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MINI-REVIEW

NADPH oxidases, essential players of hormone signalings in plant development and response to stresses

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ABSTRACT

Plasma membrane NADPH oxidases (NOXs), also named respiratory burst oxidase homologues (Rbohs), are critical generators of reactive oxygen species (ROS), which as signal molecules regulate growth and development, and adaptation to various biotic and abiotic stresses in plants. NOXs-dependent ROS production is frequently induced by diverse phytohormones. The ROS commonly function downstream of, and interplay with hormone signalings, coordinately modulating plant development and stress tolerance. In this review, we summarize recent advances on the roles and molecular mechanisms of Rbohs in mediating signalings of multiple hormones including auxin, gibberellins, abscisic acid, ethylene and brassinosteroids in plants.

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Reactive oxygen species (ROS) such as superoxide anion ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2) are byproducts of cellular metabolisms in plants. They are produced in different organelles or subcellular compartments.[1,2] Excessive ROS are harmful for plant growth and survival, and the levels of ROS in cells are efficiently and reversibly balanced by a variety of ROS scavenging systems.[1,2] During long-term evolution, plants have utilized ROS as signal molecules to regulate growth and development, and responses to diverse biotic and abiotic environmental stresses.[2–5]

ROS are synthesized by both enzymatic and non enzymatic reactions in plants. Plasma membrane NADPH oxidases (NOXs), also known as respiratory burst oxidase homologues (Rbohs), are essential producers of ROS. Rbohs transfer electrons from cytoplasmic NAD(P)H to O_2 to form $O_2^{\bullet-}$, which rapidly converts to H_2O_2 spontaneously or catalyzed by superoxide dismutase.[6–8] Rbohs have been demonstrated to be vital players of numerous cellular processes such as pathogene defense, stomatal closure, seed germination, root growth, reproductive development, and adaptations to various abiotic stress.[6–9] In Arabidopsis genome, 10 Rboh genes (AtRbohA-J) have been identified. AtRbohB serves a role in seed afterripening.[10] AtRbohC positively regulates root hair growth and cellular integrity.[11,12] AtrbohD and AtrbohF synergistically or independently function in root formation, stomatal closure, and in responding to diverse stresses.[7,8,13–17] AtrbohE is involved in modulating programmed cell death,[18] and AtrbohI regulates drought stress response in seeds and roots.[19] Both AtrbohH and AtrbohI are key regulators of pollen tube tip growth and polar root hair growth.[20,21]

NOXs also play pivotal roles in numerous cellular processes regulated by phtohormones.[9] NOXs-dependent ROS signals interact with hormone signals, coordinately regulating plant growth and development, and acclimation to diverse environmental stresses. Previously, Xia et al have discussed the crosstalks between NOXs-produced ROS and hormones in plants.[9] In this review, we focus on recent work that highlights the roles and mechanisms of Rbohs in mediating hormone signalings in plants.

NOXs exert effects in lateral root formation, polar growth and response to hypoxia modulated by auxin

Auxin is a crucial hormone that controls nearly all aspects of plant growth and development. It can induce the generation of ROS, which in turn regulate auxin signaling as well as auxin-controlled growth programmes.[9] Evidence indicated NOXs are critical for lateral root (LR) emergence regulated by auxin.[22] It was found that exogenous ROS can rescue the LR-lack phenotype of Arabidopsis double mutant *aux1 lax3* (*auxin 1, like AUX1 3*), in which the auxin influx carrier genes *AUX1* and *LAX3* are disrupted. AUX1 and LAX3 act in the accumulation of auxin in cortical and epidermal cells overlying new LR primordia (LRPs). The accumulated auxin induces the expression of cell wall remodeling genes, thereby facilitating LR initiation and emergence. ROS play significant roles in auxin-stimulated wall remodeling during LRP development, possibly through wall acidification of the cells overlying LRP.[22] Moveover, multiple AtRboh genes (*AtRbohA, AtRbohC, AtRbohD* and *AtRbohE*) are active in the cells related to LR emergence. Mutants of *AtRbohC, AtRbohD* and/or *AtRbohE* showed delayed LR development. Auxin also induces the spatial expression of several *AtRbohs* including *AtRbohA, AtRbohC, AtRbohD, AtRbohE, AtRbohF, AtRbohG* and *AtRbohI* in roots.[22] Collectively, these results suggest auxin signalings regulate the expression of *AtRbohs*,

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and subsequent production of ROS in roots, promoting LR outgrowth in *Arabidopsis*.

