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Mucosal immunology and bacterial handling in the intestine

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A B S T R A C T

The mucosal immune system has the very difficult task to protect against invaders and to promote tolerance toward food antigens and the microbiota. These activities are achieved via a complex interaction between immune cells and the local microenvironment. Under the unperturbed (steady-state) condition the immune system is set toward the activation of tolerogenic responses. During infection the immune system is prompted to initiate immunity. When these two activities are not coordinated, inflammatory conditions may arise. In this review I will summarize the characteristic features of the mucosal immune system and its interaction with the microbiota.

Introduction

The gut immune system plays two very important functions: to protect against potential pathogens and to tolerate both ingested food antigens and the huge burden of the microbiota that inhabits the gut. In addition, a new function of the mucosal immune system is emerging that is to ensure the diversification of the intestinal microbiota. Indeed, to remain innocuous, the microbiota has to reflect a balanced equilibrium between pathobionts and symbionts [1]. Pathobionts are potentially dangerous microorganisms present in the microbiota that if not checked can give rise to inflammatory diseases [2]. Hence, the mucosal immune system has many unique functions that allow controlling the growth of pathobionts and avoid tissue destruction. These include the presence of diffuse lymphoid cells in the lamina propria and organized lymphoid structures such as the isolated lymphoid follicles and Peyer's

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Patches that form the gut associated lymphoid tissue (GALT). In addition, memory and effector T lymphocytes predominate even in the absence of infection [3] as well as IgA secreting plasma cells [4,5]. Antigen presenting cells at steady-state are characterized by a tolerogenic phenotype [6].

In this review we will analyze the different activities of immune cells to control immune homeostasis in bacterial handling in the gut.

The microbiota first interacts with the epithelial barrier

Most of the microbiota does not directly interact with immune cells because it is separated by the epithelial barrier that is composed by a physical, chemical and electrical component (for comprehensive reviews see [7–9]). First, a mucous layer that differs in thickness according to the region of the gut that is analyzed, protects the epithelium from direct interaction with most but not all of the bacteria, because some bacteria such as segmented filamentous bacteria (SFB) have the capacity to enter the mucous. However, SFB colonization in humans is age dependent and the bacteria disappear by the age of three [10]. Second, the glycocalyx that is produced by epithelial cells is negatively charged and opposes most of the microorganisms that are also negatively charged. Paneth cells and epithelial cells release a battery of antimicrobial peptides that control different classes of microorganisms. Finally, epithelial cells are connected to each other by tight junctions that exclude microorganism from entering via the intercellular space. However, a subset of antigen presenting cells characterized by the expression of CX3CR1 can creep between epithelial cells and can contact directly the intestinal lumen [11,12]. However, under steady-state they do so primarily in the upper part of the intestine where the mucous layer is reduced and they can more easily extend the protrusions [13].

Gut antigen presenting cells

After the epithelial barrier, the first cells that contact microorganisms are antigen presenting cells (APCs) and intraepithelial lymphocytes. Both present characteristics of innate immune cells as they can release cytokines, chemokines and antimicrobial peptides as a first line of defense and to activate and recruit immune cells. In addition, APCs can also phagocytose and kill the ingested bacteria. Antigen presenting cells in the gut can be found scattered in the lamina propria (LP) of both small and large intestines, in the GALT and in the mesenteric lymph nodes (for extensive reviews see [8–10]). In the mouse, APCs can be divided into subgroups depending on the expression of CX3CR1 (the receptor of fraktalkine) and CD103 (α-E integrin) [11–13]. In particular, it is possible to distinguish $CX3CR1^{-}CD68^{-}CD103^{+}$ and $CX3CR1^{int}CD68^{-}CD103^{-}$ bona fide DCs, and a population of macrophages $CX3CR1^{+}CD68^{+}F4/80^{+}$. The proportions of these APC subsets may vary according to the composition of the microbiota as in mice reared under germ-free conditions the expansion of $CX3CR1^{+}$ DCs is impaired [11]. $CX3CR1^{+}$ cells derive from a monocytic precursor that may be recruited in response to the microbiota, while $CD103^{+}$ DCs derive from circulating DC precursors (pre-DCs) [14,15]. The counterpart of $CX3CR1^{+}$ APCs has not yet been described in the human system, while $CD103^{+}$ DCs have been found in human mesenteric lymph nodes (MLN) [14,15]. $CD103^{+}$ DCs are endowed with the capacity to drive T regulatory cells via a mechanism that is dependent on retinoic acid and TGF-β both in the mouse [17,18] and human [19] systems. In addition, they constitutively express IDO, which is fundamental for their tolerogenic potential [16]. $CD103^{+}$ DCs can also imprint T cells with gut homing properties in the mouse [20] and human [21] system. Hence, under steady-state conditions, $CD103^{+}$ DCs are specialized in driving mucosal tolerogenic responses. Regarding $CX3CR1^{+}$ APCs it is not yet clear what their function in vivo is as they are incapable of migrating out of the gut [16] and they are poor antigen presenting cells. However, a recent report has shown that these cells acquire migratory properties in the absence of the microbiota, indicating that they may exert a DC-like function under certain conditions [17]. $CX3CR1^{+}$ macrophages/DCs (M/DC) have been described to drive in vitro the development of Th17+ cells [12] presumably via a Flagellin [22] or ATP-dependent [23] mechanism. However, these cells are also capable of mediating oral tolerance [18] and to protect against colitis [19,20]. IL-10 signaling seems to be involved in both activities, via the restimulation of T regulatory cells and the inhibition of T cell