ANTIOXIDANTS & REDOX SIGNALING
Volume 15, Number 1, 2011

DOI: 10.1089/ars.2011.3968

Hydrogen Peroxide as a Signaling Molecule

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Abstract

Increases in hydrogen peroxide can initiate protective responses to limit or repair oxidative damage. However, hydrogen peroxide signals also fine-tune responses to growth factors and cytokines to control cell division, differentiation, and migration. Here we discuss some of the mechanisms by which hydrogen peroxide is sensed and utilized as a signaling molecule to regulate diverse biological processes. We also discuss how the localization and levels of hydrogen peroxide, antioxidants, and the cellular metal composition together influence the nature of the response. *Antioxid. Redox Signal*. 15, 147–151.

Introduction

Hydrogen peroxide is generated as a product of many enzyme-catalyzed processes, but until recently it was considered that this production was generally an unfortunate but unavoidable consequence of aerobic metabolism. Over the last decade it has become accepted that hydrogen peroxide serves important biological roles outside of its capacity to cause oxidative damage. However, it is a pervading theme of the articles in this Forum that this signaling function of hydrogen peroxide is not easily divorced from its potential for causing cell damage (Fig. 1). Here some of the mechanisms by which damage is prevented, signals are limited, and appropriate responses initiated are covered by a series of original and review articles.

Limiting Hydrogen Peroxide-Induced Oxidative Damage

Although generally considered with other reactive oxygen species (ROS) as a cause of oxidative damage, the potency of hydrogen peroxide itself as an oxidant is largely limited to proteins with susceptible cysteine thiols and Fe-S-containing proteins (Fig. 1). The chemistry of hydrogen peroxide is such that its greatest potential for damage occurs when it reacts with reduced iron (Fe^{2+}) or copper (Cu^{+}) to generate hydroxyl radicals ($OH\cdot$), which will indiscriminately oxidize the first molecule they encounter. As Fe is often found at the active or critical structural sites in proteins, this renders these proteins particularly exposed as targets for hydrogen peroxide-induced damage. The presence of abundant enzymatic and nonenzymatic antioxidants helps prevent this damage by removing hydrogen peroxide before it reaches susceptible proteins. However, as reviewed by Faulkner and Helmann, in addition to increasing the levels of antioxidant enzymes, bacteria have also evolved sophisticated mechanisms for regulating the intracellular levels of ferrous iron (Fe^{2+}) so that damage is limited under conditions of oxidative stress. In their review of the hydrogen peroxide responses of an evolutionarily divergent range of bacterial species, Faulkner and Helmann describe the increased expression of the Fe-binding protein Dps as a common feature of these responses (7). As well as increased sequestration of Fe, another common bacterial response, is to inhibit the uptake of extracellular Fe and increase uptake of Mn (and to a lesser extent Zn), possibly by replacing Fe in the active sites of many Fe proteins and thus protecting them from metal-catalyzed oxidation (MCO) by hydrogen peroxide. Indeed, as Faulkner and Helmann point out, it has been suggested that the 30-fold higher Mn/Fe ratio might be responsible for the vastly increased resistance of *Deinococcus radiodurans* to ionizing and ultraviolet radiation compared with *Escherichia coli* (7).

A key to coordination of these responses in bacteria is transcriptional regulators of antioxidant and Mn/Zn/Fe transporter gene expression, such as PerR, which directly senses hydrogen peroxide and monitors the relative levels of Mn:Fe in *Bacillus subtilis*. If the Mn/Fe ratio is low, Zn transporter and antioxidant genes are repressed by Fe-complexed PerR, which is sensitive to irreversible inactivation by hydrogen peroxide-induced MCO, resulting in increased Zn uptake and catalase expression. If the Mn/Fe ratio is already high, then the hydrogen peroxide-resistant Mn-complexed form of PerR will predominate, and transcriptional repression of PerR target genes will be maintained (7). In contrast to PerR, transcriptional activators that mediate bacterial transcriptional responses to hydrogen peroxide, such as OxyR in *E. coli*, are activated by oxidation of cysteine thiols and do not directly sense changes in the Mn/Fe ratio. However, as Faulkner and Helmann discuss, in addition to increasing expression of antioxidant genes, OxyR also coordinates alterations in metal ion transport and binding that may help

