

Innate Immune Cells: Key Regulators of Homeostasis and Inflammation in Gut and Airway Mucosae

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Abstract— The epithelial layers that line the human gut and airways have evolved into tightly regulated mechanical and functional tissue barriers, the mucosae, which have to cope with unrelenting exposure to food- and airborne contaminants. In these barriers, immune cells play a major defensive role. This review describes the most important cellular and molecular mechanisms of mucosal leukocytes during homeostasis and physiological inflammation with a major focus on innate immunity (i.e., the immediate response against potential invaders). In homeostasis, a well-defined mucus layer and the epithelial layer hinder microbes from entering the underlying tissue. In addition, mucosal macrophages are patrolling scavengers with high phagocytic capacity, but their ability to mount an inflammatory response is down-regulated. Innate lymphoid cells also have an important role in maintaining a healthy mucosa. However, if bacteria overcome the barrier they cause an inflammatory reaction aimed at eliminating the threat and re-establishing tissue homeostasis. During the inflammatory response, tissue-resident immune cells become activated and promote the recruitment of monocytes and other leukocytes from the blood to the site of inflammation. The reaction evolves the contribution of mononuclear phagocytes, mast cells, neutrophils and ILCs until the infection is eliminated, tissue damage repaired and homeostasis re-established.

Keywords — innate immunity, mucosa, leukocytes, inflammation, cytokines, gut, airways

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INTRODUCTION

The human body is constantly challenged by environmental factors such as microbes, allergens and other contaminants. Besides the skin, the internal epithelial linings of the body, the gastrointestinal, respiratory and urogenital tract mucosae, are in direct contact with the external environment and all potentially harmful agents within it. Thus, the mucosa has evolved into a specialized defensive barrier with physical and cellular features that allow to maintaining normal organ function (e.g., respiration, nutrient and water absorption) while shielding the inner parts of the body from the external agents [1, 2]. The morphology and physiology of the mucosae can differ remarkably from one tissue to another (Fig. 1). However, the different mucosae have the common goal of protecting the underlying tissue from infection or damage. When a microbe succeeds in crossing the epithelial barrier and gains access to the subepithelial space, it comes into contact with the underlying innate leukocytes and stromal cells. This contact causes an inflammatory reaction, which is a physiological defensive process to limit or block tissue invasion by microorganisms. In certain pathological conditions, this process persists or is amplified, leading to chronic inflammation, tissue destruction or tissue remodeling [3, 4]. For instance, smoking-associated chronic obstructive pulmonary disease is characterized by an exaggerated chronic inflammatory response, which results in dramatic changes in airway architecture and airflow limitation [5]. In the intestine, the group of inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn's disease, are examples of chronic inflammation with impaired barrier function and altered patterns of cytokine release, which can eventually lead to tissue destruction, fibrosis and even cancer [6]. Thus, unresolved inflammatory reactions can provoke severe changes in both the architecture and function of the mucosa.

During inflammation, activated epithelial and immune cells signal the presence of potential dangers by secreting soluble mediators, such as cytokines (Table I) and chemokines (Table II). These mediators act by coordinating the immune response to microenvironmental changes and by recruiting circulating leukocytes to the site of infection. This review focuses on the innate defensive mechanisms of the human gut and airway

mucosae. The role of innate immune cells in mucosal homeostasis, inflammation and resolution will be covered by discussing human studies in particular, but murine studies are included to provide a more complete picture. Furthermore, we will outline the general mechanisms involved in maintaining mucosal tissue homeostasis. Although adaptive immunity is not discussed here, it is important to note that innate and adaptive immune responses cross-regulate each other, and therefore a complete understanding of immunity in the mucosae cannot avoid considering also the specific immune responses.

THE EPITHELIAL BARRIER IN HOMEOSTASIS

Initial defensive features of the mucosa – epithelium, mucus and microbiome

The innate alarm and defense system of the mucosa comprises not only immune cells but also epithelial cells and several non-cellular defense mechanisms that hinder pathogens from crossing the epithelium. In order to keep off possible invaders, a mucus layer covers the mucosal epithelium. Epithelial cells of the gut and airways secrete antimicrobial peptides and proteins such as α - and β -defensins, lysozyme, lactoferrin or cathelicidin into the mucus [7-9]. The physical properties of mucus can vary significantly in the different mucosae. In the airways, pseudostratified and ciliated epithelial cells are

