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Invited Review Article

ROS and redox regulation of cell-to-cell and systemic signaling in plants during stress

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ABSTRACT

Stress results in the enhanced accumulation of reactive oxygen species (ROS) in plants, altering the redox state of cells and triggering the activation of multiple defense and acclimation mechanisms. In addition to activating ROS and redox responses in tissues that are directly subjected to stress (termed 'local' tissues), the sensing of stress in plants triggers different systemic signals that travel to other parts of the plant (termed 'systemic' tissues) and activate acclimation and defense mechanisms in them; even before they are subjected to stress. Among the different systemic signals triggered by stress in plants are electric, calcium, ROS, and redox waves that are mobilized in a cell-to-cell fashion from local to systemic tissues over long distances, sometimes at speeds of up to several millimeters per second. Here, we discuss new studies that identified various molecular mechanisms and proteins involved in mediating systemic signals in plants. In addition, we highlight recent studies that are beginning to unravel the mode of integration and hierarchy of the different systemic signals and underline open questions that require further attention. Unraveling the role of ROS and redox in plant stress responses is highly important for the development of climate resilient crops.

1. ROS, redox and stress responses

Stress causes alterations in plant metabolism and enhances the rate of reactive oxygen species (ROS; H_2O_2, $O_2^{\cdot-}$, $^1O_2$ and $HO^{\cdot}$) production in cells due to the uncoupling of different metabolic pathways and the transfer of electrons from electron transfer chains to oxygen [1–9]. Numerous studies demonstrated that the steady-state level of ROS in the cytosol, different organelles, and the apoplast is elevated in cells during responses to stress [5–9]. In addition to this type of 'metabolic' ROS production in cells during stress, the sensing of stress or pathogen infection by different stress sensors and receptors typically results in the enhanced production of ROS by dedicated enzymes, such as respiratory burst oxidase homologs (RBOHs), that are the equivalents of mammalian NADPH oxidases (NOXs; 1–4). The activation of RBOHs is considered an 'active' ROS production process during stress, and together with the metabolic ROS production that happens as a byproduct of changes in plant metabolism, the elevated ROS levels in cells during stress trigger the activation of different acclimation and defense mechanisms (Fig. 1; 1–9). The molecular mechanisms by which ROS activate acclimation and defense mechanisms during stress have been the subject of recent studies that identified important redox regulators that control these processes (Reviewed in 1, 2, 5, 6, 8, 9). While ROS can directly oxidize multiple proteins in the cell and alter their structure and function, several important regulators facilitate this protein oxidation process in a protein- and/or pathway-specific manner. These include specific glutathione peroxidases (GPXs), peroxiredoxins (PRXs), receptor-like kinases (*e.g.*, Cysteine-reach Receptor Like Kinase 5; CRK5; Hydrogen-Peroxide-induced Calcium increase 1; HPCA1), and many

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thioredoxins (TRXs), glutaredoxins (GRXs), and other proteins, as well as small molecule redox regulators, such as glutathione (GSH; 1, 2, 5–13). Together these proteins and small molecules play a major role in sensing and regulating the levels of ROS in cells, altering the structure and function of many different target proteins, such as transcription factors (TFs), kinases, phosphatases, channels, and many other proteins (*e.g., MYELOBLASTOSIS DOMAIN PROTEIN 30,* MYB30; Lesion Simulating Disease1, LSD1; Enhanced Disease Susceptibility, EDS1; Phytoalexin Deficient 4, PAD4), that activate acclimation and defense mechanisms and allow the cell to become tolerant to the stress (Fig. 1; [1–13]). For recent reviews on ROS and redox regulation of protein structure and function the reader is referred to [1,2,5,6,9].

When considering ROS and redox regulation of plant stress responses, it is also important to note that different ROS are produced in different compartments of the cell during stress (*e.g.,* 1, 2). As ROS such as H_2O_2 are relatively stable in cells and can be mobilized between different compartments through aquaporins [1,2,14], they serve an important regulatory role in communicating stress levels between different compartments, as well as between cells. Different abiotic and/or biotic stresses can therefore cause the accumulation of H_2O_2 and other ROS that will function at the compartment(s) they are produced in, as well as in other compartments. It was recently proposed that different stresses will generate different 'landscapes' of ROS in cells, and that these stress-specific landscapes will cause the activation of specific acclimation and/or defense mechanisms through the function of the different ROS sensors that are found in each different compartment of the cell (*e.g.,* GPXs, PRXs, CRK5; HPCA1; 1,2,15). ROS therefore play a key role in the sensing of stress and the activation of defense and/or acclimation responses, leading to enhanced survival of plants in response to different biotic and abiotic stress conditions (Fig. 1). As the frequency and intensity of different stresses (and their potential combinations) is predicted to increase in the coming years, due to climate change [16–18], the study of ROS signaling during stress is highly important for the development of climate resilient crops. Below we will discuss how ROS and other signal transduction molecules and mechanism mediate and regulate systemic responses of plants to different abiotic stresses.

