MECHANISMS OF DENDRITIC CELL MATURATION INDUCED BY INTRACELLULAR BACTERIA INFECTION

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ABSTRACT

Dendritic cells (DCs) are essential for the development of an immune response against pathogens such as *Listeria monocytogenes* and *Salmonella typhimurium*. This is mostly because of their unique capacity to stimulate naïve T cells. Before DCs become potent antigen presenting cells, they undergo a maturation process that enables them to efficiently stimulate naïve T cells. This process includes upregulation of costimulatory molecules such as CD80 and CD86 and production of cytokines. However, the pathway by which DCs mature can influence their capacity to induce effector functions in T cells. Thus, the aim of this thesis was to investigate the maturation and function of DCs during intracellular bacteria infection and its impact on T cell stimulation.

Conventional DCs expanded in number and upregulated costimulatory molecules in a subset- and tissue-specific manner after oral *Listeria* infection. Moreover, plasmacytoid DCs also expanded and upregulated CD86 and MHC-II although showing no tissue specificity. Conventional DCs produced significant amounts of IL-12. In addition, a complex CD11c-expressing population was identified, stratified in several subsets defined by production of TNF-α, iNOS and IL-12 alone or in combination. The production of these molecules was dependent on the subcellular compartment where *Listeria* was localized. Upregulation of CD80 and CD86 in DCs during orally acquired *Listeria* was differentially dependent on MyD88 and IFN-αβR. However, when the bacteria reached the blood stream directly, alternative pathways different than those mediated by MyD88 and IFN-αβR induced upregulation of costimulatory molecules. Remarkably, IFN-$\alpha\beta R^{-/-}$ mice expressed higher levels of CD80 and CD86, which translated into stronger naïve T cell stimulation. However, despite the significance of IFN-αβR in the early anti-*Listeria* response, it had little impact in the development of memory T cells.

Similar to *Listeria*, expression of costimulatory molecules during *Salmonella* infection was only partially dependent on MyD88 and IFN-αβR. Expression of CD80 was controlled by MyD88, whereas the MyD88-independent upregulation of CD86 was supported by IFN-α/β. Furthermore, *Salmonella*-associated DCs upregulated CD86 and CD80 to some extent even in the simultaneous absence of both MyD88 and IFN-αβR. However, DCs that matured by direct contact with the bacteria, but in the absence of these two factors, were less competent at stimulating naïve T cells than their wild type counterpart due to a decreased capacity to process bacteria-derived antigens.

Taken together, these studies expand our understanding of DC function during bacterial infection. In addition, the identification of factors involved in DC maturation addressed here can help to design more efficient approaches in the future to eliminate bacterial infections.

Keywords: *Listeria*, *Salmonella*, dendritic cells, maturation, MyD88, IFN-α/β

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I **Miguel A. Tam and Mary Jo Wick.** Differential expansion, activation and effector functions of conventional and plasmacytoid dendritic cells in mouse tissues transiently infected with Listeria monocytogenes. Cell. Microbiol. 2006 Jul; 8 (7): 1172-87.

II **Miguel A. Tam and Mary Jo Wick.** Conditional roles of MyD88 and IFN-α/β in homeostatic regulation of dendritic cell maturation but not for development of protective CD8 T cell memory response against *Listeria*. Manuscript.

III **Miguel A. Tam*, Malin Sundquist*, and Mary Jo Wick.** MyD88 and IFN-α/β are hierarchically required for functional maturation of dendritic cells and induction of CD4 T cells during infection. Submitted manuscript. *Authors contributed equally.