

TLR1- cluster of differentiation 281

Toll-like receptor 1 (TLR1) often designated as CD281 (cluster of differentiation 281), a member of the Toll-like receptor family recognizes pathogen-associated molecular pattern with specificity for gram-positive bacteria. TLR1 is a 786-residue type I transmembrane protein with a 581-amino acid leucine-rich extracellular domain (ECD), a 23-amino acid transmembrane domain (amino acids 582 to 604), and a 181-amino acid cytoplasmic Toll homology signalling domain (1, 2). TLR1 maps to chromosome 4p14 with a calculated molecular weight of 84 kDa (3, 4). TLR1 is most closely related to TLR6 and TLR10 with 68% and 48% overall amino acid sequence identity, respectively. Among members of the TLR family, TLR1 along with TLR6 comprise the most highly conserved pair and appear to have arisen more recently during evolution through a gene duplication event. Different length transcripts presumably resulting from use of alternative polyadenylation site, and/or from alternative splicing, have been noted for TLR4. In vivo, two different sized transcripts for TLR1 are observed suggesting that the mRNA is alternatively spliced to generate two different forms of the protein. TLR1 mRNA is ubiquitously expressed and found at higher levels than the other TLRs. Of the major leukocyte populations, TLR1 is most highly expressed by monocytes, but is also expressed by macrophages, dendritic cells (DCs), polymorphonuclear leukocytes, B, T, and NK cells. While TLR1 expression is most significantly upregulated by autocrine IL-6, it is also elevated by IFN- β , IL-10, and TNF- α . However, TLR1 level is unaffected by exposure to both Gram-positive and Gram-negative bacteria. TLR1 along with TLR6 functions as a co-receptor for TLR2, which confers ligand specificity and enables cell signaling. Collectively, these receptor pairs mediate immune responses to a wide variety of acylated cell wall components derived from Gram-positive bacteria, Gram-negative bacteria, mycoplasma, spirochetes, and fungi. TLR1 also heterodimerizes with TLR4, not to enhance its function, but to inhibit TLR4 activity (5, 6). Defects in the TLR1/2 signaling pathway may account for human hyporesponsiveness to OspA vaccination. Through the reciprocal exchange of extracellular domains between the human TLRs 1 and 6, it has been revealed that TLR1/2 and TLR2/6 receptor pairs exhibit different specificities toward many microbial agonists including diacylated and triacylated lipopeptides, which is determined by the region comprised of leucine-rich repeat motifs 9–12 of these receptors. A recent finding suggests that three nonsynonymous single nucleotide polymorphisms (SNPs) are located in this region of TLR1. A variant of TLR1 based upon the SNP P315L, located in the loop of LRR motif 11 (LRR11), is greatly impaired in mediating responses to lipopeptides. The P315L SNP may predispose certain individuals to infectious diseases for which the sensing of microbial cell components by TLR1 is critical to innate immune defense (7). Thus variation in the inflammatory response to bacterial lipopeptides is regulated by a common TLR1 transmembrane domain polymorphism that could potentially impact the innate immune response and clinical susceptibility to a wide spectrum of pathogens. Reference: 1. Janeway, C. A., Jr, R. Medzhitov. 2002. Innate immune recognition. *Annu. Rev. Immunol.* 20: 197-216. 2. Takeda, K., T. Kaisho, S. Akira. 2003. Toll-like receptors. *Annu. Rev. Immunol.* 21: 335-376. 3. Beutler, B., Z. Jiang, P. Georgel, K. Crozat, B. Croker, S. Rutschmann, X. Du, K. Hoebe. 2006. Genetic analysis of host resistance: Toll-like receptor signaling and immunity at large. *Annu. Rev. Immunol.* 24: 353-389. 4. Rock, F.L. et al. (1998) *Proc. Natl. Acad. Sci. USA* 95:588. 5. Ozinsky, A. et al. (2000) *Proc. Natl. Acad. Sci. USA* 97:13766. 6. Wyllie, D.H. et al. (2000) *J. Immunol.* 165:7125. 7. Katherine O. Omuetti *The Journal of Immunology*, 2007, 178: 6387-6394.

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