipic and glutamic semialdehydes, respectively, resulting in peptide bond cleavage (Stadtman 2004). Hypochlorite can oxidize lysine amino groups to carbonyl orchloramine derivatives (Stadtman and Levine 2000).

Some amino acid side chains can also interact with alkoxyl (LO•) or peroxylradicals (LOO•), which are formed during lipid peroxidation, and in addition with the lipid peroxidation end products, such as 4-hydroxy-2-nonenal (HNE) or malondialdehyde (MDA), that are covalently bound to ε-amino group of lysine, histidine imidazole group, or cysteine thiol group leading to protein aggregation and cross-linking (Shacter 2000; Stadtman 2001; Fritz and Petersen 2011; Ullery and Marnett 2012).

2.3 *Site-specific metal-catalysed protein oxidation*

The side chains of amino acid residues, mainly lysine, arginine, proline, threonine, and histidine residues, are readily oxidized by metal ion-catalysed oxidation with a site-specific mechanism, which can be briefly described as follows. Superoxide anion radical, which is formed by several prooxidant systems, is readily converted to hydrogen peroxide by the action of superoxide dismutase, one of the antioxidant enzymes. The chelate complex, which is formed by the binding of reduced form of metal ion (predominantly Fe(II) or Cu(I)) to the amino acid residue in a metal binding site of the protein/enzyme, can react with hydrogen peroxide to generate a highly reactive hydroxyl radical that will preferentially attack just the amino acid moiety in the metal binding site leading to generation of carbonyl derivatives. This site-specific mechanism is supported by the demonstration that the metal-catalysed reactions are inhibited by catalase but not by •OH scavengers, presumably because the scavengers cannot compete with the 'caged' reaction of •OH with amino acids at the metal binding site. On the other hand, other bivalent cations such as Mg(II), Mn(II), or Zn(II) may compete with Fe(II) or Cu(I) for binding to the metal binding sites on proteins and thereby prevent site-specific generation of hydroxyl radical to suppress protein damage (Stadtman and Levine 2003). The mechanism of the site-specific iron-catalysed protein oxidation of a lysine residue is illustrated in figure 2. Briefly, the reduction of Fe(III) (step 1) is followed by the binding of Fe(II) to the protein (step 2) to form a coordination complex. The H_2O_2, produced by the reduction of O_2 (step 3) may react with Fe(II) in the complex to form •OH, OH^-, and a Fe(III)–protein complex (step 4). The hydroxyl radical abstracts a hydrogen atom from the carbon atom bearing the ε-amino group to form a carbon-centered radical (step 5) that then donates its unpaired electron to Fe(III) in the complex to regenerate Fe(II) and converts the ε-amino group to an imino derivative (step 6). Finally, the imino derivative undergoes spontaneous hydrolysis whereby $NH_3$and Fe(II) are released and an aldehyde derivative of the lysyl residue is generated (step 7), which tends to proteolytic degradation (step 8) (Stadtman and Oliver 1991). However, the above mentioned reactions can proceed only in the presence of free transition metal ions, which are rarely detected in the system. Therefore, catalysis of these steps by some heme-containing proteins seems to be the probable mechanism (Bamm *et al.* 2003; Grinshtein *et al.* 2003).

2.4 *Generation of protein hydroperoxides*

Several amino acid residues (e.g. Tyr, Trp, His, Val and Pro) in the proteins have been reported to undergo oxidation in the presence of RONS (e.g. •OH, superoxide radical, singlet oxygen) to form corresponding hydroperoxide as the major product (Wright *et al.* 2002; Winterbourn *et al.* 2004; Gracanin *et al.* 2009; Das *et al.* 2014). Amino acid hydroperoxides are stable *in vitro* in the absence of exogenous catalysts (e.g. heat, light, redox-active transition metal ions) but decompose rapidly in the presence of these agents to give a variety of radicals including alkoxyl, peroxyl and carbon-centered species (Luxford *et al.* 2002). The protein hydroperoxides can further propagate oxidative damage to other biomolecules including lipids, proteins, and DNA (Luxford *et al.* 1999; Luxford *et al.* 2000; Rahmanto *et al.* 2010;

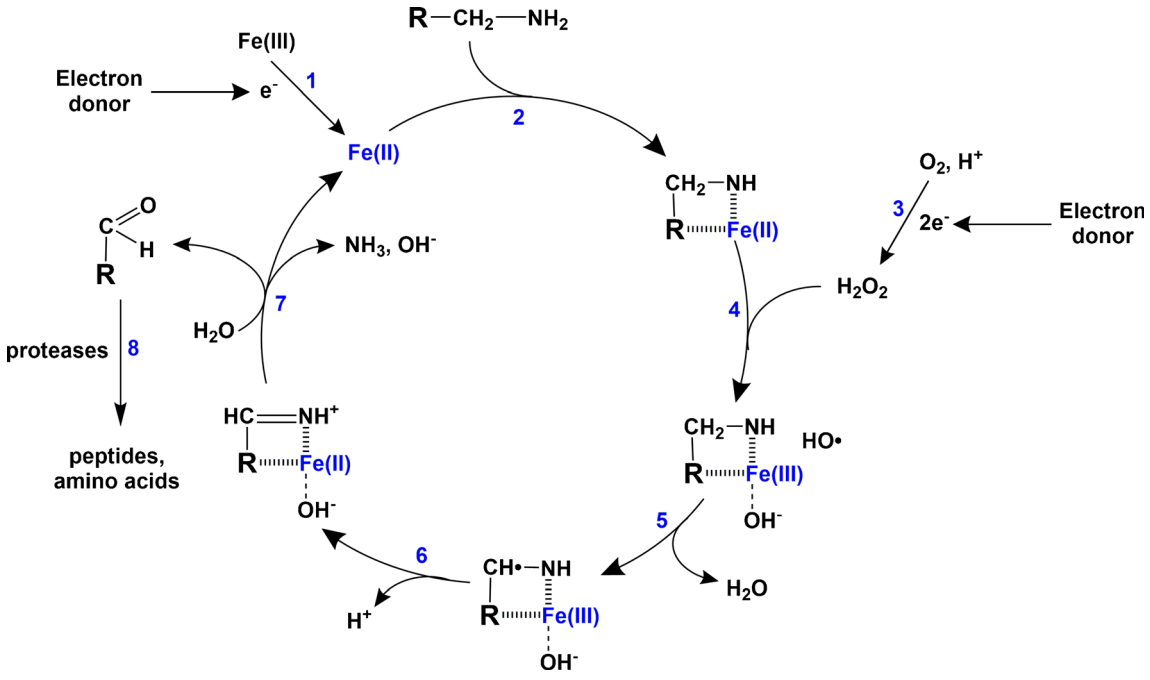

Figure 2. Mechanism of site-specific iron-catalysed oxidation of protein amino acid residues. R stands for the protein molecule.