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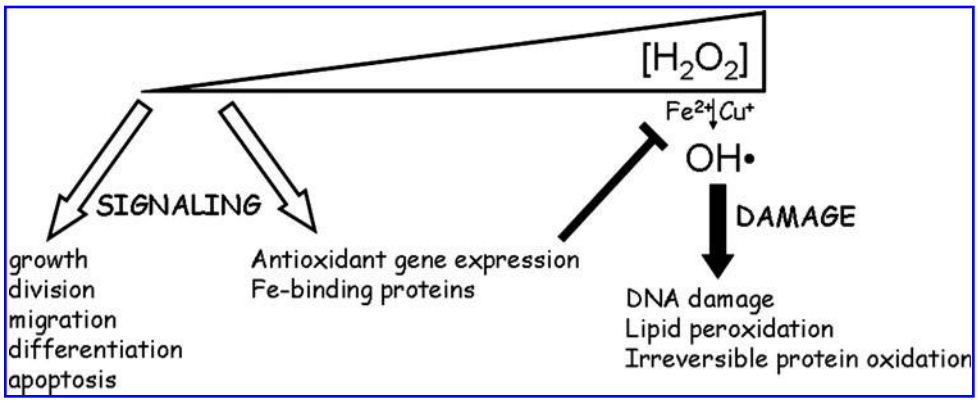

FIG. 1. The biological effect of hydrogen peroxide is dependent on its concentration. Hydrogen peroxide (H_2O_2) is a signaling molecule but can cause cellular damage, particularly after reaction with reduced iron (Fe^{2+}) or copper (Cu^{+}) ions. Consequently, signaling responses to hydrogen peroxide include changes in gene expression leading to increased removal of hydrogen peroxide (antioxidants), sequestration of iron (Fe), and altered metal ion uptake, which all act to limit reaction of hydrogen peroxide with Fe^{2+} and Cu^{+} and inhibit the generation of damaging hydroxyl radicals (OH ·). At low concentrations, hydrogen peroxide is also used as a signal to initiate diverse biological responses, including cell growth, division, differentiation, migration, and apoptosis. Where molecular mechanisms for hydrogen peroxide signaling have been established, they generally involve the reversible oxidation of low pKa protein-cysteine thiols on specific target proteins. However, these protein cysteine-thiols are also susceptible to irreversible oxidation at higher concentrations of hydrogen peroxide.

protect against MCO damage to vital enzymes under oxidative stress conditions (7). The evolution of altered metal ion homeostasis as a conserved response to hydrogen peroxide signals in diverse bacterial species likely reflects the different roles of particular metal ions in the toxicity of hydrogen peroxide (Fig. 1) (7). It will be fascinating to determine to what extent hydrogen peroxide and metal ion homeostasis are coordinately regulated in other systems too, particularly where metal ions are limiting for growth.

Responses to Hydrogen Peroxide Signals: Do or Die?

