Review Article

Reactive oxygen species-dependent wound responses in animals and plants

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ABSTRACT

Animals and plants evolved sophisticated mechanisms that regulate their responses to mechanical injury. Wound response in animals mainly promotes wound healing processes, nerve cell regeneration, and immune system responses at the vicinity of the wound site. In contrast, wound response in plants is primarily directed at sealing the wound site via deposition of various compounds and generating systemic signals that activate multiple defense mechanisms in remote tissues. Despite these differences between animals and plants, recent studies have shown that reactive oxygen species (ROS) play very common signaling and coordination roles in the wound responses of both systems. This review provides an update on recent findings related to ROS-regulated coordination of intercellular communications and signal transduction during wound response in plants and animals. In particular, differences and similarities in H_2O_2-dependent long-distance signaling between zebrafish and *Arabidopsis thaliana* are discussed.

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Introduction

Both animals and plants have evolved sophisticated mechanisms to respond to injury, a type of mechanical stress that rapidly destroys tissues and cells and exposes the organism to various types of pathogen attack. In animals, cooperation between various types of cells, such as white blood cells, platelets, epithelial cells, and vascular smooth muscle cells, is required for the wound response [1]. Multiple processes including cell migration, proliferation, and differentiation and synthesis of extracellular matrix components are initiated after injury to repair epithelial tissues and blood vessels and to kill bacteria around wound sites [1,2]. In contrast, plants do not possess mechanisms to mobilize cells in response to wounding, as cells are encapsulated inside rigid walls [3]. Wound-activated responses in plants therefore involve deposition of various compounds, such as callose and various phenolics that generate a physical barrier at the wound site and function as antimicrobials, and activation of systemic responses that are dependent on cell-to-cell signal transduction and hormones to prevent further damage to remote tissues.

Despite their toxic potential, reactive oxygen species (ROS) play important roles as signaling molecules that regulate a broad

range of biological processes [4,5]. H_2O_2, a relatively long-lived ROS, readily penetrates cell membranes and is freely diffusible between cells [6]. Diffusion of H_2O_2 that is facilitated by plasma membrane aquaporins can also influence the efficiency and perhaps even direction of H_2O_2 signaling between cells [7,8]. H_2O_2 could therefore be a strong candidate as a signaling molecule mediating cell-to-cell communication. Various types of cell-to-cell communication across cell types are essential for the regulation of both development and responses to environmental stimuli in multicellular organisms [9–11]. Previous studies have shown participation of ROS in various types of cell-to-cell communication in animals and plants, including formation of intercellular gap junctions and signal transduction in animal cells [9]; regulated apoptosis in neighboring animal cells [12]; movement via plasmodesmata, which enables transport and communication between cells in plants [10]; and intercellular movement of membrane-associated thioredoxin and transcription factors that modulate the ROS status in plants [13,14]. In addition, numerous studies have demonstrated involvement of superoxide-generating NADPH oxidases (Nox and dual oxidase (Duox) in animals and Rboh in plants), Ca^{2+}, and protein phosphorylation in coordinating various functions between cells, as well as cell-to-cell signal transduction during wound response in both animals and plants [1,5,15–17]. Recent studies uncovered the existence of H_2O_2-dependent long-distance signals induced by mechanical wounding in zebrafish and *Arabidopsis.* Niethammer et al. [16] identified a gradient of H_2O_2 generated by local epithelial cells at the wound site. This gradient extended to nearby blood vessels in zebrafish larvae and was responsible for attracting neutrophils to the wound site. Duox was identified as the source of H_2O_2 required for this signal. In *Arabidopsis,* the NADPH-oxidase homolog RbohD was shown to be required for initiation and propagation of a rapid cell-to-cell systemic signal induced by wounding. This signal was accompanied by, and dependent upon, H_2O_2 production and accumulation in the extracellular spaces between cells [15].

This review does not attempt to cover all aspects of wound response and cell-to-cell communications in animals and plants, but rather provides an update on findings related to the coordination of intercellular communications and signal transduction regulated by ROS, especially H_2O_2, during the wound response. Differences in H_2O_2-dependent long-distance signaling between zebrafish and *Arabidopsis* are also discussed. For more details on wound response and cell-to-cell communications, we refer the reader to more extensive reviews, e.g., [1,9–11,18].