2. Systemic signaling pathways during stress

The plant environment can be highly dynamic with rapid changes in conditions such as humidity, temperature, the presence of pathogens or insects, or the ambient level of different air pollutants such as ozone. While in many instances the entire plant will be simultaneously subjected to the changes in environmental conditions, in some cases certain tissues (termed 'local' tissues) will sense the change in conditions before the entire plant will. Under these conditions the local tissues that were first to sense the change in environmental condition will generate a systemic signal that will spread to other plant tissues (termed 'systemic' tissues) and alert them to the impending stress conditions that may affect them (Fig. 2; [19–24]). Classic examples for this are the activation of systemic signaling pathways by an excess light stress exposure, or pathogen infection, of one leaf (the local leaf). Under these conditions the stressed/infected tissue will generate a systemic signal that will induce systemic acquired acclimation (SAA; 25), or systemic acquire resistance (SAR; 26), in systemic tissues of the plant and make them acclimated to high light, or resistant to pathogen infection (Fig. 2). It was also shown that SAA alone in response to a local excess light stress treatment can induce SAR against virulent pathogens [27], and this was termed systemic cross-tolerance. A similar systemic signaling process occurs in plants in response to wounding, triggering a systemic wound response (SWR) that can cause the elevated expression of proteins (*e.g.,* protease inhibitors) that deter insect predation in all systemic tissues (Fig. 2; 19–23).

Over the years, researchers have identified several different systemic signals that spread from the stressed local tissue to the entire plant. These include hormones such as ethylene, jasmonic, abscisic, and salicylic acids, peptides, different metabolites, and different volatile molecules (*e.g.,* [19–28]). In addition to these, several faster ('rapid') response signals were also identified. These are mobilized within seconds to minutes from the local tissue to the entire plant and include electric, calcium, ROS, and hydraulic waves (Fig. 2). Electric waves result from rapid membrane depolarization of cells and can take several forms. They are thought to propagate on the plasma membrane of cells and to transverse long distances within seconds [29–34]. Since plant cells are connected to each other via plasmodesmata (PD; 35), the membranes of almost all cells in the plant are connected, allowing the rapid spread of electric signals over long distances [27,29–34]. In contrast to electric waves, ROS waves are a result of rapid changes in apoplastic and cytosolic steady-state ROS levels in one cell that cause a similar change in apoplastic and cytosolic steady-state ROS level in the cells adjacent to it and propagate from cell-to-cell until they reach the entire plant [36–46]. Similar to ROS waves, calcium waves propagate from cell-to-cell and are characterized by enhanced calcium level in the cytosol of cells [47–50]. Recent studies demonstrated that electric, calcium and ROS waves are generally propagating through the same cell layers of the plant. While electric and calcium waves mainly propagate through the vascular bundles of plants via phloem and xylem parenchyma cells (32–34, 49, 51; electric waves can also propagate on the surface of leaves; 34, 52), depending on the type of stress initiating the systemic signaling response, the ROS wave propagates through phloem and xylem parenchyma, or mesophyll cells [44,45]. In contrast to the electric, ROS and calcium waves, the hydraulic wave is thought to propagate through xylem vessels [53].

In addition to the different rapid systemic signals described above, changes in the redox state of cells were shown to propagate rapidly from local to systemic tissues in response to wounding or excess light stress. These changes were tied to changes in the chloroplast plastoquinone pool and linked to electric waves [25,54], as well as tied to the function of RBOHs at the plasma membrane and thereby linked to the ROS wave [55]. As changes in redox play a key role in plant acclimation to stress [1,5–8], deciphering the exact mechanisms that link the redox state of

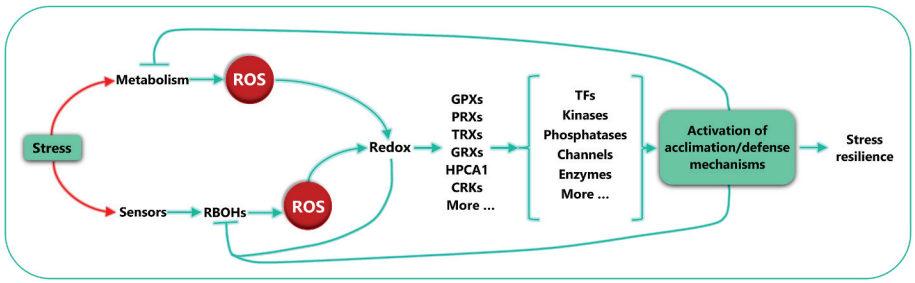

Fig. 1. ROS and redox responses in plants during stress. Stress is shown to cause ROS accumulation in cells due to alterations in plant metabolism ('metabolic' ROS production), or the activation of RBOHs following the sensing of stress ('active' ROS production). The elevated levels of ROS alter the redox state of cells and trigger the activation of different defense and acclimation mechanisms through different redox regulators such as GPXs and PRXs. Abbreviations: CRKs, cysteine-rich repeat kinases; GPXs, glutathione peroxidases; GRXs, glutaredoxins; HPCA1, H_2O_2-induced Ca^{2+} increases 1; PRXs, peroxiredoxins; RBOHs, respiratory burst oxidase homologs; ROS, reactive oxygen species; TFs, transcription factors; TRXs, thioredoxins.

