Archives of Biochemistry and Biophysics 584 (2015) 28–35

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review article

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

Huihui Fu, Jie Yuan**, Haichun Gao*

Institute of Microbiology and College of Life Sciences, Zhejiang University, Hangzhou, Zhejiang, China

ARTICLE INFO

Article history:
Received 13 July 2015
Received in revised form
19 August 2015
Accepted 20 August 2015
Available online 28 August 2015

Keywords:
Bacteria
Oxidative stress response
Regulation
Viability
OxyR
Hydrogen peroxide

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.

* Corresponding author. Institute of Microbiology and College of Life Sciences, Zhejiang University, Hangzhou, Zhejiang, 310058, China.
** Corresponding author.
E-mail addresses: jieyuan@zju.edu.cn (J. Yuan), haichung@zju.edu.cn (H. Gao).

http://dx.doi.org/10.1016/j.abb.2015.08.012
0003-9861/

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

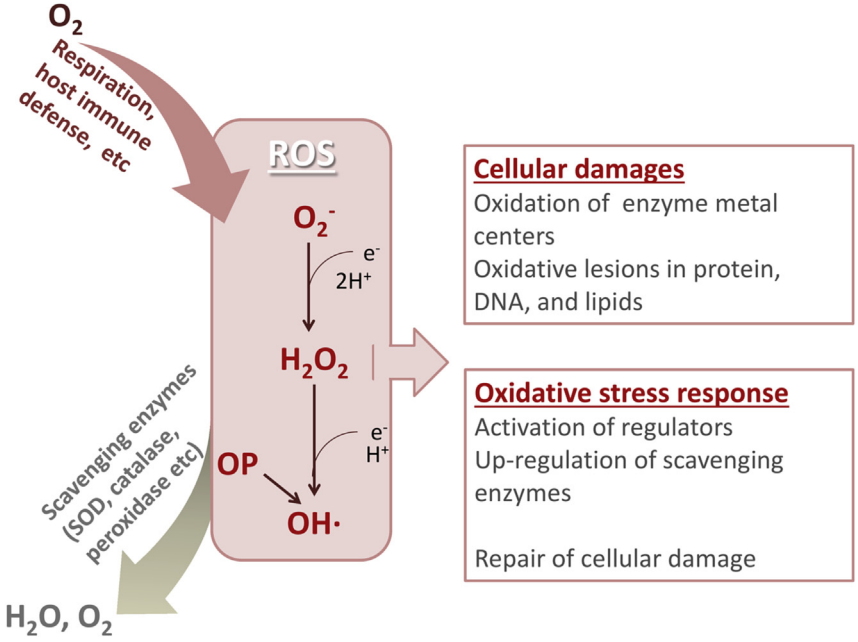

Fig. 1. Sources, sinks and consequences of reactive oxygen species (ROS) in microbes. As elaborated in the text, the sources of the ROS species discussed in this review (namely O_2^-, H_2O_2, and $OH^•$) mainly include respiration, and immune defense by animal and plant hosts. These ROS can cause various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

typically encode predicted mono- and dioxygenases, oxidoreductases and transporters directly in response of redox-cycling compounds [43–45]. It is worth mentioning that *E. coli* SoxR is not only more sensitive to O_2^- than the *Pseudomonas aeruginosa* counterpart [42] but also responsive to a wider range of oxidants, likely due to alteration of three residues that are critical to function [46].

3. H_2O_2 and OxyR

OxyR and PerR, existing in many Gram-negative and Gram-positive bacteria respectively, are two well-characterized regulators that mediate the cellular response to H_2O_2 [35,36,47,48]. Although these two regulators belong to different protein families and utilize distinct mechanisms for H_2O_2–sensing, they have evolved to control a similar set of proteins [49,50]. OxyR, a LysR family transcriptional factor, is recognized as the principle regulator for H_2O_2 response in a broad spectrum of bacteria species, including members belonging to *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* [39]. It contains a regulatory domain which senses H_2O_2 threat by formation of a reversible disulfide bond between the two conserved cysteine residues, and a DNA binding domain which modulates target gene expression directly [51,52]. Although as the case for other regulators, OxyR regulons vary among species and range from 3 to about 40 genes, those for catalases (Kat), alkylhydroperoxide reductase (Ahp), and an iron sequestration protein (Dps), are found in the regulons [53–59]. Interestingly, however, the mode of OxyR regulation on the functionally predominant catalases (Such as KatE and KatG in *E. coli*) is not conserved as much as the protein itself. In *E. coli*, *Salmonella enterica* and *Caulobacter crescentus*, OxyR positively regulates the expression of such catalases and *oxyR* null mutants are much more sensitive to H_2O_2 [32,60]. On the other hand, in *Corynebacterium diphtheria*, *Corynebacterium glutamicum R* and *Shewanella oneidensis* the regulation is negative. As a result, deletion of *oxyR* in these bacteria derepresses major catalases, leading to enhanced resistance to H_2O_2 [58,59,61]. A more complex, double-edged regulation was reported for *Neisseria meningitides* and *P. aeruginosa* PA14, in which OxyR represses expression of major catalases in the absence of H_2O_2 but activates it when H_2O_2 is present at levels sufficiently high to trigger oxidative stress response [62,63]. Ahp also contributes to H_2O_2 scavenging in many species [64–67]. Unlike catalase which is effective during high-level H_2O_2 stress, Ahp is more efficacious when H_2O_2 levels are low, thereby being the primary enzyme to remove endogenously generated H_2O_2 and maintain its levels within physiologically safe limits [68]. Additionally, Ahp is reported to have a role in scavenging other ROS species, such as OPs [66,69,70]. The discovery that *dps* and some other genes involved in iron transport and sequestration are often under OxyR regulation is conceivable because the most reactive ROS species $HO^{\bullet}$ can be readily generated from H_2O_2 in the presence of Fe^{2+}. During H_2O_2 stress, Dps is induced, resulting in substantial reduction in the intracellular levels of unincorporated iron and suppression of DNA damage [71,72].

4. Organic peroxide and OhrR

OhrR is widely reported as the sensor and regulator dedicated to managing oxidative stress related to OPs [73–75]. OhrR senses OPs via oxidation of a family-wide conserved N-terminal cysteine residue. This oxidation inactivates OhrR, leading to derepression of the *ohr* gene which codes for the major OP scavenging peroxidase. Such scheme has been uncovered in a variety of organisms, including *Brucella abortus 2308*, *Chromobacterium violaceum*, *Mycobacterium smegmatis*, and many others [66,76–78].