Reactive oxygen-dependent wound healing in animals

Wound repair in animals involves a sophisticated coordination of various types of cells required for the formation of blood clots and the repair of tissues at the wound site. In this process, ROS signals are involved in regulating important processes such as cell migration, proliferation, and differentiation, as well as synthesis of extracellular matrix components. At one of the initial steps of wound healing, collagen-activated platelets initiate a coagulation cascade and subsequent thrombin formation [1,2]. Platelets generate ROS and colocalize with other types of ROS-generating cells, including white blood cells, at the wound site [1]. Such ROS-rich environment might be significant in the regulation of platelet aggregation and downstream signaling. Indeed, platelet aggregation, associated with an H_2O_2 burst, was shown to be inhibited by the antioxidant enzyme catalase [1]. In addition, superoxide and H_2O_2 generated through the function of NADPH oxidase are required for platelet recruitment to blood clots and activation of tissue factor (TF) expression [19,20]. Platelet-derived growth factor (PDGF) is also known to play key roles in wound healing.

H_2O_2 is required for biological processes controlled by PDGF, including tyrosine phosphorylation, activation of MAPK, DNA synthesis, chemotaxis of other cells involved in wound response, and H_2O_2 generation in nonphagocytic cells [21,22]. Furthermore, the redox state of the PDGF receptor depends on H_2O_2 produced by NADPH oxidase through the functions of protein kinase C and phosphoinositide 3-kinase [23,24]. H_2O_2 also plays important roles as a signaling molecule in the regulation of blood coagulation and thrombin formation [1]. TF upregulated by H_2O_2 promotes thrombin formation. In turn, thrombin activates H_2O_2 production via the function of vascular NADPH oxidase that subsequently initiates and activates the H_2O_2-dependent thrombogenic cycle [1,25,26].

Wound closure of epithelial tissues and recovery of blood vessels are also essential steps in wound healing. Previous studies demonstrated that ROS and NADPH oxidases are able to promote migration and proliferation of cells required for the repair of epithelial tissues and blood vessels [18,27]. H_2O_2 modulates small GTPase, Ras-dependent changes in shape, actin cytoskeleton organization, adhesion, and migration of rat fibroblast cells [28]. Such modifications of morphology or motility of cells might be due to changes in the activities of Rac1, Rho, and cofilin proteins, which play key roles in the regulation of actin dynamics. Wound angiogenesis is stimulated by a low concentration of H_2O_2 and inhibited by catalase [1]. Nox1-dependent H_2O_2 was shown to induce epithelial cell proliferation and migration by controlling cell cycle via the function of cyclin D1 [5,29]. It was also reported that Nox1 is required for the migration of vascular smooth muscle cells (VSMCs) via the function of cofilin in injury-induced neointima formation in the femoral artery [30]. In addition, low concentrations of H_2O_2 at the wound site rescued phenotypes of NADPH oxidase-deficient mice in which the endogenous H_2O_2 generation and healing response is impaired [31]. Furthermore, Nox4-derived H_2O_2 plays important roles in the maintenance of VSMC differentiation [32]. ROS signaling was also involved in the fibrinolytic system that degrades excess fibrin accumulation by collagenase and enables endothelial cells to migrate to wound sites [1]. Expression of the collagenase MMP-1 is activated by Nox4-mediated H_2O_2-dependent pathways [33]. Taken together, the studies described above demonstrate that a complex network of various NADPH oxidases and ROS signaling coordinates the function of various cell types during the wound response. A key future challenge is, however, to decipher the temporal and spatial coordination of these signals at the local and whole organism levels.

Regeneration of nervous systems in response to wounding

Regeneration of the nervous system at wound sites is another integral step of wound healing. Although previous studies demonstrated induction of neurodegeneration by H_2O_2 through activation of proapoptotic pathways such as Bax, caspase, PARP, and MAPKs [34–37], an important role for H_2O_2 in the regeneration of nerve cells was also reported. Staurosporin, a specific inhibitor of protein kinase C, induces neurite outgrowth in hippocampal cells by increasing H_2O_2 generation [38]. In this study, exogenous H_2O_2 treatment also caused neurite out growth. In *Caenorhabditis elegans*, axon guidance and regeneration might be regulated by the peroxidase-like protein PXN-2, an enzyme that possesses a peroxidase catalytic domain [39]. PXN-2 was shown to be required for axon guidance in the developing nervous system but not in axon outgrowth. In response to injury, however, regeneration of adult axons was stimulated in mutants deficient in PXN-2, suggesting an inhibitory role of PXN-2 in axon regeneration during wound healing. Although H_2O_2 accumulation was

