

Dendritic Cells and the Intestinal Epithelium

with

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What is unique about the intestinal immune system?

Matt Butler and Subrata Ghosh: The lining of the intestine is coated with an epithelial cell barrier - one cell thick - separating food and bacterial antigens on one side, from the largest congregation of immune cells in the human body on the other. How do we maintain tolerance to this multitude of 'foreign' antigens, whilst preserving the ability to mount effective immune responses to true pathogens? Recent research suggests that the healthy gastrointestinal immune system is actually in a state of 'restrained' activation – constantly on but generating homeostatic rather than inflammatory responses. This condition appears to be induced by complex interactions between the gut flora, the intestinal epithelium, and the mucosal immune system. Since dendritic cells (DC) link the innate and adaptive arms of the immune system, they are likely to play a crucial role in the maintenance of intestinal homeostasis.

What is known about intestinal DCs?

Matt Butler and Subrata Ghosh: Like DC from other tissues, intestinal DC are the 'watchmen' of the immune system, continually sampling their local environment for antigens and constantly on the look out for pathogens. There are at least 3 different DC subsets in the gut and all appear to be particularly well adapted to the gut micro-environment. Myeloid, CD11c⁺/CD11b⁺/CD8 α , DC are the most numerous and can be detected in the sub-epithelial dome of Peyer's patches where they are in close contact with specialised 'M' cells in the intestinal epithelium (1). M cells efficiently transcytose antigens from the gut lumen above, and pass it to the immune cells below, thus providing DC with a 'window' on the gut contents (2). In addition, DC can actively sample the gut lumen by extending dendritic processes between epithelial cells, whilst maintaining epithelial barrier integrity by expressing tight junction proteins (3). Gut DC also appear to be specialised in their ability to stimulate naïve T lymphocytes. DC from the Peyer's patch of mice preferentially promote the development of T cells with a T helper-type 2 (Th2) cytokine profile (IL-4, IL-5, IL-10, IL-13) rather than the T helper-type 1 (Th1) profile (IFN γ , TNF α , IL-1 β) which is induced by splenic DC (4,5). Intestinal DC also influence the migration of responding T cells enabling them to home specifically to intestinal tissues. This is achieved by the induction of adhesion molecules such as α 4 β 7 integrin (binds MadCAM in the intestinal vascular system) and chemokine receptors such as CCR9 (responds to MIP3 α). Recent evidence suggests this imprinting could be controlled by retinoic acid (vitamin A) in DC (6).

Is the phenotype of intestinal DCs different from other DCs?

Matt Butler and Subrata Ghosh: the intestinal mucosa express low levels of MHC class II

and co-stimulatory molecules as compared to DC from other tissues (7). Moreover, DC from Peyer's patches express elevated levels of the immunomodulatory cytokines, IL-10 and TGF β , and preferentially skew T cells towards a Th2 response

How does the intestinal epithelium influence DC function?

Matt Butler and Subrata Ghosh: The intestinal epithelium controls the migration of DC in the steady-state via the release of chemokines, such as CCL9 and CCL20, which have been shown to attract CD11c⁺/CD11b⁺ DC to the sub-epithelial dome of Peyer's patches (9). However, epithelial cells can also modulate DC phenotype and function. In an *in vitro* co-culture model, an intact epithelial cell monolayer provides signals that inhibit DC expression of MHC class II, co-stimulatory molecules, and inflammatory cytokine production. The resulting DC are poor stimulators in an allogeneic mixed lymphocyte reaction and preferentially promote Th2 responses (10,11). In addition, co-cultured DCs show significantly reduced responses to bacterial antigens such as LPS, partly as a result of autocrine production of TGF β and down-regulation of TLR expression and activity (10). Thus, DC cultured in the presence of an intact epithelial cell monolayer, show many of the characteristics found in DC isolated from gut tissues.

Epithelial cells express a broad range of potential immuno-modulatory factors which may influence intestinal

which is vital for the generation of protective IgA antibodies (4). Gut DC also express lower levels of bacteria-sensing Toll-like receptors (TLRs) and show reduced responses towards bacterial components such as lipopolysaccharide upon stimulation *ex vivo* (8). Such adaptations to their environment may allow DC to regulate their responses to the contents of the gastrointestinal tract and promote homeostatic adaptive immune responses. Progress is now being made in understanding the nature of the modulatory signals received by DC in the intestine.

DC. Cytokines such as TGF β and lipid mediators such as PGE₂ have been shown to have potent immuno-modulatory effects on DC both *in vitro* and *in vivo* (12). Of particular interest is thymic stromal lymphopoietin (TSLP), a modulatory factor released by epithelial cells that contributes to the development of Th2 immune responses by modulating DC phenotype and function (13). While more work is required in this area, it is clear that signals encountered by DC in the gut have a critical role in shaping the resulting adaptive immune response. A healthy intestinal epithelium appears to provide one set of homeostatic signals. How DC integrate information from the tissues, and the commensal flora, is currently the subject of further investigations.

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