Comprehensive reviews are available for each of these systems [39,73–75,79,80], and understanding of these systems in the model organism *E. coli* has also been well documented elsewhere [3]. Hence we will not confine this review to these systems *per se*. Rather, we would like to highlight recent findings in oxidative stress response and regulation in environmental microbes, especially *S. oneidensis*, which add new twists to the schemes described above. Members of the genus *Shewanella* (Gram-negative γ-proteobacteria) comprise a diverse group of facultative anaerobes (more than 50 species) capable of respiring an array of organic and inorganic substances [81,82]. In light of their fascinating physiology, these organisms have biotechnological uses, from bioremediation of various environmental pollutants such as toxic elements and heavy metals, electricity generation (microbial fuel cells), to production of high-value electrofuels (microbial electrosynthesis) [83]. Importantly, the genus is increasingly being implicated as an important and developing cause of maritime-associated disease [84]. To date, an array of studies have been carried out to decipher the molecular basis underlying cellular responses to environmental perturbations, as revealed in model species *S. oneidensis* [85]. As these bacteria thrive in redox-stratified environment where ROS are likely to occur [81,82], it is not surprising that novel solutions to the oxidative threat have been developed.

5. OxyR, OhrR, and the cross-talk between them

Like many other Gram-negative bacteria, *S. oneidensis* uses OxyR and OhrR as the master regulators to mediate its response to H_2O_2 and organic peroxides respectively, but lacks an analog of SoxR [59,66]. Although both regulators largely conform to the canonical models described in previous section, significant differences are observed (Fig. 2). *S. oneidensis* OxyR functions as both an activator and a repressor as its counterparts in several bacteria, with KatB (the major functional catalase) and Dps being repressed. As a consequence, although genes under activation of *S. oneidensis* OxyR are outnumbered those under repression significantly, protection from H_2O_2 threat relies mainly on derepression of KatB and Dps. Importantly, despite the existence of two oxidative stress-sensing cysteine residues, both of which are required for function [86], *S. oneidensis* OxyR could not functionally complement the loss of *E. coli* OxyR. This is unexpected because all characterized OxyR proteins are able to do so, some of which are from microorganisms that are phylogenetically related to *E. coli* much further than *S. oneidensis* [59,87]. The most profound difference in structures between the *S. oneidensis* and *E. coli* OxyR proteins lies between two H_2O_2-sensing residues: a perfect 4-turn helix in the former and a random-coil-type arrangement in the latter. Whether this structural difference disables the functional exchangeability of these two proteins is under investigation. Unlike OxyR, OhrR characterized to date directly controls *ohr* only. However, the regulon of *S. oneidensis* OhrR consists of an additional member, SO_1563, encoding a protein of the Gpx family, some of which have been shown to function as scavengers for various ROS, including H_2O_2 and *t*BOOH (tertiary-butylhydroperoxide, an OP agent) [66,88]. Mechanistically, *S. oneidensis* OhrR differs from the well-studied model, OhrR of *Xanthomonas campestris*, in that its sensing and responding cysteine residues (C32 and C137) are not equally important for regulation [73,89].

The oxidative stress response systems are generally thought to be ROS specific, each triggered by different ROS [32], such that the most targeted and cost-effective optimal response is ensured (i.e., the relevant scavenging enzyme will not be synthesized if the threat is not present). However, when *S. oneidensis* is subjected to H_2O_2 treatment, *ohr* and *SO_1563* are highly induced along with those established OxyR regulon members [59] (Fig. 2). Intriguingly, *ohr* neither contributes to H_2O_2 scavenging nor is directly regulated by OxyR [66]. These data suggest i) that OhrR may sense and

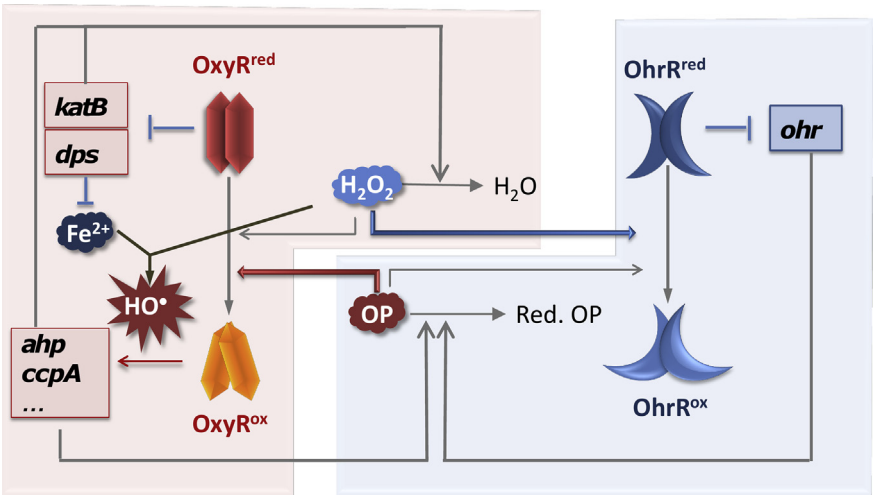

Fig. 2. Summary of the oxidative stress response characterized in *S. oneidensis*. The novel "cross-talk feature" is highlighted by thick arrows. Light red and light blue backgrounds provide visual separation of the canonical modularized oxidative stress responses induced by H_2O_2 and organic peroxide (OP) respectively.

respond to H_2O_2 in addition to OPs; ii) that a yet-unidentified H_2O_2-sensing regulator participates in regulation of *ohr* expression. Conversely, members of the OxyR regulon, including KatB, AhpC, and Dps are also found to be induced by *t*BOOH treatment [66]. This induction appears to be OxyR dependent and persisted in the *ohrR* null mutant, implying that OxyR also responds to OPs. Such cross-talk should not be lightly dismissed as promiscuity of the sensor, since Ahp is regulated by OxyR but contributes to OP clearance [66]. One of probable explanations to the cross-talk is that H_2O_2 and OPs may coexist in redox-stratified environments where *Shewanella* thrive. This notion gains support from a recent finding that H_2O_2 could promote OP formation from organic acids such as salicylic acid on mineral surfaces [90]. Therefore, it might be of great advantage for organisms living in mineral-rich environment, such as *Shewanella*, to prepare for OP assault when H_2O_2 is likely to be formed.