Lopez-Alarcon *et al.* 2014). They have been demonstrated to consume important cellular reductants (such as ascorbate or glutathione) via redox reactions (Simpson *et al.* 1992). These species are able to generate radicals in the presence of metal ions andto oxidize thiols essential to cellular function via non-radical reactions (Rahmanto *et al.* 2010; Michalski *et al.* 2014).The protein hydroperoxides can be quantified using the oxidation of ferrous ion monitored with xylenol orange (FOX assay) (Morgan *et al.* 2008, 2012) and iodometric assays (Thomas *et al.* 1989), which cannot be used in real time measurements. For the real-time measurement of these compounds, the boronate-based assay has been recently introduced (Michalski *et al.* 2014).

2.5 *Generation of protein carbonyl derivatives*

Protein carbonyl derivatives (ketones and aldehydes) are highly reactive compounds produced by different mechanisms such as direct metal-catalysed oxidation of lysine, arginine, proline, and threonine residues (Requena *et al.* 2003), or oxidative cleavage of the peptide backbone via the α-amidation and glutamic acid oxidation pathways (Berlett and Stadtman 1997). Furthermore, carbonyl derivatives of proteins can be also formed by the interaction of protein amino acid side chains (i.e. histidine imidazole groups, lysine amino groups, and cysteine thiol groups) with lipid peroxidation products (e.g. HNE, MDA), or with reactive carbonyl derivatives (ketoamines, ketoaldehydes, deoxyosones) generated as a consequence of the reaction of reducing sugars and their oxidation products with lysine residues of proteins (glycation and glycoxidation reactions) (Stadtman 2004). In addition, interactions of protein lysine residues with lipid peroxidation and glycation/glycoxidation products can lead to the formation of *N*-*ε*-carboxymethyllysine (CML) derivatives, which possess strong chelating ability and thus are able to promote the generation of carbonyl groups by metal-catalysed reactions (Requena and Stadtman 1999; Saxena *et al.* 1999). As carbonylation results in the introduction of reactive aldehyde or ketone groups in the protein, they are easily quantifiable and are indeed considered in practice as reliable markers of oxidative stress, aging, and age-related diseases (Dalle-Donne *et al.* 2005, 2006; Akagawa *et al.* 2009; Madian and Regnier 2010; Baraibar *et al.* 2013; Fedorova *et al.* 2014).

2.6 *Oxidation-dependent generation of protein–protein cross-linkages*

Protein oxidation is implicated in the generation of many various kinds of inter- and intra-protein cross-linked derivatives by several different mechanisms such as the direct interaction of two carbon-centered radicals to form –C–C– protein cross-links, the oxidation of protein thiol groups to form disulphide –S–S– cross-linked proteins, the oxidation

of tyrosine residues to form –Tyr–Tyr– (bityrosine) cross-linked derivatives (Miller and Shaklai 1994), the interaction of carbonyl groups obtained in direct oxidation of amino acid side chains with lysine amino groups to form Schiff-based cross-linked products, the interaction of glycation/glycoxidation derived protein carbonyls with either a lysine or an arginine residue of the same or a different protein molecule to form Schiff-based cross-linked products (Thorpe and Baynes 2003; Ansari *et al.* 2011), and the Michael addition reaction of either cysteine thiol groups, lysine amino groups, or histidine imidazole groups of proteins with the double bonds of aldehydes obtained by the lipid peroxidation (e.g. HNE, MDA) to form Schiff-based cross-linked derivatives (Grune and Davies 2003). Some cross-linked derivatives are not only resistant to proteolytic degradation by the proteasome but in addition they are potent inhibitors of the proteolytic degradation of other oxidatively modified proteins. Therefore, they may contribute to the accumulation of oxidized forms of proteins during aging and age-related diseases (Grune and Davies 2003; Agou *et al.* 2004; Stadtman 2004).

2.7 *Non-enzymatic glycoxidation of proteins as a complex protein damage*

Non-enzymatic glycation/glycoxidation (also known as Maillard reaction), which leads to the onset and progression of many human diseases (e.g. diabetes mellitus and its related complications, atherosclerosis, and Alzheimer's disease) (Sell *et al.* 2005; Goh and Cooper 2008; Monnier *et al.* 2013; Ramos-Fernandez *et al.* 2014; Tajes *et al.* 2014; Genuth et al. 2015), is an elaborate process of covalent damage of proteins usually accompanied by oxidative steps (West 2000). It is initiated as the non-enzymatic reaction between amino groups of proteins and carbonyl groups of reducing sugars (e.g. glucose), their reactive metabolites (e.g. α-oxoaldehydes), or other carbohydrate relatives (e.g. ascorbic acid) leading to generation of advanced glycation end products (AGEs) via early (Schiff bases) and intermediate (Amadori or Heyns products) glycation products (Schalkwijk *et al.* 2004). The AGEs represent complex and heterogeneous molecules (figure 3) that cause significant changes in physico-chemical properties of proteins, e.g. a considerable increase in their molecular weight, an ability of aggregation and cross-links formation, a yellow-brown pigmentation, or a fluorescence generation (Ulrich and Cerami 2001; Nass *et al.* 2007).

