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With the synchrotron and beyond the synchrotron towards the structure of the TIR-domain signalosome

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TIR (Toll/interleukin-1 receptor, resistance protein) domains are key components of innate immunity signaling pathways. They are found in animals, plants and bacteria, for example in TLRs (Toll-like receptors) and TLR adaptors in animals, NLRs (nucleotide binding, leucine-rich repeat receptors) in plants, and virulence factors interfering with immune responses in bacteria. While it has been well established that signaling depends on regulated self-association and homotypic association of TIR domains, 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 used the Australian Synchrotron to determine a number of TIR-domain crystal structures and study association using SAXS, including those from the human TLR adaptor proteins MAL [2] and SARM (unpublished), the bacterial protein TcpB from *Brucella melitensis* [3] and the plant immune proteins L6 from flax [4], RPS4 and RRS1 from *Arabidopsis* [5], SNC1 and RPP1 from *Arabidopsis* and MrRPV1 from grapevine (unpublished). These crystal structures have started revealing common trends in the TIR-domain association modes, in particular for bacterial and plant TIR domains. Furthermore, for the TLR adaptors MAL and MyD88, we have been able to reconstitute large assemblies and determine the structure for the former by cryo-electron microscopy (unpublished), while we are characterizing the structure of the latter by synchrotron and X-FEL-based serial crystallography. Jointly, these studies suggest a general mechanism of function of TIR domains, which involves “signalling by cooperative assembly formation (SCAF)” with prion-like features that is consistent with signaling in other innate immunity pathways.

References

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Keywords or phrases (comma separated)

crystallography, SAXS, higher-order assembly signalling

Are you a student?

No

Do you wish to take part in the Student Poster Slam?

No

Are you an ECR? (<5 yrs</br>since PhD/Masters)

No

What is your gender?

Male

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