not monitored in this study, stimulation of axon regeneration in the mutant lacking the peroxidase-like enzyme could implicate involvement of H_2O_2 in the regeneration of nervous system during wound response. In addition, Nogo-A, an inhibitor of axon regeneration, antagonized ROS production [40]. Such inhibition of ROS production by Nogo-A could play an important role in the protection of the nervous system from oxidative stress caused by H_2O_2. These results suggest a dual role for H_2O_2 in the nervous system as both a stimulator of axon regeneration in response to injury and a trigger for apoptosis.

A recent study demonstrated that H_2O_2 promotes injury-induced peripheral sensory axon regeneration in the zebrafish skin [41]. Injury to zebrafish fins strongly promoted the regeneration of sensory axons and H_2O_2 production around wound sites. Exposure of zebrafish larvae to sublethal levels of exogenous H_2O_2 promoted growth of severed axons. Interestingly, blocking of H_2O_2 production by inhibition of the NADPH oxidase Duox1 prevented the promotion of axon activity, suggesting that Duox-dependent H_2O_2 production is necessary for promotion of injury-induced axon regeneration. A gradient of H_2O_2, as proposed for the roles in leukocyte recruitment [16], is not, however, thought to be required for promotion of axon regeneration. In addition, H_2O_2-induced axon regeneration was not inhibited in a mutant lacking blood cell and macrophage recruitment in larvae. These results suggest that H_2O_2-dependent axon regeneration is independent of H_2O_2 function in the inflammatory response. However, the integration of axon regeneration and the inflammatory response is still poorly understood.

Involvement of reactive oxygen signaling in the wound inflammatory response

The inflammatory response is characterized by migration of white blood cells into wound sites and a burst of superoxide and H_2O_2 [2]. ROS generated during the inflammatory response participate in signal transduction as well as protection of host cells by killing invading bacteria [2,42]. Nox2 is highly expressed in phagocytes [43] and plays an essential role in the inflammatory response. Alteration in Nox2 activity resulted in deregulation of inflammatory processes leading to chronic granulomatous [42]. Activation of adhesion molecules is a critical step in the migration of leukocytes during the inflammatory response. ROS-activated NF-κB plays a key role in the release of inflammatory cytokines that induce expression of adhesion molecules [44,45]. An inflammatory cytokine, tumor necrosis factor α, was not able to induce the expression of the adhesion molecule ICAM-1 in coronary microvascular endothelial cells from mice lacking a subunit of Nox2 [46], suggesting involvement of Nox2 in migration of leukocytes that is regulated by the activation of inflammatory cytokines and adhesion molecules. It was also reported that lipopolysaccharides increase the expression of ICAM-1 in human aortic endothelial cells in an NF-κB-dependent manner through the function of Nox4 [47]. Several recent studies, however, reported negative regulation of inflammatory responses by NADPH oxidases [18,48].

H_2O_2 induces an attractant signal that controls migration of leukocytes or acts as a chemoattractant itself [49–52]. Previous studies demonstrated that H_2O_2-induced chemoattractants such as transforming growth factor β and MCP1 are involved in recruitment of monocytes to wound sites in humans [49,50]. Duox was also shown to be required for migration of embryonic hemocytes toward the wound sites in *Drosophila* [53]. More recently, Moreira et al. [54] revealed that H_2O_2 functions not only as an attractant signal that guides *Drosophila* hemocytes to wound sites, but also as an essential molecule that differentiates between

damaging signals and standard developmental signals during wound responses. These results suggest that H_2O_2 generated via NADPH oxidases might be required for the appropriate guidance of leukocytes to wound sites. Interestingly, a recent study using zebrafish larvae provided clear evidence showing that a gradient of H_2O_2 generated from local epithelial wound sites is responsible for attracting neutrophils, and inhibition of this H_2O_2 gradient by an NADPH oxidase inhibitor blocks the wound inflammatory response ([16]; discussed in detail below).

