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Review Article

Pathophysiological importance of aggregated damaged proteins

Annika Höhn, Tobias Jung, Tilman Grune *

Department of Nutritional Toxicology, Institute of Nutrition, Friedrich-Schiller-University Jena, 07743 Jena, Germany

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ABSTRACT

Reactive oxygen species (ROS) are formed continuously in the organism even under physiological conditions. If the level of ROS in cells exceeds the cellular defense capacity, components such as RNA/DNA, lipids, and proteins are damaged and modified, thus affecting the functionality of organelles as well. Proteins are especially prominent targets of various modifications such as oxidation, glycation, or conjugation with products of lipid peroxidation, leading to the alteration of their biological function, nonspecific interactions, and the production of high-molecular-weight protein aggregates. To ensure the maintenance of cellular functions, two proteolytic systems are responsible for the removal of oxidized and modified proteins, especially the proteasome and organelles, mainly the autophagy–lysosomal systems. Furthermore, increased protein oxidation and oxidation-dependent impairment of proteolytic systems lead to an accumulation of oxidized proteins and finally to the formation of nondegradable protein aggregates. Accordingly, the cellular homeostasis cannot be maintained and the cellular metabolism is negatively affected. Here we address the current knowledge of protein aggregation during oxidative stress, aging, and disease.

Contents

Introduction

Free radicals are defined as molecules or atoms containing one or more unpaired electrons in an atomic orbital. The presence of an unpaired electron results in common properties shared by radical species. Several radicals are unstable and highly reactive. They can either donate or accept an electron from other molecules, therefore serving as oxidants or reductants. Important oxygen-containing free radicals derived by the partial reduction of oxygen are the superoxide anion radical ($O_2^{\bullet -}$) and the hydroxyl radical ($HO^{\bullet}$). In addition to radicals, reactive oxygen species (ROS)[1] also include a number of nonradical molecular species such as singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2). In biological systems,

Abbreviations: Aβ, β-amyloid; AGE, advanced glycation end product (here: proteins modified by AGEs); Atg, autophagy-related gene; CMA, chaperone-mediated-autophagy; 3-DG, 3-deoxyglucosone; FIP200, focal adhesion kinase family-interacting protein of 200 kDa; IP3, inositol trisphosphate; JAK, Janus kinase; LC3, microtubule-associated protein light-chain-3; NF-κB, nuclear factor "κ-light-chain enhancer" of activated B cells; PA28, proteasome activator 28 kDa; PA700, proteasome activator 700 kDa; PE, phosphatidylethanolamine; PHF, paired helical filament; polyQ, polyglutamine; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; ULK1/2, UNC-51-like kinase 1/2; UPS, ubiquitin–proteasome system; UVRAG, ultraviolet irradiation resistance-associated gene

* Corresponding author. Fax: +49 3641949672.

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ROS are often derived from superoxide, which is generated by adding a single electron to molecular oxygen and is only moderately reactive itself. Superoxide can rapidly be converted into hydrogen peroxide, ultimately yielding the highly reactive hydroxyl radical in the presence of reduced iron (Fe^{2+}) or copper (Cu^{+}) via the Fenton reaction. In the aerobic metabolism the generation of ROS is an inevitable event of metabolic and energy-transferring processes. ROS are derived either from exogenous sources such as exposure to X-rays, environmental pollutants, ozone, cigarette smoke, drugs/pharmaceuticals, alcohol, pesticides, and industrial solvents, or from essential endogenous metabolic processes (Fig. 1). ROS formation occurs continuously in the cells as a consequence of both enzymatic and nonenzymatic reactions. A number of ROS sources are known in mammalian cells, including the mitochondria (mainly the respiratory chain, but also monoamino oxidase, α-ketoglutarate dehydrogenase, and glycerol phosphate dehydrogenase [1]) and the endoplasmic reticulum (mainly cytochrome P-450 enzymes, endoplasmic reticulum (ER) oxidoreductin 1, and diamine oxidase [2]). In peroxisomes H_2O_2 is a byproduct of fatty acid β-oxidation [3] and also the synthesis of fatty acids can produce $O_2^{\bullet-}$ via acyl-CoA oxidase-catalyzed electron transfer to oxygen [4]. Cytochrome P-450 enzymes, whose function is to dispose of foreign substances, are also able to reduce molecular oxygen to superoxide. Furthermore, H_2O_2 can be produced by the oxidation of lysine side chains by the enzyme lysyl oxidase, which catalyzes the cross-linking of collagen and elastin fibers in the extracellular matrix [5].

