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Common and distinct features of TIR domain function

S. Williams[1], M. Alaidarous[1], T. Ve[1], X. Zhang[1], E. Valkov[1], M. Bernoux[2], K. Sohn[3], J. Jones[3], P. Dodds[2], B. Kobe[1]

[1]University of Queensland, School of Chemistry and Molecular Biosciences, Brisbane, Australia, [2]CSIRO, Plant Industry, Canberra, Australia, [3]John Innes Centre, The Sainsbury Laboratory, Norwich, UK

TIR (Toll/interleukin-1 receptor, resistance protein) domains feature in diverse proteins with functions in the immune system, such as animal TLRs (Toll-like receptors), plant NLRs (nucleotide binding, leucine-rich repeat) and bacterial virulence factors. It has been well established, especially through the work on TLRs, that signalling depends on regulated self-association of TIR domains. However, every single TIR domain structure has revealed a different association mode [1]. In the search for common features, we have targeted a number of TIR domains from mammals, plants and bacteria to characterize structurally. We have determined the crystal structures of the TIR domains from the human TLR adaptor protein MAL [1], the bacterial protein TcpB from Brucella melitensis [2] and the plant immune proteins L6 from flax [3] and SNC1, RPS4 and RRS1 from Arabidopsis (unpublished). In the case of the proteins RPS4 and RRS1, which work together as a protein complex to confer resistance to three different bacterial and fungal pathogens, we have determined, using linker-assisted crystallization, the first structure of a hetero-dimeric complex of TIR domains (Fig. 1). The association interface in this complex is conserved in the crystals of the TIR domains of RPS4 and RRS1 on their own, as well as in those of SNC1 and another Arabidopsis protein AT1G72930. Similarly, the dimerization interface observed in the structure of TcpB is conserved in the structure of the TIR domain-containing protein from Paracoccus denitrificans. We validated the association interfaces by site-directed mutagenesis coupled with a variety of cellular assays. As self-association is key to TIR domain function, our studies are finally revealing common features of the molecular function of TIR domains across phyla.

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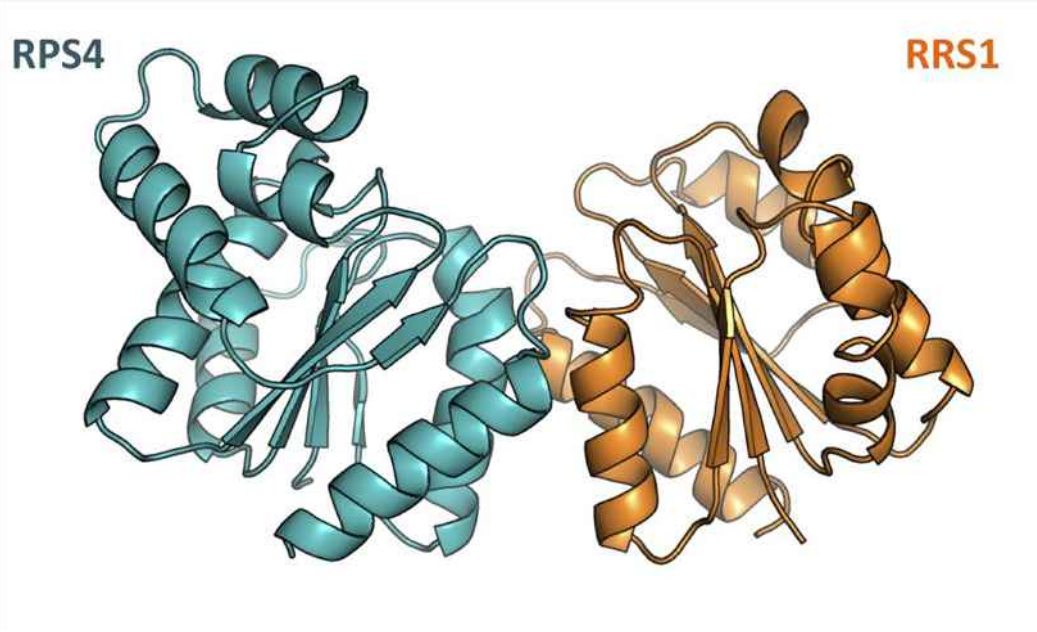

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