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Oxidative pathways of chemical toxicity and oxidative stress biomarkers in marine organisms

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ABSTRACT

The antioxidant system of marine organisms consists of low molecular weight scavengers and antioxidant enzymes which interact in a sophisticated network. Environmental pollutants can unbalance this system through closely related mechanisms, indirect relationships and cascade effects acting from pre-transcriptional to catalytic levels. Chemically-mediated pathways have the potential to greatly enhance intracellular formation of reactive oxygen species (ROS); at the same time, excessive levels of oxyradicals down-regulate xenobiotics metabolism, with important environmental implications for organisms exposed to chemical mixtures. Interactions between different classes of chemicals, generation of ROS and onset of oxidative stress conditions are partly modulated by changes in levels and functions of redox-sensitive signaling proteins and transcription factors. The Nrf2–Keap1 pathway still remains largely unexplored in marine organisms, despite the elevated degree of identity and similarity with homolog transcripts and proteins from different species. Recent evidences on transcriptional up-regulation of this system are consistent with the capability to provide a prolonged expression of ARE-regulated cytoprotective genes, and to efficiently switch off this mechanism when oxidative pressure decreases.

Although gene expression and catalytic activities of antioxidants are often measured as alternative biomarkers in monitoring biological effects of contaminants, conflicting results between molecular and biochemical responses are quite frequent. The links between effects occurring at various intracellular levels can be masked by non-genomic processes affecting mRNA stability and protein turnover, different timing for transcriptional and translational mechanisms, metabolic capability of tissues, post-transcriptional modifications of proteins, bi-phasic responses of antioxidant enzymes and interactions occurring in chemical mixtures. In this respect, caution should be taken in monitoring studies where mRNA levels of antioxidants could represent a snapshot of cell activity at a given time, not an effective endpoint of environmental pollutants.

1. The antioxidant network

Reactive oxygen species (ROS) are naturally produced during several cellular pathways of aerobic metabolism including oxidative phosphorylation, electron transport chains in mitochondria and microsomes, the activity of oxido-reductase enzymes producing ROS as intermediates or final products, or even immunological reactions such as active phagocytosis (Halliwell and Gutteridge, 2007). The main ROS generated by cellular metabolism are the singlet oxygen $^1O_2$, the superoxide anion (O_2^{-}), the hydrogen peroxide (H_2O_2) and the hydroxyl radical (HO•); these compounds can rapidly react to form other molecules like peroxynitrite (HOONO), hypochloric acid (HOCl), peroxyl radicals (ROO•) and alkoxyl radicals (RO•), to cite a few. Despite all these molecules are generally termed as ROS, they greatly differ in terms of cellular reactivity and potential to cause toxic insults to lipids, proteins and DNA (Regoli and Winston, 1999).

Under basal conditions, the adverse effects of oxyradicals are prevented by the antioxidant system, consisting of a wide array of low molecular weight scavengers and antioxidant enzymes which interact in a sophisticated network with both direct and indirect effects (Fig. 1). Scavengers neutralize ROS by direct reaction with them, thus being temporarily oxidized before being reconverted by specific reductases to the active form. Scavengers can act as antioxidants in the cytoplasm or are intended to arrest the propagation of lipid peroxidation reactions on the membranes. The most abundant cytosolic scavenger is reduced glutathione (GSH), a tripeptide (γ-glutamyl–cysteinyl glycine), which directly neutralizes

