

P012 Negative regulatory activity of soluble Toll-like receptor 2: mechanism and biological relevance

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Following our finding of a natural soluble form of TLR2 (sTLR2), we engineered a sTLR2 form resembling plasma sTLR2, and found that it conferred hyposensitivity to TLR2 stimulation. Ligand-induced mobilization of CD14 and TLR2 to lipid rafts was impaired by sTLR2, which acted as a decoy receptor, but also disrupted ligand-independent CD14-TLR2 interaction by associating with CD14. PBMC sensitivity to lipopeptide was higher in the presence of sTLR2-depleted serum, indicating sTLR2 physiological activity. sTLR2 was also tested in a mouse model of Gram-positive bacteria-induced peritoneal inflammation. sTLR2 lowered the peritoneal levels of the neutrophil (PMN) chemoattractant, KC, PMN numbers, and late apoptotic PMN. Levels of endogenous sTLR2 increased, and mononuclear cell recruitment remained unaffected. Peritoneal mesothelial cells were targeted by sTLR2. Notably, sTLR2 inhibited the uptake of Gram-positive bacteria, and PMN superoxide production, thus pointing to the absence of bacterial burden inhibition by sTLR2. These findings define sTLR2 as a physiological negative regulator of TLR2 responses that, by targeting the co-receptor CD14 and TLR2 ligands, can act as a novel therapeutic to control pro-inflammatory responses.