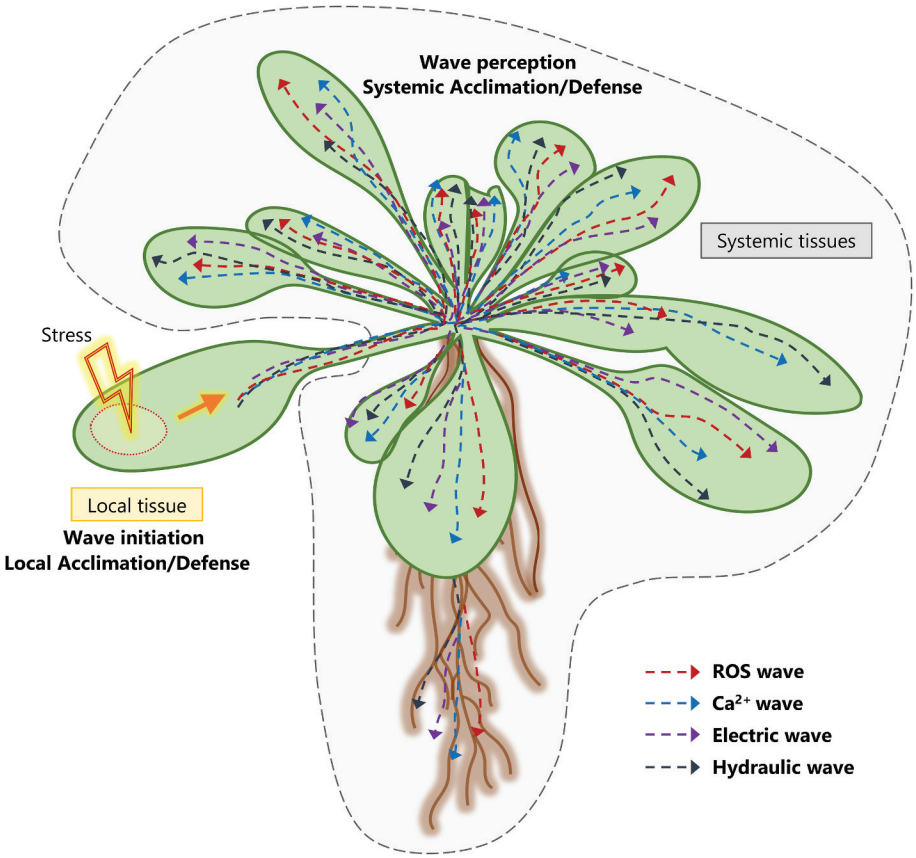

Fig. 2. Systemic signaling in plants during stress. The sensing of stress by one leaf (the 'local' tissue) is shown to activate several different rapid systemic signals (electric, calcium, ROS, redox and hydraulic) that travel from the local tissue to other tissues of the plant (the 'systemic' tissues), activate defense and acclimation mechanisms, and induce a state of systemic acquired resistance or acclimation in them, hardening the plant against further, or additional stress conditions. Ca^{2+}, calcium; ROS, reactive oxygen species.

one plant cell to the other should be the focus of future studies. The importance of redox changes to plant acclimation was recently demonstrated in mutants that lack the redox-regulated TF MYB30 [37,56]. In these mutants the ROS wave occurred in response to a local stimulus, but plant acclimation (SAA) was impaired [37]. These finding suggest that systemic changes in redox levels play a key role in plant acclimation to stress.

One of the key questions that awaits discovery in the systemic signaling field is the hierarchy and integration of different systemic signals (electric, calcium and ROS). In addition, the cell and tissue types that mediate these signals, as well as the role of key regulators of each signal and their potential to integrate different signals, need to be further clarified [57]. The electric and calcium waves were shown, for example, to be dependent on the glutamate receptor like channels (GLRs) GLR3.3 and GLR3.6. In their absence (*i.e.,* in a *glr3.3glr3.6* double mutant), both waves are suppressed in response to wounding [32,33,49]. Although GLRs can function as calcium permeable channels [50], during responses to salinity stress the calcium wave was also linked to other calcium channels such as two pore calcium channel 1 (TPC1; 47, 48). Further studies are therefore needed to determine what are the different calcium channels involved in the electric and calcium waves. Similarly, in the absence of a functional Photosystem II Subunit S (PsbS) protein (*i.e.,* non-photochemical quenching mutant *npq4-1*) electrical and ROS signaling, cellular light memory and plant acclimation responses are deregulated [27,51,52]. While the calcium and electric waves are dependent on GLRs and PsbS, the ROS wave, as well as different types of electric waves, were found to depend on RBOHs [36,38,46]. Interestingly, during systemic responses to wounding, all 3 waves (electric, calcium and ROS) were dependent of GLR function [38]. In contrast, during systemic responses to excess light stress, only the calcium and electric waves depended on GLRs, while the ROS wave was not [40]. In a recent study it was also shown that the H_2O_2 receptor HPCA1 and the calcium permeable channel mechanosensitive ion channel 3 (MSL3) are both required for the calcium and ROS waves during responses to excess light stress [42]. It therefore appears that in response to different types of stresses, different tissues and regulatory proteins may be involved in mediating and regulating systemic signaling responses. These interactions and their underlying mechanisms should be the subject of future studies, as they may reveal how specificity is determined during systemic signaling in plants. Below we will discuss the different mechanisms that mediate cell-to-cell signaling during systemic responses to stress in plants.

