Abstract

Toll-like receptors are a family of pattern-recognition receptors of the innate immune system. TLRs recognize conserved products of microbial metabolism, such as lipo-polysaccharide (LPS) and peptidoglycan, thus detecting the presence of microbial infection. Upon recognition of their ligands, TLRs induce signaling pathways that induce inflammation and initiate the immune responses directed at the invading pathogens. TLRs activate NF-kB and MAP kinase signaling pathways, as well as IRF-3/IFN-inducing pathways (in the case of TLR3 and TLR4). Different TLRs can engage distinct signaling pathways in order to induce the appropriate set of immune responses tailored to the nature of the infectious agents. The differential signaling is achieved, in part, by the use of several signaling adapter molecules, including MyD88, TIRAP and TRIF. Stimulation of TLRs by their cognate ligands can lead to direct activation of a variety of effector mechanisms of the innate immune system, including production of antimicrobial proteins and peptides, generation of reactive oxygen and nitrogen intermediates, activation of phagocytes, etc.

In addition to the induction of innate immune responses, TLRs play a critical role in the control of adaptive immunity. TLRs activate specialized antigen-presenting cells, dendritic cells (DCs), which in turn initiate T-cell activation. By inducing DC maturation, TLR signaling couples pathogen recognition with antigen presentation and expression of co-stimulatory signals. In addition, TLRs induce expression by DCs of a variety of cytokines and chemokines that participate in T-cell recruitment, activation and differentiation. We have recently demonstrated that, in addition to the control of co-stimulation, TLRs control T-cell activation by a different mechanism that has to do with regulation of regulatory T-cell (Tr cell) function. Tr cells play an essential role in the maintenance of peripheral tolerance by suppressing activation of self-reactive T cells. Tr cells however do not interfere with the activation of T cells specific to pathogen-derived antigens. This is achieved, at least in part, by TLR-induced IL-6 production by DCs. IL-6, in turn, acts on T helper cells and renders them refractory to the suppressive effect of Tr cells. We believe that this mechanism plays a fundamental role in the control of immunity. The follow-up and several implications of these studies (especially for cancer vaccine design) will be presented and discussed at the meeting.

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