Monocytes and macrophages are known to release high-mobility group box 1 (HMGB1) proteins that accelerate the inflammatory response during wounding [55]. Tang et al. [56,57] demonstrated an important role for H_2O_2 in active HMGB1 release via a MAPK and chromosome region maintenance 1-dependent mechanism. In addition, previous studies suggested a role for H_2O_2 in the regulation of adhesion between neutrophils or macrophages and cytokine signals involved in the survival of monocytes and macrophage at the wound site [1,58].

Reactive oxygen signals involved in the wound response of plants

When dealing with wound responses in plants and animals it is important to remember that plants do not have an immune system involving various types of circulating cells, nor do they have a network of nerve cells to rapidly transmit signals from the wound site. Wound responses in plants are therefore limited to the activation of various local signals such as ROS and calcium, the activation of cell death pathways if needed, and the generation of long-distance signals that involve ROS and electric waves, as well as various hormones.

ROS, calcium (Ca^{2+}), protein phosphorylation, and wound-inducible hormones such as jasmonic acid (JA), ethylene, and abscisic acid (ABA) play pivotal roles in the wound response of plants [3,17,59–61]. At an early stage of the wound response, plants transiently produce superoxide and H_2O_2 that might play important roles in signal transduction [3,62,63]. Wounding induces the expression of the cytosolic H_2O_2-detoxifying enzyme, ascorbate peroxidase 2 (APX2) [64]. Wound-induced expression of APX2 is independent of other wounding signals such as JA or ABA, but requires photosynthetic electron transport. In addition, wound-induced APX2 expression was suppressed by the NADPH oxidase inhibitor diphenyleneiodonium (DPI). These results suggest that NADPH-dependent H_2O_2 signals could contribute to the activation of specific wound signals not activated by the JA- or ABA-dependent pathways. The cellular steady-state level of ROS is tightly regulated by a complex network involving Ca^{2+}, protein phosphorylation, and ROS-scavenging/producing enzymes during the wound response. Mechanical wounding induces a burst of superoxide, as well as an apoplastic peroxidase that might possess both oxidative and peroxidative activities [65]. In addition, wounding of *Arabidopsis* roots elicits Ca^{2+}-dependent activation of RbohC, resulting in H_2O_2 production at the cell wall [60], suggesting positive regulation of H_2O_2 signaling by Ca^{2+}. Furthermore, a recent study reported that *Arabidopsis* mitogen-activated protein kinase 8 (MPK8) plays important roles in coordinating various signals such as protein phosphorylation, Ca^{2+}, and H_2O_2 in the wound response [17]. MPK8 is activated in response to wounding through the binding of calmodulin in a Ca^{2+}-dependent manner and phosphorylation by the MAPK kinase MKK3. In contrast to RbohC-mediated H_2O_2 production in roots, the MPK8 pathway negatively regulates H_2O_2 accumulation by controlling the expression of RbohD, implicating a pivotal role for Ca^{2+} in modulation of cellular H_2O_2 level in response to wounding.

Programmed cell death was previously associated with hormone signaling and enhanced accumulation of H_2O_2 [66–68]. Antisense suppression of a wound-response JA synthesis enzyme, OsHI-LOX, in rice resulted in enhanced tolerance to infestation of phloem-feeding herbivores accompanied by increased cell death as well as enhanced accumulation of H_2O_2 and salicylic acid (SA) [66]. Oh et al. [68] analyzed transgenic plants silenced for a negative regulator of JA signaling, NaJAZh, in tobacco. The suppression of NaJAZh resulted in enhanced tolerance of plants to herbivores. Interestingly, NaJAZh-silenced plants demonstrated spontaneous development of leaf necrosis associated with enhanced expression of programmed cell death genes and accumulation of H_2O_2 and SA during the transition to the reproductive stage. Furthermore, these transgenic plants accumulated significantly higher levels of H_2O_2 in wounded leaves compared to wild-type plants. These results suggest that JA could play a key role in the regulation of cell death associated with H_2O_2 and SA signaling.

