MS25-1-5 Structural Basis of Higher-order Assembly Formation In Toll-Like Receptor 1 and 2 Signalling Pathway #MS25-1-5

B.B.O.S. Kobe [1], N. Jeff [1], Y.A.N.L. Yan [1], X. Hongyi [2], P. Laura [2]
[1]The University of Queensland - Brisbane (Australia), [2]Stockholm University - Stockholm (Sweden)

Abstract
Toll-like receptors (TLRs) detect pathogens and endogenous danger-associated molecules, initiating innate immune responses that lead to the production of pro-inflammatory cytokines. Signaling by TLRs is initiated by dimerization of their cytoplasmic TIR (Toll/interleukin-1 receptor [IL-1R]) domains, followed by recruitment of the TIR-containing adaptor proteins, including MyD88 (myeloid differentiation primary response gene 88) and MAL (MyD88 adaptor-like/TIRAP). In previous works, we showed the MAL TIR domain can reversibly and spontaneously form filaments in vitro. They also form co-filaments with TLR4 TIR domain and nucleate the assembly of MyD88 TIR domain into crystalline arrays. These results suggest signalling by cooperative assembly formation (SCAF), a prevalent mechanism in innate immunity and cell death pathways. The structural basis of higher-order assembly formation in the TLR1/2 signalling pathways remains obscure.
Here, we show that TLR2 TIR domain directly interacts with the MyD88 TIR domain, and nucleates the assembly of MyD88 TIR domain in vitro. Microcrystal electron diffraction (Micro-ED) is the crucial technique to address the assembly structure. The structure shares a high similarity with the previous MAL TIR domain induced MyD88 TIR domain higher-order assembly. Conformational changes are found at key regions for signalling (e.g., BB loop) compared to the monomeric X-ray structure. We also found that TLR1 TIR domain can co-assemble with MAL into filaments, electron microscopy (EM) studies indicate that the filaments have a different morphology compared with MAL filaments alone. The results shed lights on a conserved SCAF model in the TLR1/2 signalling pathway but may involve more complicated TIR: TIR interactions.