3. Cell-to-cell signaling during systemic responses to stress

Cell-to-cell signaling is fundamental to multicellular organisms. The four basic types of cell-to-cell signaling are paracrine, autocrine, endocrine, and juxtacrine. Cell-to-cell signaling is used in plants and animals to communicate signals over short or long distances, however with some key differences. While in animals long-distance signaling is primarily mediated by neurons and/or blood vessels (Fig. 3A), in plants long-distance signaling is mediated by cell-to-cell signaling involving many cells that touch each other, each transmitting the signal to the next (Fig. 3B; 57,58). This type of cell-to-cell communication primarily involves paracrine (through the apoplast and cell wall), and juxtacrine (through PDs) signaling, and is similar to local communication between animal cells that involves paracrine and juxtacrine (Fig. 3C; 58). Since each plant cell involved in such a signaling pathway transmits the electric, calcium and ROS waves, each cell could be considered 'activated' or 'excited' once the signal reaches it and turns it 'on' [1,22]. Thus, much like neurons that excite each other, transmitting a signal over long distances, plant cells excite each other using the electric, calcium and ROS waves. As the electric wave is the fastest out of these three, it will reach the receiving cells first, followed by the calcium and ROS waves, that are linked together [42]. It is therefore possible that the electric wave primes each cell to the coming calcium and ROS waves,