6. Involvement of global regulators

ROS generation is coupled to aerobic respiration, thus the rate of endogenous ROS production is closely correlated with the respiratory activity of cells [91]. Such relationships have triggered the idea that respiration-related global regulatory systems might be involved in oxidative stress response. So far, evidence for participation of global regulators, including Arc (*aerobic respiration control*), Fnr (*fumarate and nitrate reduction regulatory*), Crp (*cAMP receptor protein*), and even RpoS (a sigma factor), has all been put forward. More explicitly, Arc and Fnr have been implicated in the resistance to ROS. Fnr, the primary regulator controlling respiratory transition in *E. coli*, possesses a $[4Fe–4S]^{2+}$ cluster for oxygen sensing, and is thought to participate in the oxidative stress response [92,93]. The *E. coli yhiA* gene, encoding a predicted cytochrome *c* peroxidase which plays a role in peroxide stress response under anaerobic condition, is regulated both by Fnr and OxyR [94]. However, *S. oneidensis* Fnr has no significant role in mediating gene expression in response to oxygen availability [95,96]. Moreover, physiological impacts of this regulator are extremely minor, with no evident phenotype being elicited by its loss or no influence on expression of genes which contain conserved Fnr-binding sites in their promoter regions [97,98]. It is hence not surprising that Fnr is dispensable in oxidative stress response in *S. oneidensis* [99].

The Arc two-component (ArcA and ArcB) signal transduction system is second to Fnr in controlling the transition from aerobic to anaerobic growth in *E. coli* and its regulon members are mostly involved in the TCA cycle and energy metabolism [93]. The ArcB sensor kinase senses oxygen indirectly, undergoes autophosphorylation and transfers a phosphoryl group to ArcA, a DNA binding protein that activates or represses the expression of downstream genes [100–102]. Compared to Fnr, the Arc system is involved in oxidative stress response more broadly and deeply. In *Haemophilus influenza*, mutants lacking ArcA was susceptible to H_2O_2 due to the increased expression of multiple respiration genes and the loss of activation of oxidative stress genes including *dps* [103]. In *E. coli*, situation is much the same as that in *H. influenza* but caused by the deficiency in amino acid assimilation and protein synthesis [104]. In *S. enterica*, loss of the Arc system increases the influx rate of H_2O_2 by derepressing the most abundant porin, leading to enhanced sensitivity [105]. Different from the reasons discussed above, the sensitivity of the *S. oneidensis* ArcA null mutant to H_2O_2 is mainly the result of impaired cell envelope [99]. The defect in the cell envelope appears to be associated with the outer-membrane, based on a substantially increased sensitivity to sodium dodecyl sulfate (SDS). The underlying mechanism is at least in part attributed to overexpressed SO_1915, an outer-membrane bound serine protease under the direct repression of ArcA. It is suggested that overproduced SO_1915 leads to an augment of degradation of proteins that have a role in maintaining the envelope integrity [99]. The profound involvement of the Arc system in bacterial oxidative stress response may be explainable in the sense of evolution. The Arc system emerges at the time that oxygen is becoming a major component of the atmosphere and the system may have originally evolved as an oxidative stress response mechanism that is later co-opted by emerging facultative anaerobes to facilitate the exploitation of aerobic environments [106]. It is worth mentioning that *S. oneidensis* and other sequenced *Shewanella* possess an atypical Arc system in which function of the sensory kinase is fulfilled by two proteins, ArcS and HptA [107–110]. The sensor protein ArcS differs substantially from the *E. coli* ArcB in that it contains two additional signal sensing domains. Such arrangement naturally leads to the speculation that the *S. oneidensis* Arc system might be capable of sensing more external stimuli than its canonical counterparts [106].

Crp is a cAMP-dependent transcriptional factor mediating carbon catabolite repression, a common phenomenon among bacteria

whereby the synthesis of catabolic proteins is inhibited when growing on preferable sugars [111]. Under oxidative stress *E. coli* mutant strains lacking Crp fails to increase *oxyR* expression during exponential growth and is more sensitive to H_2O_2 [112]. In contrast, loss of cAMP-Crp confers uropathogenic *E. coli* remarkable resistance to H_2O_2, owing to the elevated catalase activity attributable in part to RpoS (σ^S) [113,114]. Despite the phenotypic differences, these findings suggest that the influence of Crp seems to be achieved through other regulators, such as OxyR and σ^S. As a sigma factor, σ^S controls expression of a large number of genes for stress response and transition from the exponential phase to stationary phase. Its involvement in H_2O_2 resistance has been reported in multiple organisms. In *E. coli*, σ^S regulates catalase coding gene *katE* in the stationary phase [115], as well as other genes important for oxidative stress resistance including *dps* [116], *xthA* [113], *sodC* [117], and *katN* [118]. Negative regulation of *oxyR* by σ^S has been reported in *E. coli* [105], while the opposite situation exists in *Burkholderia pseudomallei* [119]. In addition, OxyS, an untranslated RNA induced by OxyR, inhibits translation of *rpoS* by altering activity of Hfq, an RNA binding protein [120]. Both Crp and σ^S homologues also exist in *S. oneidensis*. While the role that σ^S plays in *S. oneidensis* physiology remains uninvestigated, Crp takes the role of *E. coli* Fnr as the predominant regulator mediating aerobic and anaerobic respiration [97,98,121–124]. Along with its role in carbon utilization, Crp is the most critical regulator for survival and growth of *S. oneidensis* [96]. Nevertheless, evidence that supports its direct involvement in oxidative stress response remains elusive [99]. Furthermore, based on findings from the *E. coli* paradigm these global regulators might be functionally intertwined with respect to oxidative stress. For instance, Crp could modulate σ^S activity in response to H_2O_2 stress [113] and Fnr regulates the activity of the *rpoS* promoter [125,126]. Thus, it is safe to say that participation of these important global regulators ties oxidative stress response into a greater picture of cell growth and survival, and reflects the importance of proper regulation of related cellular functions.

7. Viability of *oxyR* mutant

Given the unavoidable endogenous generation of ROS, it is not surprising to learn that loss of OxyR can lead to multiple defects in various biological processes. In many bacteria in which OxyR functions as an activator only, including *E. coli*, *Vibrio cholerae*, *Shigella flexneri*, and *Haemophilus influenzae*, *oxyR* null mutants grow at a reduced rate compared to the wild-type [127–129]. This is the natural consequence of compromised production of ROS scavenging enzymes, especially Ahp and catalases. Interestingly, the decrease in growth rate is less significant when grown in liquid medium than on plates made of the same medium [112,130]. Additionally, the *oxyR* mutants also display a plating defect (reduced viability) on the rich-medium plate in general [127,131,132]. Given that this plating defect can be rescued by addition of exogenous catalase or spent culture supernatants containing the major catalase, the cause is attributed to some external ROS.

