Immunity in the Gut

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The large intestine (colon) has a large resident population of microbiota, consisting of at least 10^{12} organisms per gram of luminal contents. These organisms, together with the antigenic load provided by the diet and the constant threat of potential pathogens, means the intestinal immune system encounters more antigen than any other part of the body.

The Balance

As many pathogens enter the body via the intestinal mucosa, it is vital the gut-associated lymphoid tissues can provide effective immune responses when necessary. However, inappropriate responses against innocuous food and commensal antigens lead to inflammatory disorders such as **coeliac disease** and **inflammatory bowel disease** (**IBD**).

Gut-associated lymphoid tissue (GALT)

The lymphoid elements of the gut comprise organised lymphoid tissues such as the Peyer's patches (PP), and the mesenteric lymph nodes (MLN). The effector sites of the intestine are the mucosal epithelium and underlying lamina propria (LP). Here there are many different immune cells including activated T cells, plasma cells, mast cells, dendritic cells and **macrophages** (**Figure 1**) even under normal conditions. That this does not result in overt tissue pathology reflects the fact that the effector cells present are actively held in check by potent regulatory mechanisms.

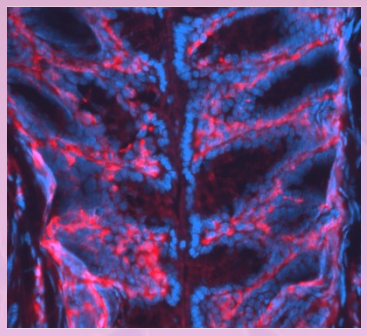

Figure 1. Macrophages (F4/80+; red) are abundant in the resting LP of the colon

Immune protection in the gut

Although composed of only a single cell layer, the intestinal epithelium forms a barrier against penetration of microbes. Defects in barrier function contribute to the development and perpetuation of inflammation in IBD. Epithelial cells of the small intestine are coated in a glycocalyx of **mucins** and other glycoproteins that can interact with and trap bacteria in the mucus. In addition, anti-microbial peptides such as **defensins** are secreted by Paneth cells located at the bottom of the intestinal crypts. Epithelial cells also act as **microbial sensors** by secreting factors such as IL-8, MCP-1, RANTES, TNFα and IL-6 in response to bacterial entry. This results in the recruitment of neutrophils, eosinophils, monocytes, **phagocytic macrophages** and T cells, and so enhances the induction of protective immunity. Although many of these cells are also present in the normal intestine, under physiological conditions, they are **conditioned by factors in the local environment to be non-inflammatory**. The normal and inflamed intestine contains many specific immune cells, including IgA-secreting plasma cells, **CD4+** and **CD8+ T cells**, **regulatory T cells** and **γδT cells**.

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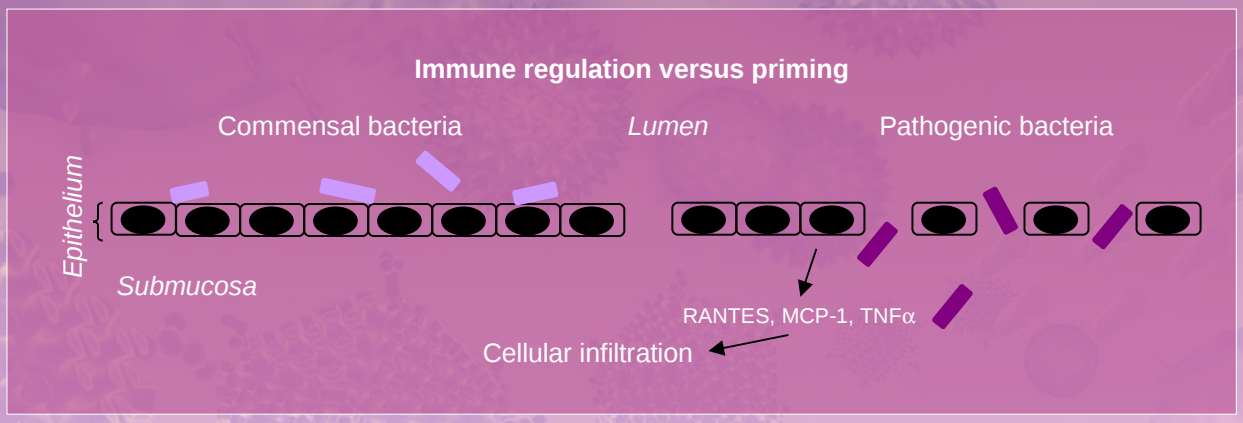

Figure 2. Immune regulation versus priming

Commensal bacteria and pathogens share many factors which can be detected by pathogen recognition receptors such as toll-like receptors (**TLR**). So how do commensals fail to trigger inflammatory responses (also see **Figure 2**)?

- Modulation of innate activating receptors such as CD14 and CD89 on gut macrophages.
- High levels of immunomodulatory factors: IL-10, TGFβ, TSLP, retinoic acid which can 'condition' local cells.
- Reduced function of TLRs in intestinal DC.
- Commensals are **non-invasive**. Whereas pathogens penetrate the epithelium and trigger inflammatory responses both locally and more widely, commensal bacteria only penetrate the epithelium after uptake by local DC and are then transported to the draining MLN, where their progress is halted. This results in the production of secretory IgA in the gut which limits commensal numbers and regulatory T cells which dampen inflammatory responses. Local, non-inflammatory macrophages also ingest and kill the rare commensals which enter.