

How dendritic cells respond to nucleic acid adjuvants

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Dendritic cells (DCs) sense nucleic acid adjuvants and produce type I interferon (IFN) in a subset-dependent manner. Among nucleic acid sensors, TLR7 and TLR9 are peculiar in that they recognize not only pathogen- but also host-derived nucleic acids. In this context, TLR7 and TLR9 have a potential danger to cause autoimmunity. This danger is contained in physiological conditions, but manifested in the presence of anti-nucleic acid antibodies, antimicrobial peptides or intranuclear proteins that can transport the host-derived nucleic acids into the endosome of DCs. Such conditions can be observed in autoimmune diseases or chronic inflammations with massive cell death. In fact, accumulating evidences suggest that TLR7/9-induced type I IFN production play important roles in pathogenesis of autoimmune disorders such as SLE. Therefore, clarifying the TLR7/9 signaling mechanisms should contribute to the development of therapeutic manipulation for such diseases.

Plasmacytoid DC (PDC) is distinct from conventional DC (CDC) and a unique DC subset expressing nucleic acid sensors, TLR7 and TLR9. PDC can produce vast amounts of type I IFN, especially IFN- α , in response to TLR7/9. Meanwhile, TLR7/9-stimulated CDC can produce some amounts of IFN- β , but not IFN- α . PDC does not express the other TLRs or cytosolic nucleic acid sensors. Thus PDC can be regarded as a type I IFN producing DC subset by sensing nucleic acids through TLR7/9.

TLR7 and TLR9 are quite similar in their amino acid structures and can activate similar signaling pathways, which depend on a cytoplasmic adapter molecule, MyD88. At the downstream of MyD88, signaling pathways are bifurcated into NF- κ B and IRF-7 activation pathways, leading to the induction of inflammatory cytokines and type I IFNs, respectively. We have clarified that a serine threonine kinase, I κ B kinase- α (IKK α), plays critically roles in this type I IFN induction pathway in PDC. IKK α associates with and phosphorylate IRF-7, thereby inducing IRF-7 activation. IRF-7 is critical for type I IFN induction and constitutively highly expressed in PDC. However, CDC increases IRF-7 expression with various stimuli, but still fails to produce IFN- α in response to TLR7/9 signaling, indicating that PDC should have certain mechanisms to exhibit type I IFN producing ability. We will present characteristics of DC subsets and the molecular mechanisms for responses to nucleic acid adjuvants.