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Review article

Microbial oxidative stress response: Novel insights from environmental facultative anaerobic bacteria

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ABSTRACT

Facultative bacteria can grow under either oxic or anoxic conditions. While oxygen provides substantial advantages in energy yield by respiration, it can become life-threatening because of reactive oxygen species that derive from the molecule naturally. Thus, to survive and thrive in a given niche, these bacteria have to constantly regulate physiological processes to make maximum benefits from oxygen respiration while restraining oxidative stress. Molecular mechanisms and physiological consequences of oxidative stress have been under extensive investigation for decades, mostly on research model *Escherichia coli*, from which our understanding of bacterial oxidative stress response is largely derived. Nevertheless, given that bacteria live in enormously diverse environments, to cope with oxidative stress different strategies are conceivably developed.

Contents

1. Overview of oxidative stress response

Over two billion years of hard work by photosynthetic organisms brought about this wonderful earth with adequately oxygenated atmosphere, with which higher energy-yield aerobic respiration, faster growth, greater capacity to explore the evolutionary space, and advent of higher organisms became possible [1]. Along with numerous benefits, comes an unavoidable pitfall—threat from the damaging reactive oxygen species (ROS).

Abbreviations: ROS, reactive oxygen species; O_2^-, superoxide; H_2O_2, hydrogen peroxide; $HO^\bullet$, the hydroxyl radical; OP, organic peroxide; TCA, the tricarboxylic acid; LB, lysogeny broth; PFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

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The most common ROS include superoxide (O_2^-), hydrogen peroxide (H_2O_2) and the hydroxyl radical ($HO^•$), all of which are direct byproducts of oxygen reduction [2,3]. Unlike O_2^- and $HO^•$, H_2O_2 is not a free radical, but is chemically more active than molecular oxygen [2]. In aerobic cells these species can be formed endogenously by consecutive addition of electrons to oxygen. Simultaneous generation of both O_2^- and H_2O_2 occurs when molecular oxygen collides with redox enzymes, flavoenzymes in particular such as NADH dehydrogenase II, lipoamide dehydrogenase, and fumarate reductase, and abstracts their electrons [4–7]. Both O_2^- and H_2O_2 can be released into the bulk solution although the former is usually rapidly converted to the latter by dismutation in the living cell. In addition, H_2O_2 can also be generated endogenously through the turnover of committed oxidases, such as aspartate oxidase and phenylethylamine oxidase [8–10]. In spite of these processes, it should be noted that the source of a significant fraction of the endogenous H_2O_2 yield remains unknown [9,10]. $HO^•$, an extremely powerful oxidant that reacts with nearly all macromolecules, especially DNA, is a natural product of Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow OH^- + HO^• + Fe^{3+}$) [11].

Equally critically, most if not all, ROS can be generated exogenously both by other organisms and by chemical processes. H_2O_2 is generated and excreted by lactic acid bacteria to inhibit their competitors in proximity [12]. Some ROS, including organic peroxides (OP), are immune defense "bombs" generated by plant and animal hosts against microbial pathogens [13–15]. When a plant recognizes an attacking pathogen, one of the first induced reactions is to rapidly produce O_2^- and/or H_2O_2 to strengthen the cell wall and confine the infection [16,17]. In the mammalian host, production of ROS is induced as an antimicrobial defense [18–20]. In parallel, environmental O_2^- and H_2O_2 are formed either by oxidation of reduced metals and sulfur species at anoxic/oxic interfaces or by UV/visible radiation of extracellular chromophores [21].