surrounded by a watery periciliary mucus, on top of which a more viscous mucus layer is located [10]. Ciliary beating propels the overlaying mucus, thereby ensuring the removal of pathogens trapped within the denser mucus. In contrast, the small intestine is equipped with a single unattached mucus layer, which is easily removed by an intense motor activity and secreted liquid. Thus, entrapped bacteria are moved distally towards the colon, where the highest number of commensal bacteria resides. In the colon, under the unattached mucus layer is present a constantly renewed, dense and fixed mucus layer. While commensal bacteria of the colon are able to thrive well in the outer layer, the inner layer is impenetrable to these microbes [11]. Compared to pathological microorganisms, commensal bacteria are less invasive and their sheer abundance restrains the colonization of the gut by potential pathogens [3]. The coevolved interactions between the intestinal microbiome and the host's innate defensive mechanisms are important for their mutual homeostasis. Thus, on the one hand sensing of commensal bacteria by innate immune receptors is necessary for a stable microbiome to occur. On the other hand the microbiome is involved in the development and functionality of innate immunity (reviewed in [12]). In particular, murine studies on impaired innate immune signaling underlined the major role of innate immune mechanisms in maintaining a homeostatic balance with the microbiome [12]. For instance, deficiency in the intracellular

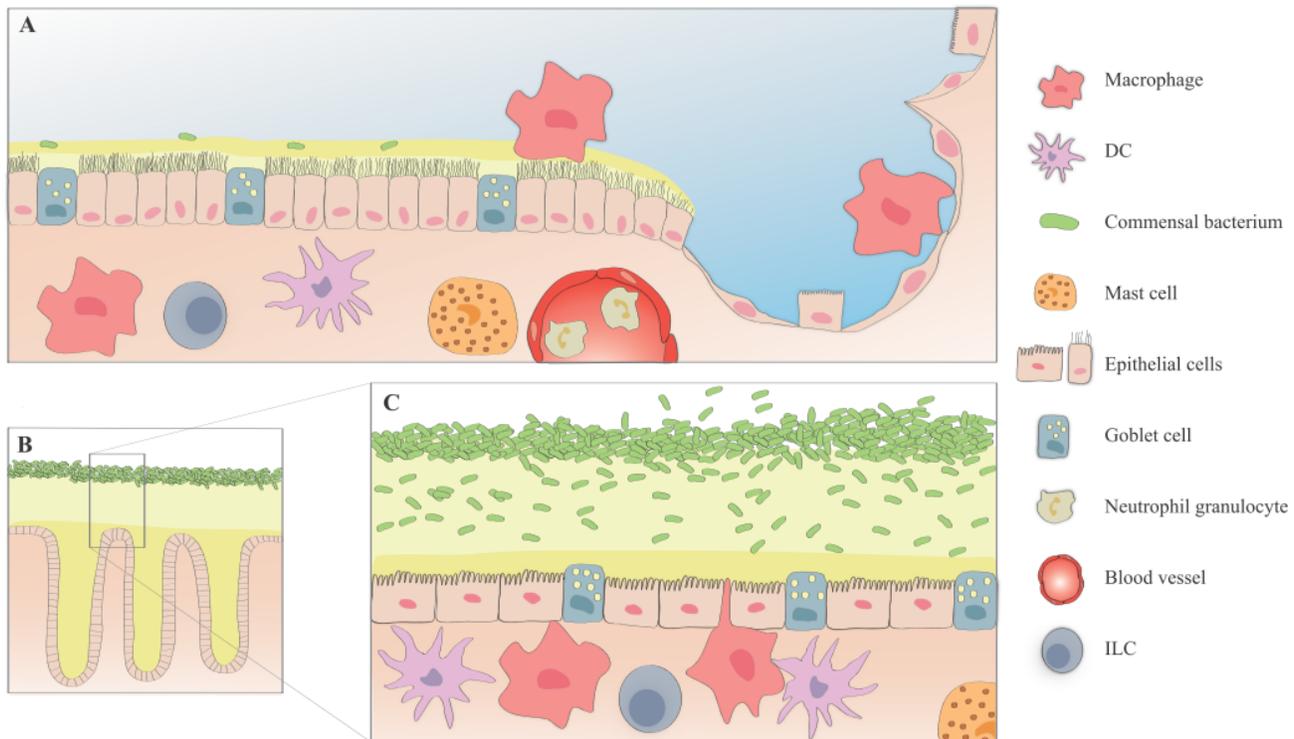


Fig. 1. Innate immune features and mucosal architecture of the airways (A) and the colon (B and C) during homeostasis. In the lung, stratified ciliated epithelial cells can remove potential dangers, entrapped in an outer viscous mucus layer by pushing them towards the trachea. In contrast, in the colon a high number of commensal bacteria thrive in a permissive, thick outer mucus layer. Beneath the mucus, epithelial cells form an impenetrable lining connected by tight junctions. In the gut, the underlying macrophages are able to penetrate the epithelial monolayer but preserve the epithelial barrier by expressing tight junction proteins. In this way macrophages are able to get in contact with luminal antigens. These antigens can be transferred to dendritic cells (DCs) via the expression of gap junctions between macrophages and DCs. In both tissues, the lamina propria encompasses macrophages, DCs, mast cells and innate lymphoid cells (ILCs), while in the airways (towards the alveoli) alveolar macrophages (AM) are found attached to the luminal side of the epithelium.

