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Innate and acquired plasticity of the intestinal immune system

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The principal function of the intestines is to process food through digestion and to take up and transport the digested nutrients across the epithelium, i.e. from the lumen to the bloodstream. The intestinal mucosa constitutes a vast surface area covered by a monolayer of epithelial cells dedicated to the above-mentioned functions. Intestinal epithelia are therefore constantly exposed to large quantities and a wide variety of (i) food antigens and (ii) resident microorganisms forming the commensal flora (about 10^{11-12} per gram of lumenal material in the colon) [1]. From time to time, food and water supplies introduce exogenous pathogenic microbes that are specifically equipped to invade the mucosa [2]. Hence, gut homeostasis requires immunological 'ignorance' of the large amount of food antigens and commensal flora as well as effective protection from incessant and abundant environmental challenges and injuries. The aim of the following set of reviews is to describe how innate and adaptive immunity closely discriminates between and regulates hyporesponsiveness or specific immune deviation for 'beneficial' antigens (so-called oral tolerance) on the one hand and mechanisms which defend against 'harmful' antigens on the other.

The review by Rumbo and Schiffrin describes the mechanisms involved in the development of intestinal tissue (especially the formation of epithelial cell tight junctions and the acquisition of digestive and defense functions) and the organization of mucosa-associated lymphoid tissue (MALT). Even though the intestinal immune system is built up through programmed gene expression, signals delivered from the external environment during the embryonic and neonatal periods also play a role in this process. A stunning example comes from studies in Jeff Gordon's laboratory showing that the introduction of commensal bacteria into axenic animals modulates various intestinal functions – including immunity [3].

A major contribution of the intestinal epithelia to immunity is the barrier function that prevents interaction between lumenal material and cells lining the gut. In addition to factors such as impermeability, rapid renewal and peristalsis, the epithelial layer is protected first by mucus produced by goblet cells and second by a myriad of antimicrobial molecules such as cryptdins, lysozyme, phospholipases and chemokines. As reviewed by Müller and colleagues, these natural microbicidal or microbiostatic compounds impair the proliferation of a broad range of microorganisms, thereby blocking much of the ongoing colonization prior to mucosal invasion. Recent observations have shown that mammalian genomes code for a number of cryptdin-related homologues and that these polypeptides associate in homo- or heterodimers [4]. This system provides a wide variety of soluble antimicrobial factors, thereby increasing the spectrum of targeted microbes and boosting synergistic, antimicrobial activity. Whereas the biochemical barrier is essential under steady-state conditions, external signals also induce or increase expression of antimicrobial molecules likely to potentiate the barrier during neonatal microbial colonization, pathogen assault or other injury [5, 6]. These signals also initiate the mobilization of phagocytic cells via chemokine gradients and mucosal remodeling [7, 8]: the recruited phagocytes subsequently engulf and eliminate any undesirable microbes.

Although innate mechanisms are sufficient for protecting the gut in most instances, the memory properties of the adaptive immune system's effector lymphocytes enable pathogens to be eliminated more specifically and more efficiently when the latter are re-encountered. Thus, the

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digestive tract is a major site of immunological memory and indeed constitutes the body's main reservoir of B and T lymphocytes. The review by Kunisawa and Kiyono summarizes how adaptive immunity is elicited via anatomically distinct mucosal inductive sites and mucosal effector sites: the mucosal immune system is therefore compartmentalized [9]. A prerequisite for an antigen-specific response is antigen sampling through the mucosal epithelium and delivery to underlying MALT or lymph nodes draining mucosa. Peyer's patches (PPs) were originally described as being the only small intestine MALT structures involved in these functions. The recent identification of specialized sampling cells (known as M cells) and isolated lymphoid follicles scattered throughout the villi suggests that a large area of small intestine is competent for antigen uptake and induction of adaptive immunity [10–12]. However, it remains to be seen whether the development of intestinal inductive sites is totally determined by a genetic program or is also controlled by nutrients and microbial signals, as recently reported for the lung [13]. Kunisawa and Kiyono also present the mechanisms involved in the compartmentalization of mucosal immunity, i.e. the generation and homing of mucosal effector cells including plasma cells, producing secretory immunoglobulins (SIgs).

Dubois and colleagues describe recent progress in understanding oral tolerance to food antigens and the commensal microbes of the intestinal flora. Their review presents various scenarios accounting for the development of immunosuppressive responses within the gut. Oral tolerance is essential for preventing inflammatory responses to the huge quantity of luminal antigens encountered. Local expression of cytokines such as interleukin 10 or transforming growth factor beta plays a key role in the control of intestinal inflammation and disease. Oral tolerance depends on dynamic immune processes that require specific activation of $CD4^+$ T cells and/or regulatory T cells within MALT. In turn, lymphocytes specific for beneficial antigens are functionally inactivated by deletion, anergy and the production of anti-inflammatory/immunosuppressive cytokines. In terms of the professional antigen-presenting cells, dendritic cells (DCs) are not only essential for setting up the platform for blockade of gut-damaging responses but are probably also involved in local propagation of tolerance to other lymphocytes, i.e. infectious tolerance or bystander tolerance [14].

