Plant Signaling & Behavior ›
Volume 7, 2012 - Issue 6

Mini Review

N-rich protein (NRP)-mediated cell death signaling

A new branch of the ER stress response with implications for plant biotechnology

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Pages 628-632 | Published online: 14 May 2012

Cite this article https://doi.org/10.4161/psb.20111

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attenuates dehydration-induced cell death and promotes a better adaptation of BiP-overexpressing transgenic lines to drought.

Keywords: :

ERD15 GmNAC6 N-rich proteins NRP-A NRP-B cell death response endoplasmic reticulum stress osmotic stress

The endoplasmic reticulum is a key signaling organelle involved in the activation of cellular stress responses in eukaryotic cells. One such well-characterized signaling event is the unfolded protein response (UPR), which is activated to cope with the disruption of ER homeostasis that results in the accumulation of unfolded or misfolded proteins in the lumen of the organelle. In mammalian cells, the UPR has been associated with other stress response pathways through shared components.[1] In plants, the potential of the ER stress response to accommodate adaptive pathways and its connection with other environmentally induced responses have been the subjects of studies in recent years.[2,3] One plant-specific, ER stress-shared response is ER and osmotic stress-integrated signaling, which converges on N-rich proteins (NRPs) to transduc l death signaling ls for full activatio

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transducers. Under normal conditions, the molecular chaperone BiP is bound to the luminal domain of these receptors, rendering them inactive. The accumulation of misfolded proteins in the ER increases the need for the molecular chaperone activity of BiP, and thus, upon ER stress, BiP is released from these receptors. BiP dissociation causes the activation of the three transducers. The activation of PERK suppresses protein synthesis through the phosphorylation of translation initiation factor 2 α (IF2α). Upon BiP release, Ire1 undergoes dimerization, which sequentially activates its kinase and ribonuclease activity to induce the spliceosome-independent splicing of XBP1 (X-box binding protein-1) mRNA to generate mature mRNA that encode an active transcription factor. The activation of ATF6 promotes its translocation to the Golgi, where it is specifically cleaved by the proteolytic enzymes SP1 and SP2. Upon proteolytic hydrolysis of the transmembrane, the transcriptional activation domain of ATF6 detaches from the membrane and is directed to the nucleus. In the nucleus, XBP1 and ATF6 act in concert to activate the expression of ER-resident molecular chaperones, foldases and components of the ER-associated degradation (ERAD) system to increase the protein folding and processing capacity of the ER under stress conditions. Thus, on a physiological level, the activation of UPR triggers three protective cellular responses: (i) attenuation of protein translation through the PERK-mediated phosphorylation of IF2α, (ii) upregulation of ER chaperones and (iii) degradation of misfolded proteins by the proteasome (ERAD). However, the failure to restore ER homeostasis under stress condition[illegible]ways as an ultimate[illegible]rtite module,[illegible] and ATF6 transduc[illegible]

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and activates the stress-inducible BiP3 promoter.[10] More recently, it has been demonstrated that upon ER stress, bZIP60 mRNA is spliced in an IRE1b-mediated process to generate an alternatively spliced transcript that lacks the transmembrane domain-encoding sequences.[7,9] This splicing leads to the synthesis of a soluble and functional bZIP60 transfactor that can be translocated to the nucleus, where it activates ER stress inducible promoters, such as the BiP3 promoter. Likewise, OsbZIP74 or OsbZIP50 from rice, an ortholog of Arabidopsis AtbZIP60, is regulated through the IRE1-mediated splicing of its RNA to render the activation of ER stress-inducible promoters.[11,12]

The second branch of UPR in plants mechanistically resembles the ATF6-mediated transduction of the ER stress signal. The membrane-associated Arabidopsis ATF6 homologs are bZIP17 and bZIP28, and they have canonical S1P sites in their C-terminal tails that face the ER lumen and appear to be processed by S1P and S2P. Upon ER stress, bZIP17 and zZIP28 are relocated to the Golgi, where their transcriptional domains are proteolytically released from the membrane by SP2.[13] The transcriptional activator components of these transmembrane transfactors are then translocated to the nucleus, where they promote the expression of stress response genes.[14-16,2] Thus, the bipartite cellular response to ER stress in plants is mediated through Ire1-like receptors and ATAF6 analog transducers to induce ER-resident molecular chaperones andthe ER-associated protein degradation machinery as a protective measure. Howeve rtheless, little is k cell death in plants. F as been shown t ll death in Arabidop AGB1) of the heterotr unicamycin (Tm), a vith the dem ty to ER stress a ble mutant.[8] Although g ER stress-induced strated through istically control t

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and osmotic stress signals into a full response.[18] This integrative pathway was first identified through genome-wide approaches and expression profiling, which revealed the existence of a modest overlap of the ER and osmotic stress-induced transcriptomes in soybean seedlings treated with PEG (an inducer of osmotic stress) or tunicamycin and AZC (potent inducers of ER stress).[18] The co-regulated genes were first considered to be downstream targets of the integrated pathway based on similar induction kinetics and a synergistic response to the combination of osmotic and ER stress-inducing treatments. Based on these criteria, the selected downstream components of this ER and osmotic stress response-integrating pathway demonstrated the strongest synergistic induction, encoding proteins with diverse roles, such as plant-specific development and cell death (DCD) domain-containing proteins (NRP-A and NRP-B), an ubiquitin-associated (UBA) protein homolog and NAC domain-containing proteins (GmNAC6). NRP-A and NRP-B share a highly conserved C-terminal DCD (development and cell death) domain and possess a high number of asparagine residues at their more divergent N terminus.[19] NRPs are critical mediators of ER and osmotic stress-induced cell death in soybeans.[4] The cell death response mediated by NRPs resembles a programmed cell death event. The overexpression of NRPs in soybean protoplasts induces caspase-3-like activity and promotes extensive DNA fragmentation. Furthermore, the transient expression of NRPs in plants causes leaf yellowing, chlorophyll loss, malondialdehyde production, ethylene evolution and the induction of senesce