In eukaryotes, as in bacteria, hydrogen peroxide-activated signaling pathways increase the expression of antioxidant and phase 2 detoxification genes as a vital part of adaptive responses to oxidative stress. In addition, it is clear from an increasing number of studies that eukaryotes also utilize hydrogen peroxide to direct the activity of key signal transduction pathways toward biological outcomes that do not merely reflect mechanisms to protect against damaging levels of oxidants (Table 1). Nonetheless, hydrogen peroxide is potentially a significant cause of cellular damage. Indeed, many of the signaling pathways that respond to hydrogen peroxide act to prevent or repair cellular damage or to initiate apoptosis and eliminate a potentially cancerous damaged cell. For instance, as discussed by Runchel *et al*., mitogen-activated protein kinase (MAPK) activated by ROS plays important roles in initiating cell-protective responses to potential damage but can also trigger cell proliferation or apoptosis (24). Hence, hydrogen peroxide can potentially initiate very different biological outcomes through regulation of the same signaling pathways. Analogies with responses in single-cell systems suggest that the levels of hydrogen peroxide and antioxidant defenses, together with the particular effector molecules that are present, will determine the response of each cell. For instance, previous work in the fission yeast *Schizosaccharomyces pombe* has shown that distinct transcriptional responses are initiated in response to low, sublethal doses of hydrogen peroxide, to which the yeast can adapt and grow, and high doses to which prolonged exposure is lethal. Accordingly, the activities of the Pap1 and Atf1 transcription factors that are important for these transcriptional responses are subject to concentration-dependent regulatory mechanisms involving a hydrogen peroxide-sensitive thiol peroxidase, the 2-Cys peroxiredoxin Tpx1 (3, 31). Here, Quinn *et al*. present studies that suggest that a two-component system (TCS) is important specifically at high concentrations of hydrogen peroxide for regulating the activity of a third transcriptional regulator involved in these responses, Prr1, the *S. pombe* member of the fungal Skn7 family of transcription factors (23). TCS proteins are widely found in bacteria, where they initiate and control responses to a huge variety of stimuli. Although absent from metazoans, phylogenetic analysis suggests that lateral transfer events have resulted in the presence of a limited number of TCS in fungi and plants. For instance, in yeast, TCS comprising histidine kinase (HK), phosphorelay, and response regulator proteins feed into conserved p38/JNK-related MAPKs to regulate responses to stress. In *S. pombe* a TCS comprising two HKs (Mak2 and Mak3), phosphorelay protein (Mpr1), and response regulator (Mcs4) is important for the activation of the Sty1 MAPK by hydrogen peroxide. Quinn *et al*. have identified two domains in the *S. pombe* HK Mak2 that are required for peroxide signal transduction. Moreover, domain swap experiments with a HK, Chk1, from the fungal pathogen *Candida albicans* suggest that the presence of the PAS domain in Mak2 might be particularly important for hydrogen peroxide sensing. PAS domains in other proteins, such as FixL, have been previously identified as redox/oxygen sensors through their ability to bind redox-sensitive cofactors. However, it remains to be determined how the PAS domain in Mak2 senses hydrogen peroxide to elicit activation of Sty1.

Hydrogen Peroxide Signals Regulate Diverse Biological Processes

NADPH oxidase-generated ROS have long been established as an important weapon in the innate defenses of plants and animals (Table 1). However, a key discovery suggesting that hydrogen peroxide might have biological roles outside of targeted cell killing was the finding that NADPH oxidase complexes were also present in nonimmune cells (26). Indeed, as illustrated in Table 1, NADPH oxidase complexes generate

Table 1. Examples of Biological Processes Involving Hydrogen Peroxide as a Signal

Phyla	*Biological process*	*Source of hydrogen peroxide*	*Biological effect*	*Reference*
Eubacteria	Biofilm differentiation and dispersal	Lysine oxidase	Cell death	(15)
Fungi	Morphogenesis	Exogenous	Differentiation of budding yeast	(18)
	Hyphal growth	NADPH oxidase	Enforces apical dominance	(25)
	Sexual differentiation	NADPH oxidase	Differentiation of cleistothecia	(13)
Planta	Stomatal closure	Copper amine oxidase	Activates calcium channel to cause guard cell swelling	(1, 22)
	Root growth	NADPH oxidase	Activates Ca^{2+} channel leading to cell elongation	(8)
Flies	Haematopoietic cell differentiation	Mitochondrial electron transport chain	Enhances differentiation	(20)
	Cell division	Mitochondrial electron transport chain	G1-S arrest	(21)
Zebrafish	Wound healing	Dual oxidase	Leukocyte recruitment to wound	(19)
Mammals	Cardiac differentiation	NADPH oxidase	Cell differentiation	(14)
	Vascularization	NADPH oxidase	Promotes cell migration and proliferation	(12, 28)
	Angiogenesis	NADPH oxidase and lipoxygenase	Endothelial cell proliferation and migration	(4, 30)
	Innate immunity	NADPH oxidase	Neutrophil chemotaxis	(10)

hydrogen peroxide signals in many different cell types to initiate responses to a multitude of stimuli. However, cells will also detect and respond to any increases in the level of hydrogen peroxide generated during aerobic metabolism or after exposure to environmental agents.