The wound response in plants involves accumulation of various compounds such as callose and various phenolics that generate a physical barrier at the wound site and function as antimicrobials. Callose is thought to participate in strengthening of cell walls and closing of plasmodesmata to prevent the spread of invading pathogens [10]. Callose accumulation is triggered by an oxidative burst in response to pathogen attack, the activation of programmed cell death, or ozone stress [10,69–71]. Various phenolic compounds that accumulate after an oxidative burst during injury in plant tissues are also part of a defense response against microbes [72–74]. Lignin biosynthesis is a key process required for the strengthening of plant cell walls. In response to cell wall damage, it is regulated by cross talk between H_2O_2- and JA-dependent signaling [75]. During early stages of lignin biosynthesis, H_2O_2 is required to induce a secondary oxidative burst and JA accumulation. During late stages of lignin biosynthesis, RbohD-dependent H_2O_2 and JA–isoleucine form a negative feedback loop that modulates lignin accumulation. The studies described above indicate extensive cross talk between wound and pathogen responses, as well as between the oxidative burst and the production of various secondary compounds in plants.

Reactive oxygen-dependent systemic wound response in plants

Being sessile organisms and unable to mobilize cells to a wound site, plants rely on the activation of wound response mechanisms in the entire plant in response to a local injury. This type of response limits damage that might occur if the injury spreads or appears in remote tissues, as well as helping to prevent further damage to remote tissues in case the injury is caused by an insect that is mobile. In plants JA plays a central role in the systemic wound response. Wound-induced systemic signaling depends on both biosynthesis of JA at the site of wounding and the ability to perceive a jasmonate signal in systemic tissues [59,76]. Involvement of H_2O_2 in systemic signaling, activated during plant immunity, wound response, or high light acclimation, was initially addressed more than decade ago by Alvarez et al. [77], Orozco-Cardenas and Ryan [78], and Karpinski et al. [79], respectively. Wound-induced increases in H_2O_2 and methyl jasmonate in systemic tissues were shown to be sensitive to the NADPH oxidase inhibitor DPI, suggesting that NADPH oxidase is required for the activation of systemic wound responses [80]. Sagi and co-workers [81] demonstrated that wound-induced expression of a marker protein of systemic wound response, proteinase inhibitor II, was compromised in antisense lines of RbohD, supporting the requirement of Rboh-dependent H_2O_2 production for systemic wound responses. Recently, we demonstrated that
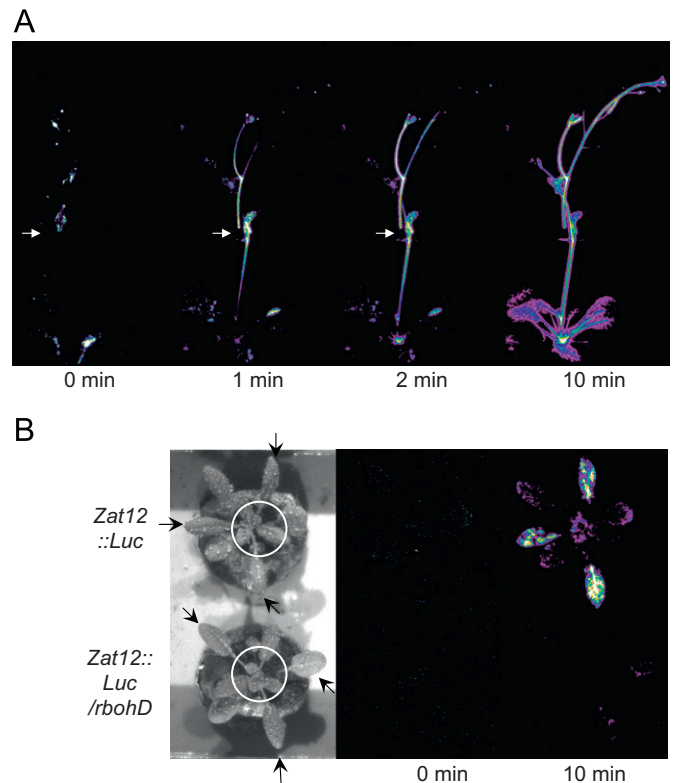

Fig. 1. Imaging of the wound-induced systemic signal in *Arabidopsis* using a luciferase reporter gene fused to the promoter of the zinc-finger protein ZAT12 [15]. (A) Time-lapse imaging of a systemic ROS signal propagating throughout an entire *Arabidopsis* plant in response to wounding at the middle of the stem (white arrows). (B) Suppression of the wound-induced systemic signal in wounded rosette leaves (black arrows) and in systemic unwounded leaves (white circles) of a plant lacking the NADPH oxidase RbohD gene.