Due to the complexity of non-enzymatic glycoxidation, no universal method exists for its powerful monitoring and assessment which would help in finding of convenient strategy for its suppression. One of the possibilities for its monitoring is application of methods which study changes in structural and catalytic properties of proteins and enzymes (Gugliucci *et al.* 2009; Bousova *et al.* 2011). Powerful approach for monitoring of glycoxidation process includes identification and quantification of arising metabolic intermediates (e.g. α-oxoaldehydes) and AGEs mostly by immunochemical (Nagai *et al.* 2008), spectrofluorimetric (Wu and Yen 2005), or chromatographic (Wu *et al.* 2008; Zmatlikova *et al.* 2010) methods. Pentosidine and CML are used as good biomarkers of glycoxidation as well as oxidative stress, respectively (Moreira *et al.* 2005; Kuang *et al.* 2014).

Several strategies for inhibition of the protein glycation and AGE-mediated damage have been developed: inhibition of AGEs formation by carbonyl-blocking agents or by antioxidants, reducing AGEs deposition using cross-link breakers or by enhancing cellular uptake and degradation, and finally inhibition of the receptors for AGEs (RAGE) by neutralizing antibodies or suppression of post-receptor signalling using antioxidants (Ahmed 2005; Bousova *et al.* 2012). Numerous compounds have been investigated *in vitro* and *in vivo* for anti-glycation activity but their use in humans is still debatable (Kaushik *et al.* 2010; Martini *et al.* 2010). Among compounds with antioxidant activity, which have received interest, are, for example, aminoguanidine (Thornalley 2003), curcumin (Hu *et al.* 2012; Fleenor *et al.* 2013), and various plant-derived flavonoids (e.g. quercetin) (Matsuda *et al.* 2003). The effects of these compounds on the disease onset/progression are ambiguous and require further studies.

2.7.1 *Role of AGEs formation in the development of diabetic microvascular complications:*

Diabetes mellitus is commonly associated with both microvascular and macrovascular complications. Diabetic macroangiopathy is a collective term for all atherosclerotic manifestations in main arteries of diabetics, while microvascular complications are represented by diabetic neuropathy, nephropathy and retinopathy. All these complications are caused by glycation of various proteins including proteins of extracellular matrix. Moreover, AGEs can contribute to the development of diabetic complications also via their interaction with specific receptors on the cell surface (Singh *et al.* 2014). The role of AGEs formation and protein oxidation in the development of diabetic microvascular complications is discussed in the following text.

Diabetic nephropathy Diabetic nephropathy is the most common cause of end-stage renal disease in the world, and could account for disability and high mortality rate in patients with diabetes. Various hyperglycaemia-induced metabolic and hemodynamic imbalances (e.g. increased AGEs formation, oxidative stress, activation of protein kinase C, polyol pathway and renin-angiotensin system) are considered to contribute to the development and progression of diabetic nephropathy (Yamagishi and Matsui 2010). Various structural

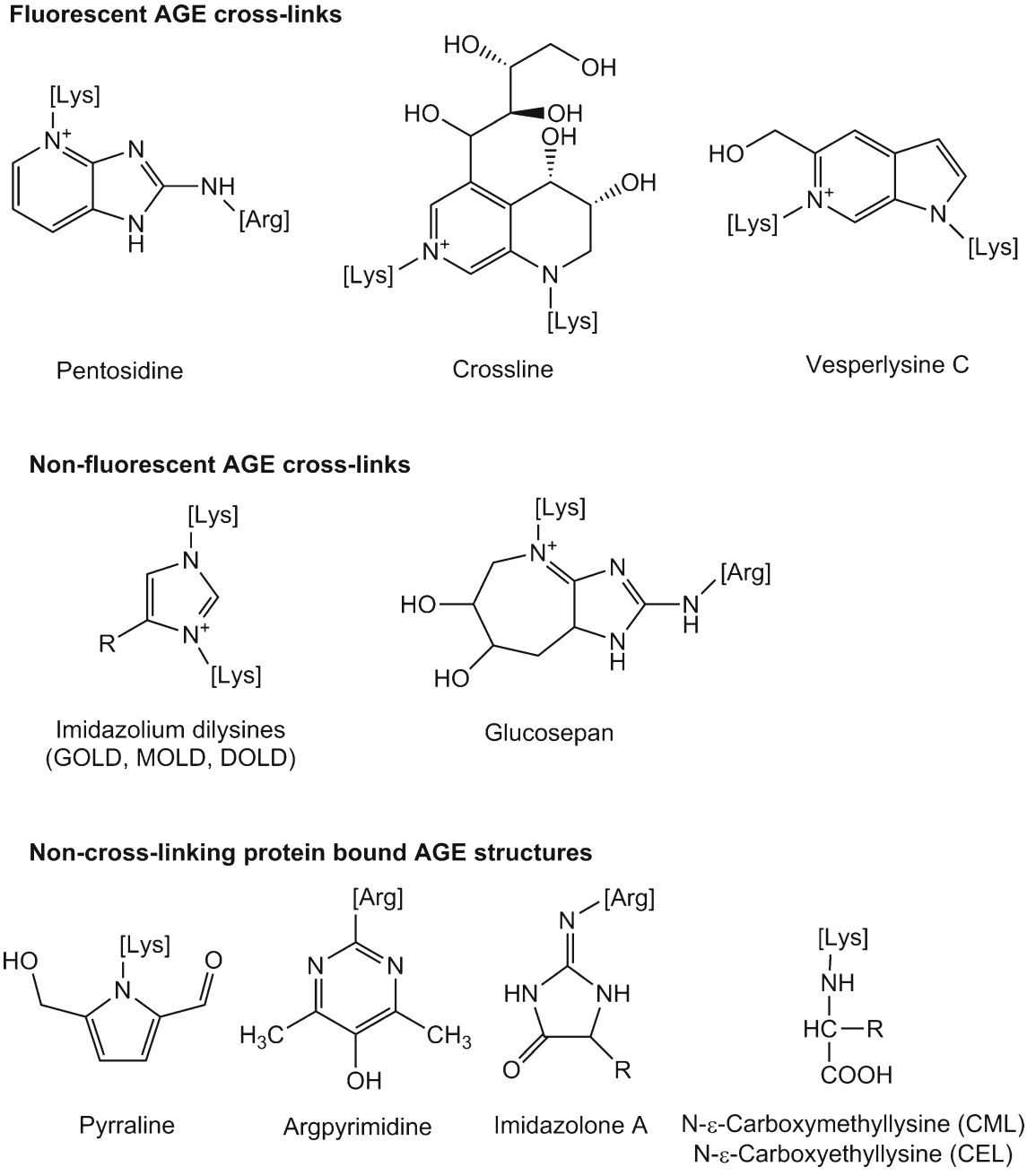

Figure 3. Classification of AGEs formed under physiological conditions including severalexamples to each group. [Lys] represents a desamino-lysine residue; [Arg] stands for adesguanidino-arginine residue; R represents either hydrogen atom (GOLD, CML), methyl group(MOLD, CEL), 1,2,3-trihydroxypropyl (DOLD) or 2,3,4-trihydroxybutyl group (imidazolone A).

abnormalities in glomeruli including basement membrane thickening, mesangial expansion and hypertrophy as well as podocyte loss have been observed (Teng *et al.* 2014).