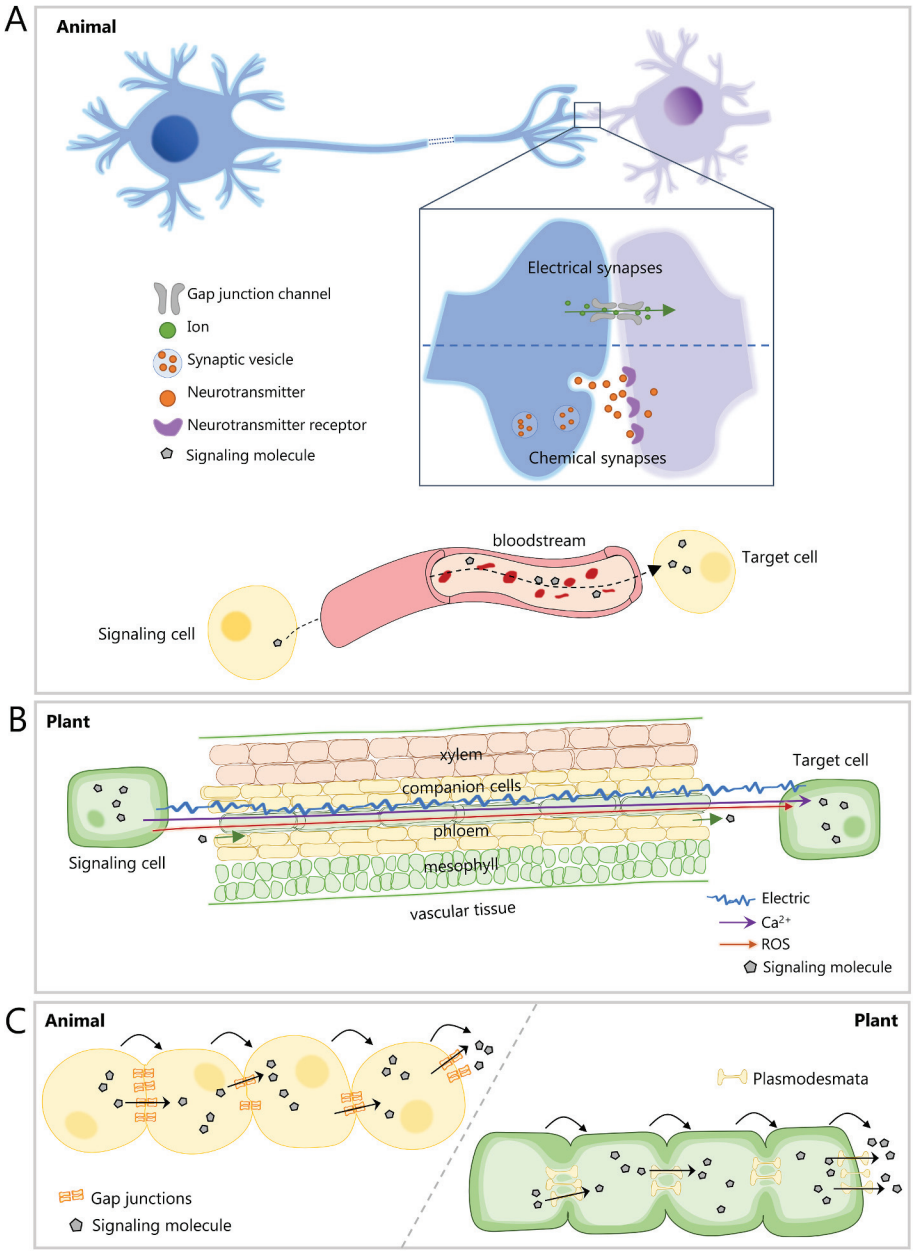

Fig. 3. Similarities and differences between systemic signaling in plants and animals. **A.** Long distance signaling is mediated in animals through neurons and blood vessels. **B.** In plants long distance signaling is mediated via systemic cell-to-cell signaling. **C.** Local cell-to-cell signaling in animals and plants can be mediated via paracrine and juxtacrine signaling. In plants juxtacrine signaling is mediated through plasmodesmata, while in animal cells it is mediated through gap junction and tunnelling nanotubes. Ca^{2+}, calcium; ROS, reactive oxygen species.

but that true activation of acclimation and defense mechanisms that results from changes in redox, calcium, protein phosphorylation/dephosphorylation, and other signaling events, as well as opening of PD, requires the ROS and calcium waves that are dependent on each other [34,40,42,43,46].

4. Apoplastic, symplastic, and membrane signaling during systemic responses to stress

The transmission of systemic signals such as electric, calcium, ROS, and redox waves requires the function of apoplastic, symplastic, plasma membrane (PM), and PD associated mechanisms (Fig. 4). Electric waves that are triggered by a mechanical injury or other abiotic stresses are thought to propagate on the plant PM and to be affected by the ion and pH differences between the cytosol and the apoplast (Fig. 4A; 19, 29, 50). They need however to transvers PDs along their path and could be subjected to regulation by PD-localized mechanisms (Fig. 4A; 38). In addition, because the PD pores contain membrane extensions of the endoplasmic reticulum (ER) system that connects cells, and some GLRs are localized to the ER membrane [59], it is also possible that PDs transmit electric signals between the ER membrane systems of adjacent cells (Fig. 4A). In addition, it was shown that abiotic stresses, such as light stress, can trigger electric waves suggesting that chloroplasts and other organelles that are in contact with the PM or the ER, may also produce electric signals (Fig. 4A; 27, 34, 51). Since electric waves play a canonical role in systemic signaling in plants, further studies are needed to determine how they are transferred between cells during systemic responses to stress.

In contrast to electric waves that are transferred via cellular membranes or on the surface of a leaves, calcium waves occur in the cytosol of plants. The elevation in calcium levels in the cytosol could be a result of stored calcium being mobilized from the apoplast, ER or the vacuole (Fig. 4B). Since, like other small molecules, calcium can transverse the PD, it is likely that changes in cytosolic calcium levels in one cell will affect calcium concentrations in a neighboring cell. In addition, if ER stores of calcium are used for the calcium wave, then the triggering of