A more extensively investigated case was presented in *S. oneidensis*. Compared to the wild-type, the *oxyR* null mutant of this organism grows significant slower and displays severe colony formation defect on Lysogeny broth (LB) agar plate but not in liquid LB [59,133]. It appears puzzling because the loss of OxyR confers *S. oneidensis* an increased rate of H_2O_2 degradation as the regulator functions as repressor for major catalase [59]. The plate defect of the *S. oneidensis oxyR* null mutant can be rescued either by external supplementation of catalase or by drastically overproduced catalase intracellularly [133]. The underlying mechanism is simple but surprising: ROS, likely mainly H_2O_2, can be generated by autoxidation of constituents in LB under aerobic condition, with peptides and amino acids being the main source of abiotic H_2O_2 generation [131,133]. Consistently, defined media devoid of peptides and amino acids are not subject to abiotic H_2O_2 generation and supplementation of antioxidants such as thiourea, mannitol, tiron, and manganese to LB plate can also repress the plating defect to some extent. However, it is not immediately obvious that addition of exogenous iron can also suppress the plating defect. One possibility is that although free iron in an H_2O_2 abundant environment readily sets stage for Fenton reaction to generate most deadly $HO^{\bullet}$, which would react primarily with agar rather than cells. Hence, the Fenton reaction probably serves as a mechanism for scavenging H_2O_2. In short, iron species function either as a scavenger for H_2O_2 or a stimulator for an OxyR-independent response to help cells cope with oxidative stress [133].

Based upon revelation of exogenous H_2O_2 as the major factor for the plating defect, a model is proposed to explain the plating defect of the *oxyR* mutant on LB plate [133]. In liquid LB, some of *oxyR* mutant cells lyze after inoculation, releasing catalase into the culture, which decomposes H_2O_2 and facilitates survival and growth. On the plate, catalase from dead cells is immobile and thus could not make such contribution. When from diluted cultures, cells on plates are likely separating from one another and have to cope with H_2O_2 produced abiotically in medium individually. Through some unknown mechanisms, *oxyR* mutant cells become vulnerable to extracellular H_2O_2 and die quickly (Fig. 3A). When cultures of high cell density are spread on plates, by average less H_2O_2 is applied to each cell and therefore less resulting oxidative damage. In addition, under this condition cells exist in close proximity and form cell patches which shield vulnerable cells from ambient H_2O_2 of lethal dose, allowing cells to survive and proceed to replicate (Fig. 3B). Suppression of the plating defect can be achieved either by adding exogenous H_2O_2 scavenging agents such as catalase and iron species or by enhancing intracellular H_2O_2-scavenging ability of cells (Fig. 3C & 3D). While in the former case growth is allowed simply because H_2O_2 is effectively and efficiently removed, the latter is associated with H_2O_2 fluxes. The permeability coefficient of membranes for H_2O_2 is ~1.6×10^{-3} cm/s, allowing formation of a H_2O_2 gradient across the cytoplasmic membrane when extracellular H_2O_2 is present [68]. In cells overproducing KatB or Ahp, internal H_2O_2 concentrations decrease rapidly. As a result, the flux of H_2O_2 into the cell is accelerated, promptly lowering concentrations of H_2O_2 in proximity to levels permissive for survival and growth.

8. Lipid peroxidation

Lipid peroxidation is the universal damage of ROS in eukaryotic organisms in which polyunsaturated lipids are abundant [134]. Naturally, this type of peroxidation is not to be expected in most bacteria since their membranes usually consist of saturated and monounsaturated fatty acids only [135]. However, recent works have suggested that peroxidation damage of membranes in several bacteria including *E. coli*, *Staphylococcus aureus*, and *Pseudomonas syringae* pv *tomato*, is the major cause for antibiotic-induced oxidative stress and metal-mediated contract killing [136–139]. Such membrane damage corresponds well with the observed plating defect phenotype described in the previous section, since the external ROS directly destroy lipids from the outside, nullifying the protection from internal ROS scavenging enzymes. In addition, some bacteria are more liable to lipid peroxidation as they incorporate host polyunsaturated fatty acids (PFAs) into their own membranes. *Borrelia burgdorferi* is such an example, whose membranes are the primary targets of ROS [30].

In fact, lipid peroxidation covers oxidative deterioration of any polyunsaturated compound that contains multiple carbon–carbon

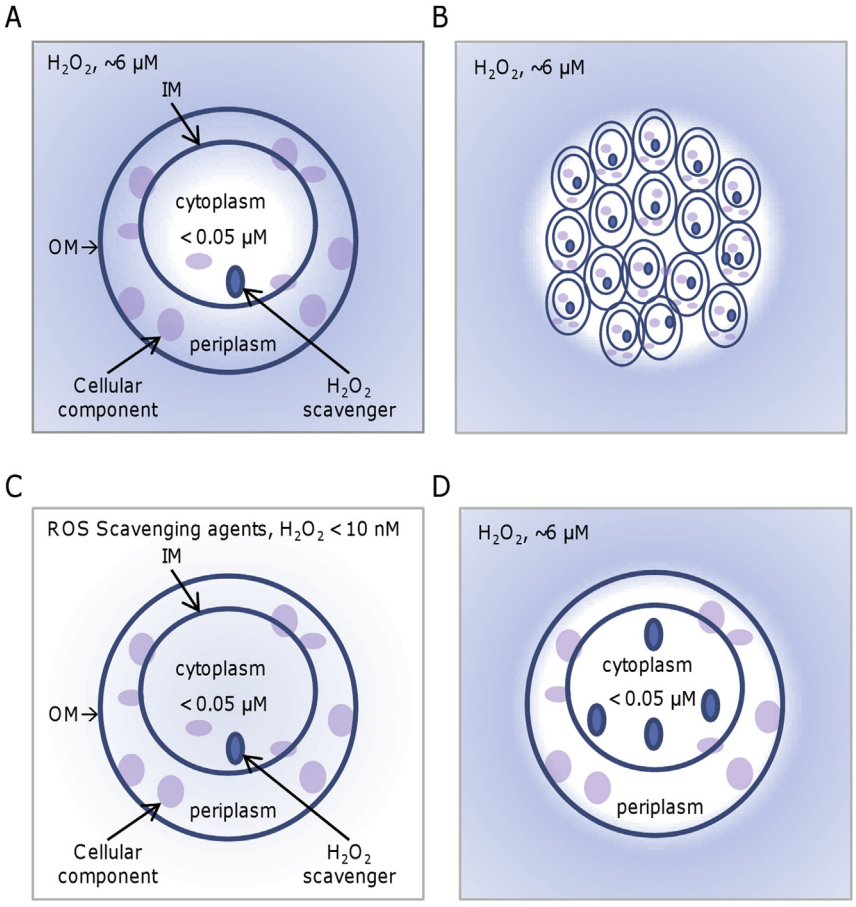

Fig. 3. Model illustrating the mechanism underlying the plating defect of the *oxyR* mutant. The *oxyR* mutant carries pleiotropic defects and is vulnerable to extracellular H_2O_2 although H_2O_2 scavengers are able to keep intracellular H_2O_2 levels below 0.05 μM. H_2O_2 generated abiotically in LB plates is ~6 μM (light blue background) and intracellular H_2O_2 is lower than 0.05 μM (white background). A H_2O_2 gradient forms from the extracellular space to the cytoplasm membrane because of the H_2O_2 influx. OM, outer membrane; IM inner membrane. A. Cells from diluted cultures plated onto LB plate. Cells die quickly. B. Cells from high cell-density cultures plated onto LB plate. Cells survive and grow because i) there is Less H_2O_2 per cell and so less oxidative damage; ii) cells form patches, which shield come cells from a lethal dose of H_2O_2. C. Cells from diluted cultures on plated onto LB plate containing H_2O_2 scavengers such as catalase, iron species, or others. Cells survive and grow because extracellular H_2O_2 is removed. D. Catalase-overproducing cells from diluted cultures on plated onto LB plate. Cells survive and grow because increased H_2O_2-degrading capacity promptly removes intracellular H_2O_2 and speeds up the H_2O_2 influx, reducing the concentration of H_2O_2 in proximity.