the NADPH-oxidase homolog RbohD is required for the initiation and amplification of a rapid autopropagating systemic signal that travels at the rate of approximately 8.4 cm/min and is induced by various abiotic stimuli including mechanical wounding (Fig. 1) [15]. Development of this signal is accompanied by, and dependent upon, H_2O_2 production and accumulation in the extracellular spaces [15]. The potential involvement of electric signals was also implicated in RbohD-triggered rapid systemic signaling during wounding [15,82,83]. Recent studies reported on wound-induced electric signals in plant species other than *Arabidopsis*. These signals were faster than 8.4 cm/min and propagated for longer distances [82,84]. Electric signals with a maximum velocity of 10 cm/min or 20.9 cm/s were induced by mechanical wounding in *Vicia faba*, barley [82], or avocado tree [84], respectively. In avocado tree the signals propagated over distances of 30 to 100 cm [84]. Electric signals induced by wounding could therefore play a significant role in the propagation of rapid long-distance signaling in various plant species.

Comparison of H_2O_2-dependent long-distance signaling between plants and zebrafish

In a recent study, the dynamics of H_2O_2 signaling in response to wounding was monitored in a larval zebrafish tailfin using a fluorescent H_2O_2 sensor protein revealing a function for H_2O_2 as an initial chemoattractant signal for the migration of leukocytes to wound sites (Fig. 2A) [16]. The sustained rise in H_2O_2 at the wound margin reached concentrations of 0.5–50 µM and the H_2O_2 gradient extended approximately 200 µm; far enough to
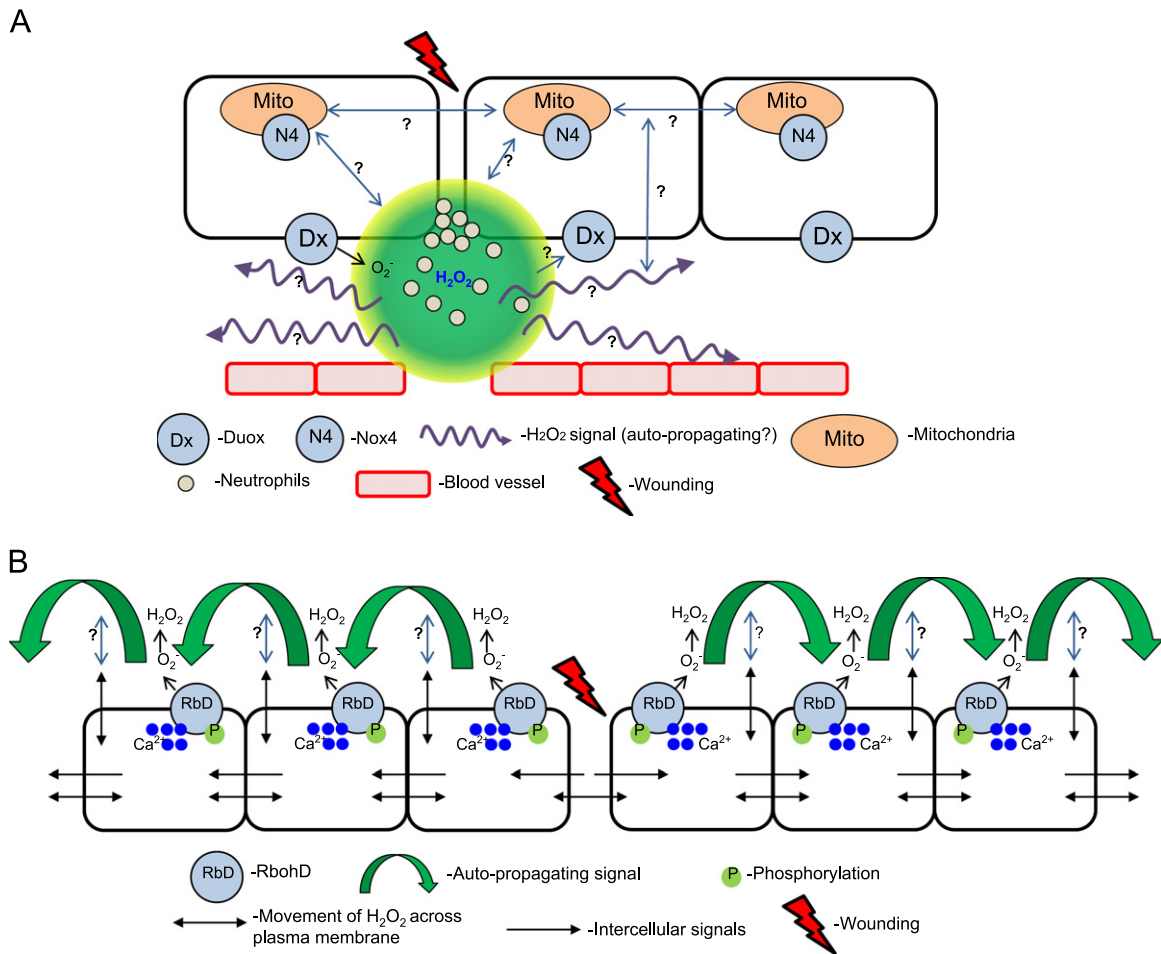
Fig. 2. A model for H_2O_2-dependent long-distance signaling in response to wounding in *Arabidopsis* and zebrafish. (A) Long-distance signaling in zebrafish. An H_2O_2 gradient is generated from local epithelial wound cells in zebrafish larvae. This gradient is responsible for attracting neutrophils to the wound site. Dual oxidase (Dx) is required as the source of H_2O_2 [16]. Green circle with color gradation indicates H_2O_2 gradient. (B) Rapid systemic signaling in *Arabidopsis*. The NADPH oxidase homolog RbohD (RbD) is required for the initiation and propagation of wound-induced rapid systemic signaling. This signal is accompanied by, and dependent upon, ROS production and accumulation at the extracellular spaces [15]. The ROS-dependent long-distance signal is autopropagating and is amplified by each of the various cells along its path.