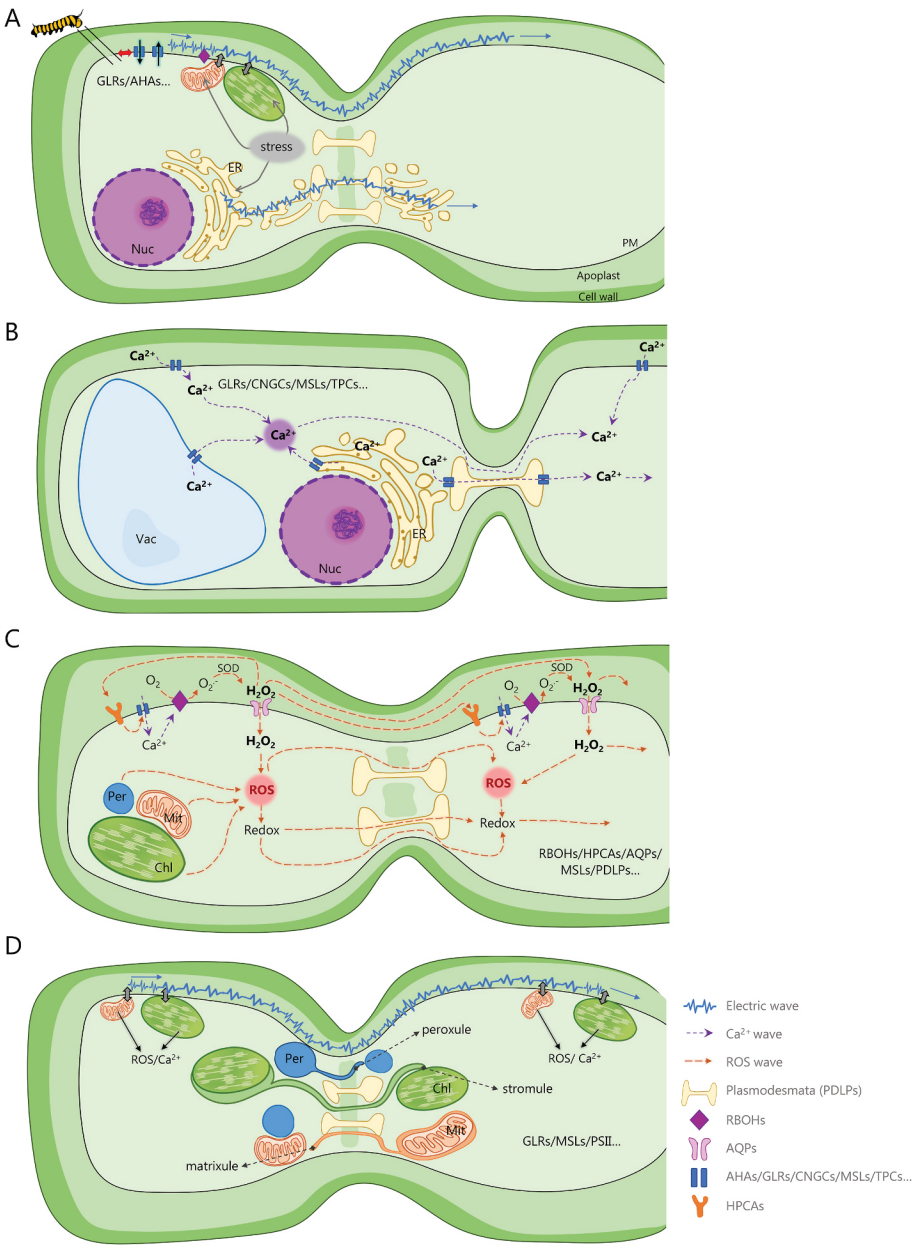

Fig. 4. Proposed modes of systemic cell-to-cell transmission of signals between plant cells during systemic signaling. The mode of cell-to-cell electric (**A**), calcium (**B**), ROS and redox (**C**), and organelle (**D**) signaling is highlighted. Electric, calcium, ROS/redox, and organelle signaling are shown be mediated through symplastic (through plasmodesmata), and/or apoplastic (the extracellular space of plant cells) pathways in cells. Please see text for more details. Abbreviations: AHAs, H^+-ATPases; AQPs, aquaporins; Ca^{2+}, calcium; Chl, chloroplast; CNGCs, cyclic nucleotide-gated ion channels; ER, endoplasmic reticulum; GLRs, glutamate receptor-like channels; H_2O_2, hydrogen peroxide; HPCAs, H_2O_2-induced Ca^{2+} increases; Mit, mitochondria; MSLs, mechanosensitive ion channels-like; N, nucleus; O_2^-, superoxide; PDLPs, plasmodesmata-localized proteins; Per, peroxisome; PM, plasma membrane; PSII, photosystem II; RBOHs, respiratory burst oxidase homologs; ROS, reactive oxygen species; SOD, superoxide dismutase; TPCs, two pore calcium channels; V, vacuole.

calcium release from the ER of one cell can be linked to the other via the ER membrane connections of cells that occur through the PD (Fig. 4B). Of course, because the PM of all plant cells are connected, depolarization of the PM (or ER) of one cell can also affect the activity of calcium channels in the other, linking the calcium levels of different cells. The absolute dependence of the wound response-triggered electric and calcium waves on GLRs, that are localized to the ER and PM [32,33,49], suggest that both compartments are involved in linking electric and calcium waves (Fig. 4B). Further studies are however needed to determine how the electric and calcium waves are integrated during the systemic response of plants to different stresses.

The ROS wave is dependent on the function of PM-localized RBOHs that produce superoxide at the apoplastic side of the cell; which can be rapidly converted into H_2O_2 by extracellular superoxide dismutase (SOD; 1, 36–46, 57, 58). The produced H_2O_2 can enter cells through aquaporins (AQPs) and/or activate cytosolic calcium signaling via PM-localized HPCA1 (Fig. 4C; 40, 42). Once H_2O_2 enters cells through AQPs, it can alter the redox sate of the cell and trigger acclimation and defense mechanisms (Fig. 4C; 1, 55). As ROS produced in the apoplast of one cell can affect a neighboring cell via HPCA1, or AQPs, located on the neighboring cell, the ROS wave can be mobilized between cells through the apoplast (Fig. 4C). Interestingly, recent studies have shown that in addition to RBOHs, the ROS wave is also dependent of on PD-localized proteins 1 and 5 (PDLP1 or PDLP5; 38, 40). Moreover, it was shown that ROS produced by RBOHs is triggering an enlargement of PD pores that facilitates rapid cell-to-cell transport, in a process that is dependent on PDLPs (Fig. 4C; 40; this process is likely to be transient, as PD are usually closed due to callose deposition at later stages of pathogen infection or stress; 60, 61). Since H_2O_2 and the redox state of cells can be mobilized through PDs to neighboring cells [60,61], it is possible that the ROS wave is also propagating through the PDs of cells (Fig. 4C). Our current understanding of the ROS wave is therefore that it requires both apoplastic (RBOHs, and HPCA1) and symplastic (PDLPs) functions, and that it can propagate between cells through the apoplast and/or PDs, but that both compartments are needed for its cell-to-cell mobilization (Fig. 4C). Additional studies are of course needed to determine how the ROS wave regulates PD functions and how it is mobilized between cells.