Sato and Iwasaki provide further insights on the role of gut DCs as the principal cellular players in induction and regulation of mucosal immune responses. Compared with peripheral DCs, MALT-associated DCs have distinct migratory and functional properties: this is partly due to the gut-specific microenvironment. Depending on the nature of the antigen (harmful versus beneficial), mucosal DCs will drive an appropriate immune response for controlling homeostasis, be it activation of effectors and/or development of regulatory cells. Thus, PP DCs instruct T and B lymphocytes to induce maturation of B cells into immunoglobulin A (IgA)-producing plasma cells – an effector arm that is central to mucosal immunity. Whether resident or recently recruited, DCs within MALT or gut-draining lymph nodes also acquire specific features that enable them to imprint homing abilities on intestinal lymphocytes [15, 16]. Interestingly, vitamin A (which is generally delivered by food) influences the imprinting of T cell gut homing, thereby emphasizing a crucial role of external factors in regulation of the intestinal immune system [17]. It remains to be established whether commensal or gut-specific pathogenic microorganisms play a similar role.

In the neonate, microbial colonization (which occurs in successive waves) shapes the mucosal immune system. The review by Collier-Hyams and Neish reveals that commensalism has strong effects on intestinal epithelial cells. Commensals and the mammalian host co-exist in a mutually beneficial relationship, since (i) the resident flora not only improves digestive capabilities and the barrier function but also competes with harmful microbes and (ii) the host provides a nutrient-rich environment. Moreover, the interaction stimulates a broad immune response, characterized by massive production of SIgA and expansion/activation of mucosa-associated, invariant T cells in the lamina propria [18, 19]. Disruption of mutualism triggers the onset of inflammatory bowel diseases such as Crohn's disease or ulcerative colitis. These findings imply that commensal bacteria can still elicit an inflammatory response similar to that observed during intestinal infection by a bacterial pathogen [20]. The cross-talk between the microbes and their mammalian host depends on a variety of signals (such as sugar/nutrient availability), but it remains to be seen whether specific microbial factors influence the host. On the host side, surface and cytosolic pattern-recognition receptors (PRRs) expressed in the gut are involved in the detection of highly conserved microbial molecular motifs called pathogen-associated molecular patterns, or PAMPs. Since commensal microorganisms share these signatures, the term 'MAMP', for microbe-associated molecular pattern, has been proposed and should be used in preference to PAMP. The cognate PRR-MAMP interaction is instrumental in triggering signaling and leads to the transcriptional activation of genes encoding pro-inflammatory molecules. Collier-Hyams and Neish first describe strategies used by commensals to escape this detection machinery and then illustrate the resulting pro-inflammatory responses: they hypothesize that MAMP-dependent signaling might affect anti-apoptotic as well as pro-apoptotic processes. In addition, recent findings confirm that commensal-mediated PRR activation is a prerequisite for effective gut epithelium homeostasis [21, 22].

Of the PRRs, the Toll-like receptor (TLR) family has been extensively investigated over the last 5 years. TLRs are expressed in intestinal cells and have been found to be essential in various mucosal infection models. For instance, TLR signaling stimulates epithelial cells to produce the chemokines involved in neutrophil and DC recruitment. The review by Alexopoulou and Kontoyiannis provides insights into how TLR-triggered signaling cascades modulate mucosal immune responses. In view of the fact that TLR signaling activates nuclear factor kappa B (NF-κB)-dependent transcription of pro-inflammatory genes, mechanisms for the resolution of this process and reversion to a steady state are also required. The review shows that TLR activation occurs in various intestinal cell types and that it induces sequential waves of information transfer in a given cell. This temporal control depends on transcriptional and post-transcriptional events, which mediate the stability of messenger RNA (mRNA) and proteins. Finally, signaling via a specific TLR can be sequentially regulated by various ligands, including MAMPs initially and then endogenous ligands generated upon MAMP detection. Deciphering the features of responding cells and the signaling outcomes in a time- and space-dependent manner will be instrumental to understanding how PRRs shape mucosal immunity.

The following reviews give a broad overview of the specific features of gut immunity: constitutive innate defenses, the anti-inflammatory environment, immune signaling in response to environmental factors, imprinting functions in dendritic cells and effector compartmentalization. Although we are starting to understand the molecular basis for the induction of tolerance versus immunity in the gut, mucosal immunology still faces many challenges. By deciphering how innate immunity influences adaptive immunity and how memory effector cells can reach mucosal sites, future research will help design new avenues for controlling gut infections and chronic immune disorders.

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