Structural and Functional analysis of the TIR-domain in Toll-like receptors 7, 8 and 9 signaling and the Interactions with adaptor proteins

Xiaoqi Qian*1, Jeffrey Nanson1, Boštjan Kobe1

1.School of Chemistry and Molecular Biosciences, Faculty of Science, The University of Queensland, Australia.
b.kobe@uq.edu.au

Keywords: TIR domain, Toll-like receptors, Structural biology

Toll-like receptors (TLR) recognize pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs) via their leucine rich repeat (LRR) domains and initiate innate immune system signaling in response to detected threats [1][2]. TLRs are critical for host defense and dysfunctional TLR signaling is strongly associated with pathogenesis of inflammatory and autoimmune diseases. TLRs contain a cytoplasmic TIR (Toll/interleukin-1 receptor/resistance protein) domain, upon PAMP/DAMP binding by the non-cytoplasmic TLR LRR domain. The cytoplasmic TIR domain recruits downstream adaptors and effector enzymes such as MAL (MyD88 adaptor-like) and MyD88 (myeloid differentiation primary response gene 88) to initiate immune system signaling [3].

Among ten identified TLRs, TLR7, TLR8 and TLR9 are localized to endosomal membranes and sense nucleic acids. Once activated, TLR7/8/9 recruit MyD88 to the membrane of the endosome, initiating the downstream signaling. Abnormal activation of TLR7/8/9 signaling leads to autoimmune diseases, including psoriasis and systemic lupus erythematosus. However, the underlying mechanism causing these diseases remains elusive [4]. Given the similarity of TLR7/8/9, this project aims to 1) express and purify the protein TLR7/8/9 TIR; 2) identify the structural basis of human TLR7/8/9 TIR, 3) analyze the intermolecular interactions between human TLR7/8/9 TIR and their adaptor proteins MAL or MyD88. The hypotheses of the project are 1) TLR7/8/9TIR dimerize and interact with adaptor proteins through TIR-TIR interactions, 2) TLR7/8/9TIR directly interact with MAL or MyD88 to initiate immune system signaling, 3) TIR domains of TLR7/8/9 can induce formation of MAL or MyD88 assemblies. Our research will shed light on drugs targeting on autoimmune diseases.

References