double bonds, such as unsaturated fatty acids, phospholipids, glycolipids, cholesterol, and polyunsaturated hydrocarbon. Thus, it is possible that polyunsaturated compounds other than eukaryotic-like PFAs are among the main targets in bacteria. In recent years, many genes predicted to encode enzymes for the biosynthesis of polyunsaturated compounds have been identified from a variety of sequenced environmental bacteria (marine psychrophilic and/or piezophilic in particular), including *Shewanella*, suggesting that a great portion of environmental bacteria may have polyunsaturated species in their membranes, deviating significantly from the current understanding of membrane composition derived from model enterobacteria. The ability of *Shewanella* species to produce polyunsaturated compounds has been confirmed experimentally. While some such as *Shewanella pneumatophori* and *Shewanella marinitestina* are able to synthesize PFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [140,141], most, if not all, produce a polyolefinic hydrocarbon (3,6,9,12,15,19,22,25,28-hentriacontanonaene) synthesized by the conserved *oleABCD* gene cluster [142,143]. Similar to unsaturated fatty acids, these polyunsaturated species play a beneficial role in membrane organization and cell division under low temperatures [144]. With respect to oxidative stress response, the polyunsaturated compounds confer bacteria resistance to extracellular H_2O_2 as mutants deficient in their production are more sensitive [140]. Importantly, engineered EPA-producing *E. coli* strains have significantly enhanced resistance to H_2O_2 [145,146]. It is proposed that polyunsaturated compounds, such as EPA, may affect the membrane permeability, reducing the diffusing rate of H_2O_2 across the membrane [141]. To date, at least two mechanisms, regulated transport via pores and simple diffusion, have been suggested to account for the regulation of membrane permeability for H_2O_2 [147]. Although it is premature to completely exclude the involvement of regulated transport in *S. oneidensis*, its major porins have no significant role in the H_2O_2 transport [99]. Hence, simple diffusion seems to play a large role, which is consistent with increased H_2O_2 sensitivity of *S. oneidensis* strains deficient in production of polyunsaturated compounds [140]. It is suggested that phospholipids with polyunsaturated compounds have a more highly packed structure than those with less unsaturated species, leading to reduced membrane permeability for H_2O_2 [141]. Thus, although polyunsaturated species are cellular compounds that are easily oxidized when exposed to oxidants [148], they may behave differently when they are present as mass substance.

9. Conclusive remarks

Thanks to intensive studies in *E. coli* and other model bacteria, our understanding of bacterial oxidative stress response has been unprecedentedly rich and profound. Nevertheless, some basic questions remain unanswered. For instance, most of ROS targets identified to date reside inside the cell, but the plating defect of *oxyR* mutants indicates that some life-critical cellular components outside the cytoplasm are vulnerable to exogenous H_2O_2. Therefore, additional targets of ROS remain to be found. More importantly, in recent years much evidence emerged from work on other microorganisms has amended or to some extent challenged the established paradigm. As environmental circumstances that bacteria face in their daily life are so diverse, it is conceivable that distinct strategies may evolve to cope with the oxidative stress. Unraveling these mechanisms would therefore provide new insights into an incredibly complex network utilized by bacteria to tackle the life-threatening crisis accompanying the appearance of oxygen.

Acknowledgement

This research was supported by National Natural Science Foundation of China (31270097, 41476105) to HG; and by National Natural Science Foundation of China (31100600), Fundamental Research Funds for the Central Universities (2014FZA6002), and Ministry of Education Science and Technology Development Center (20120541) to JY.