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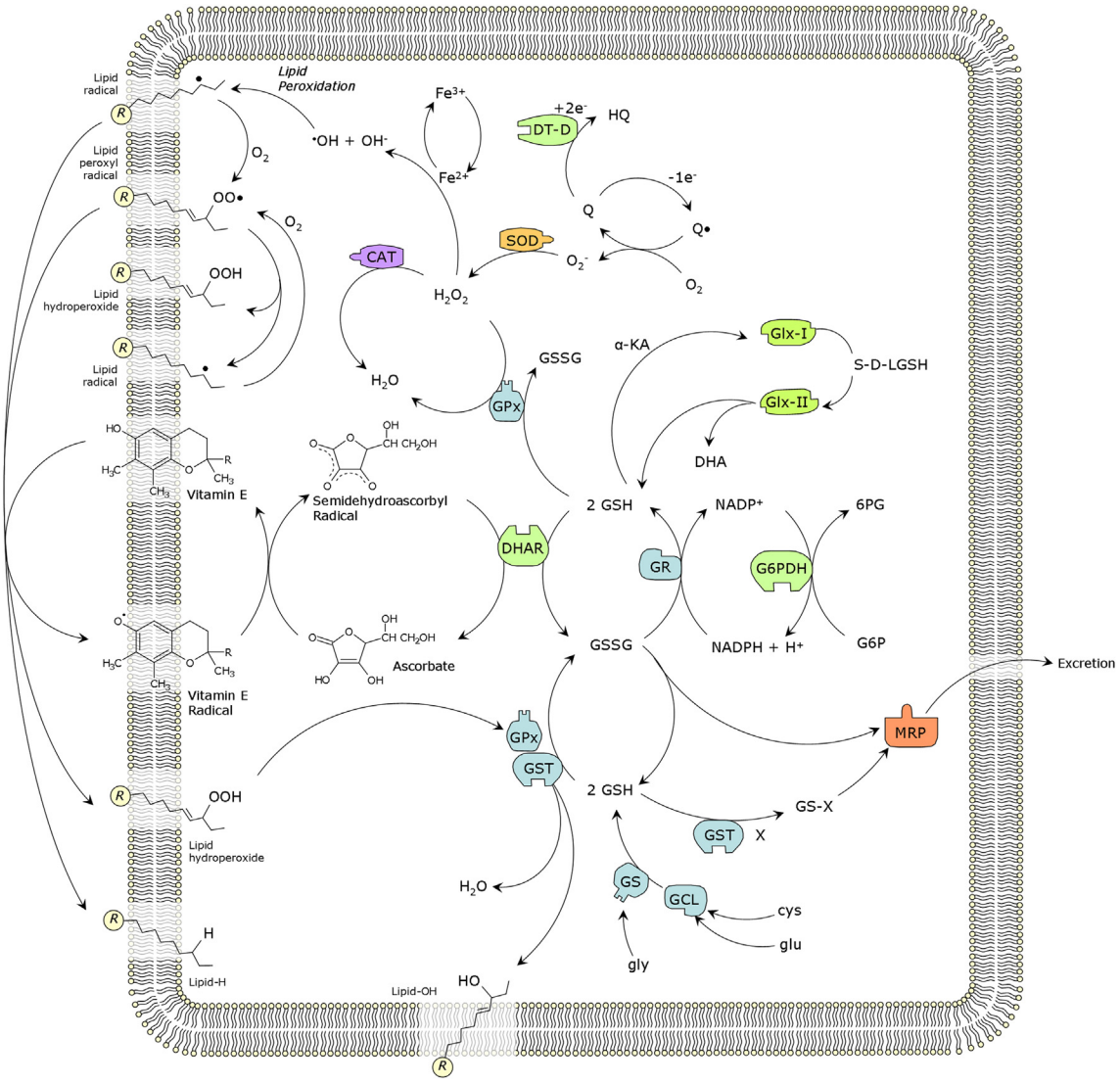

Fig. 1. Main cellular antioxidant defences and antioxidant pathways (arranged in alphabetical order): 6 PG: 6-phospogluconate; CAT: catalase; cys: cysteine; DHA: D-hydroxyacid; DHAR: dehydroascorbate reductase; DT-D: DT-diaphorase; G6P: glucose 6-phosphate; G6PDH: glucose 6-phosphate dehydrogenase; GCL: γ-glutamylcysteine synthetase; Glx-I: glyoxalase I; Glx-II: glyoxalase II; GPx: glutathione peroxidases; GR: glutathione reductase; gly: glycine; glu: glutamic acid; GS: glutathione synthetase; GSH: reduced glutathione; GSSG: oxidized glutathione; GST: glutathione S-transferases; GS-X: GSH conjugated xenobiotic; HQ: hydroquinone; αKA: α-keto aldehydes; MRP: multidrug resistance-related protein; Q: quinone; Q: semiquinone radica; S-D-LGSH: S-D-Lactoylglutathione; SOD: superoxide dismutase; X: xenobiotic (adapted from Regoli et al., 2011b). See text for explanations.

several reactive species through its oxidation to GSSG; in addition, GSH acts as a cofactor of several antioxidant glutathione-dependent enzymes.

Cytosolic scavengers also include ascorbic acid (vitamin C) and uric acid, the latter found at high levels in some marine invertebrates like sea anemones (Regoli and Winston, 1998); in these organisms it acts as a reducing agent for many ROS (H_2O_2, O_2^-, HO• and lipid hydroperoxides) with an efficiency comparable to that of ascorbate (Muraoka and Miura, 2003).

Among lipid soluble scavengers, α-tocopherols (vitamin E) are the main antioxidants localized within cell membranes where, due to the presence of a hydroxyl group, efficiently react with unpaired electrons of ROS, thus arresting the propagation of lipid peroxidation. Also carotenoids, assumed by organisms with diet, represent important membrane-associated antioxidants against lipid peroxidation.

Besides direct reactions with ROS, cytosolic and lipid-soluble scavengers are functionally connected each other (Fig. 1). Lipid peroxidation is initiated by the abstraction of a hydrogen atom, and the formed lipid radical (L•) reacts with O_2 to produce the lipid peroxyl radical (LOO•); the latter readily removes a hydrogen from another lipid, thus yielding a lipid hydroperoxide (LOOH) and a new lipid radical which sustains again the reaction (propagation phase). Lipid peroxidation is terminated when L• or LOO• are quenched by a lipid-soluble radical scavenger like α-tocopherol; the resulting vitamin E radical is reduced again to the functionally active form by the ascorbate on the cytosolic side, while the semidehydroascorbyl radical is recycled by the dehydroascorbate reductase (DHAR), which use GSH as cofactor (Fig. 1); the oxidized glutathione (GSSG) is finally reconverted to GSH by glutathione reductase using NADPH as the reducing agent.

Compared to scavengers, which interact with more than one type of ROS, enzymatic antioxidants catalyze highly specific reactions with specific substrates; however, these reactions still appear closely connected through several pathways (Fig. 1). Superoxide anion can be generated through multiple cellular