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Article Addendum

TPR Proteins in Plant Hormone Signaling

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Addendum to:

The Arabidopsis Tetratricopeptide Repeats Containing Protein TTL1 is required for Osmotic Stress Responses and ABA Sensitivity

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ABSTRACT

There is a large number of proteins in nature containing Tetratrico Peptide Repeats (TPRs). TPR motifs are defined as a protein-protein interaction module involved in regulation of different cellular functions. We have recently identified TTL1 as a protein containing TPR motifs required for abscisic acid responses and osmotic stress tolerance. In recent years several of these proteins have been found to be essential for responses to other hormones such ethylene, cytokinin, gibberelling and auxin in *Arabidopsis*. Thus, proteins containing TPRs are emerging as essential determinants for signal transduction pathways mediated by most plant hormones.

THE TETRATRICO PEPTIDE REPEAT MOTIF

The tetratrico peptide repeat (TPR) motif is a 34 amino acid consensus sequence reported more than 15 years ago in yeast proteins involved in the cell cycle.[1,2] Since these reports many proteins containing TPRs have been identified involved in a plethora of cellular functions.[3] The TPR motif is a protein-protein interaction module, commonly found in multiple copies in the same protein, that facilitates specific interactions with a partner protein(s).[4] Therefore, proteins do not normally contain an individual TPR motif, but consists of three to 16 tandem-repeats of TPRs that can be grouped or dispersed throughout the protein.[5] Because most TPR proteins contain three repeats it is likely that this is the minimum number required to form a functional domain. Sequence analysis of many proteins indicates that TPRs are defined by a pattern of small and large hydrophobic amino acids rather than a pattern of conserved amino acid residues. In fact, no invariant positions are found in TPRs. Three-dimensional structure data have shown that a TPR motif contains two antiparallel α-helices such that tandem arrays of TPR motifs generate a right-handed helical structure with an amphipathic channel that might accommodate the complementary region of a target protein.[4] Interestingly, there are other interaction domains that resemble the TPR motif in secondary structure; the paired amphipathic helix (PAH) motif and helix-loop-helix (HLH) motif, identified in certain transcription factors and endonucleases[6-8] and the antiparallel α-helices of 14-3-3 proteins.[9] The similarity in structure between these motifs most likely reflects a case of convergent evolution toward essential domains for protein interaction, which in turn may explain the abundance and functional importance of TPRs in nature.

DEFINING FUNCTIONS FOR TPR PROTEINS

In addition to their role in the cell cycle in yeast, many additional functions have been assigned to proteins containing TPRs such as, neurogenesis, protein folding and transport, and transcriptional control.[4,10] Interestingly, mutations in TPR proteins have been found to produce several human diseases indicating essential roles in cell function. Because of their role in protein-protein interaction the identification of binding partners is a common strategy and a requisite to fully understand the function of TPR proteins on a molecular level.

A CENTRAL ROLE OF TPR PROTEINS IN PLANT HORMONE SIGNALING

Proteins containing TPR domains are becoming a common theme in plant hormone signaling. There have been recent reports on TPR proteins involved in gibberellin, cytokinin and auxin responses as well as ethylene biosynthesis.[11-13] In Arabidopsis, the ETO1 (ETHYLENE-OVERPRODUCER1) protein negatively regulates ethylene

biosynthesis in seedlings through direct interaction of its TPR domains with a 1-aminocyclopropane-1-carboxylate synthase isoform.[13,14] The spindly (*spy*) mutant was selected because of its capacity to germinate in the presence of an inhibitor of gibberellin (GA) biosynthesis.[15] The SPY protein contains TPR domains in its N terminus, whereas the C terminus sequence shows high homology to Ser/Thr O-linked N-acetylglucosamine (O-GlcNAc) transferases (OGTs) from animals.[16,17] The TPR domains of SPY physically interact with two transcription factors forming complexes that act as negative regulators of GA responses.[18] Mutations in the ETO3/STG1b enhanced the auxin-dependent phenotype of the auxin-receptor mutant tir1-1 mutant. SGT1b was previously identified as a factor involved in plant disease resistance signaling.[19] The ETA3/SGT1b protein is required for SCFTIR1-mediated degradation of Aux/IAA proteins, although the molecular mechanism has not been yet established.[12]

IDENTIFICATION OF TTL1, A TPR PROTEIN INVOLVED IN ABA SIGNALING

We have recently identified ttl1 an Arabidopsis mutant hypersenstive to osmotic stress. Further analysis indicated that *ttl1* was affected in ABA sensitivity.[20] *TTL1* encodes a plant-specific 699 amino acids protein with two domains based on sequence analysis: the centre of the protein contains the TPR motifs whereas the last 100 amino acids show homology to thioredoxins. TTL1 protein is predicted to be cytoplasmic based on sequence analysis and preliminary GFP fusion experiments data (not shown). TTL1 contains six TPRs, the first of which is located 226 amino acids from the initial methionine. The exact mode of action of TTL1 has not been established since we have been unable to find interacting proteins of TTL1. Analysis of a subset of genes involved in ABA biosynthesis and degradation indicated that ABA metabolism is not affected in *ttl1* and therefore TTL1 likely acts downstream in the ABA signal transduction pathway. Only a subset of genes was altered in *ttl1* and their analysis did not provided straightforward information about the role in the ABA signal transduction pathway. Additional research is needed in order to gain further insight into the TTL1 function.

TTL1 BELONGS TO A FAMILY COMPOSED BY FOUR MEMBERS IN ARABIDOPSIS

Analysis of genes in the Arabidopsis genome revealed the presence of three additional genes showing homology to TTL1. These three genes, TTL2, TTL3, and TTL4 have similar intron-exon structure and the position of the encoded TPRs and thioredoxin-like domains are very well conserved. The most variable region among the TTLs corresponds to the N-terminus and is probably not essential for ABA sensitivity as identification of a mutant lacking the N-terminus behaved similar to the wild type.[20] The presence of proteins with high homology to TTL1 raises the possibility of functional redundancy. In fact, the isolation and analysis of mutants in all TTL genes revealed that TTL2, the closest homolog to TTL1, is also required for ABA sensitivity (data not shown).

Seventy nine genes encoding TPR proteins have been identified in the Arabidopsis genome.[3] The role of several of these proteins such as in hormone signaling, defense response,[19] photosystem I assembly,[21] and mRNA processing and stability[22,23] has been established, however the function of most of them remains elusive. Further research on the TTL family such as analysis of double, triple or even quadruple mutants will help to determine the role of these proteins in plants.

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