Although ROS can be beneficial [22], they are generally regarded to be detrimental to living organisms since they react with proteins, DNAs, lipids, and other bio-molecules that are commonly thought to be stable, leading to enzyme dysfunction, genetic mutation, and lipid peroxidation [23] (Fig. 1). The most vulnerable macromolecules identified to date include Fe–S dehydratases [24,25], mononuclear iron proteins [26], DNA [27–29], and lipids [30]. As lipids in most bacteria are not prone to peroxidation because of the lack of polyunsaturated fatty acids, the primary targets of ROS are believed to be in the cytoplasm [3]. This coincides with the fact that most of ROS scavenging enzymes also reside intracellularly, which are usually present in a surprisingly large number in a given bacterium [21]. These proteins not only comprise the basal line of defense to limit intracellular ROS levels generated endogenously during normal growth, but also function as the crucial part of the oxidative stress response system once the ROS and associated cellular damages are over the physiologically safe limit [31].

While oxidative stress response systems typically involve activation of dedicated (redox-sensitive) regulators, up-regulation of expression of genes encoding scavenging enzymes, and action of cellular repair systems, molecular details differ for individual ROS to ensure accurate regulation and specificity of defense [32]. The well characterized systems for sensing and responding to oxidative stress induced by different ROS species are discussed briefly below.

2. O_2^- and SoxRS system

SoxRS system encompasses a redox sensor/regulator SoxR and a downstream second regulator SoxS [33–36]. The canonical mode of action is that SoxR becomes active by oxidation of its two [2Fe–2S] clusters under O_2^- producing conditions and activates SoxS expression subsequently. SoxS, in turn, controls the expression of over a hundred genes battling on multiple fronts against O_2^- threat, including superoxide dismutase, the well-known O_2^- scavenging enzyme converting O_2^- to H_2O_2 [37–39]. Although the molecular mechanism of SoxRS system in *Escherichia coli* has been characterized and reviewed in great details, the exact nature of the SoxR-activating oxidants is still controversial, with both O_2^- and redox-cycling drugs being suspects [40–42]. Interestingly, this debate echoes with the fact that, outside the Enterobacteriaceae family, SoxR works *in solo*. It regulates a handful of target genes that

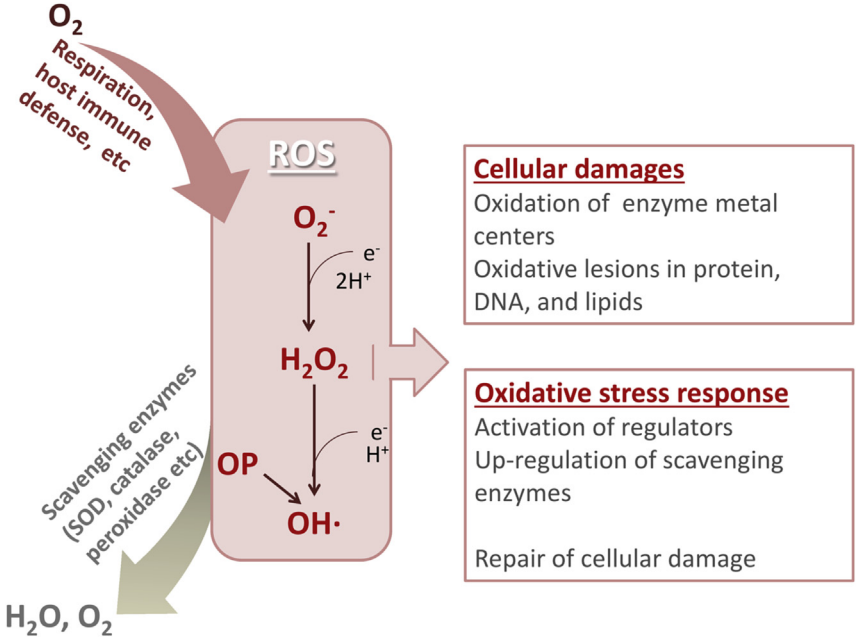

Fig. 1. Sources, sinks and consequences of reactive oxygen species (ROS) in microbes. As elaborated in the text, the sources of the ROS species discussed in this review (namely O_2^-, H_2O_2, and $OH^•$) mainly include respiration, and immune defense by animal and plant hosts. These ROS can cause various cellular damages and induce oxidative stress response. Dedicated scavenging enzymes are responsible for cleansing out the damaging O_2^- and H_2O_2.