Journal of Bacteriology and Mycology

Austin Publishing Group

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Editorial

Delineating the Oxidative Stress Response in Shewanella Oneidensis

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Received: August 16, 2014; **Accepted:** August 18, 2014; **Published:** August 18, 2014

Editorial

Emergence of the ability to respire on O_2 in prokaryotes had been a great evolutionary success story, leading way to more efficient energy use, faster growth, greater cell populations for natural selection to act upon, and eventually to the birth of higher organisms [1]. However, every coin has two sides, along with all the benefits of aerobic respiration come the Reactive Oxygen Species (ROS) and oxidative stress [2].

Superoxide (O_2^-), H_2O_2 and Organic Peroxides (OP) are all ROS species commonly encountered by microbes [3,4]. They are damaging to DNA, RNA, protein, lipids, and virtually any cellular component, causing oxidative stress [2, 5]. The bad news is, beside radiation and other external factors, one major source of ROS is the process of aerobic respiration *per se*, rendering ROS an unavoidable drag of the aerobic lifestyle [1,5]. In defense, microorganisms have evolved sophisticated mechanisms to sense, respond, and battle against ROS.

Figure 1 summarizes the oxidative stress response dedicated to battling against various ROS and their damages. Although a diversity of genes are involved, and specific genes differ for different ROS species, oxidative stress response can be broadly divided into two tiers of defense. The primary defense focuses on removing the ROS (e.g., H_2O_2 induces catalase and peroxidase, and O_2^- induces superoxide dismutase), and the secondary defense is concerned with cellular component repair or removal [4,5]. Also illustrated in Figure 1 are the four major sensor-transcriptional regulators well characterized in model organisms, OxyR, PerR, OhrR, and SoxRS. As shown, each of these regulators specializes in coping with a set of different ROS species, with OxyR and PerR for H_2O_2 but usually found in different organisms, OhrR for OPs, and SoxRS for superoxide.

While studies in model organisms undoubtedly helped us put together a general picture of oxidative stress response, it is also of great value to expand the territory by characterizing other interesting organisms, especially those thriving in redox-stratified environments prone to ROS generation, and investigate their specific strategies. *Shewanella oneidensis* MR-1, a gram-negative facultative anaerobe, is such a representative. Endowed by the diverse collection of iron or *heme* containing respiratory proteins encoded in its genome, MR-1 is able to respire on oxygen, nitrate, Fe(III), Cr(VI) and even more exotic electron acceptors [6]. These characteristics all put MR-1 in the front seat for ROS attack [2,5], and our study aims to shed light on how this organism defends itself. We have identified analogues of OxyR and OhrR MR-1 [7,8]. And our recent research had revealed that the regulation of oxidative stress response in MR-1 (summarized in Figure 2) differ considerably from the general model shown in Figure 1.

S. oneidensis OxyR represents a relatively rare H_2O_2-responding regulator, which functions as both an activator and a repressor as in *Neisseria* [9]. Although three catalases (KatB, KatG-1, and KatG-2) are encoded in the genome, only KatB appears to be functional. In addition, several peroxidase genes of the OxyR regulon are under positive control of the regulator but their contribution in combating H_2O_2 is negligible. Instead, the predominant force protecting the microorganism from harmful H_2O_2 relies on de repression of the

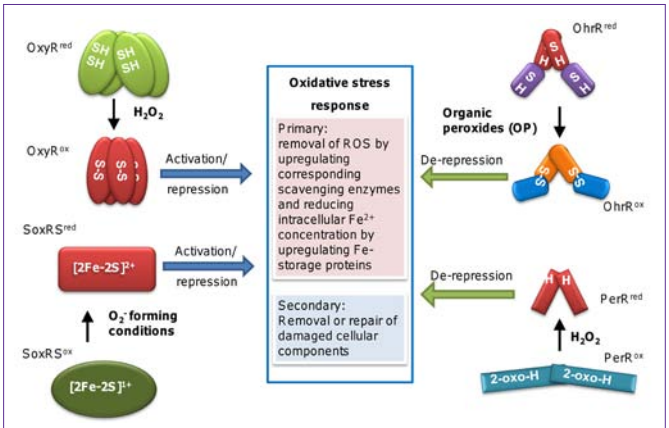

Figure 1: Summary of general oxidative stress response and known major ROS sensor-transcriptional regulators. OxyR is the principle H_2O_2-responding regulator governing the expression of a similar set of genes (OxyR regulon) across species. OxyR features a key Cysteine residue (C199 in *E. coli*) prone to H_2O_2 oxidation, although still a point of debate, this oxidation most likely results in the formation of a disulfide bond (between C199 and C208 in *E. coli*) which leads to OxyR activation and eventually increased expression of genes for scavenging enzymes such as peroxidase and catalase (Ahp and KatG) and other proteins having a role in oxidative stress response. Although OxyR is widely distributed, *Bacillus subtilis* employs PerR in its place. PerR is a repressor that can be deactivated by H_2O_2 through oxidation of a histidine residue, its regulon overlaps to a great extent with OxyR. It is interesting to contemplate how such distinct H_2O_2-sensing mechanisms had evolved, but no compelling hypothesis had been put forward. SoxR senses superoxide-generating conditions (rather than O_2^- *per se*) through redox reaction of its 2Fe-2S clusters and often modulates oxidative stress response by regulating the expression of its cognate transcriptional regulator SoxS. OhrR senses OP in a manner similar to OxyR with H_2O_2, except that it functions mainly as a repressor. In *Xanthomonas campestris* OhrR, OP-triggered formation of the intermolecular disulfide between the sensory residue C22 and the C127 residue of the other subunit of the homodimeric protein leads to the de-repression of Ohr. A subset of OhrR proteins known as Cys-1 contains only one conserved sensing cysteine (e.g., C15 in *B. subtilis*). It forms either mixed disulfide with cellular free thiol or cyclic sulfonamide with the amino group of a nearby amino acid upon organic peroxide oxidation. For thorough reviews, please refer to [3-5].

