

P053 Toll-like receptor cross-hyporesponsiveness is functional in IRAK-1 deficient mice

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Toll-like receptors (TLRs) recognize and signal in response to a wide range of microbial structures. This results in e.g. production of proinflammatory cytokines and subsequent activation of the adaptive immune system. Although it is important to respond to invading pathogens, it is equally important to downregulate excessive cytokine production causing tissue destruction and cell death. TLR signalling is negatively regulated at many levels. It is known that repeated in vitro stimulation of macrophages with the TLR4 ligand Lipopolysaccharide (LPS) leads to downregulation of the cytokine production, so-called endotoxin tolerance. Furthermore, repeated stimulation with the TLR2 ligand Lipoteichoic acid (LTA), or combinations of LPS and LTA (cross-tolerance) also leads to hyporesponses. Signalling convergence between different TLR as well as common use of downregulating molecules partly explains the downregulated immune response. However, the exact mechanisms and the biological importance of LPS-, LTA and cross-tolerance are still unknown. IRAK-1 is a central molecule for TLR signalling coupling MyD88 to TRAF6. IRAK-1 is also known as a potential substrate for several downregulating molecules e.g. IRAK-M and Tollip. We used IRAK-1 deficient peritoneal macrophages to investigate if we could induce cross-tolerance after repeated stimulation with combinations of LPS and LTA. Our results demonstrate that IRAK-1 deficient peritoneal macrophages display functional cross-tolerance as well as signalling, compared to WT controls.