

TLR6- cluster of differentiation 286

Toll-like receptor 6 (TLR6) often designated as CD286 (cluster of differentiation 286), is a member of the Toll-like receptor family, a highly conserved series of ancient innate immune pattern recognition receptors. TLR6 was first described by Takeuchi et al in 1999 as a 91.9-kDa, 796 amino-acid polypeptide. The gene for TLR6 has been mapped to human chromosome 4p13. It has a single exon, and contains an N-terminal signal peptide, 20 tandemly repeated extracellular leucine-rich motifs, and a cytoplasmic domain homologous to interleukin-1 receptor (IL1R), similar to other TLRs (1). TLR6 is most closely related to TLR1, TLR10, and TLR2 with 68%, 46%, and 31% overall AA sequence identity, respectively. (2) In vivo, TLR6 transcript is observed in thymus, spleen, and lung. TLR6 mRNA expression is highest in B cells and monocytes. In vitro, TLR6 mRNA expression is upregulated in THP-1 cells upon PMA-induced differentiation. Further, TLR6 is moderately upregulated by autocrine IFN- γ ; IL-1 β ; However, TLR6 mRNA expression in THP-1 cells is unaffected by exposure to both Gram-positive and Gram-negative bacteria. Ex vivo, monocyte and, in particular, granulocyte TLR6 expression is down-regulated upon exposure to Gram-negative bacteria. (3, 4, 5). Coexpression of TLR2 and TLR6 at the cell surface is crucial for recognition of diacylated lipopeptide and peptidoglycan and subsequent cellular activation in human cells. TLR6 was expressed, although at a lower level than TLR2, on the cell surface in monocytes, monocyte-derived iDCs, and neutrophils, but not on B, T, or NK cells. Confocal microscopic analysis revealed that TLR6 was colocalized with TLR2 at the plasma membrane of monocytes (6). Like TLR1, TLR6 is thought to specify or enhance the pathogen-associated molecular patterns (PAMP) sensitivity of TLR2 and contribute to its signaling capabilities through heterodimerization. TLR2/6 heterodimers recognize diacyl lipopeptides such as MALP2 (the Mycoplasma-derived macrophage-activating lipopeptide 2). CD14 was reported to enhance the responses of TLR2/TLR6 complexes to their ligands. CD36 helps TLR2/6 to further discriminate among their ligands because it contributes to the response to MALP2 and lipoteichoic acid (from gram-positive bacteria), but not to zymosan. Upon ligand recognition, TLR2/TLR6 complexes recruit both the sorting adaptor TIRAP and the signaling adaptor MyD88, and initiate the MyD88-dependent pathway, activating the transcription factors nuclear factor (NF)- κ B and activator protein-1 (AP-1), leading to inflammatory cytokine production. (7) Reference: 1. Tantisira Genes and Immunity (2004) 5, 343–346. 2. O. Takeuchi Gene (1999) Volume 231, Issues 1-2, 29,pp 59-65 3. Takeuchi, O. et al. (1999) Gene 231:59. 4. Zarembler, K.A. & P.J. Godowski (2002) J. Immunol. 168:554. 5. Hornung, V. et al. (2002) J. Immunol. 168:4531. 6. Yoshiya Nakao (2005) The Journal of Immunology, 174: 1566-1573. 7. Myeong Sup Lee (2007) Annual Review of Biochemistry Vol. 76: 447-480.

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