

Role of the Toll pathway in the control of immune responses

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Toll-like receptors play a critical role in innate immune recognition of infectious microorganisms. Different members of the Toll family have evolved to recognize distinct microbial products. Upon recognition of microbial structures, TLRs induce production of inflammatory cytokines, chemokines, and co-stimulatory molecules. At the cellular level, triggering of the TLRs leads to activation of macrophages and dendritic cells, and thus couples microbial recognition with the induction of antigen-specific adaptive immune responses. Several signaling components are now known to function downstream of TLRs. These include the adapter protein, MyD88, a protein kinase, IRAK, and an E3 ligase, TRAF6. All these components are activated by all tested TLRs as well as by the members of the IL-1 Receptor family. Although all of the known signaling components activated by TLRs and the IL-1R are identical, some of the signaling pathways and cellular responses induced by the different TLRs and the IL-1Rs are distinct, suggesting that additional signaling components may exist that account for differential signaling by the TLRs. Results will be presented on characterization of one such component – a TIR domain containing adapter protein (TIRAP). TIRAP functions downstream of TLR4, but not downstream of IL-1Rs, TLR2, or TLR9. Thus TIRAP is the first Toll signaling component that is differentially involved in signaling by different members of the Toll family and therefore responsible for at least some of the signaling specificities of the TLRs.

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