The role of dendritic cells in the induction of oral tolerance and immunity

Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, MD, and *Departments of Pediatrics and Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN, USA

Marina FLEETON, Akiko IWASAKI, Nikhat CONTRACTOR, Francisco LEON, Jianping HE, Denise WETZEL*, Terence DERMODY* and Brian KELSALL

Dendritic cells (DC) play a central role in the generation of immune responses in the intestine. DC induce differentiation and tolerance of T cells, and may have a direct role in B-cell switching to IgA. Four distinct subsets of CD11c+ DC are present in murine Peyer's patches (PP), which represent primary sites for the induction of mucosal T and B cell responses. In vitro, CD11b+ DC produce high levels of IL-10 and induce the differentiation of IL-4+ and IL-10-producing T cells, while CD8α+ DC and CD11b+/CD8α− DC produce little IL-10, high levels of IL-12, and induce only IFN-γ-producing Th1 cells. Ly6c+/B220+ plasmacytoid DC (pDC) reportedly produce IFN-α and IL-12, and may have a propensity for the induction of IL-10-producing regulatory T cells. These in vitro studies suggest that CD11b+ DCs or pDCs may be specialized for the induction of regulatory T cells, while all subsets may be involved in responses to pathogens. Despite these studies, the involvement of PP DC subsets in immunity to infection or in the induction of oral tolerance in vivo is not at all clear. We are currently using reovirus, type-I Lang (TIL) to explore the role of DC populations in mucosal immunity in vivo. This is because oral administration of live TIL to mice induces strong mucosal and systemic anti-viral immune responses, while oral administration of inactivated TIL results in tolerance to viral proteins. We have found that primary infection with TIL occurs in epithelial cells of the PP follicle-associated epithelium, but that DCs in the sub-epithelial dome region (SED) are loaded with TIL antigens in the absence of active DC infection. As least a portion of this antigen is associated with cell fragments from apoptotic epithelial cells, demonstrating that SED DCs cross present antigens from apoptotic epithelial cells. In vitro, in contrast to exposure to several TLR-ligands or anti-CD40, DCs are not activated to mature or to produce cytokines by direct exposure to the virus, despite clear loading of the DCs with viral antigens. These data suggest that TIL is taken up by a "silent" receptor on DCs, and that the induction of immunity to TIL is dependent on signals from non-DCs following active viral infection that induce DC maturation. Thus, the decision between tolerance and immunity to this virus likely depends on the active infection of epithelial cells by TIL, which results in the elaboration of molecules, such as cytokines, that induce DC maturation.