International Symposium 2-1

Intestinal M cells and sampling of the gut microbiota

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The mucosal immune system in the mammalian intestine is charged with establishing a stable mutualistic relationship with the resident gut microbiota while simultaneously maintaining an active surveillance program aimed at containing pathogenic and potentially pathogenic microbes located at the mucosal interface. The innate and the adaptive immune systems have evolved to form specialized intestinal lymphoid structures including cryptopatches, isolated lymphoid follicles (ILF) and Peyer's patches (PP) that serve as immune hubs facilitating the maintenance of gut homeostasis. A prerequisite for immune cells within these hubs to initiate appropriate responses to individual components of the complex gut microbiota is direct exposure to antigenic components of the microbiota.

Microfold (M) cells are a specialized lineage of phagocytic epithelial cells derived from intestinal stem cells restricted to the epithelium overlying ILF and PP and capable of avid uptake of particulate antigens in the gut lumen and transcytosis of this material into the subepithelial space for delivery to myeloid antigen-presenting cells. In 2009 my laboratory identified the TNF superfamily protein RANKL as an essential M-cell inducing cytokine made locally in the ILF and PP microenvironment by subepithelial stromal cells (Knoop et al., *The Journal of Immunology*, 2009, 183:5738-5747). After this initial observation my group and other laboratories sought a more detailed understanding of the transcriptional mechanisms underlying RANKL-driven commitment to the M cell lineage. TRAF6, canonical and non-canonical NF-κB heterodimers, and the ETS transcription factor Spi-B all play crucial roles in RANKL-induced M cell differentiation. Another line of investigation has focused on determining the in vivo consequences in mice of conditionally disrupting the RANKL signal transmitted by M-cell inducing stromal cells to RANK-expressing intestinal epithelial cells. The absence of intestinal M cells observed in both RANK and RANKL conditional knockout mice interferes with the full normal maturation of ILFs and PPs and compromises the normal post-weaning secretory IgA response that is temporally associated with a large expansion of the density of the commensal microbiota. These in vivo findings support the conclusion that M cells play a nonredundant role in contributing to the normal establishment of immune homeostasis with the commensal gut microbiota.