References

[1] M.T. Madigan, J.M. Martinko, D.A. Stahl, D.P. Clark, Brock Biology of Microorganisms, D.E.*e. al.*, thirteenth ed., Pearson Education, Inc., San Francisco, CA, 2012.
[2] C.C. Winterbourn, Nat. Chem. Biol. 4 (2008) 278–286.
[3] J.A. Imlay, Nat. Rev. Microbiol. 11 (2013) 443–454.
[4] V. Massey, S. Strickland, S.G. Mayhew, L.G. Howell, P.C. Engel, R.G. Matthews, M. Schuman, P.A. Sullivan, Biochem. Biophys. Res. Commun. 36 (1969) 891–897.
[5] J.A. Imlay, I. Fridovich, Free Radic. Res. Commun. 1 (1991) 59–66, 12-13 Pt.
[6] K.R. Messner, J.A. Imlay, J. Biol. Chem. 274 (1999) 10119–10128.
[7] K.R. Messner, J.A. Imlay, J. Biol. Chem. 277 (2002) 42563–42571.
[8] S. Korshunov, J.A. Imlay, J. Bacteriol. 188 (2006) 6326–6334.
[9] S. Korshunov, J.A. Imlay, Mol. Microbiol. 75 (2010) 1389–1401.
[10] S.R. Kumar, J.A. Imlay, J. Bacteriol. 195 (2013) 4569–4579.
[11] C. Walling, Acc. Chem. Res. 8 (1975) 125–131.
[12] C.D. Pericone, K. Overweg, P.W.M. Hermans, J.N. Weiser, Infect. Immun. 68 (2000) 3990–3997.
[13] C. Lamb, R.A. Dixon, Annu. Rev. Plant Physiol. Plant Mol. Biol. 48 (1997) 251–275.
[14] B. Rada, T.L. Leto, Contrib. Microbiol. 15 (2008) 164–187.
[15] A.V. Garcia, H. Hirt, Front. Microbiol. 5 (2014) 141.
[16] M.A. Torres, Physiol. Plant 138 (2010) 414–429.
[17] S. Stael, P. Kmiecik, P. Willems, K. Van Der Kelen, N.S. Coll, M. Teige, F. Van Breusegem, Trends Plant Sci. 20 (2015) 3–11.
[18] T.L. Leto, M. Geiszt, Antioxid. Redox Signal 8 (2006) 1549–1561.
[19] C.J. Harrison, Minerva Pediatr. 61 (2009) 503–514.
[20] C. Deffert, J. Cachat, K.H. Krause, Cell. Microbiol. 16 (2014) 1168–1178.
[21] S. Mishra, J. Imlay, Arch. Biochem. Biophys. 525 (2012) 145–160.
[22] E. Owusu-Ansah, U. Banerjee, Nature 461 (2009) 537–541.
[23] J.A. Imlay, Annu. Rev. Microbiol. 57 (2003) 395–418.
[24] C.F. Kuo, T. Mashino, I. Fridovich, J. Biol. Chem. 262 (1987) 4724–4727.
[25] M.A. Wallace, L.-L. Liou, J. Martins, M.H.S. Clement, S. Bailey, V.D. Longo, J.S. Valentine, E.B. Gralla, J. Biol. Chem. 279 (2004) 32055–32062.
[26] J.M. Sobota, J.A. Imlay, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 5402–5407.
[27] S.B. Farr, R. D'Ari, D. Touati, Proc. Natl. Acad. Sci. U. S. A. 83 (1986) 8268–8272.
[28] E.S. Henle, Z. Han, N. Tang, P. Rai, Y. Luo, S. Linn, J. Biol. Chem. 274 (1999) 962–971.
[29] S. Park, X. You, J.A. Imlay, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 9317–9322.
[30] J.A. Boylan, K.A. Lawrence, J.S. Downey, F.C. Gherardini, Mol. Microbiol. 68 (2008) 786–799.
[31] S.B. Farr, T. Kogoma, Microbiol. Rev. 55 (1991) 561–585.
[32] J.A. Imlay, Annu. Rev. Biochem. 77 (2008) 755–776.
[33] J.T. Greenberg, P. Monach, J.H. Chou, P.D. Josephy, B. Demple, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 6181–6185.
[34] I.R. Tsaneva, B. Weiss, J. Bacteriol. 172 (1990) 4197–4205.
[35] B. Demple, Annu. Rev. Genet. 25 (1991) 315–337.
[36] B. Demple, C.F. Amábile-Cuevas, Cell 67 (1991) 837–839.
[37] J. Wu, B. Weiss, J. Bacteriol. 174 (1992) 3915–3920.
[38] P.J. Pomposiello, B. Demple, J. Bacteriol. 182 (2000) 23–29.
[39] S.M. Chiang, H.E. Schellhorn, Arch. Biochem. Biophys. 525 (2012) 161–169.
[40] S.I. Liochev, L. Benov, D. Touati, I. Fridovich, J. Biol. Chem. 274 (1999) 9479–9481.
[41] M.Z. Gu, J.A. Imlay, Mol. Microbiol. 79 (2011) 1136–1150.
[42] M. Fujikawa, K. Kobayashi, T. Kozawa, J. Biol. Chem. 287 (2012) 35702–35708.
[43] M. Palma, J. Zurita, J.A. Ferreras, S. Worgall, D.H. Larone, L. Shi, F. Campagne, L.E.N. Quadri, Infect. Immun. 73 (2005) 2958–2966.
[44] L.E. Dietrich, T.K. Teal, A. Price-Whelan, D.K. Newman, Science 321 (2008) 1203–1206.
[45] A. Mahavihakanont, N. Charoenlap, P. Namchaiw, W. Eiamphungporn, S. Chattrakarn, P. Vattanaviboon, S. Mongkolsuk, J. Bacteriol. 194 (2012) 209–217.
[46] R. Sheplock, D.A. Recinos, N. Mackow, L.E. Dietrich, M. Chander, Mol. Microbiol. 87 (2013) 368–381.
[47] J.-W. Lee, J. Helmann, Biometals 20 (2007) 485–499.