As responses to hydrogen peroxide in each kingdom of life are likely to have originated in mechanisms to cope with its toxicity, it is plausible that many will remain connected to adaptive responses or other processes in which hydrogen peroxide is involved. For instance, although long recognized that cells actively generate hydrogen peroxide as a weapon against invading pathogens, recent studies have suggested that hydrogen peroxide produced *in vivo* at the site of wounding also protects against infection by stimulating migration of leukocytes to promote wound healing (10, 19). Similarly, hydrogen peroxide is utilized by plants to protect against pathogens by a variety of mechanisms, including as a signaling molecule to regulate stomatal opening/closure and abscission (1, 2).

Spatial Regulation of Hydrogen Peroxide Signals

Although the signaling functions of hydrogen peroxide probably arose from the need to prevent or repair the damaging effects of ROS, antioxidants that limit the potential for hydrogen peroxide to cause damage also limit its signaling capacity. Thus, an outstanding question is how the signaling functions of hydrogen peroxide are maintained against the backdrop of potential toxicity and the presence of considerable cellular oxidative defenses. An enormous literature, generated over many years, has established the importance of spatial regulation of calcium signals, localized release of calcium from intracellular stores, and the presence of localized channels all work to spatially localize signals. Despite its ability to diffuse through membranes, similar constraints are likely to be applied to hydrogen peroxide signals through the relative localization of peroxide sources, antioxidants, and signaling molecules. In addition, recent studies have suggested that aquaporin regulates the passage of hydrogen peroxide across membranes (16). Indeed, other studies have suggested that hydrogen peroxide is generated in very specific locations close to the responsive signaling molecules (29). Moreover, some of the antioxidants that damp down hydrogen peroxide signals have been shown to be spatially regulated through inhibition of their activity by post-translational modification at particular locations. For instance, at the site of wounding in mice the thioredoxin peroxidase activity of Prx1 is inhibited by phosphorylation (33). Intriguingly, analogies with work in Zebrafish suggest that this could be important for establishing a hydrogen peroxide gradient to promote the migration of cells involved in wound healing (19). Some of the intracellular sources of hydrogen peroxide are discussed by Szypowska and Burgering in relation to their roles in insulin regulation/responses (27). The relative localization of these ROS sources and signaling molecules are likely to contribute to the specificity of hydrogen peroxide signaling. This is supported by the article of Cuddihy *et al.* in this Forum using a cell system where ROS are generated and utilized in the propagation of EGF signals through the reversible inhibition, by oxidation, of the phosphoprotein tyrosine phosphatase PTP1B (5). A 2D gel analysis of cell lysate by Cuddihy *et al.* failed to detect any proteins consistently undergoing thiol oxidation in response to EGF. Indeed, they found that the vast majority of the peroxide-sensitive peroxiredoxins Prx1 and Prx2 remained in reduced form after EGF treatment (5). Although this study only examined a single cell line and used an approach insufficiently sensitive to detect the oxidation of the (less abundant) phosphatases that are oxidized in response to growth factors and hydrogen peroxide, it is consistent with the work of Woo *et al.* that also demonstrated that the redox state of the majority of Prx1 and Prx2 was not significantly affected by PDGF-induced generation of hydrogen peroxide (33). Instead, studies of Woo *et al*. suggest that mechanisms to inhibit the peroxidase activity of these enzymes are restricted

to pools of peroxiredoxin located close to the site of hydrogen peroxide generation (33). This is proposed to allow hydrogen peroxide to react with and inactivate nearby PTPs while maintaining a spatial limit to these signals and preventing damage.

