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HOP3 a new regulator of the ER stress response in Arabidopsis with possible implications in plant development and response to biotic and abiotic stresses

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ABSTRACT

HOPs (heat shock protein 70 (HSP70)-heat shock protein 90 (HSP90) organizing proteins) are a highly conserved family of cytosolic cochaperones. In a recent study we showed that HOP3, a member of the HOP family in Arabidopsis, plays an essential role during endoplasmic reticulum (ER) stress in plants. Interestingly, we also demonstrated that AtHOP3 interacts with binding immunoglobulin protein (BiP), a major ER-resident chaperone. All these data suggest that HOP3 could assist BiP in protein folding in the ER. These findings open the exciting possibility that HOP3, through its role in the alleviation of ER stress, could play an important function during different developmental processes and in response to different biotic and abiotic stresses.

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HOPs, HSP70-HSP90 organizing proteins, are a family of cochaperones with representative members in different eukaryotes including diverse plant species.[1] At the structural level HOP proteins are defined by the presence of 3 tetratricopeptide repeat (TPR) domains (called TPR1, TPR2A and TPR2B) that mediate the interaction with the molecular chaperones HSP70 and HSP90.[2] Due to its involvement in the folding and maturation of important proteins, as the glucocorticoid receptor,[3] the sequences and domains involved in HOP interaction with HSP70 and HSP90 have been deeply studied in mammals.[4-6]

We have recently demonstrated that HOP3, one of the 3 member of the HOP family in Arabidopsis, interacts *in vivo* with cytosolic HSP90 and HSP70, indicating that it is a functional member of the HOP family in Arabidopsis. Interestingly, we have shown that HOP3 interacts specifically with BiP, a major endoplasmic reticulum (ER) chaperone that belongs to the HSP70 family, through a non-canonical interaction that involves BiP's ATPase domain.[7] This observation opened the possibility that HOP could have a prominent role in protein folding at the ER, an aspect unexplored before in other eukaryotes, but with potential implications in important developmental and adaptation processes.

The ER hosts the synthesis and folding of membrane and secreted proteins by a complex orchestra of ER-located foldases and chaperones (being BiP one of the major representatives).[8] ER protein folding capacity is limited and, when exceeded, the strong accumulation of misfolded or unfolded proteins in the ER causes the so called ER stress. ER stress promotes a strong protein imbalance that leads to cell death when the system is overwhelmed.[9,10]

In addition to HOP3 interaction with BiP, we have demonstrated that Arabidopsis *hop3* loss-of-function mutants show a hypersensitive phenotype in the presence of the ER stress inducer agents dithiothreitol (DTT) and tunicamycin (TM) and that this phenotype is reverted by the addition of tauroursodeoxycholic acid (TUDCA), a compound that relieves ER stress in plants. These data, along with its partial localization at the ER and *HOP3* induction by ER stress inducer agents, highlight the prominent role of HOP3 in the ER stress response.[7]

Besides its major role as the gateway to the secretory pathway, the ER is also a central regulator of plant adaptation to abiotic and biotic stresses.[11-13] Probably the best illustrative example of the role of the ER in environmental stresses is the response to pathogen attack, since this response is mainly based on the production of pattern recognition receptors (PRRs) and resistance (R) proteins that mostly are folded and matured in the ER.[14,15] In the same sense, it has been speculated that, under other environmental stresses, the strong demand for folding of proteins involved in the stress response exceeds the folding capacity of the ER, which jeopardizes ER homeostasis and cell viability.[16,17] Despite it is not completely clear, the involvement of ER stress in the response to environmental challenges is supported by the observation that the unfolded protein response (UPR) is activated under different stress conditions and that mutants in different components of