reach nearby blood vessels. The H_2O_2 gradient was established within 10 min of injury, resulting in recruitment of leukocytes to wound sites. Inhibition of NADPH oxidase using antisense RNA or chemical inhibitors revealed that Duox is the source of H_2O_2. In addition, suppression of Duox with antisense caused a significant decrease in wound-induced H_2O_2 generation and subsequent leukocyte recruitment to wound sites without reducing the number of leukocytes. A dual role for Nox enzymes in innate immunity after wounding was suggested in a previous review [85].

Recently, we demonstrated that the NADPH-oxidase homolog in *Arabidopsis,* RbohD, is required for the initiation and propagation of a rapid systemic signal that travels at the rate of 8.4 cm/min and is induced by wounding (Fig. 2B) [15]. This signal is also triggered by various abiotic stimuli such as heat, cold, and high light, and its amplification depends on H_2O_2 production and accumulation at the extracellular spaces. The rapid rate of the H_2O_2 signal and its ability to travel in both up and down directions (along the stem of the plant) at the same rate indicate that the signal is actively propagating and is independent of normal diffusion of H_2O_2. In addition, transcriptome analysis showed that transcripts responsive to H_2O_2 account for the majority of transcripts upregulated in systemic tissues in response to wounding. The propagation of the rapid systemic signal was suppressed by catalase that decomposes H_2O_2. Taken together, it is likely that superoxide produced by RbohD is rapidly dismutated to H_2O_2

spontaneously or through the action of apoplastic superoxide dismutases such that H_2O_2 primarily mediates the rapid systemic signal.

In contrast to the chemoattractant signal in zebrafish that is dependent on a gradient of H_2O_2 produced by a group of cells at the injury site, the systemic H_2O_2 signal produced in *Arabidopsis* is autopropagated to distant cells without loss of signal intensity (Fig. 2B). Application of an NADPH oxidase inhibitor, or catalase, at the wound site, or as far as 10–15 cm from it, was found to block further propagation of the signal [15]. This finding indicated that each cell along the path of the systemic signal was actively producing H_2O_2 in a type of H_2O_2-induced H_2O_2-production mechanism (Fig. 2B). Such active propagation of Nox- or Duox-dependent signals in animals has not been reported. Based on the results obtained with plants, it would be important to investigate whether active propagation of similar ROS signals exists in animals. Nox4 was recently found to play an important role in mediating mitochondrial oxidation during pressure overload [86]. In heart cells, the mitochondrial energy state is synchronized across a mitochondrial network via waves of superoxide-induced superoxide release [83,87]. Such a communication between mitochondria might be similar to the mechanisms that propagate long-distance cell-to-cell signaling in plants [15] and could occur among different groups of animal cells. It would also be interesting to study what the contributions of Nox4 and the mitochondrial ROS network are to the propagation of ROS signaling in animals (Fig. 2A).