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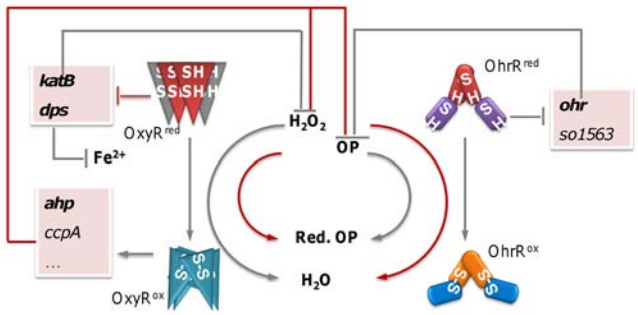

Figure 2: Summary of the oxidative stress response characterized in *S. oneidensis* MR-1 recently. Grey line indicates reactions or relationships existing in *E. coli*, and red lines indicate those that are in MR-1 but not *E. coli*.

katB and *dps* genes upon inactivation of OxyR, whose products ensure rapid removal of the oxidant and restriction of intracellular iron concentrations, respectively [7]. One striking difference between the *S. oneidensis* OxyR regulon and those characterized to date is that $OxyR_{So}$ seems not to be involved in the regulation of genes encoding proteins participating in the secondary defense, such as those for *heme* synthesis, FeS cluster assembly, or divalent cat ion import. This observation may partially account for the hypersensitivity of *S. oneidensis* (in comparison to *E. coli*) to H_2O_2 [7].

Loss of $OxyR_{So}$ results in substantial defects in both growth and viability. While we do not yet know the mechanism underlying the slow growth, impaired viability is certainly associated with iron [7]. Addition of Fe^{3+} fully rescues the defect, whereas Mn^{2+} does not have such effect, despite that replacement of vulnerable Fe^{2+} by Mn^{2+} in many proteins is believed to be a critical strategy against oxidative stress in *E. coli* [5]. This observation is clearly out of expectation because extra iron is usually blamed for exasperating the stress via Fenton reaction, leading to generation of the most deadly ROS, hydroxyl radical. Moreover, $OxyR_{So}$ cannot functionally complement $OxyR_{Ec}$ or vice versa. As far as we are aware, this is the first case that an OxyR analogue could not work as a functional replacement in *E. coli*.

The most distinctive feature we have observed in *S. oneidensis* is the cross talk between OxyR and OhrR systems [8]. More specifically, these two regulators can both respond to H_2O_2 as well as OPs; and Ahp contributes considerably to OP scavenging. Finally, it is also worth mentioning that the OhrR regulon of *S. oneidensis* differs from its characterized counterparts in that it at least contains one extra member SO1563 (glutathione peroxidase), in addition to Ohr (Organic hydroperoxide resistant protein), although its role in ROS stress response remains elusive.

These intriguingly unusual arrangement (in comparison to *E. coli*) and the observation that MR-1 is far more sensitive to H_2O_2 (but not to OP) than *E. coli*, prompted us to the postulation that organic peroxides are probably more of a threat than H_2O_2 in the natural habitat of MR-1. Given that *E. coli* usually dwells in human gut, it probably often encounters H_2O_2 attack from the host immune system [10]. In contrast, MR-1 most typically resides in aqueous environments relatively rich in organic matters and mineral. A recent report [11] had demonstrated that simple organic matters can be effectively converted to acyl hydro peroxides in the presence of H_2O_2 and minerals such as Fe_2O_3, Al_2O_3, TiO2 mineral, supporting our theory.

Last but not least, we would like to acknowledge that these findings just opened up the investigation of *S. oneidensis* oxidative stress response, the molecular detail of how OxyR and OhrR senses both types of ROS remains to be elucidated, whether the KatG-1 and KatG-2 are just useless evolutionary leftovers or a secret arsenal against some other ROS threat would be interesting, not to mention that despite owning a SOD in the genome, no Sox analogues was detected in MR-1. All these puzzles invite further studies to put together a complete roadmap of *S. oneidensis* oxidative stress response.

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J Bacteriol Mycol - Volume 1 Issue 1 - 2014
ISSN : 2471-0172 | www.austinpublishinggroup.com

Citation: Yuan J and Gao H. Delineating the Oxidative Stress Response in Shewanella Oneidensis. J Bacteriol Mycol. 2014;1(1): 2.