[48] G. Storz, L. Tartaglia, B. Ames, Antonie Van Leeuwenhoek 58 (1990) 157–161.
[49] H.-J. Choi, S.-J. Kim, P. Mukhopadhyay, S. Cho, J.-R. Woo, G. Storz, S.-E. Ryu, Cell 105 (2001) 103–113.
[50] J.-W. Lee, J.D. Helmann, Nature 440 (2006) 363–367.
[51] C. Lee, S.M. Lee, P. Mukhopadhyay, S.J. Kim, S.C. Lee, W.S. Ahn, M.H. Yu, G. Storz, S.E. Ryu, Nat. Struct. Mol. Biol. 11 (2004) 1179–1185.
[52] I. Jo, I.Y. Chung, H.W. Bae, J.S. Kim, S. Song, Y.H. Cho, N.C. Ha, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 6443–6448.
[53] U.A. Ochsner, M.L. Vasil, E. Alsabbagh, K. Parvatiyar, D.J. Hassett, J. Bacteriol. 182 (2000) 4533–4544.
[54] A. Harrison, W.C. Ray, B.D. Baker, D.W. Armbruster, L.O. Bakaletz, R.S. Munson Jr., J. Bacteriol. 189 (2007) 1004–1012.
[55] R. Ieva, D. Roncarati, M.M. Metruccio, K.L. Seib, V. Scarlato, I. Delany, Mol. Microbiol. 70 (2008) 1152–1165.
[56] Y.J. Heo, I.Y. Chung, W.J. Cho, B.Y. Lee, J.H. Kim, K.H. Choi, J.W. Lee, D.J. Hassett, Y.H. Cho, J. Bacteriol. 192 (2010) 381–390.
[57] H. Wang, S. Chen, J. Zhang, F.P. Rothenbacher, T. Jiang, B. Kan, Z. Zhong, J. Zhu, PLoS One 7 (2012) e53383.
[58] H. Teramoto, M. Inui, H. Yukawa, FEBS J. 280 (2013) 3298–3312.
[59] Y. Jiang, Y. Dong, Q. Luo, N. Li, G. Wu, H. Gao, J. Bacteriol. 196 (2014) 445–458.
[60] V.C.S. Italiani, J.F.D. Neto, V.S. Braz, M.V. Marques, J. Bacteriol. 193 (2011) 1734–1744.
[61] J.S. Kim, R.K. Holmes, PLoS One 7 (2012) e31709.
[62] R. Ieva, D. Roncarati, M.M.E. Metruccio, K.L. Seib, V. Scarlato, I. Delany, Mol. Microbiol. 70 (2008) 1152–1165.
[63] Y.-J. Heo, I.-Y. Chung, W.-J. Cho, B.-Y. Lee, J.-H. Kim, K.-H. Choi, J.-W. Lee, D.J. Hassett, Y.-H. Cho, J. Bacteriol. 192 (2010) 381–390.
[64] S.R. Kumar, J.A. Imlay, J. Bacteriol. 195 (2013) 4569–4579.
[65] I. Derecho, K.B. McCoy, P. Vaishampayan, K. Venkateswaran, R. Mogul, Astrobiology 14 (2014) 837–847.
[66] N. Li, Q. Luo, Y. Jiang, G. Wu, H. Gao, Environ. Microbiol. 16 (2014) 1821–1834.
[67] F.L. Zuo, R. Yu, G.B. Khaskheli, H.Q. Ma, L.L. Chen, Z. Zeng, A.J. Mao, S.W. Chen, Res. Microbiol. 165 (2014) 581–589.
[68] L.C. Seaver, J.A. Imlay, J. Bacteriol. 183 (2001) 7182–7189.
[69] G. Wang, R.C. Conover, S. Benoit, A.A. Olczak, J.W. Olson, M.K. Johnson, R.J. Maier, J. Biol. Chem. 279 (2004) 51908–51914.
[70] H.-W. Wang, C.-H. Chung, T.-Y. Ma, H.-c. Wong, Appl. Environ. Microbiol. 79 (2013) 3734–3743.
[71] S. Park, X. You, J.A. Imlay, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 9317–9322.
[72] A. Harrison, B.D. Baker, R.S. Munson Jr., J. Bacteriol. 197 (2015) 277–285.
[73] J.M. Dubbs, S. Mongkolsuk, J. Bacteriol. 194 (2012) 5495–5503.
[74] M. Hillion, H. Antelmann, Biol. Chem. 396 (2015) 415–444.
[75] V.V. Loi, M. Rossius, H. Antelmann, Front. Microbiol. 6 (2015) 187.
[76] C.C. Caswell, J.E. Baumgartner, D.W. Martin, R.M. Roop, J. Bacteriol. 194 (2012) 5065–5072.
[77] J.F. da Silva Neto, C.C. Negretto, L.E. Netto, PLoS One 7 (2012) e47090.
[78] S. Saikolappan, K. Das, S. Dhandayuthapani, J. Bacteriol. 197 (2015) 51–62.
[79] J.L. Rosner, G. Storz, in: R.S. Earl, P.B. Chock (Eds.), Current Topics in Cellular Regulation, Academic Press, 1997, pp. 163–177.
[80] V.I. Lushchak, Biochem. (Mosc.) 66 (2001) 476–489.
[81] H.H. Hau, J.A. Gralnick, Annu. Rev. Microbiol. 61 (2007) 237–258.
[82] J.K. Fredrickson, M.F. Romine, A.S. Beliaev, J.M. Auchtung, M.E. Driscoll, T.S. Gardner, K.H. Nealson, A.L. Osterman, G. Pinchuk, J.L. Reed, D.A. Rodionov, J.L. Rodrigues, D.A. Saffarini, M.H. Serres, A.M. Spormann, I.B. Zhulin, J.M. Tiedje, Nat. Rev. Microbiol. 6 (2008) 592–603.
[83] K. Rabaey, R.A. Rozendal, Nat. Rev. Micro 8 (2010) 706–716.
[84] J.M. Janda, S.L. Abbott, Crit. Rev. Microbiol. 40 (2014) 293–312.
[85] J. Yin, H. Gao, Stress responses of *Shewanella*, Int. J. Microbiol. 2011 (2011). Article ID 863623.
[86] H. Antelmann, J.D. Helmann, Antioxid. Redox Signal 14 (2010) 1049–1063.

