**Conference contribution: ICMI Berlin 2015**

**Abstract:**

**IRF8-dependent DCs Play a Key Role in the Regulation of CD8 T Cell Responses to Epithelial-derived Antigen in the Steady State but not in Inflammation**

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The intestinal immune system has the complex task of generating tolerance towards harmless antigens derived from our diet, commensal microflora or tissue, while maintaining the ability to mount protective immune responses to mucosal pathogens. Much of our understanding regarding the regulation of mucosal T cell responses stems from studies on CD4+ T cells. However, the intestinal mucosa is a major entry site for intracellular pathogens, whose control requires cross-presentation of cell-associated antigens for the induction of protective CD8+ T cell responses. To assess the regulation of mucosal CD8+ T cell priming and differentiation in the steady state and inflammatory setting, we utilized IFABP-tOva mice, in which Ovalbumin (Ova) is expressed as an epithelial-derived antigen in the small intestine. In this model Ova-specific CD8+ T cells were found to differentiate into two distinct subsets, CD107a/b+ cytotoxic T cells (CTLs) and FoxP3+ CD8+ T cells with regulatory potential. Interestingly, neither IRF8 nor IRF4 expression by intestinal dendritic cells (DCs) was crucial for the expansion of CTLs. In contrast, presence of IRF8- but not IRF4-dependent DCs was critical for the development of FoxP3+ CD8+ T cells in the steady state. However in the inflammatory setting, expansion of the FoxP3+ subset was not affected by the absence of IRF8-dependent DCs, suggesting that other subsets of intestinal antigen presenting cells (APCs) can compensate their function in an inflammatory milieu. Collectively these findings further our understanding of the mechanisms regulating CD8+ T cell responses in the intestinal mucosa and have potential implications for mucosal vaccine design.

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