Advanced glycation end-products pentosidine (Beisswenger *et al.* 1993; Tanji *et al.* 2000), CML (Tanji *et al.* 2000; Lieuw *et al.* 2004), *N*-ε-carboxyethyl-lysine (CEL) (Lieuw *et al.* 2004; Beisswenger *et al.* 2013) and methylglyoxal-derived hydroimidazolones (Beisswenger *et al.* 2013) have been reported in diabetic patients suffering from nephropathy. In diabetic kidneys, CML was the major AGE detected in mesangium, glomerular basement membranes, tubular basement membranes, and vessel

walls, while pentosidine was preferentially located in interstitial collagen (Tanji *et al.* 2000). Due to the slow turnover, proteins of extracellular matrix are highly susceptible to AGEs formation, which causes changes in their structure and function. Structural alterations observed in diabetic nephropathy comprise changes in packing density and surface charge, manifested by increased stiffness, reduced thermal stability, and resistance to proteolytic digestion (Forbes *et al.* 2003). Glycation of laminin and fibronectin, the key components of extracellular matrix, have been reported in diabetic animals (Thallas-Bonke *et al.* 2004). This process causes reduction in polymer self-assembly and decrease in binding of type IV collagen and heparan sulphate proteoglycan, other major components of the basement membrane (Goode *et al.* 1995). Glycated proteins of extracellular matrix may have decreased susceptibility to enzymatic hydrolysis by matrix metalloproteinases, which would allow them to accumulate in the extracellular space. Moreover, glycation of heparan sulphate proteoglycans reduces their electronegativity and thus modifies the charge-selective filtration properties of the basement membrane, resulting in microalbuminuria (Kanwar *et al.* 2011). Heparan sulphate proteoglycan is a strong inhibitor of mesangial growth and its reduced content in glomerular basement membrane was found to be associated with mesangial expansion due to the overproduction of other matrix components (Vernier *et al.* 1992; Deyneli *et al.* 2006). Moreover, interaction of AGEs with RAGE localized on the mesangial cells stimulates platelet-derived growth factor secretion, which in turn mediates mesangial expansion (Lu *et al.* 2011). Moreover, hyperglycaemia induces intracellular formation of ROS in mesangial cells leading to the increased expression of extracellular matrix proteins (Ha and Lee 2000; Iglesias-De La Cruz *et al.* 2001; Ha *et al.* 2002).

Diabetic neuropathy Diabetic neuropathy is a life-threatening complication, and both autonomic and peripheral nerves are affected. The clinical symptoms of diabetic neuropathy manifest in a time-dependent manner as a positive symptoms (i.e. pain, hypersensitivity, tingling, cramps, cold feet, etc.) during its early stages and by a loss of function (i.e. loss of sensory perception, delayed wound healing, etc.) predominating in the later stages (Hidmark *et al.* 2014). Although the pathogenesis of diabetic neuropathy remains unclear, hyperglycaemia-induced formation of AGEs as well as other mechanisms (e.g. activation of protein kinase C, polyol pathway, oxidative stress, excessive release of cytokines) play a key role in its pathogenesis (Yagihashi *et al.* 2011). Oxidative stress in turn increases formation of glycoxidation AGEs such as CML and pentosidine (Ryle *et al.* 1997; Haslbeck *et al.* 2002).

Peripheral nerves of diabetic rats contained significantly elevated levels of CML, CEL, fructosyl-lysine, methylglyoxal- and 3-deoxyglucosone-derived hydroimidazolones compared to controls (Thornalley *et al.* 2003). The perineurium, axons, endothelial cells and pericytes of endoneurial microvessels as well as myelinated and unmyelinated nerve fibres of diabetic patients contained AGEs (Sugimoto *et al.* 1997; Misur *et al.* 2004). Modification of several neural proteins, including myelin, cytoskeletal proteins and protein components of extracellular matrix by non-enzymatic glycation has been reported. Glycation of myelin protein alters its antigenicity, rendering it vulnerable to the phagocytic attack of monocytes, macrophages, and neutrophils from blood circulation and tissue, and of glial cells from nervous system. In addition, the activated immune cells secrete the pro-inflammatory cytokines and various proteases contributing to demyelination (Vlassara *et al.* 1985; Shi *et al.* 2013). Formation of AGEs on major axonal cytoskeletal proteins (e.g. actin, tubulin, neurofilament), which are central to the maintenance of axonal function and structure, may cause alteration of the structural and functional properties of the axon, thereby contributing to the axonal atrophy, degeneration, and impairment of axonal transport (McLean *et al.* 1992; Juranek *et al.* 2013). AGEs in extracellular matrix proteins (e.g. laminin, collagen), the major constituents of basal lamina, impair peripheral nerve regeneration (Duran-Jimenez *et al.* 2009). Glycation of laminin, collagen type IV as well as collagen type IV reduces neurite overgrowth in cell culture (Luo *et al.* 2002) and experimental animals (Ozturk *et al.* 2006). Moreover, it has been demonstrated that binding of AGEs to RAGE in the perineurium, epineurial vessels and in part in endoneurial vessels activates transcription factor NF-κB, which in turn induces expression of pro-inflammatory cytokines. Activation of AGE/RAGE/NF-κB pathway contributes to the development of polyneuropathy in diabetics (Haslbeck *et al.* 2005).