[87] J.F. Heidelberg, I.T. Paulsen, K.E. Nelson, E.J. Gaidos, W.C. Nelson, T.D. Read, J.A. Eisen, R. Seshadri, N. Ward, B. Methe, R.A. Clayton, T. Meyer, A. Tsapin, J. Scott, M. Beanan, L. Brinkac, S. Daugherty, R.T. DeBoy, R.J. Dodson, A.S. Durkin, D.H. Haft, J.F. Kolonay, R. Madupu, J.D. Peterson, L.A. Umayam, O. White, A.M. Wolf, J. Vamathevan, J. Weidman, M. Impraim, K. Lee, K. Berry, C. Lee, J. Mueller, H. Khouri, J. Gill, T.R. Utterback, L.A. McDonald, T.V. Feldblyum, H.O. Smith, J.C. Venter, K.H. Nealson, C.M. Fraser, Nat. Biotech. 20 (2002) 1118–1123.
[88] F.A. Arenas, P.C. Covarrubias, J.M. Sandoval, J.M. Pérez-Donoso, J.A. Imlay, C.C. Vásquez, PLoS One 6 (2011) e15979.
[89] W. Panmanee, P. Vattanaviboon, L.B. Poole, S. Mongkolsuk, J. Bacteriol. 188 (2006) 1389–1395.
[90] Y. Zhao, D. Huang, L. Huang, Z. Chen, Environ. Sci. Technol. 48 (2014) 10614–10623.
[91] B. Gonzalez-Flecha, A. Boveris, Biochim. Biophys. Acta 1243 (1995) 361–366.
[92] J. Crack, J. Green, A.J. Thomson, J. Biol. Chem. 279 (2004) 9278–9286.
[93] J. Green, M.S. Paget, Nat. Rev. Micro 2 (2004) 954–966.
[94] J.D. Partridge, R.K. Poole, J. Green, Microbiology 153 (2007) 1499–1507.
[95] T.M. Maier, C.R. Myers, J. Bacteriol. 183 (2001) 4918–4926.
[96] H. Gao, X. Wang, Z.K. Yang, J. Chen, Y. Liang, H. Chen, T. Palzkill, J. Zhou, PLoS One 5 (2010) e15295.
[97] H. Fu, H. Chen, J. Wang, G. Zhou, H. Zhang, L. Zhang, H. Gao, Environ. Microbiol. 15 (2013) 2198–2212.
[98] G. Zhou, J. Yin, H. Chen, Y. Hua, L. Sun, H. Gao, ISME J. 7 (2013) 1752–1763.
[99] F. Wan, Y. Mao, Y. Dong, L. Ju, G. Wu, H. Gao, Sci. Rep. 5 (2015) 10228.
[100] D. Georgellis, A.S. Lynch, E.C. Lin, J. Bacteriol. 179 (1997) 5429–5435.
[101] D. Georgellis, O. Kwon, E.C.C. Lin, Science 292 (2001) 2314–2316.
[102] M. Bekker, S. Alexeeva, W. Laan, G. Sawers, J. Teixeira de Mattos, K. Hellingwerf, J. Bacteriol. 192 (2010) 746–754.
[103] S.M. Wong, K.R. Alugupalli, S. Ram, B.J. Akerley, Mol. Microbiol. 64 (2007) 1375–1390.
[104] C. Loui, A.C. Chang, S. Lu, BMC Microbiol. 9 (2009) 183.
[105] E. Morales, I. Calderon, B. Collao, F. Gil, S. Porwollik, M. McClelland, C. Saavedra, BMC Microbiol. 12 (2012) 63.
[106] Y. Dong, F. Wan, J. Yin, H. Gao, J. Bacteriol. Mycol. 1 (2014) 27.
[107] J.A. Gralnick, C.T. Brown, D.K. Newman, Mol. Microbiol. 56 (2005) 1347–1357.
[108] H. Gao, X. Wang, Z. Yang, T. Palzkill, J. Zhou, BMC Genomics 9 (2008) 42.
[109] J. Lassak, A.L. Henche, L. Binnenkade, K.M. Thormann, Appl. Environ. Microbiol. 76 (2010) 3263–3274.
[110] N.P. Shroff, M.A. Charania, D.A. Saffarini, J. Bacteriol. 192 (2010) 3227–3230.
[111] A. Kolb, S. Busby, H. Buc, S. Garges, S. Adhya, Annu. Rev. Biochem. 62 (1993) 749–797.
[112] B. Gonzalez-Flecha, B. Demple, J. Bacteriol. 179 (1997) 382–388.
[113] E. Barth, K.V. Gora, K.M. Gebendorfer, F. Settele, U. Jakob, J. Winter, Microbiology 155 (2009) 1680–1689.
[114] G.T. Donovan, J.P. Norton, J.M. Bower, M.A. Mulvey, Infect. Immun. 81 (2013) 249–258.
[115] A. Ivanova, C. Miller, G. Glinsky, A. Eisenstark, Mol. Microbiol. 12 (1994) 571–578.
[116] S. Altuvia, M. Almiron, G. Huisman, R. Kolter, G. Storz, Mol. Microbiol. 13 (1994) 265–272.
[117] T. Dong, H.E. Schellhorn, Mol. Genet. Genom. 281 (2009) 19–33.
[118] V. Robbe-Saule, C. Coynault, M. Ibanez-Ruiz, D. Hermant, F. Norel, Mol. Microbiol. 39 (2001) 1533–1545.
[119] W. Jangiam, S. Loprasert, D.R. Smith, S. Tungpradabkul, Microbiol. Immunol. 54 (2010) 389–397.
[120] A. Zhang, S. Altuvia, A. Tiwari, L. Argaman, R. Hengge-Aronis, G. Storz, EMBO J. 17 (1998) 6061–6068.
[121] D.A. Saffarini, R. Schultz, A. Beliaev, J. Bacteriol. 185 (2003) 3668–3671.
[122] Y. Dong, J. Wang, H. Fu, G. Zhou, M. Shi, H. Gao, PLoS One 7 (2012).
[123] G. Wu, N. Li, Y. Mao, G. Zhou, H. Gao, Front. Microbiol. 6 (2015) 374.
[124] H. Zhang, Q. Luo, H. Gao, Y. Feng, MicrobiologyOpen 4 (2015) 282–300.
[125] Y. Kang, K.D. Weber, Y. Qiu, P.J. Kiley, F.R. Blattner, J. Bacteriol. 187 (2005) 1135–1160.
[126] T. Dong, M.G. Kirchhof, H.E. Schellhorn, Mol. Genet. Genom. 279 (2008) 267–277.
[127] A. Daugherty, A.E. Suvarnapunya, L. Runyen-Janecky, Microbiol. Res. 167 (2012) 238–245.
[128] I. Maciver, E.J. Hansen, Infect. Immun. 64 (1996) 4618–4629.
[129] H. Wang, S. Chen, J. Zhang, F.P. Rothenbacher, T. Jiang, B. Kan, Z. Zhong, J. Zhu, PLoS One 7 (2012) e53383.
[130] J.-S. Hahn, S.-Y. Oh, J.-H. Roe, J. Bacteriol. 184 (2002) 5214–5222.
[131] D.J. Hassett, E. Alsabbagh, K. Parvatiyar, M.L. Howell, R.W. Wilmott, U.A. Ochsner, J. Bacteriol. 182 (2000) 4557–4563.
[132] T. Vinckx, S. Matthijs, P. Cornelis, FEMS Microbiol. Lett. 288 (2008) 258–265.
[133] M. Shi, F. Wan, Y. Mao, H. Gao, J. Bacteriol. 197 (2015) 2179–2189.
[134] A. Catalá, Chem. Phys. Lipids 157 (2009) 1–11.
[135] B.H. Bielski, R.L. Arudi, M.W. Sutherland, J. Biol. Chem. 258 (1983) 4759–4761.
[136] M. Becerra, P. Páez, L. Laróvere, I. Albesa, Mol. Cell. Biochem. 285 (2006) 29–34.
[137] S.J. Yoon, J.E. Park, J.H. Yang, J.W. Park, J. Biochem. Mol. Biol. 35 (2002) 297–301.
[138] R. Hong, T.Y. Kang, C.A. Michels, N. Gadura, Appl. Environ. Microbiol. 78 (2012) 1776–1784.
[139] H. Semchyshyn, T. Bagnyukova, K. Storey, V. Lushchak, Cell Biol. Int. 29 (2005) 898–902.
[140] T. Nishida, N. Morita, Y. Yano, Y. Orikasa, H. Okuyama, FEBS Lett. 581 (2007) 4212–4216.
[141] H. Okuyama, Y. Orikasa, T. Nishida, K. Watanabe, N. Morita, Appl. Environ. Microbiol. 73 (2007) 665–670.
[142] D.J. Sukovich, J.L. Seffernick, J.E. Richman, K.A. Hunt, J.A. Gralnick, L.P. Wackett, Appl. Environ. Microbiol. 76 (2010) 3842–3849.
[143] D.J. Sukovich, J.L. Seffernick, J.E. Richman, J.A. Gralnick, L.P. Wackett, Appl. Environ. Microbiol. 76 (2010) 3850–3862.
[144] J. Kawamoto, T. Kurihara, K. Yamamoto, M. Nagayasu, Y. Tani, H. Mihara, M. Hosokawa, T. Baba, S.B. Sato, N. Esaki, J. Bacteriol. 191 (2009) 632–640.
[145] T. Nishida, Y. Orikasa, K. Watanabe, H. Okuyama, FEBS Lett. 580 (2006) 6690–6694.
[146] T. Nishida, Y. Orikasa, Y. Ito, R. Yu, A. Yamada, K. Watanabe, H. Okuyama, FEBS Lett. 580 (2006) 2731–2735.
[147] V.I. Lushchak, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 153 (2011) 175–190.
[148] B. Halliwell, J.M.C. Gutteridge, Free Radicals in Biology and Medicine, fourth ed., Clarendon Press, Oxford, 2006.