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MULTI-AUTHOR REVIEW

Between vigilance and tolerance: the immune function of the intestinal epithelium

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Introduction

Only three decades ago, gut mucosal immunology largely focused on secretory immunoglobulin A (SIgA), mucins, and secreted enzymes such as lysozyme, lactoferrin, and peroxidase [1]. The intestinal epithelium was regarded as passive physical barrier separating the bacterially colonized gut lumen from the largely sterile underlying tissue. During the following decades, however, fuelled by an increasing interest in the pathogenesis of inflammatory bowel disease and exciting discoveries in mucosal immunology and microbial pathogenesis, the spectrum of mechanisms examined was dramatically extended. For example, cell development, tissue homing and functional characteristics of the various T helper and T effector (and later again, also regulatory) lymphocyte subsets and antigen presenting cells, as well as the structural and spatial organization of the different mucosal lymphoid compartments, became an area of intense research [2]. The identification of intestinal stem cells and the characterization of developmental aspects of the remarkable small intestinal crypt-villus architecture and the rapid cell turn over illustrated the complex biology behind the epithelial surface structure of the intestinal mucosa [3]. Research on the pathogenesis of enteric infectious diseases unravelled the molecular basis of attachment, cell invasion and epithelial translocation by many important enteropathogenic bacteria, viruses and parasites [4]. The characterization of antimicrobial mechanisms of the host on the one hand but also microbial immune evasion strategies on the other hand as a result of the long co-evolution illustrated the intense bidirectional host–microbial interaction [5]. Finally, the generation of animals bred in the absence of a viable microbiota, colonized by only one single bacterial strain, or a controlled bacterial flora highlighted the significant influence of commensal bacteria on the host [6, 7]. The more recent findings of the specific effect of selected members of the microbiota and the susceptibility of the microbiota composition to exogenous influences (e.g. co-housing) as a potential disease-promoting mechanism once again illustrated the great dynamic and complexity of the host–microbial interaction and its far-reaching downstream effects, an area that keeps attracting much attention and providing unexpected results [8–10].

With the prediction and subsequent discovery of innate immune receptors and accumulating evidence that intestinal epithelial cells also express a selection of these receptors, the active functional role of the intestinal epithelium as part of the host's mucosal immune system both during homeostasis and intestinal disease emerged [11–14]. The active contribution of intestinal epithelial cells both to host–microbial homeostasis and inflammatory diseases was subsequently corroborated by the findings obtained from genome-wide association studies (GWAS) analyzing patients with chronic inflammatory bowel diseases as well as a variety of elaborated genetic animal models [15, 16]. This led to the current model that the intestinal epithelium senses the presence of environmental and microbiota-derived innate immune receptor ligands and actively contributes to mucosal homeostasis, inflammation and tissue repair. Epithelial innate immune receptor stimulation was shown to result in the release of proinflammatory, chemoattractive and regulatory mediators, epithelial apoptosis, and the production and secretion of antimicrobial peptides

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and nitrogen and oxygen radicals. The epithelium receives information from underlying cells of the *lamina propria* and instructs professional immune cells that reside within the mucosal tissue [17]. These secreted mediators exhibit target cell specificity and selectively influence the epithelium or cells of the underlying tissue [18]. Individual epithelial cells also communicate horizontally among themselves and forward the information of bacterial challenge to allow a coordinated mucosal response [19]. Epithelial cells thus represent an intrinsic interactive player of the mucosal immune system and actively contribute to mucosal homeostasis [20].

The identification of functional innate immune receptor expression at the intestinal epithelium in the presence of high concentrations of a variety of microbial ligands early on illustrated the requirement for regulatory control to avoid inappropriate innate immune activation, mucosal inflammation and organ dysfunction intensifying the research on negative regulatory mechanisms of innate immune signalling [21]. Various negative regulatory mechanisms provided by the microbiota, the underlying *lamina propria* or epithelial cells have since been proposed. The mechanisms that allow rapid reconstitution of the severely damaged mucosal tissue, e.g. after infection with invasive bacterial pathogens or chemically-induced cell damage, have, however, largely remained an enigma. But the regulatory network that governs, restricts and terminates innate immune activation is likely to play a significant role in the host–microbial interaction both during inflammation and homeostasis.

Of note, the enteric mucosal surface is covered not by one single intestinal epithelial cell but rather by different highly specialized cell types. The epithelial cell types are generated by the regenerating stem cell localized in the intestinal crypts and comprise the antimicrobial peptide-producing Paneth cells, the mucus-secreting goblet cells, the regulatory peptide hormone-releasing neuroendocrine cells and, finally, the absorptive enterocytes that together cover the intestinal surface, but reside in different anatomical niches, and are present in varying numbers in different anatomical sites of the intestine. Although the main functions of the different enteric epithelial cell types have been characterized, novel features continue to arise. For example, Paneth cells have recently been shown to provide essential growth factors and to foster the nearby stem cells [22]. In addition to the different epithelial cell types, the phenotype of enterocytes depends on its position along the crypt–villus axis since the migration along the crypt–villus axis is accompanied by continuous cell differentiation. The continuous cell proliferation, crypt–villus migration and differentiation have important consequences: first, the analysis of epithelial cells always includes a great variety of different cell types and differentiation stages; and second, individual epithelial cells are rapidly exchanged due to the rapid cell turnover with complete renewal of the epithelial surface every 3–5 days.

The present collection of review articles aims at drawing an admittedly incomplete but hopefully stimulating picture of the active role of intestinal epithelial cells and their contribution to enteric mucosal immunology. The contribution from Nita Salzman and Charles Bevins includes a comprehensive description of the enteric microbiota and host mechanisms such as Paneth cell-derived antimicrobial peptides that influence its composition and might turn out to critically contribute to establishing and maintaining the host–microbial balance and prevent the development of an adverse colitogenic flora composition. Gunnar Hansson, Malin Johannson and collegues draw attention to the structure and function of the surface overlaying mucus, which, although principally known for a long time, is still ill-understood with its sophisticated composition, localization and function. The current understanding of the rapidly expanding field of epithelial innate immune receptor expression and function in intestinal epithelial cells is illustrated in the article from Rute Marques and Ivo Boneca. Richard Siggers and David Hackam shed light on the mechanisms that lead to intestinal epithelial apoptosis observed in various human diseases. Silvia Stockinger and the two of us summarize our understanding of the processes that facilitate adaptation of the fetal gut epithelium to microbial colonization and pathogenic challenge during the postnatal period. Arthur Kaser, Lukas Niederreiter and Richard Blumberg describe the recent progress made to understand inherited epithelial dysfunctions and their contribution to human disease. Chittur Srikanth, Regino Ricardo-Lubo, Kelly Hallstrom, and Beth McCormick analyze the intimate molecular interaction between an intestinal pathogen and the host's epithelium, using the example of the well-studied human enteropathogen *Salmonella enterica* subsp. *enterica* sv. Typhimurium. Finally, Julien Royet illustrates recent findings made to better understand the mechanisms of gut epithelial homeostasis using the striking model of the fruit fly *Drosophila melanogaster*. Thus, the present reviews illustrate both the peculiarities of the epithelial cells as well as their integrated function within the mucosal immune system. They will hopefully stimulate further interest and the development of novel approaches to improve our understanding of the active role of the intestinal epithelium during mucosal inflammation and host–microbial homeostasis.

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