While the role of the apoplast, cytosol and PDs in systemic signaling

has been extensively investigated (Fig. 4A–C), the possible involvement of organelle-to-organelle communication between cells during systemic cell-to-cell signaling requires more attention [62–64]. Electric waves were shown to coordinate the chloroplastic response of different cells within a plant to wounding and high light stress [27,31,51,52]. Moreover, it was shown that chloroplastic responses to stress in one plant can be transferred by electric signals to other plants that are physically touching it (via leaves) under humid conditions, coordinating the chloroplastic response of the different (touching) plants to stress [34]. This phenomenon was termed network acquired acclimation (NAA; 34). The observations described above open the possibility that organelles that are touching the PM (or ER) in different cells communicate stress signals with each other by sending and receiving electric waves (Fig. 4D). In addition, it is possible, but not shown yet, that membrane extensions of different organelles can cross the PDs of cells creating an organelle cell-to-cell network (Fig. 4D). Further studies are of course needed to determine the role of organelle-to-organelle communication during systemic responses to stress in plants.

5. Systemic signal integration and pending questions

The hierarchy and mode of integration of the electric, calcium and ROS waves remain open questions. Undoubtfully, the electric wave is the fastest of the three, but how and whether it triggers the calcium and ROS waves is unknown. The electric and calcium waves propagate through the same cell layers of the plant and require GLRs for their function (*e.g.,* 32, 33, 49), raising the possibility that membrane depolarization and/or apoplastic/cytosolic changes in pH, potentially associated with the electric wave, could trigger GLRs and/or Arabidopsis H^+-ATPases (AHAs) function and subsequently activate the calcium wave (Fig. 5A; 50,65). The changes in cytosolic calcium levels could directly activate RBOHs and calcium dependent protein kinases (CPKs) that will phosphorylate and further activate RBOHs, or open additional calcium channels such as MSLs and cyclic nucleotide-gated ion channels (CNGCs) that would cause the activation of RBOHs through similar mechanisms (Fig. 5A; [40,42,66–68]). H_2O_2 produced by RBOHs and SODs will be sensed then by HPCA1, further opening calcium channels such as MSL3 (or other channels), to support and amplify the calcium wave [42]. The calcium and ROS wave may therefore be intertwined in a continuous amplification loop that propagates from cell-to-cell over long distances [42]. Changes in PM membrane potential, as a result of RBOHs activation (transfer of electrons from the cytosol to the apoplast during RBOHs function), could also amplify and support the electric wave (Fig. 5A; 38, 46). Finally, the elevated ROS levels will alter the cellular redox state of cells through GPXs, PRXs, and other redox regulators, turning 'on' the redox wave [55]. Since changes in the redox state of cells could cause the enhanced expression of ROS detoxifying mechanism and or turnover/suppression of RBOHs, the redox wave could suppress the ROS wave (Fig. 5A; 1,69), and thereby function as a negative feedback loop for all other waves. This hypothetical chain of events and integration scheme of the different waves (Fig. 5A) requires further studies. In addition, in response to different types of stress (or stress combinations) such as wounding and excess light stress, it may be different. Thus, for example, while the ROS