Diabetic retinopathy Diabetic retinopathy, which is classified into non-proliferative diabetic retinopathy and proliferative diabetic retinopathy, is characterized by retinal neovascularization, vascular occlusion, angiogenesis, loss of pericytes from retinal capillaries, increased retinal capillary permeability, thickening of the capillary basement membrane and infarction affecting the retina of the eye. This condition (mainly proliferative diabetic retinopathy) is a leading cause of blindness in people of the working age. A number of interconnecting biochemical pathways (e.g. increased polyol pathway flux, accelerated AGEs formation, oxidative stress, increased expression of various growth factors, activation of the renin-angiotensin-aldosterone system, hemodynamic changes, and activation of diacylglycerol-protein kinase C pathway) have been proposed as potential links between hyperglycaemia and diabetic retinopathy (Tarr *et al.* 2013).

Increased levels of pentosidine and CML, the glycoxidation products, have been detected in eyes of patient

with diabetic retinopathy, suggesting that both glycation and oxidation may contribute to the onset and progression of retinopathy (Endo *et al.* 2001; Nakamura *et al.* 2003). Formation of AGEs has been reported in different eye compartments such as vitreous, inner retina, retinal pericytes, and retinal pigment epithelium. Cross-linking of collagen fibrils by AGE adducts in vitreous leads to their dissociation from hyaluronan and resulting destabilization of the gel structure. Moreover, AGEs on vitreous collagen are linked to light exposure-mediated depolymerization of hyaluronan, which is a key component of the liquefaction process leading to proliferative diabetic retinopathy (Katsumura *et al.* 2004). Furthermore, increased levels of protein carbonyls have been found in vitreous of patients suffering proliferative diabetic retinopathy (Loukovaara *et al.* 2014). Accumulation of AGEs in the inner retina of diabetics, mainly within the collagenous matrix of the lamina cribrosa, has been described. AGE-mediated cross-linking of the lamina cribrosa, which supports ganglion cell axons, may reduce flexibility and perhaps induce age-related optic nerve damage (Albon *et al.* 1995; Albon *et al.* 2000). AGE-induced cross-linking of proteins in the vessel wall increases vascular stiffness and modification of extracellular matrix proteins decreases retinal pericyte adherence. AGEs are toxic to retinal pericytes possessing AGE receptors, because AGE-RAGE binding activates a variety of signalling pathways, leading to increased oxidative stress and synthesis of local growth factors, cytokines and adhesion molecules (Singh *et al.* 2014). Retinal pigment epithelium, a highly oxygenated and glucose-enriched region, is highly susceptible to lipid peroxidation due to the high content of polyunsaturated fatty acids. Lipid peroxidation leads to the formation of reactive aldehydes (e.g. acrolein, malondialdehyde, 4-hydroxynonenal), which are in turn able to interact with proteins to form stable advanced lipoxidation end-products (Januszewski *et al.* 2003). Moreover, retinal pericytes accumulate AGEs negatively influencing their cell function and survival during experimental diabetes in animal models (Yamagishi *et al.* 2005).

Diabetic cataract Cataract, a major cause of blindness in the world, is characterized by the loss of lens transparency. Progression of this disease is increased diabetic patients and hyperglycaemia leading to the formation of coloured AGEs is thus one of the risk factors for cataract development. Also sunlight (mainly UVA-visible light) constitutes a risk factor for cataract development, underlying the importance of photo-processes that take place in the eye (Avila *et al.* 2012). Post-translational modifications that occur with aging are thought to be one of the causative factors in human cataract development because of their effects on crystallin structure and interactions. Several post-translational modifications altering crystallin stability, solubility, and function have already been identified in human lenses, including glycation, deamidation, oxidation of Met, Trp, and Tyr, disulphide bonding formation, transglutaminase-mediated cross-linking, methylation, phosphorylation, and truncation of crystallins (Fan *et al.* 2006; Hains and Truscott 2007; Asomugha *et al.* 2010). Among other mechanisms significantly contributing to the cataract development are the polyol pathway (increased activity of aldose reductase), oxidative-nitrosative stress, poly(ADP-ribose) polymerase activation, and protein kinase C activation (Obrosova *et al.* 2010).

A wide range of AGEs including pentosidine (Kessel *et al.* 2002), glucosepane (Biemel *et al.* 2002), argpyrimidine (Padayatti *et al.* 2001; Kessel *et al.* 2002), methylglyoxal-lysine dimer (Degenhardt *et al.* 1998), and CML (Franke *et al.* 2003) has been reported in human eye lens. AGEs induce irreversible changes in lens proteins such as protein aggregation and conformational changes ultimately leading to the light scattering, decrease in eye lens transparency and vision loss (Nagaraj *et al.* 2012). Moreover, AGEs have been described as photosensitizers when they are exposed to UVA-visible light at low oxygen concentration (5%), which is the physiological condition of the eye lens (Avila *et al.* 2010). In the case of the protein-bound AGEs, the sensitizing damage is circumscribed to the nearby space surrounding the sensitizer (Avila *et al.* 2008). Generation of ROS during photoxidation reactions proceeds via two mechanisms, known as type I and type II. In the type I mechanism, the excited photosensitizer can interact directly with the substrate and/or solvent via an electron transfer reaction or hydrogen transfer generating radicals, which rapidly react with oxygen molecules producing ROS (e.g. superoxide radical, hydrogen peroxide, hydroxyl radical), capable of oxidizing a variety of biomolecules. In the type II, the excited photosensitizer interacts with oxygen molecules generating singlet oxygen ($^1O_2$) through an energy transfer process. The singlet oxygen-mediated photooxidative processes are often more efficient than radical processes due to the higher diffusibility of $^1O_2$ and the higher reaction rate constants with substrates (Ochsner 1997). Several studies have supported the idea that type I photosensitizing mechanism is predominant for AGEs at the low oxygen concentration found in the lens, in which the main process is the direct interaction between triplet AGEs and reactive amino acids within the proteins. This photo-process leads to the cross-linking of lens proteins mainly through radical reactions (Avila *et al.* 2008, 2012; Fuentealba *et al.* 2009). The amino acids more prone to generate radical species by a type I mechanism, giving rise to protein dimers, are tryptophan and tyrosine (Avila *et al.* 2008). Simultaneously with protein cross-linking, oxidation of amino acids residues (assessed as protein carbonyl content) and peroxide formation proceed (Fuentealba *et al.* 2009). However, production of $^1O_2$, which can cause depletion of antioxidant defence of the eye lens (Argirova and Breipohl 2002) as well

as impairment in proteasome activity, has been reported (Zetterberg *et al.* 2003).

