Regulation of inflammatory and anti-apoptotic responses through the IL-1RI/TILRR complex.

Eva E. Qwarnstrom
University of Sheffield, Sheffield S102RX UK

Members of the toll-like and IL-1 receptor family (TIR) are central regulators of immune and inflammatory responses. Signal activation is induced through ligand binding and controlled by system specific co-receptors.

The IL-1RI co-receptor TILRR is a splice variant of FREM-1. TILRR association with the signalling receptor magnifies IL-1–induced activation of the canonical and non-canonical NF-κB network, by enhancing signal amplification at the level of the receptor complex and potentiate recruitment of the MyD88 adapter and PI3 kinase.

TILRR-controlled MyD88 dependent activation of the canonical pathway is regulated in a Ras-dependent manner, reflected in alterations in cytoskeletal structure and cell adhesion. The changes induced provide a process for rapid control of NF-κB, involving sequestration and release of cytoskeletal bound IκBα through a mechanism controlled by TILRR signal amplification. *In silico* simulations using agent based modelling of the NF-κB network predict cytoskeletal control of inhibitor levels to provide a mechanism for signal calibration, and to enable activation-sensitive regulation of NF-κB induced inflammatory responses.

Our studies have identified two functional sites within the TILRR core protein, which selectively control inflammatory and anti-apoptotic responses. The mechanisms underlying distinct network amplification, and the relevance of pathway-specific regulation of canonical and non-canonical NF-κB activation will be discussed.

References

Zhang, X., Shephard, F., Kim, HB., Palmer, IR., McHarg, S., Fowler, GJ., O'Neill, LA., Kiss-Toth, E., and Qwarnstrom, EE. *J Biol Chem*. 2010, 285: 7222-7232.

Zhang, X., Montagut-Pino, G., Shephard, F., Kiss-Toth, E. and Qwarnstrom E E. *J. Biol. Chem.* 2012, 287: 12348-12352

Rhodes, D., Smith S., Holcombe, M. and Qwarnstrom E.E. *PLoS One*. 2015, **10:** e0129888. doi: 10.1371/journal.pone.0129888.

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