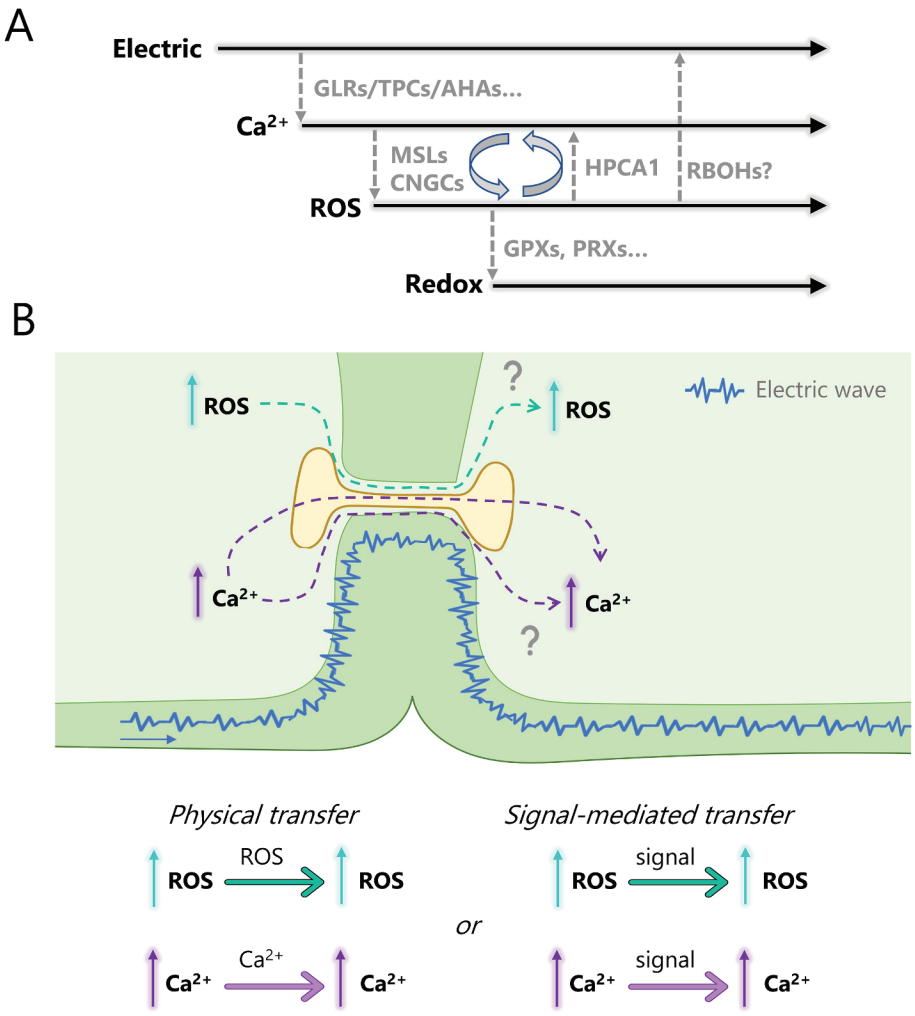

Fig. 5. Hierarchy and integration of different systemic signals and an important open question. **A.** A proposed model for the hierarchy and integration of rapid systemic signals in plants. The electric wave is shown to activate the calcium wave that activates the ROS wave. The calcium and the ROS wave are shown to be dependent on each other. The ROS wave is shown to activate the redox wave. Key proteins involved in these integration steps are indicated. Please see text for more details. **B.** The levels of ROS and calcium are shown to be altered in adjacent cells during systemic signaling. However, whether ROS and or calcium are physically transported from one cell to the other is highlighted as a key question that should be answered. Since the electric wave is mobilized between the two adjacent cells through membrane structures at the plasmodesmata, it could function for example as a signal that triggers ROS and calcium responses in the two cells (without ROS and/or calcium being physically transported from cell to cell). Please see text for more details. Abbreviations: AHAs, H^+-ATPases; Ca^{2+}, calcium; CNGCs, cyclic nucleotide-gated ion channels; GLRs, glutamate receptor like channels; GPXs, glutathione peroxidases; HPCA1, H_2O_2-induced Ca^{2+} increases 1; MSLs, mechanosensitive ion channels; PRXs, peroxiredoxins; RBOHs, respiratory burst oxidase homologs; ROS, reactive oxygen species; TPC, two-pore channel.

wave is dependent on GLR function during responses to wounding, it is not dependent of GLRs during responses to excess light stress [38,40]. In addition, subcellular localization of calcium or ROS to the vicinity of specific membrane domains or protein complexes within cells, and the intracellular gradients of calcium and ROS generated from these subcellular localizations, could also regulate the different waves and integrate them [70,71].

In addition to the question of hierarchy and integration of the different waves (Fig. 5A), there is also the question of direct transfer of the different signals from one cell to the other (Fig. 5B). While it is easy to imagine how electric waves are transferred between cells through the plasma and/or ER membrane connections of the PD, there is very little evidence for the direct transfer of calcium or H_2O_2 between cells through the apoplast or PDs during rapid systemic signaling. We cannot therefore rule out the possibility that each cell along the path of the cell-to-cell signal is altering its own levels of ROS and calcium, and that the connection between cells is not mediated by physical transfer of ROS and/or calcium between cells (Fig. 5B). The electric wave, or other signals, could for example trigger changes in ROS and calcium levels in each cell, but these changes will not be linked to each other by direct physical transfer of calcium and/or H_2O_2 molecules between cells (Fig. 5B). While grafting experiments between WT and different mutants, the use of genetically encoded sensors for calcium and ROS, the demonstration that opening of PDs results in the facilitated mobility of a fluorescent compound from cell-to-cell, as well as the external application of different scavengers or inhibitors, such as catalase that cannot enter cells, diphenyleneiodonium (DPI), or calcium signaling blockers and chelators (*e.g.,* 36–49,55), support the hypothetical models shown in Fig. 4, direct measurements of calcium and H_2O_2 transfer between cells during rapid systemic signaling are needed to substantiate them. In addition to this question, the relationship between apoplastic and cytosolic H_2O_2 levels needs to be addressed. Measurements of the ROS wave were conducted at the apoplast [36] and cytosol [39] of cells, but how are AQPs, HPCA1, and other proteins at the interface between the apoplast and cytosol regulate these levels is also an open question. Moreover, the biological function of the different regulators, rapid systemic signals, and pathways such as SAA and SAR, identified in laboratory studies, needs to be examined under field conditions [72]. There are many differences between field and laboratory conditions [73], including basal levels of different hormones, redox status, and other signaling pathways that may be altered under field conditions, and the function and biological relevance of the different systemic signaling pathways described above could be different under these conditions [72–75]. Finally, because plant pathogens can also produce ROS, and/or manipulate ROS production by plants for their own benefit [76], further studies are needed to determine how local and systemic ROS and redox signaling are affected by different pathogens, and the interactions between these different pathogens and other abiotic conditions such as temperature, humidity, atmospheric CO_2 levels, and light intensity.

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