Role of Hydrogen Peroxide in Disease and Aging

Despite the long-standing association of many diseases and aging with increased oxidative damage, several recent studies have questioned whether ROS-induced oxidative damage is actually a cause of aging. For example, although inhibition of insulin/insulin-like signaling leads to increased expression of many antioxidant genes, there is little evidence that any one of these genes is particularly important for the associated slower aging (6). However, in some cases, such as the genetic manipulation of superoxide dismutase (SOD) genes, the accompanying changes in ROS metabolism may not always be as simple as increasing/reducing "damaging ROS." For example, genetic manipulation of the SOD genes to increase or reduce the levels of superoxide is likely to have the opposite effect on hydrogen peroxide levels and thus influence the activity of hydrogen peroxide-regulated signaling pathways. In their review, Szypowska and Burgering describe how ROS help to potentiate insulin signaling but are also likely to be involved in many of the processes leading to both type I and II diabetes (27). It is evident that any interventions to prevent or treat diabetes and other diseases using antioxidants must take into account both the signaling roles and toxicity of hydrogen peroxide and maintain the appropriate redox balance.

Recent genetic studies in mammals, flies, worms, and yeast have suggested that inhibition of translation has a conserved role in increasing stress resistance and extending lifespan (11). Moreover, a recent study in *C. elegans* indicated that inhibition of translation can increase the activation of phase 2 detoxification/antioxidant gene expression through activation of SKN-1, a transcription factor required for both phase 2 detoxification gene expression and the antiaging effects of reduced insulin signaling (32). Although transcript profiling has established that many cells initiate substantial changes in gene expression after exposure to hydrogen peroxide, similar levels of hydrogen peroxide often lead to a global decrease in the rate of protein synthesis such that these changes are unlikely to be rapidly translated into changes in the proteome. Grant's review describes and provides valuable insight into the various mechanisms by which both global and specific mRNA translations are regulated to produce appropriate changes in the proteome in response to oxidative stress (9). As the role of ROS-induced oxidative damage in aging is challenged, understanding ROS-mediated regulation of translation will be vital to fully understand the role of ROS in the complex phenotype of aging.

Conclusions and Future Directions

As hydrogen peroxide becomes increasingly studied for its roles as a signaling molecule, many of the attributes that make it suitable for this role, such as the ability to target specific proteins, are better appreciated. It is also becoming clear that, similar to calcium and inositol signaling, spatial regulation of responses through concentration gradients extending from sites of generation and the specific intracellular location or expression pattern of responsive molecules and transporters are likely to play critical roles. Moreover, the threshold of hydrogen peroxide that initiates a particular response may be determined not only by the concentration of hydrogen peroxide and antioxidant enzymes but also by other considerations such as the intracellular metal composition.

Recent work has begun to elucidate how the signaling functions of hydrogen peroxide in eukaryotes are performed despite the presence of considerable cellular oxidative defenses and without causing cell damage (33). However, further investigations into the spatial separation of peroxide generators and signal transducers and examination of how different concentrations of hydrogen peroxide affect the activity of signaling molecules are areas of research likely to continue to provide important insight. The recent development of more specific and targeted peroxide sensors, allowing measurement of *in vivo* changes in peroxide levels, should expedite these studies (17). Measurement of the levels and cellular and subcellular distributions of antioxidants and particular metal ions may also turn out to be vitally important to understand how responses to hydrogen peroxide are coordinated.

Acknowledgments

We would like to thank the authors of each article for contributing their work and also the many anonymous reviewers whose helpful comments have been invaluable in the preparation of this Forum. In addition, we would like to thank Brian Morgan, Chris Grant, John Helmann, Janet Quinn, and members of the Veal lab for comments on this editorial. We are grateful to the BBSRC and MRC for funding.

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Date of first submission to ARS Central, February 28, 2011; date of acceptance, March 6, 2011.

Abbreviations Used

HK = histidine kinase
MAPK = mitogen-activated protein kinase
MCO = metal-catalyzed oxidation
ROS = reactive oxygen species
SOD = superoxide dismutase
TCS = two component system

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