pattern recognition receptor (PRR) Nod2 resulted in an increased load of commensal bacteria and an increased ability of pathogens to colonize the murine small intestine [13]. Furthermore, antimicrobial α -defensins affect the microbiome composition, while having no influence on total bacterial load [14]. In parallel the innate immune mechanisms are influenced by the microbiome, for instance the secretion of an antibacterial C-type lectin seems to be related to microbial colonization in the mouse gut [15]. Moreover, microbial tryptophan catabolites are able to induce interleukin (IL)-22 expression in the murine gut. This cytokine is able to improve epithelial barrier functions [16]. While the intestine harbors a vast amount of microorganisms, it was believed for a long time that the airways are sterile [17]. Interestingly, recent studies have pointed out the existence of microbial communities in the healthy human lung [18], and that dysregulation of the host's microbial ecosystem can lead to chronic lung inflammation [19]. However, more research is needed to improve the knowledge on the lung microbiome.

Beneath the microbiome and mucus of the gut and airways a heterogeneous population of epithelial cells is arranged to form a highly structured and impenetrable physical barrier, kept together by intercellular junction complexes comprising tight and adherence junctions [20]. Epithelial cells of the gut and airways are the first cells to encounter microbes and are therefore able to recognize a broad range of pathogen-associated molecular patterns (PAMPs). These cells recognize PAMPs by expressing PRRs, such as Toll-like receptors (TLRs) [21, 22]. Since PRRs recognize molecular patterns that are not specific to pathogens but that can be shared by the commensal microflora, it is very important that expression of these receptors is polarized. Thus, plasma membrane-expressed TLRs are located on the basolateral surfaces of the epithelial cells, thereby ensuring recognition exclusively of invading microorganisms. The lack of TLR expression on the apical epithelial surface avoids receptor stimulation by luminal commensal bacteria, thereby ensuring tissue integrity. In this way, the epithelium does not mount potentially detrimental inflammatory responses to non-invasive microbes (reviewed in [3]). A group of intracellular PRRs known as NLRPs (NOD-like receptor family pyrin domain containing) has also been recently found to be important in maintaining gut homeostasis and in regulating inflammation severity (reviewed in [23]). NLRPs play a central role in initiating the inflammatory response as they are part of inflammasomes, multiprotein complexes that are able to cleave and thereby activate the precursors of IL-1 β and IL-18. Interestingly NLRP6 deficient mice showed a decrease in IL-18 and a higher susceptibility to chemically induced colitis. Furthermore, an altered microbiome with higher colitogenic properties was observed in these mice indicating that the NLRP6 inflammasome pathway and the produced IL-18 are involved in maintaining mucosal homeostasis [24].

This homeostatic, hyporesponsive state of the epithelium is furthermore sustained by down-regulation of TLR signaling through expression of molecules such as Toll-interacting protein (TOLLIP) or single immunoglobulin IL-1R-related molecule (SIGIRR) [25-27]. TOLLIP, an intracellular protein, interacts with IL-1R associated kinases (IRAKs), and in this

way is able to inhibit TLR2 and TLR4 downstream signaling. In intestinal epithelial cells, an up-regulation of TOLLIP was reported upon continuous stimulation of these cells with bacterial components [25]. SIGIRR, expressed in epithelial cells of the gut and airways, is an orphan receptor of the IL-1R family and does not bind to any known member of the IL-1 cytokine family. However, it is able to interfere with TLR and IL-1R signaling after these receptors bind to their ligands. Thereupon, the intracellular domain of SIGIRR competitively binds signaling molecules and in this way dampens the response of epithelial cells to TLR and IL-1R ligands [28]. Deficiency of SIGIRR was associated with both dramatic intestinal inflammation [29] and an increased susceptibility to acute lung infection [30]. During inflammation, however, SIGIRR expression is reduced in intestinal epithelial cells in order to ensure proper TLR signaling [31]. Moreover, expression of the TLR4 adaptor molecule MD2 is supposedly low in intestinal epithelial cells in order to reduce inflammatory reactivity to bacterial cell wall components [27].

