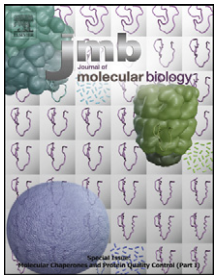
Review



Protein Quality Control under Oxidative Stress Conditions

Jan-Ulrik Dahl, Michael J. Gray and Ursula Jakob

Department of Molecular, *Cellular, and Developmental Biology, University of Michigan, Ann Arbor, MI 48109-1048, USA*

Correspondence to Ursula Jakob: *ujakob@umich.edu*
http://dx.doi.org/10.1016/j.jmb.2015.02.014
Edited by J. Buchner

Abstract

Accumulation of reactive oxygen and chlorine species (RO/CS) is generally regarded to be a toxic and highly undesirable event, which serves as contributing factor in aging and many age-related diseases. However, it is also put to excellent use during host defense, when high levels of RO/CS are produced to kill invading microorganisms and regulate bacterial colonization. Biochemical and cell biological studies of how bacteria and other microorganisms deal with RO/CS have now provided important new insights into the physiological consequences of oxidative stress, the major targets that need protection, and the cellular strategies employed by organisms to mitigate the damage. This review examines the redox-regulated mechanisms by which cells maintain a functional proteome during oxidative stress. We will discuss the well-characterized redox-regulated chaperone Hsp33, and we will review recent discoveries demonstrating that oxidative stress-specific activation of chaperone function is a much more widespread phenomenon than previously anticipated. New members of this group include the cytosolic ATPase Get3 in yeast, the *Escherichia coli* protein RidA, and the mammalian protein α2-macroglobulin. We will conclude our review with recent evidence showing that inorganic polyphosphate (polyP), whose accumulation significantly increases bacterial oxidative stress resistance, works by a protein-like chaperone mechanism. Understanding the relationship between oxidative and proteotoxic stresses will improve our understanding of both host–microbe interactions and how mammalian cells combat the damaging side effects of uncontrolled RO/CS production, a hallmark of inflammation.

The Origin of Oxidative Stress

Reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^{\bullet}OH$) are metabolic by-products, which occur naturally in all organisms that live an aerobic lifestyle. They are constantly produced during electron transfer in the respiratory chain [1], by enzymes such as NADPH oxidases [2,3], and in organelles such as the peroxisomes [4]. Non-physiologically low levels of ROS negatively affect cell growth, development, and differentiation [5–7], illustrating the importance of ROS as second messengers that control metabolic processes and signaling pathways (Fig. 1) [8]. Non-physiologically high levels of ROS, on the other hand, can cause irreversible oxidative modifications of virtually all cellular macromolecules, including lipids, DNA, and proteins (Fig. 1) [9]. Maintaining redox homeostasis requires a concerted cellular effort, involving expression of a variety of different ROS-detoxifying enzymes (e.g., superoxide dismutase, peroxiredoxin, and catalase), oxidoreductases of the thioredoxin (Trx) and glutaredoxin (Grx) systems, NADPH-regenerating systems such as the nicotinamide nucleotide transhydrogenase, and the production of the small redox-buffering tripeptide glutathione (GSH) [10]. Together, these systems keep cytosolic protein thiols reduced and protect cells against the accumulation of toxic oxidants (Fig. 1) [5,11].

However, even the best systems sometimes fail. When they do, such as during aging, age-related neurodegenerative diseases (e.g., Parkinson's disease), or metabolic diseases (e.g., diabetes) [12], ROS begin to accumulate in the cell, causing cells to experience a stress condition commonly known as oxidative stress. Oxidative stress can be caused by a variety of different mechanisms, including defects in specific antioxidant or redox-maintaining systems,

ROS production during host defense, UV light, gamma and X-rays, pollutants and smoke, or due to metal-catalyzed Fenton reactions [13]. All of these processes produce free radicals, capable of oxidizing cellular structures [14–16]. Apart from lipid peroxidation and DNA damage, ROS are especially known for their high reactivity toward sulfur-containing amino acids and metal-containing cofactor sites in proteins, causing reversible and irreversible inactivation of many different proteins and representing a major threat toward the cellular proteome [17]. It is thought that oxidative damage to a cell's proteome contributes to the etiology of a variety of different human protein-folding diseases, including Alzheimer's, Parkinson's, and prion disease [18].