Active propagation of long-distance signals might be important for animal systems, even those with an efficient circulatory system. It was reported that H5N1 influenza virus infection elicited high levels of proinflammatory cytokines in whole lungs and primary human macrophages [88]. Moreover, pulmonary arteries constrict, whereas systemic arteries dilate under hypoxic conditions to improve gas exchange in the lung and to increase the delivery of blood to other hypoxic tissues [89]. Mitochondrial redox signaling associated with ROS might be involved in O_2 sensing in these vascular responses [89]. These findings could suggest that long-distance signaling in animals is required to prevent further damage to nearby cells caused by viruses or to regulate cellular homeostasis in various systemic tissues.

Species-specific H_2O_2 responses were revealed by a comparison of transcriptome profiling data between various organisms, including plants and humans [90], indicating diversity in H_2O_2 signaling between different organisms. The broad range of processes associated with the wound response of different organisms might, however, be regulated by a conserved network of ROS-producing NADPH oxidases and depend on Ca^{2+} and protein phosphorylation. Similarities among NADPH oxidases in structure, subcellular localization, tissue distribution, and function have been previously described between animals and plants [5,85,91,92]. Diversity in H_2O_2 signaling between different organisms could thus be attributed to differences in spatial or temporal coordination of NADPH oxidase activity and other regulatory mechanisms such as Ca^{2+} and MAPKs. Indeed, different types of wound-response pathways associated with Ca^{2+} signaling seem to be activated at different times during the wound response. For example, wounding induced early (within 5 min) and late (after 1 h) calcium waves in bovine corneal endothelial cells [93]. Interestingly, suppression of wound healing occurred only after the inhibition of the late Ca^{2+} waves [93]. In *C. elegans,* formation of the actin ring was initiated within minutes after mechanical wounding and the ring gradually closed over the next 1–2 h [94]. Moreover, in plants, early wound response signals associated with H_2O_2 and MAPKs were activated within 10 min or earlier [15,17], and defense mechanisms, such as JA accumulation, reached a maximum level at 1 or 2 h after wounding [95]. These results suggest that species-specific processes, such as wound healing in animals and defense response in plants, might be activated at relatively later stages of the wound response, after early signaling events that could be conserved among different species. Dissection of wound responses with respect to different Ca^{2+} waves activated at different times might be key to elucidating the diversity of H_2O_2-dependent wound response signaling between different organisms. The similarities and differences between long-distance H_2O_2 signaling in zebrafish and *Arabidopsis* should be further studied especially in the context of NADPH oxidase networking and the various pathways that function up- or downstream along the signal path. It would also be interesting to find out whether animal cells are capable of generating autopropagating H_2O_2 signals that cover long distances along various tissues or entire organs. In plants it would be interesting to find out how the functions of different Rboh genes expressed in different tissues are coordinated. For example, can the RbohD-dependent systemic signal generated in leaves be integrated with signals generated in roots via the root-specific RbohC enzyme [60]. In future studies the complex coordination between various ROS signals or ROS and other wound-specific signals should be further addressed.

Conclusions

Wound responses in animals and plants are largely dependent on cell-to-cell communication events that are partially regulated by H_2O_2. Animals evolved sophisticated ROS signaling pathways to coordinate the dynamics of the wound response, promote immune responses, and initiate tissue regeneration. These pathways function on a local scale and involve a gradient of H_2O_2 that spreads on a tissue scale (extended approximately 200 µm from the wound site). In contrast, plants use ROS to trigger local wound responses, as well as to generate an autopropagating systemic signal that travels from the wound site to the entire plant (often as far away as 20 cm from the wound site in *Arabidopsis*). NADPH oxidases, such as Duox or RbohD, are the driving force behind this local and long-distance signaling. It is unclear, however, whether animal cells use a similar autopropagating mechanism to send ROS signals across entire organs or large tissues. Such a system could facilitate or amplify the immune response in animals allowing for a more comprehensive networking of various cells.

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