Understanding the structural basis of TIR-domain assembly formation in TRAM- and TRIF-dependent TLR signalling

Mengqi Pan, Jeff Nanson, Andrew Hedger, Bostjan Kobe

the University of Queensland, St Lucia, 4102, Australia

m.pan@uq.edu.au

Toll-like receptors (TLRs) detect pathogens and endogenous danger, initiating immune responses that lead to the production of pro-inflammatory cytokines. At the same time, TLR-mediated inflammation is associated with a number of pathological states, including infectious, autoimmune, inflammatory, cardiovascular and cancer-related disorders. This dual role of the pathways has attracted widespread interest from pharmaceutical industries. Cytoplasmic signalling by TLRs starts by their TIR (Toll/interleukin-1 receptor) domain interacting with TIR domain-containing adaptor proteins MyD88, MAL, TRIF and TRAM. Combinatorial recruitment of these adaptors via TIR:TIR domain interactions orchestrates downstream signalling pathways, leading to induction of the pro-inflammatory genes. Although many constituents of the TLR pathways have been identified, the available information on their coordinated interactions is limited. Such information is crucial for a mechanistic understanding of TLR signalling, development of therapeutic strategies, and understanding of the molecular basis of the consequences for human disease of adaptor polymorphic variants. We have discovered that TIR domains can form large assemblies. We hypothesized that TIR domain signalling occurs through a mechanism involving higher-order assembly formation. In this study we aim to determine the molecular architecture of higher-order assemblies formed by TIR domains with a focus on TRAM-TRIF assemblies in the TLR4 and TLR3 pathway.

Keywords: TLR signalling pathway, innate immune system