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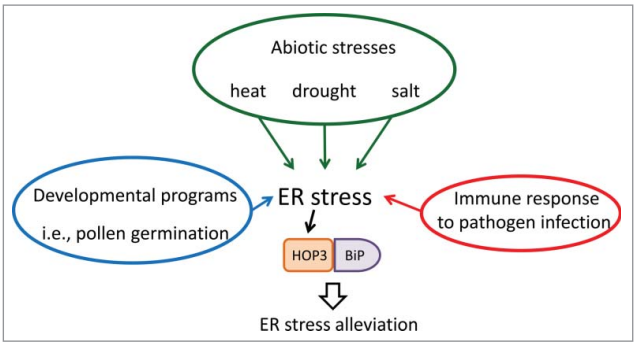

Figure 1. During specific plant developmental programs and in response to different environmental challenges as abiotic stresses or pathogen infection, the folding capacity of the ER is exceeded leading to ER stress. This ER stress should be promptly alleviated to successfully complete the developmental program or adapt to the environmental stress. ER stress promotes *HOP3* induction and HOP3, as it is also the case of its interactor BiP, plays an important role in ER stress alleviation, opening the possibility that HOP3 could be involved in the response to different biotic and abiotic stress and other ER-dependent developmental programs.

the ER stress (sensors, chaperones and cochaperones) have an altered response under different abiotic and biotic threats as heat, drought, salt, osmotic stresses and pathogen defense.[17,16,13] Previous data from our laboratory demonstrated that HOP3 is highly induced under high temperatures[18,19] and a closer view to the microarray available data points out that AtHOP3 could be also induced in a wide range of stresses (http://jsp.weigelworld.org/expviz/expviz.jsp). These observations suggest that HOP3, through its prominent function in the ER stress response, could play a major role in the response to a wide range of environmental conditions (Fig. 1). In line with this possibility, HOP was recently involved in blast fungus immunity in rice, promoting the efficient transport of the chitin elicitor receptor kinase 1 (CERK1) to the plasma membrane.[20] In addition, HOP was proposed as a cell-intrinsic virus restriction factor of the mitochondrial *Carnation Italian ringspot tombusvirus* (CIRV) in *N. benthamiana*.[21] Despite the emerging function of HOP in these two quite divergent plant defense responses, the role of HOP3 or of the different members of the HOP family in response to other biotic or abiotic stresses remains largely unknown constituting an exciting field of study in plants.

Our data also revealed that *hop3–1* mutant shows a reduction in pollen germination,[7] a developmental process especially vulnerable to disturbances in ER protein homeostasis.[22] In line with this evidence, it is tempting to speculate that HOP3 could have a major impact on other developmental processes with special demand in protein folding or secretion, as it is the case of seed maturation[23] (Fig. 1). This speculation seems to be supported by the high induction of *HOP3* in seeds (http://jspweigelworld.org/expviz/expviz.jsp). The study of the possible role of HOP3 or of the other members of the family in developmental processes constitutes a new avenue for exploring HOP function in plants.

Remarkably, the ER stress response is highly conserved in eukaryotes, and so are HOP and BiP (known as GRP78 in mammals). Therefore, we are confident that the description of BiP and HOP3 interaction could be also relevant, not only for plants, but for other eukaryotes including yeast, insects or mammals. In mammals, GRP78 plays a main role in tumor proliferation, metastasis and resistance to a wide variety of anticancer therapies.[24] In addition, neurodegenerative disorders including Parkinson and Alzheimer diseases and progressive retinal degeneration are characterized by activation of ER stress and altered expression of *GRP78*.[25] Indeed, the alleviation of the ER stress by *GRP78* upregulation has been proven a successful therapeutic target for the treatments of some of these disorders in animal models of neurodegeneration.[26-30] In line with these data, mammaliam *HOP* shows an altered expression in cancer cells and a protective effect against the progression of prion and neurodegenerative diseases.[1]Therefore, this study opens an exciting field of research in which the HOP interaction with BiP could be also explored in relation to the occurrence of these disorders and the development of novel therapies to tackle these important human diseases.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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