2.8 *Consequences of oxidative protein damage and related diseases*

A protein radical can: (1) be immediately and fully repaired by direct reaction with an antioxidant; (2) react with oxygen molecule to form the corresponding peroxyl radical; or (3) undergo intramolecular long-range electron transfer to relocate the free electron to another amino acid residue (Gebicki *et al.* 2010). Oxidized derivatives of sulphur-containing amino acid residues can be reduced (Vogt 1995; Stadtman 2004), while repair of carbon-centered amino acid radicals carried out by ascorbate, urate and to a lesser extent also by glutathione can be accompanied by alterations in the stereochemistry of the intermediate amino acid(s) radical (Gebicki *et al.* 2010; Domazou *et al.* 2012). Instead, the damaged proteins are targeted to degradation to amino acid constituents by the action of various endogenous proteases, including cathepsin C, calpain, trypsin, and especially the 20S proteasomes (Jung *et al.* 2013), whose activity is also under metabolic control by diverse regulatory factors, including the concentrations of enzyme substrates, ubiquitinylation and various inhibitors (e.g. cross-linked proteins, glycation/glycoxidation protein conjugates) (Davies 2001; Grune and Davies 2003). Decrease in the efficiency of proteolysis causes their accumulation in the cellular content, which can lead to disruption of cellular function either by loss of catalytic and structural integrity or by interruption of regulatory pathways. The intracellular accumulation of oxidized forms of proteins is a complex function of pro-oxidants (e.g. ROS generation, metals), antioxidant activities (i.e. protective antioxidant system), and the concentrations and activities of the proteases that degrade the oxidized proteins and is dictated by prevailing environmental, genetic, and dietary factors (Berlett and Stadtman 1997; Davies 2001). For example, as stated above, some oxidized proteins (e.g. cross-linked proteins) can become more resistant to proteolysis and thus can contribute to their accumulation in the organism. Moreover, they can also inhibit the ability of proteases to degrade the oxidized forms of other proteins (Friguet *et al.* 1994; Grune and Davies 2003). Generally, biochemical consequences of protein oxidative modifications, which may play a key role in the pathogenesis of various diseases, include the loss/gain of enzymatic activity (e.g. isocitratelyase, creatine kinase BB, superoxide dismutase, carbonic anhydrase III vs. protein kinase C), loss of protein function (e.g. fibrinogen/fibrin clotting), loss of protease inhibitor activity (e.g. α1-antitrypsin, α2-macroglobulin), protein aggregation (e.g. α-synuclein, prion protein, α-crystalline, LDL, immunoglobulin G, amyloid protein), enhanced susceptibility to proteolysis (e.g. iron-responsive element-binding protein 2, glutamine synthetase, hypoxia-induced factor 1α), diminished susceptibility to proteolysis, abnormal cellular uptake (e.g. LDL), modified gene transcription (e.g. SoxR protein, IκB), and increased immunogenicity (e.g. 4-hydroxynonenal- and acrolein-LDL, ovalbumin) (Shacter 2000; Balafanova *et al.* 2002; Nguyen and Donaldson 2005; Nagaraj *et al.* 2012).

In addition, the generation of protein oxidation products in the organism and consequently their accumulation and action is closely connected with the development of many age-related diseases including atherosclerosis and cardiovascular diseases (Elahi *et al.* 2009), neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's diseases (Gella and Durany 2009; Jomova *et al.* 2010; Martinez *et al.* 2010; Sorolla *et al.* 2010; Tunez *et al.* 2011; Miotto *et al.* 2014), amyotrophic lateral sclerosis (Niebroj-Dobosz *et al.* 2004), diabetes mellitus and metabolic syndrome (Lyons 1995; Cohen and Tong 2010; Whaley-Connell *et al.* 2011), rheumatoid arthritis (Gelderman *et al.* 2007), cataractogenesis (Yanshole *et al.* 2013; Linetsky *et al.* 2014), progeria (Trigueros-Motos *et al.* 2011), Werner's syndrome (Harrigan *et al.* 2007), carcinogenesis (Pan *et al.* 2009; Klaunig *et al.* 2010), acute respiratory distress syndrome (Manzanares *et al.* 2007; Sarker *et al.* 2011), muscular dystrophy (Tidball and Wehling-Henricks 2007; Iwasaki *et al.* 2013), cystic fibrosis (Kettle *et al.* 2004; Starosta *et al.* 2006; Thomson *et al.* 2010), essential hypertension (Simic *et al.* 2006), and many others. In some of these diseases, more than one kind of oxidative protein modification has been demonstrated. A causative link between oxidative damage and aging is almost universally accepted (Stadtman 2004; Romano *et al.* 2010). However, serious doubts concerning the oxidative stress theory of aging have been recently raised (Gems and Doonan 2009; Perez *et al.* 2009; Blagosklonny 2010; Lapointe and Hekimi 2010; Pun *et al.* 2010).

Description of the mechanisms involved in the pathogenesis of all the above-mentioned diseases as a result of the protein oxidation modifications would highly exceed the extent of this review. Therefore, a causative role of protein oxidation in the development of Huntington's disease is described in detail as an example of such modification. Till date, 18 carbonylated and oxidized proteins have been identified in human striatum of patients suffering from Huntington's disease (Sorolla *et al.* 2008; Sorolla *et al.* 2010; Fox *et al.* 2011). Oxidation and the resulting inactivation and/or degradation of important proteins can explain the impairment of several metabolic pathways observed in Huntington's disease (Sorolla *et al.* 2012). Energy deficiency described in this disease can be explained by oxidative damage of enzymes involved in energy metabolism and ATP synthesis (e.g. enolase, glyceraldehyde-3-phosphate

