

Membrane-tethered transcription factors provide a connection between stress response and developmental pathways

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Membrane-tethered transcription factors (MTTFs) are proteins that are targeted to membranes and are capable of regulating gene expression. In this way, they are physically restrained from entering the nucleus and are innately dormant. Upon specific signal recognition cues, MTTFs are activated through cleavage by a protease that releases the transcription factor domain into the cytosol thus allowing it to translocate to the nucleus where it can regulate gene expression. MTTFs are classically thought to provide an advantage to an organism by allowing for rapid signal transduction in response to cellular and environmental stresses. However, recent findings suggest that MTTFs may not only act as a means to respond quickly to stress but also are able to regulate developmental pathways, illustrating a point of interaction between stress and development.

Membrane-tethered transcription factors (MTTFs) are proteins that contain both transmembrane and transcription factor domains and can regulate gene expression only after they have been proteolytically released from the membrane.¹ Transcriptional regulation through MTTFs represent an evolutionarily conserved mechanism for gene expression from bacteria and yeast to plants and metazoans, and generally aid organisms as a means to rapidly respond to stress.¹ Regulation of MTTF activity occurs through a series of events. First, a specific signal is detected either by the MTTF directly or by a protein that closely associates with the MTTF.¹ This signal

recognition allows the MTTF to interact with a protease or the proteasome that is then able to release the protein from the membrane, resulting in activation of the MTTF.^{2,3} Proteolytic cleavage of the MTTF allows the truncated form of the protein, containing the transcription factor domain, to translocate to the nucleus where it regulates gene expression.¹

Previously characterized MTTFs have largely been shown to play a role in stress response. For example, in mammalian systems, SREBP (sterol regulatory element-binding protein) has been shown to respond to depleted sterol levels and to regulate genes that are involved in cholesterol homeostasis.⁴ Additionally, ATF6 has been shown to respond to the unfolded protein response in the ER and to regulate genes related to ER stress response pathways and is a conserved mechanism to responding to ER stress in eukaryotic cells.⁵

In light of previously characterized MTTFs in many model organisms, their classical role has been established as a means of coping with cellular stress and stressful environmental conditions. However, there is evidence that supports a role for MTTFs in organogenesis and other developmental processes in addition to their role in stress response, suggesting that holistic roles of MTTFs have yet to be elucidated.

There are 85 predicted MTTFs in *Arabidopsis*,⁶ yet only nine have been characterized to date. These include members from the bZIP family (AtbZIP17, 28 and 60), members from the NAC family (NTM1, NTL6, 8 and 9 and ANAC089) and most recently, a member of the

Key words: membrane-tethered transcription factors, unfolded-protein response, NAC, bZIP, R2R3-MYB

Submitted: 04/22/11

Accepted: 04/25/11

DOI: 10.4161/psb.6.8.16047

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Addendum to: Slabaugh E, Held M, Brandizzi F. Control of root hair development in *Arabidopsis thaliana* by an endoplasmic reticulum anchored member of the R2R3-MYB transcription factor family. *Plant J* 2011; 67:395-405. PMID: 21477080; DOI: 10.1111/j.1365-313X.2011.04602.x

R2R3-MYB family of transcription factors (maMYB).⁷⁻¹⁰

All three characterized members that belong to the bZIP family have been shown to be activated in response to stress signals, such as the unfolded protein response in the ER, and also to activate the expression of genes involved in stress response, such as ER chaperones.^{7,8} AtbZIP17 has been shown to be activated in response to salt and ER stress and results in the upregulation of salt stress related genes.¹¹ Likewise, AtbZIP28 was shown to be involved in heat stress response by demonstrating that the expression of AtbZIP28 is upregulated in response to heat stress, is activated by heat stress and regulates the expression of genes related to ER stress.¹² And AtbZIP60 was also shown to be activated in response to ER stress and to regulate the expression of ER-stress related genes including ER chaperones and calnexin.¹³ Though MTTFs of the bZIP family largely play a role in stress response, it has been recently shown that this stress response pathway may serve additional functions as well. Specifically, it was demonstrated that activated forms of AtbZIP17 and AtbZIP28 can also regulate genes involved in the brassinosteroid signaling pathway, thereby identifying a point of integration between ER stress response and growth and development pathways.¹⁴

Previously characterized MTTFs that belong to the NAC family have also been shown to be involved in stress response but also regulate developmental processes in Arabidopsis. NTM1 was one of the first MTTFs to be characterized in Arabidopsis and was shown to mainly regulate genes involved in cell division through interactions with cytokinins.¹⁵ Additionally, it was shown that NTM1 is also regulated by environmental stresses, in that the expression of NTM1 is induced under conditions of high salinity and abiotic stress, indicating that regulation of the cell cycle may be implicated in stress response pathways.¹⁶ NTL6 has been found to be induced by cold and abscisic acid and regulates genes involved in pathogenesis.¹⁶ Another member of the NAC family, NTL8, was demonstrated to be activated by salt stress and to regulate genes involved in germination and flowering.¹⁷ Additionally, NTL9 was found to

be induced by osmotic stress and to regulate genes involved in senescence. And the latest MTF to be characterized that belongs to the NAC family is ANAC089. The overexpression of the truncated form of ANAC089 results in repression of several major flowering genes and a delayed flowering phenotype. However, the signal that results in the activation of ANAC089 has not yet been identified. Collectively, most membrane-tethered NAC proteins are induced by specific stress conditions,¹⁶ but many of these proteins not only regulate genes directly identified as being related to a specific stress response, but rather regulate developmental and physiological processes to allow the plant to cope with environmental stresses, providing yet another integration between stress response and morphogenesis.

Lastly, maMYB was recently identified in Arabidopsis as being involved in root hair elongation, likely through interaction with an auxin signaling pathway.¹⁰ This case documents a membrane-tethered R2R3-MYB transcription factor, which appears to be unique to land plants, with a functional role in cell-specific morphogenesis. Although the putative transcription factor domain of maMYB has been shown to regulate gene expression and downregulation of *maMyb* affects root hair elongation, the precise signal that results in the activation of maMYB remains to be determined.¹⁰ This leaves open the possibility that maMYB may play additional roles in yet unidentified stress response pathways that somehow affect root hair elongation.

Previously, the biological advantage of MTTFs has largely been restricted to the perception and response to stress related signals. However, more evidence is emerging that implies that MTTFs are beneficial not only to immediate stress response pathways, but can participate in signaling that results in more global, long lasting morphological changes to help organisms cope with stress. By further studying MTTFs, future work in the field will not only add to our growing knowledge about their function and regulation but may also identify potential points of cross-talk between stress signaling and developmental regulation, thereby more finely elucidating the relationship between the two.

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