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Review Article

Antioxidant responses and cellular adjustments to oxidative stress

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ABSTRACT

Redox biological reactions are now accepted to bear the Janus faceted feature of promoting both physiological signaling responses and pathophysiological cues. Endogenous antioxidant molecules participate in both scenarios. This review focuses on the role of crucial cellular nucleophiles, such as glutathione, and their capacity to interact with oxidants and to establish networks with other critical enzymes such as peroxiredoxins. We discuss the importance of the Nrf2-Keap1 pathway as an example of a transcriptional antioxidant response and we summarize transcriptional routes related to redox activation. As examples of pathophysiological cellular and tissular settings where antioxidant responses are major players we highlight endoplasmic reticulum stress and ischemia reperfusion. Topologically confined redox-mediated post-translational modifications of thiols are considered important molecular mechanisms mediating many antioxidant responses, whereas redox-sensitive microRNAs have emerged as key players in the posttranscriptional regulation of redox-mediated gene expression. Understanding such mechanisms may provide the basis for antioxidant-based therapeutic interventions in redox-related diseases.

Contents

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1. Introduction

Free radicals and oxidant species may behave as deleterious and toxic products, involved in cellular and tissular dysfunction. Overproduction of these species may result in DNA, lipid and protein damage. Nevertheless, low or moderate concentrations of reactive oxygen species (ROS) or reactive nitrogen species (RNS) are also involved in physiological responses as part of signaling processes and defense mechanisms against infectious agents. In fact, ROS protect the cell against ROS damage by inducing different antioxidant responses and re-establishing or maintaining redox homeostasis. For the sake of clarity in this review we will focus on endogenous antioxidant systems and the different factors involved in their regulation.

2. Glutathione and glutathione-related post-translational modifications

Antioxidant molecules are in fact nucleophilic and reductant molecules able to react with oxidants, which are generally electrophiles, giving them one or two electrons. Glutathione (GSH) is considered the most abundant molecule among endogenous antioxidants. GSH is a reduced peptide consisting of three-residues (γ-L-glutamyl-L-cysteinyl glycine) which can donate an electron with the consequence that two electron donating GSH molecules form oxidized GSSG. In humans, GSH is almost uniquely present in a quite high concentration (1–10 mM) which allows to scavenge ROS either directly or indirectly [1]. It can directly react with $O_2^{\bullet}$ and some other ROS, but its indirect ROS-scavenging functions, such as revitalizing other antioxidants, are likely more important; e.g. it can reduce dehydroascorbic acid which is formed in the reconversion of α-tocopheroxyl radical to α-tocopherol, a lipophilic chain breaking antioxidant, which interacts with the polyunsaturated acyl groups of lipids, stabilizes membranes and scavenges various reactive oxygen species and lipid oxy-radicals [2,3]. As an antioxidant it reacts with ROS, RNS and radicals produced in association with electron transport, xenobiotic metabolism and inflammatory responses [4,5]. GSH is synthesized from its constituent amino acids forming a tripeptide thiol and this synthesis requires two ATP-dependent steps (Fig. 1). The first and limiting synthesis is catalyzed by γ-glutamyl-cysteine ligase (GCL) and the second step mediated by GSH synthetase (GS). GCL is a heterodimeric enzyme composed by a heavy subunit, GCLc (73 kDa) with catalytic activity and a smaller one, GCLm (33 kDa) that has a regulatory role on the other subunit [6]. GSH homeostasis in the cell is not only regulated by its de novo synthesis, but also by other factors such as utilization, recycling and cellular export. This redox cycle is known as the GSH cycle and incorporates other important antioxidant, redox-related enzymes. Aerobic respiration may result in an increase in hydrogen peroxide, which will be metabolized by glutathione peroxidase (GPx) by converting 2 GSH molecules to its oxidized form (GSSG). GSH is recycled by the action of glutathione reductase (GR, see below). Moreover, GSH is also able to react with critical Cys residues in proteins, by forming mixed disulfides (see below). This is a labile process that can be reverted by glutathione S-transferase (GST). Another cellular mechanism used to prevent redox unbalance is exporting GSSG to the extracellular medium. In addition, the biosynthetic capacity to form

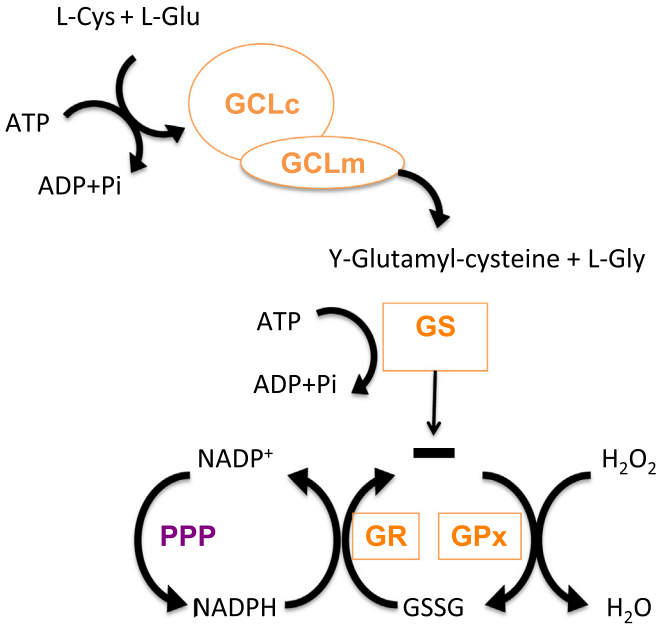

Fig. 1. GSH biosynthetic route and GSH cycle. GSH biosynthesis occurs in two different and ATP-dependen steps. The first and limiting step is carried out by GCL, formed by two subunits GCLc and GCLm. In this step L-Glu and L-Cys react to form γ-glutamyl-cisteine. GS is responsible of the second step, that joins L-Gly forming γ-glutamyl-cisteinyl-glicine (GSH). As well as aerobic respiration or other ROS sources increase H_2O_2, that should be metabolized, in this case GPx generating GSSG. This GSSG could be reduced to GSH again with the help of GR GR, creating a redox cycle, using as reducing agent NAPDH, from Penthoses Phosphate Pathway (PPP).

GSH is also regulated by allosteric mechanisms and substrate abundance. An excess of GSH in the cell produces a competitive inhibition in GCLc, while L-Cys is one of the limiting substrates [6,7].

Alterations in the ratio of the redox pair 2GSH/GSSG towards a more oxidized status form the biochemical basis of targeting redox-sensitive cysteine residues in proteins by generating mixed disulfides between the thiol and GSH [2,8]. However, the calculation and quantification of this ratio is not easy and depends on the detection method, the tissue of interest and the abundance of recycling enzymes such as GPx1 [9]. This post-translational modification, known as S-glutathionylation, is a reversible process, which has been extensively reviewed elsewhere [10,11]. S-glutathionylation may result in the activation or inactivation of protein function [12]. Thereby S-glutathionylation is able to modulate different cellular pathways, and affect gene expression profiles by affecting different transcription factors as Nrf2 (see below), or NF-κB. Although these mechanisms were initially proposed to be part of a protective pathway against other irreversible oxidative modifications [2,8], it was recently shown that S-glutathionylation of eNOS at Cys689 and Cys908 leads to eNOS uncoupling, diminished NO production, and enhanced oxidative stress and superoxide anion production [13]. Thus, S-glutathionylation may be a double-edged sword in the sense that it may promote antioxidant or pro-oxidant responses.