dehydrogenase, pyruvate kinase, citrate synthase, aconitase, creatine kinase, subunit 2 of cytochrome b-c1-complex III, and the alpha subunit of ATP synthase). Oxidation of several heat shock proteins (e.g. HSP90, HSC71 and TCP-1) and transitional endoplasmic reticulum ATPase can account for the impairment of protein folding and degradation. Oxidation of two enzymes involved in the vitamin B6 metabolism (i.e. pyridoxal kinase and antiquitin 1) could result in decreased availability of pyridoxal phosphate, a necessary cofactor in transamination reactions, the kynurenine pathway and the synthesis of glutathione, GABA, dopamine and serotonin, all of which have a key role in the pathology of this disease (Sorolla *et al.* 2008, 2010). Moreover, oxidation products of N-terminal fragments from mutant huntingtin are more prone to form soluble oligomeric species that are potentially more toxic than aggregates or inclusion bodies (Sanchez *et al.* 2003; Arrasate *et al.* 2004). This idea may also apply to other neurodegenerative diseases (such as Alzheimer's disease), where there is evidence that soluble oligomers may be particularly important for toxicity (Shankar *et al.* 2008; Sanchez *et al.* 2003).

2.9 *Determination of protein oxidative modifications*

Due to a complexity of the protein oxidation process there is no universal method for its powerful monitoring and assessment. A wide range of techniques is available to investigate oxidative posttranslational modifications including gel-based and non-gel-based separation approaches to be combined with sophisticated methods of detection, identification, and quantification of these modifications (Charles *et al.* 2014; Ckless 2014). Each method of investigation provides different information and possesses its advantages as well as disadvantages. The identification and mapping of the post-translational modifications in proteins have been dramatically improved during the last decade due to increases in the sensitivity, speed, accuracy and resolution of mass spectrometry (MS) (Cerny *et al.* 2013; Tveen-Jensen *et al.* 2013; Ghesquiere and Gevaert 2014; Raftery 2014; Thornalley and Rabbani 2014; Vasil'ev *et al.* 2014). A great attention has been also dedicated to enrichment and separation of post-translationally modified proteins (Cerny *et al.* 2013). The methodological approaches can be divided to those measuring the levels of reactive species and those measuring the damage that they cause (Halliwell 2001; Hawkins *et al.* 2009).

The first approach includes methods for detection and/or quantification of radical and non-radical intermediates. However, these methods are of limited applicability to cells and organisms and therefore most clinical studies focus on the measurement of the end products of damage (Halliwell 2001). Free radicals can be detected either by direct methods based on detection techniques such as UV/visible spectroscopy, resonance Raman spectroscopy, conductivity, and electron paramagnetic resonance (EPR) spectroscopy (Irwin *et al.* 1999; Hawkins *et al.* 2009). Indirect methods such as EPR spin trapping (Kleschyov *et al.* 2007; Lardinois *et al.* 2008; Hawkins and Davies 2014) and immuno-spin trapping (Hawkins *et al.* 2009; Gomez-Mejiba *et al.* 2014) are also applicable. Spectroscopic detection of protein radicals is only usable for some amino acids and requires the use of fast kinetic techniques. For instance, radiolysis technique can be successfully used to explore the mechanisms of free radical modifications in proteins (Houee-Levin and Bobrowski 2013). At present, various commercial kits to measure protein radicals generated by the presence of RONS are readily available, e.g. those combining the EPR technology with the enzyme-linked immunosorbent assay (ELISA) as detection. Also non-radical intermediates can be used as biomarkers of oxidative protein modifications, e.g. quantification of the hydroperoxides using several separation and detection techniques (Bou *et al.* 2008; Morgan *et al.* 2008; Grintzalis *et al.* 2013; Santas *et al.* 2013), chloramines by high-performance liquid chromatography with electrospray ionization detection (HPLC-ESI-MS) (Raftery 2007), or sulphenic acid using Western blotting with chemiluminescence detection (Saurin *et al.* 2004).Various strategies for the detection of protein sulphenic acid are described in recent reviews (Kettenhofen and Wood 2010; Burgoyne and Eaton 2011; Charles *et al.* 2014; Gupta and Carroll 2014).

The second approach involves determination of changes in parent amino acid residues by quantification of the loss of specific amino acids. Hawkins *et al*. have described various methods of standard amino acid analysis by HPLC with spectrophotometric, fluorimetric, or mass spectrometry (MS) detectionin detail (Hawkins *et al.* 2009). Various determinations of thiols and disulphides are summarized in recent reviews (Burgoyne and Eaton 2011; Winther and Thorpe 2014). The other possibility is to detect and quantify specific oxidation products. Modification of aromatic side chains can be used as a sensitive marker of protein oxidation and cellular oxidative damage, as these moieties are readily oxidized and often yield stable products (mentioned above) that are readily quantified (Dalle-Donne *et al.* 2006). Three major methods involving gas chromatography with MS detection, HPLC with different types of detection, and immunological methods (Western blotting/ELISA) have been developed to quantify these products (Hawkins *et al.* 2009). One of the most harmful irreversible oxidative protein modifications is protein carbonylation. Protein carbonyls are formed not only by ROS-mediated protein damage but also by lipid peroxidation (i.e. covalent binding of aldehyde end products of lipid peroxidation such as malondialdehyde and 4-hydroxynonenal) (Yarian *et al.* 2005; Grintzalis *et al.* 2013; Li *et al.* 2013; Spickett 2013; Zhang *et al.* 2013; Vasil'ev *et al.* 2014) and by glycation/glycoxidation