NOXs are responsible for auxin-modulated root hair growth. Mangano et al observed that auxin-controlled auxin response factor (ARF) like ARF5, ARF7, ARF8 and ARF19 transcriptionally activate the bHLH transcription factor RSL4 (Root hair defective six-like 4), which up-regulates the expression of genes encoding AtrbohC, AtrbohJ and AtrbohH, as well as class III peroxidases.[21] The NOXs and peroxidase catalyze the synthesis of ROS, further promoting root hair cell elongation.[21]

NOXs also modulate auxin signal transduction under oxygen deficiency in *Arabidopsis*.[23] Under submergence condition, mutants of *AtrbohI* shows clearly decreased survival rate and chlorophyll contents, and reduced expression levels of hypoxia responsive genes including *AtHRE1* (*Hypoxia responsive ethylene-responsive transcription factor 1), AtADH1* (*Alcohol dehydrogenase 1), AtLDH* (*Lactate dehydrogenase*), and *AtSUS1* (*Sucrose synthase 1*). Oxygen deprivation substantially increases the expression of *AtrbohI*. The increased effects are markedly inhibited by auxin transport inhibitor 1-naphthylphthalamic acid (NPA). Moreover, lack of auxin causes the reduction of the transcriptional abundances of *AtSUS1* in *AtrbohI* mutants. Disruption of *AtrbohI* lowers the increases in the expression of auxin-responsive genes induced by oxygen starvation,[23] indicating that *AtrbohI* is involved in auxin signaling under oxygen deprivation. Auxin regulates hypoxia response likely through affecting ethylene biosynthesis under hypoxia in *Arabidopsis*.[23]

NOXs positively regulate gibberellins-induced seed germination

Gibberellins (GAs) serve vital roles in modulating many aspects of plant growth and development including activating α-amylase in aleurone cells and promoting seed germination.[24] ROS has been demonstrated to positively influence seed germination, and NOXs are an important player during the process.[25] During barley seed germination, NOX genes are highly expressed in embryotic cells, and a large amount of NOXs-dependent ROS are generated, which stimulate GA biosynthesis in embryos through increasing the expression of *HvGA20ox1* (*GA20-oxidase 1), HvGA3ox1, HvGA2ox4* and *HvKAO1* (*Ent-kaurenoic acid oxidase 1*), key genes involved in GA synthesis. NOXs also positively regulate α-amylase activities induced by GA in embryotic cells. The combined effects of NOXs significantly promote seed germination in barley.[25,26] Additionally, NOXs activity in aleurone cells enhances after treatment with GA. GA most likely induces the enhancement of Ca^{2+} in aleurone cells, further activating NOXs in barley seed germination.[25]

NOXs promote seed germination through degradation of ABA

ABA plays pivotal roles in plant responses to various biotic and abiotic stresses, as well as in regulating stomatal closure, and growth and development.[27,28] Evidence reveals that NOXs function in barley seed germination via affecting ABA catabolism.[25] During barley seed germination, NOXs inhibitor DPI (Diphenylene iodonium) clearly decreases endogenous ABA levels in embryos, and suppresses the expression of *HvABA8'OH-1* (*ABA8'-hydroxylase-1*), a gene required for ABA catabolism. This indicates that NOXs may stimulate ABA catabolism through impacting the expression of *HvABA8'OH-1*, further inducing seed germination. ABA also inhibits the expression of *HvRbohB1, HvRbohE, HvRbohF1* and *HvRbohF2*, and activity of NOXs and ROS production in embryos of barley.[25]

NOXs play roles in scald development and response to abiotic stresses regulated by ethylene

Ethylene is involved in regulating plant growth including cell expansion and fruit ripening, senescence, and multiple stress responses.[29] It also acts in apple scald development after exposure to cold stress. Zermiani et al investigated the action and mechanisms of ethylene regulating the scald formation in apple fruit superficies in response to cold stress, and found that ethylene negatively modulates the ROP-GAP rheostat, and progressively impairs apoplastic H_2O_2 homeostasis, further promoting the scald development.[30] NOXs, as key components of ROP-GAP rheostat, are essential for maintainance of the ROS equilibrium. Ethylene downregulates the expression of *MdRbohF* and particularly *MdRbohC*, leading to the disturbance of the apple ROP-GAP rheostat machinery and 'ROS gene network', thereby disruption of apoplastic ROS homeostasis during cold exposure.[30]

Rbohs also function in AtERF73 (Ethylene-responsive factors73)/HRE1-mediated feedback regulation of hypoxia signaling in *Arabidopsis*.[31] AtERF73/HRE1 is a central regulator of ethylene responses under hypoxia.[32] It is also regulated by ROS, the key components of oxygen deficiency signaling. Under oxygen starvation, NOXs-dependent ROS are rapidly generated, which affect ethylene signaling, and trigger downstream transcriptional responses of hypoxia-inducible genes including *AtERF73/HRE1*.[32,33] Recently, Yang et al found that hypoxia-induced production of H_2O_2 in mutants of *AtERF73/HRE1* significantly reduces.[31] Moreover, the expression of *AtRbohB* and *AtRbohD* clearly enhances while that of *AtRbohG* decreases in *AtERF73/HRE1* mutants. The transcriptional abundances of *AtRbohI* also markedly alter in the *AtERF73/HRE1* mutants.[31] These results imply that AtERF73/HRE1 regulates H_2O_2 generation through impacting the hypoxia-stimulated expression of many AtRboh genes under oxygen deficiency.