It should be kept in mind that ROS are both physiological intermediates and mediators of oxidative stress. At low levels, ROS participate in several physiological mechanisms such as cellular signaling, gene expression, and pathogen elimination [6]. However, at high levels ROS can cause irreversible and detrimental cellular damage. Yet, cells are not defenseless and complex antioxidant protection mechanisms have evolved to protect cells from ROS, including enzymatic and nonenzymatic systems. Antioxidant enzymes include superoxide dismutases (SODs), catalase, glutathione peroxidases, and peroxiredoxins. But although very important to regulate the levels of ROS in cells, antioxidant compounds and enzymes are not fully effective in preventing oxidative stress and damage. Closely related to ROS are the reactive nitrogen species (RNS). RNS are various nitric oxide ($^{\bullet}NO$)-derived compounds such as nitroxyl anion (NO^{-}) and nitrosonium cation (NO^{+}), higher oxides of nitrogen, *S*-nitrosothiols, and dinitrosyl iron complexes. RNS also play an important role in redox biology by acting as important intracellular signaling molecules but are in the same way able to cause cellular damage. $^{\bullet}NO$ per se is not very reactive, but the damaging effect is due to its reaction with $O_2^{\bullet-}$ leading to the formation of the highly reactive peroxynitrite ($ONOO^{-}$). This product is a strong oxidant with a formation rate that has been determined to be three times faster than the scavenging of $O_2^{\bullet-}$ by SOD [7]. Oxidative/nitrosative stress represents an imbalance between the formation of reactive oxygen and nitrogen species and their elimination by various reducing or antioxidant systems that destroy reactive intermediates and prevent or repair the resulting damage. In the following the general summarizing terms "ROS" (including ROS and RNS) and "oxidative stress" will be used. The term "oxidative stress" itself was first used by Helmut Sies who described it as "an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage" [8]; in 2006 this definition was extended to include the "disruption of redox signaling" [9]. Oxidative stress results in direct or indirect ROS-mediated cellular damage and has been implicated in carcinogenesis [10], neurodegenerative diseases [11], diabetes [12], atherosclerosis, and aging [10,13].

Targets of ROS include all kinds of molecules in the body; therefore, oxidative stress causes irreversible oxidative damage to DNA bases, lipids, and proteins, interfering with vital cellular functions. Because proteins are most abundant in cells they are major targets for oxidative stress and modifications in cells.

Protein oxidation and formation of aggregates

Critical factors determining the degree of protein oxidation are the location of the protein, the protein structure, as well as location and concentration of oxidants and antioxidants. Oxidative protein damage in vivo can impair the functioning of receptors, transport proteins, and enzymes, with effects on various cellular downstream processes. Furthermore, oxidized proteins may be identified as foreign by the immune system triggering antibody formation and possibly autoimmunity [14]. Proteins with modified moieties are able to diffuse or be transported to other cellular parts potentiating the damaging effect [15]. Moreover, secondary damage of other biomolecules can result from protein oxidation as well, e.g., DNA damage as a result of oxidative damage of DNA repair enzymes and histones.

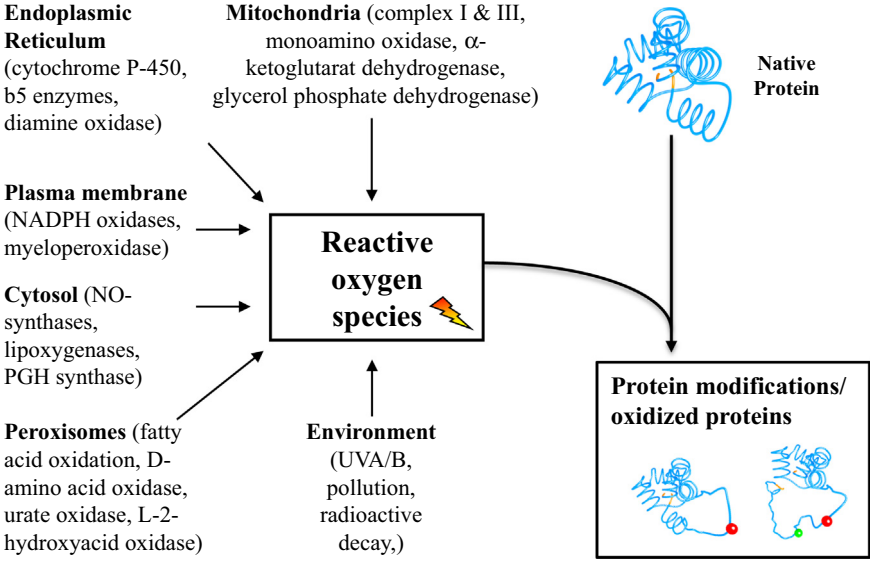

Fig. 1. Endogenous and exogenous sources of ROS and protein oxidation, according to [1,2,293–296].