Similar t s strongly induced nsion cells. It is synerg ls, and induces toplasts.[20,21] GmNAC containing proteins genes repre stered into 15 differ opment and stress re e that consists called the NAC don nd length, which fu ately regulate RPs

expression of NRPs activates the GmNAC6 promoter and induces GmNAC6 expression, suggesting that GmNAC6 is located downstream of NRP in the ER and osmotic stress-induced cell death response.[21]

An upstream component of the NRP-mediated cell death response, GmERD15 (Glycine max Early Responsive to Dehydration 15), has been recently identified using one-hybrid screening that targeted the NRP-B promoter in yeast.[23] GmERD15 is induced by ER and osmotic stress to activate the expression of NRP genes. GmERD15 binds to and activates the NRP-B promoter in vitro and in vivo, exhibits transcriptional activity, is localized in the nucleus and induces the expression of the NRP-B gene when transiently expressed in soybean protoplasts. GmERD15 belongs to a class of ssDNA binding proteins and specifically recognizes the 12-bp palindromic sequence -511AGCAnnnnTGCT-500 in both SS (single-stranded) and DS (double-stranded) configurations of the NRP-B promoter. As an upstream component of ER stress-induced NRP-mediated signaling, GmERD15 associates stress in the ER with an osmotic stress-induced cell death signal.

The binding protein inhibits NRP-mediated cell death signaling and confers tolerance to drought

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In addition to alleviating ER stress,[30] the overexpression of BiP in plants has also been shown to increase their tolerance to water deficits.[32-34] The apparent increase in BiP-mediated drought tolerance was not associated with typical short and long-term avoidance responses or with other known tolerance mechanisms.[34] The only variations observed in the BiP-overexpressing (OE) lines are a delay in drought-induced leaf senescence and an inhibition of the drought-mediated downregulation of ER molecular chaperone transcripts that occurs under prolonged osmotic stress. Recently, it has been shown that the enhanced expression of BiP in soybean (Glycine max) attenuated ER and osmotic-stress-mediated cell death.[31] In transgenic lines, BiP overexpression attenuates ER and osmotic stress-induced cell death phenotypes, such as foliar necrotic lesions and wilting, percentage of dead cells, induction of senescence-associated gene markers, DNA fragmentation, caspase activity, lipid peroxidation and induction of the cell death marker genes NRP-A, NRP-B and GmNAC6. Accordingly, the prosurvival effect of BiP was associated with the modulation of the ER and osmotic stress-induced NRP-mediated cell death signaling, as determined in transgenic tobacco lines with enhanced and suppressed BiP levels. The enhanced expression of BiP prevented NRP- and NAC6-mediated cell death, whereas the silencing of endogenous BiP accelerated the onset of leaf senescence mediated through the ectopic expression of NRPs and GmNAC6 in tobacco leaves. These results implicate BiP as a negative regulator of the stress-induced NRP-mediated cell death response. Thus, it is not surprising that the overexp ybean plants a water deprivat

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necrotic lesions, resembling those of the hypersensitive response phenotype, and induces the expression of pathogenesis-related genes.[21] Finally, ERD15, the transcriptional activator of NRP expression, was first described in Arabidopsis as a dehydration-induced gene[36] that functions as a negative regulator of the abscisic acid (ABA)-mediated response and a positive regulator of the salicylic acid (SA)-dependent defense pathway.[37]

Conclusions

Since the discovery of the stress-induced NRP-mediated cell death response, many aspects of this signaling pathway induced by prolonged ER and osmotic stress have been elucidated. We now know that this pathway integrates the ER and osmotic-stress signals to synergistically increase the expression of N-rich proteins (NRP-A and NRP-B) and the NAC domain-containing protein GmNAC6, which are critical mediators of stress-induced cell death in plants. We also know that NRP-B expression is controlled by the novel ER and osmotic stress-induced transcriptional factor GmERD15 (Glycine max Early Responsive to Dehydration 15). However, several key players of this stress-induced signaling pathway are unknown, and many questions remain unanswered. What is the ER receptor that molecularly links the ER stress signal with the cell death respons sma membra at are the molecul onse? The synergis of ER and osmotic cell death signals a xpression. Which u gnal? The identi nNAC6 trans plant ER stress tr signaling respons

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to modulate the osmotic stress-induced NRP-mediated cell death response. The positive effect of the modulation of the NRP-mediated cell death pathway on plant adaptation to stress might implicate this pathway as an excellent target for engineering superior crops. Because the NRP-mediated cell death signaling pathway represents a shared response to multiple stress signals in plants, it might permit coordinate adaptive cellular responses under a large array of stress conditions.

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