Interactions of Toll-like receptor- and RIG-like receptor-mediated signals in plasmacytoid dendritic cells

Innate immunity is a conserved host defense mechanism and its key functions of are 1) to differentiate between harmful and non-harmful materials; 2) to initiate the first line of immune response; and 3) to recruit and prime the effector cells of the adaptive immune system. Dendritic cells are key participants of these processes as part of the network of professional antigen presenting cells. More than a decade after the discovery of myeloid DCs, researchers identified the plasmacytoid DCs, a small subset of DCs. Plasmacytoid DCs have a prominent role in antiviral immunity as professional type I interferon-producing cells, recognizing viruses in their endosomal compartment by Toll-like receptors. In contrast to recognition of viral replication intermediates in the cytoplasm of other cells by RIG-I-like helicase molecules (RLHs), this mechanism does not depend on viral replication and effectively detects non-replicating viruses. Multiple studies suggest that plasmacytoid DCs exclusively employ TLR-mediated viral recognition under steady-state conditions; however, the potential collaboration of TLRs and RLHs was not investigated. We have recently demonstrated that plasmacytoid DCs up-regulate RIG-I expression upon treatment with TLR7 and 9 ligands (Szabo et al. 2014). The up-regulation of RIG-I is independent of type I IFN autocrine feedback regulation. Co-stimulation with a TLR7 and TLR9 ligand showed inhibitory rather than synergistic effect on the up-regulation of RIG-I in primary plasmacytoid DCs. Our results suggest that Toll-like receptors and cytoplasmic nucleic acid sensors might act in co-operation during viral infection. The detection of non-replicating viral particles by endosomal TLRs might sensitize and prepare plasmacytoid DCs for the appearance of viral replication intermediates in the cytoplasm. This concept represents a novel synergy between various innate immune recognition pathways.