(Akagawa *et al.* 2005; Villaverde and Estevez 2013; Fedorova *et al.* 2014; Thornalley and Rabbani 2014). Their measurements are often performed to assess the extent of oxidative stress in the context of cellular damage, aging and different age-related disorders (Madian and Regnier 2010; Baraibar *et al.* 2013; Fedorova *et al.* 2014; Thornalley and Rabbani 2014). Various analytical techniques are available to detect and quantify protein-bound carbonyls. Several current reviews are dedicated to this actual topic (Madian and Regnier 2010; Yan and Forster 2011; Baraibar *et al.* 2013; Cerny *et al.* 2013; Fedorova *et al.* 2014). Briefly, there are three categories of methods to determine reactive carbonyls: biochemical and immunological techniques such as immunoblotting and ELISA to provide global information on the modified proteins and carbonylation levels, spectrophotometric and chromatographic assays to determine the total protein carbonyl content, and MS for identification of the modified proteins (Madian and Regnier 2010; Baraibar *et al.* 2013; Fedorova *et al.* 2014). In addition, other types of ROS-mediated damage protein products are used for assessment of post-translational protein modifications, e.g. the determination of methionine sulphoxide (Ghesquiere and Gevaert 2014), dityrosine (DiMarco and Giulivi 2007), 3-nitrotyrosine (Nuriel *et al.* 2008; Sharov *et al.* 2008; Diaz-Moreno *et al.* 2013; Feeney and Schoneich 2013;), chloramine derivatives (Mouls *et al.* 2009), various mono- or di-hydroxyphenylalanine (DOPA) derivatives (Sharov *et al.* 2008), or cross-links and aggregates and their degraded products (Leavell *et al.* 2004; Lee 2008; Leitner *et al.* 2010), advanced glycation end products such as determination of pentosidine and argpyrimidine by HPLC with fluorimetric detection (Slowik-Zylka *et al.* 2004; Gomes *et al.* 2005; Scheijen *et al.* 2009), CEL and CML by liquid chromatography–tandem mass spectrometry (LC-MS/MS) (Sternberg *et al.* 2010; Kuang *et al.* 2014), or precursors of AGEs such as 3-deoxyglucosone, glyoxal, or methylglyoxal that can be quantified by HPLC method with fluorimetric detection (Hurtado-Sanchez Mdel *et al.* 2012) or by ultra-performance liquid chromatographywith electrospray ionization time-of-flight mass spectrometry (UPLC-ESI-TOF-MS) (Min *et al.* 2012). In addition, there are various commercial kits available to quantify different stable biomarkers of oxidative posttranslational modifications, e.g. determination of protein carbonyls, using different types of detection (i.e. spectrophotometric, fluorimetric, immunoblotting, or ELISA), detection of 3-nitrotyrosine, total AGEs and specific AGEs formation such as CEL, CML and methylglyoxal using ELISA, or 3-nitrotyrosine and CML by immunoblotting.

2.10 *Inter-relationships in oxidative damage of organism*

As it has been described above, RONS at high concentrations are able to attack and damage virtually all important biomolecules. The inter-relationship among oxidative damage of proteins and other important biomolecules such as lipids and nucleic acid is displayed in figure 4. Proteins may not be attacked directly by RONS but they can be damaged by lipid peroxidation products (e.g. HNE, MDA). If unrepaired, also the oxidized forms of DNA and RNA can lead to transcription/translation errors, and therefore to the

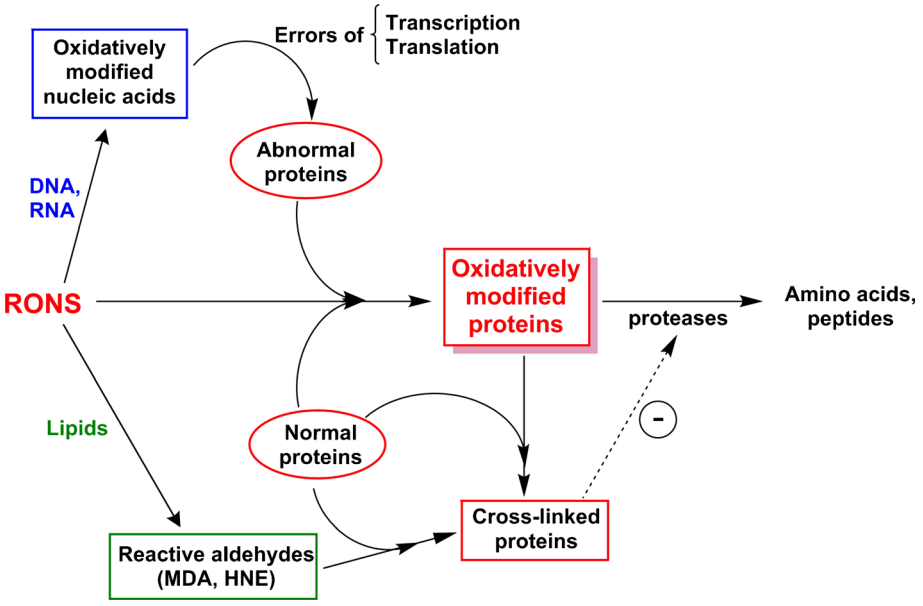

Figure 4. Interrelationships among RONS-dependent modifications of lipids, nucleic acids and proteins in protein degradation.

synthesis of abnormal proteins that are prone to RONS-mediated oxidation (Stadtman 2004). Two cellular proteolytic systems are responsible for the removal of oxidized and modified proteins, especially those of the proteasome and organelles, mainly the autophagy-lysosomal systems (Sitte *et al.* 1998; Jung *et al.* 2006). However, protein aggregates of highly oxidized and cross-linked proteins (such as lipofuscin) are able to inhibit the proteasomal degradation of oxidized proteins. Thus, increased protein oxidation and oxidation-dependent impairment of proteolytic systems lead to an accumulation of oxidized proteins and finally to the formation of non-degradable protein aggregates (Sitte *et al.* 2000; Hohn *et al.* 2011). Accordingly, the cellular homeostasis cannot be maintained and the cellular metabolism is negatively affected (Jung *et al.* 2006; Hohn *et al.* 2014).For example, oxidized apoprotein B100, the only apoprotein of low density lipoprotein particles (LDL), is no longer recognized by LDL receptor and is removed from the circulation via phagocytosis mediated by scavenger receptors present on monocytes and macrophages. The oxidized LDL then mediates transformation of these macrophages to lipid-laden foam cells, which is the beginning of atherosclerotic process (Lusis 2000).

3. Conclusions

The oxidative modification of proteins caused especially by RONS is very complicated process, which plays not only a key role in numerous physiological processes within cells but is also implicated in the development/progression of many human diseases as well as physiological process of aging. The protein oxidation and its impact on living organisms including the human body is extensively studied from different perspectives in order to reduce generation of oxidatively modified proteins and to moderate their deleterious manifestation. This review brought a brief overview of the protein oxidation focused on the oxidation, including the non-enzymatic glycoxidation, as an important factor of protein damage.

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