

P040 SARM is a negative regulator of TRIF dependent TLR signalling

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Engagement of TLRs with their ligands results in receptor dimerisation and the recruitment of TIR –domain containing adaptors, via the TIR domain located in the cytoplasmic tail of the receptor. This leads to IRAK recruitment which in turn results in the activation of TRAF6 which ultimately leads to NF- κ B activation and expression of pro-inflammatory genes. Five TIR adaptors exist, MyD88, Mal, TRIF, TRAM and SARM. With the exception of SARM the function of the other adaptors has been well established. For example TRIF is involved in NF- κ B and IRF3/7 activation by TLR3 and TLR4. Studies undertaken by our group have demonstrated that human SARM is a specific inhibitor of TRIF dependent TLR signaling. Transient expression of SARM inhibited both TLR3 and TLR4 mediated transcription factor activation and cytokine release, while signals dependent upon IL-1 or RIG-I were not affected. We have demonstrated an interaction between TRIF and SARM and have identified the motifs in SARM necessary for the observed inhibition. siRNA mediated knockdown of SARM message led to enhanced TRIF dependent gene induction and cytokine release both in transformed and primary human cells. In addition we have shown that LPS treatment leads to SARM protein stabilisation, providing a mechanism for negative feedback for TLR4/TRIF signalling. We have extended our studies to murine SARM and have determined that other TLR ligands also induce SARM protein stability. Thus SARM, the fifth mammalian TIR adaptor to be characterized, is a negative regulator of TRIF function.