Studied showed that NOXs have effects in ethylene-induced aerenchyma formation under oxygen limited conditions.[34] In rice, the expression of *OsRbohH* is highly induced in root cortical cells. Mutation of *OsRbohH* or inhibition of NOX activity significantly suppresses ROS production and ethylene-stimulated aerenchyma formation. OsRbohH is activated by CDPK5 (Calcium-dependent protein kinase 5) and CDPK13 in *N. benthamiana* leaves, and Ca^{2+} signaling is involved in aerenchyma formation in rice roots.[34] These results demonstrated that CDPK5- and/or CDPK13-mediated Ca^{2+} stimulates OsRbohH-dependent ROS generation, further promoting ethylene-induced aerenchyma formation in rice roots under hypoxia.

Similarly in sunflower, ROS showed to mediate ethylene-induced aerenchyma formation in stem. In addition, pretreatment with DPI partially inhibits the aerenchyma formation modulated by ethylene,[35] pointing to the importance of NOXs in ethylene signaling. Yet, which NOX subunits play a role in the processes is unexplored.

Additionally, NOXs are responsible for the resistance to multiple abiotic stresses controlled by ERF74.[36] ERF74 positively regulates *Arabidopsis* tolerance to drought, high light, heat and aluminum stresses through inducing ROS burst in the early stages of various stresses. The ROS burst relys on the high expression of *AtRbohD*. ERF74 directly binds to the GCC *cis*-elements of *AtRbohD* promoter and activates its expression under the abiotic stresses. Also, *AtRbohD*-dependent ROS burst is required for inducing the expression of many stress marker genes involving in flooding, drought and aluminum stress, and in ROS scavenging enzyme genes under different stresses in *Arabidopsis*.[36]

NOXs function in brassinosteroids-mediated stomatal closure, systemic resistance and seedling growth

Brassinosteroids (BRs) are key growth promoting hormones. They modulate cell division, elongation and vascular differentiation, and stress response.[37] BRs positively and negatively affect ABA-induced stomatal closure.[38] BR mutant *bri1-301* shows decreased sensitivity to ABA-promoted stomatal closure, suggesting BR signaling is required for ABA modulated stomatal closure. However, high levels of BR suppress ABA-evoked stomatal closure. Further studies revealed that BR inhibits the enhancements in expression of *AtrbohD, AtrbohF, AtNIA1* (*Nitrate reductase 1*) and *ATNIA2* elicited by ABA, thereby repressing ABA promotion of ROS production and nitric oxide (NO) synthesis.[38] This suggests that BR suppresses ABA-mediated stomatal closure at least partially through inhibiting ABA-induced expression of *AtrbohD* and *AtrbohF*.

NOXs also essential for BR-induced systemic virus resistance in *Nicotiana benthamiana*.[39] BR has shown to trigger system resistance to virus, and the accumulation of ROS and NO in leave of *Nicotiana benthamiana*. The ROS are originated from NOXs, particularly NbRbohB because silencing of the gene *NbRbohB* notably suppresses BRs-stimulated ROS production and systemic immunity response. Moreover, in the presence of BRs, NbRbohB-mediated ROS accumulation is regulated by BR receptor kinase NbBRI1 (BR insensitive 1).[39]

Recently, Song et al observed that the reduction in BR levels or deficiency of BR receptor promotes the sensitivity of tomato plants to the nematode *Meloidogyne incognita* while application of BR has the opposite effects.[40] Further study reveals that lack of BR leads to marked decreases in apoplastic ROS generation and the expression levels of *Rboh1*, and the activation of mitogen-activated protein kinase 1/2 (MPK1/2) and MPK3 in roots. Compared with the wild-type plants, the silenced lines of *Rboh1, MPK1, MPK2* and *MPK3* genes showed elevated susceptibility of roots to nematode infection, and arrested resistance against the nematode triggered by BR. These results indicate that the Rbohs-mediated the activation of MPK cascade plays significant roles in BR-induced systemic resistance against the nematode in tomato.

NOXs have been demonstrated to mediate BR controlled *Arabidopsis* seedling development (including hypocotyls elongation and root meristem development), Tian et al reported that H_2O_2 stimulates the oxidation of the key BR signaling transcription factor BZR1 (Brassinazole-resistant 1), further increasing the transcriptional activity of BZR1 by promoting its interaction with the crucial auxin-signaling regulator ARF6 (Auxin response factor 6) and the key light-signaling regulator PIF4 (Phytochrome interacting factor 4), thereby facilitating seedling growth.[41] DPI significantly represses BR-induced H_2O_2 generation and BR-promoted hypocotyl elongation and cell division of root quiescent center (QC). Moreover, double mutant *atrbohd/atrbohf* is hyposensitive to BR-modulated hypocotyl elongation and QC cell division,[41] highlighting the great importance of AtrbohD and AtrbohF in BR regulated growth and development.

In summary, recent evidence reveals that NOXs play crucial roles in the multiple hormone signalings. However, the molecular mechanisms for most hormones activating NOXs during growth or under some specific stresses are largely unknown. The regulation mechanisms for NOXs mediating hormone signalings in many cases also remain to be thoroughly investigated in the future.

Disclosure of potential conflicts of interest

The authors declare that they have no conflicts of interest in the research.

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