The Benefit of Oxidative Stress—ROS and RCS as Physiological Antimicrobials

Oxidative stress is not always a bad thing; in fact, production of high levels of ROS and the related reactive chlorine species (RCS) [17] plays an important physiological role in the innate immune response, where it provides a powerful strategy for killing invading pathogens [19]. When bacteria are taken up by neutrophils, NADPH oxidases localized in the phagosomal membrane catalyze the reduction of molecular oxygen to superoxide ($O_2^{\bullet -}$). After being rapidly dismuted to H_2O_2 by superoxide dismutases, myeloperoxidases convert H_2O_2 and chloride ions into the RCS hypochlorous acid (HOCl). HOCl is extremely reactive and bactericidal even at low micromolar concentrations [20], making it one of the most powerful physiological oxidants known (for a comprehensive overview, see Refs. [17] and [19]). Not surprisingly, HOCl is the active ingredient of household bleach and is one of the most commonly used disinfectants in medical, industrial, and domestic settings [21]. Once released into the phagosome, HOCl evokes a very rapid toxic effect on bacteria, contributing to the effective neutrophil-mediated killing of invading microbes [22–24].

In addition to the role of HOCl production in the antimicrobial action of neutrophils, HOCl might also be involved in controlling bacterial colonization of mucosal barrier epithelia, such as the airways and the intestine [25,26]. Epithelial cells express the enzyme dual oxidase (DUOX), a member of the nicotinamide adenine dinucleotide phosphate oxidase family. DUOX, like myeloperoxidase, has been suggested to convert peroxide into HOCl [27]. It is also possible, however, that the antimicrobial function of DUOX is primarily due to the production of H_2O_2, which is rapidly converted to the highly bactericidal hypothiocyanite by lactoperoxidases [154]. In either case, knockdown of the *duox* gene in the fly gut leads to increased bacterial colonization and a significantly increased rate of death caused by infections [27,28]. Duox$^{-/-}$ mice show a significant decrease of neutrophil invasion during the development of allergic asthma in a murine model and increased levels of pathogens that colonize the intestinal epithelial cells [29]. These results emphasize the physiological importance of oxidative stress in general and HOCl production, in particular, in

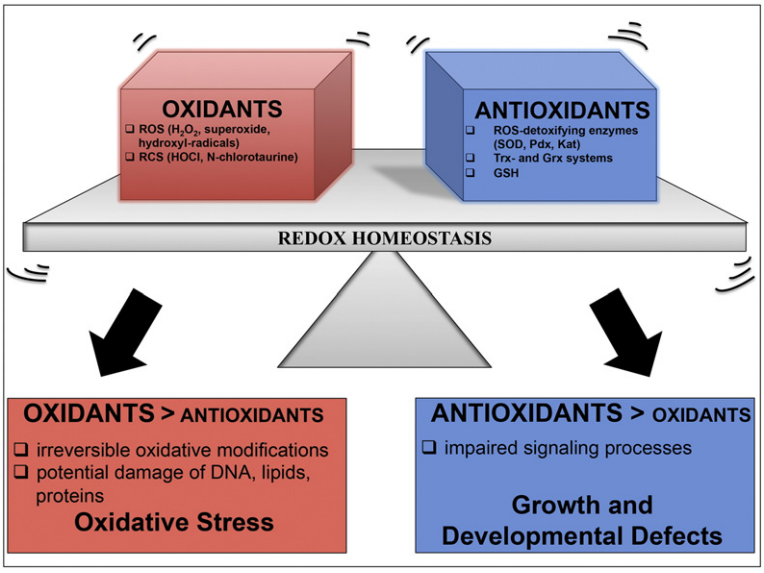


Fig. 1. Redox homeostasis—A balance between oxidants and antioxidants. ROS and RCS are constantly produced as by-products of cellular processes. They are involved as second messenger in signaling pathways, influencing a variety of different cellular processes. Antioxidant systems [including ROS-detoxifying enzymes, such as superoxide dismutase (SOD), peroxiredoxin (Prx), and catalase (Kat); oxidoreductases including the thioredoxin (Trx) and glutaredoxin (Grx) system; and the non-protein thiol glutathione (GSH)] work together to maintain a reducing environment and prevent accumulation of oxidants beyond physiological levels. However, defects in antioxidant systems or exposure to increased concentrations of RO/CS can shift this ratio. While accumulation of RO/CS causes widespread oxidative damage and is thought to be involved in aging and many age-related diseases, diminished levels of RO/CS affect growth, development, and differentiation.