Macrophages and DCs cross-talk with the epithelium to maintain a healthy mucosa

Myeloid cells of the mucosa, a heterogeneous population of mononuclear cells, include monocytes, macrophages and DCs. Some tissue-resident phagocytes such as alveolar macrophages (AM) derive from embryonic precursors and are able to self-renew *in situ* [32]. However, in general, mucosal mononuclear phagocytes in the gut and airways (in the *lamina propria*) require constant replenishment by newly recruited blood monocytes that differentiate into macrophages once in the tissue [33, 34]. Tissue-resident and monocyte-derived macrophages are able to keep the gut and airway mucosae in a healthy state by controlling epithelial renewal. In addition, they have a key role in tissue patrolling, and in protective immunity and controlled hyporesponsiveness to microbiota and ingested or inhaled components. For instance, a study has demonstrated that commensal bacteria can promote intestinal homeostasis through cytokine cross-talk between tissue-resident macrophages and other innate leukocytes. This interaction involves the production of GM-CSF from innate lymphoid cells (ILCs), which acts on mononuclear phagocytes by inducing the anti-inflammatory mediator IL-10 [35].

Macrophages, the main innate immune cells of the mucosa, are variously distributed in the different tissue locations. For instance, the gut contains the largest pool of macrophages in the body, which accounts for the high load and diversity of microbiota and the need for constant epithelial turnover [36]. Furthermore, most human intestinal macrophages are found in the colon [37]. In both the gut and respiratory tract, macrophages are located within the subepithelial *lamina propria* and are in close proximity to luminal microbes. In addition, the lower respiratory tract (alveoli and bronchioles) contains AM. These macrophages adhere on the luminal side of the epithelium to allow effective and direct clearance of microbes [1].

Macrophage activation has been recently classified into two subtypes, the classical (M1) activation and the alternative (M2) functional phenotype [38, 39]. The two activation stages



are characterized by the expression of selective panels of mediators and surface receptors [40, 41]. Resident gut macrophages show functional characteristics of both subtypes. They can express significant levels of M1 markers such as major histocompatibility complex (MHC) II and produce tumor necrosis factor (TNF)- α [34, 42], while showing features of M2 macrophages such as the expression of cluster of differentiation (CD) 206 and CD163 and release of IL-10 [43]. During steady-state, the physiological role of resident macrophages is to maintain the integrity and proper function of tissues by clearing apoptotic, senescent and anomalous cells [37, 44]. The process by which macrophages eliminate apoptotic cells is known as efferocytosis and is mainly mediated by scavenger receptors such as CD36 [45]. Another important feature of macrophages during tissue homeostasis is the release of soluble mediators that contribute to maintaining tissue integrity. For example, intestinal macrophages can stimulate the proliferation of epithelial progenitors cells in intestinal crypts *via* release of prostaglandin E2 [46]. They also express the triggering receptor expressed on myeloid cells 2 (TREM2), a phagocytic receptor that facilitates the entrapment of bacteria [47].

Under healthy conditions, both epithelial cells and macrophages are in a low reactive state, in order to avoid reactivity to local commensal bacteria and consequent tissue damage. Although mature human intestinal macrophages express a full range of TLRs and high phagocytic activity, they are able to remain hyporesponsive to inflammatory triggers. Among the mechanisms underlying the reduced inflammatory reactivity of tissue-resident macrophages, the down-regulation of adaptor molecules such as CD14 and MD2, which are normally required for inflammatory activation *via* TLR signaling, has been reported [48, 49]. Also, the abundant anti-oxidative mechanisms displayed by resident

macrophages dampen the ROS-induced NLRP3 activation and the consequent release of inflammatory mediators [50]. The abundant presence of IL-10 [51] and transforming growth factor (TGF)- β [52] in the *lamina propria* of the healthy mucosae are also important drivers of macrophage hyporesponsiveness. Interestingly, chemokine receptors such as CCR5 and CXCR4 are differentially expressed in human mucosal macrophages during steady-state. While down-regulated in AM, intestinal macrophages lack such receptors, a process regulated by the proteasome pathway [53, 54]. Thus, both intestinal and AM are unable to respond to CCR5 ligands, such as CCL3, CCL4 and CCL5, and the CXCR4 ligand CXCL12. In human AM, mannose receptors also play a critical role in suppressing the release of inflammatory cytokines upon recognition of unopsonized bacteria *in vitro* [55]. In fact, this effect, driven by the ligation of mannose receptors leads to a reduction of TLR4-mediated TNF- α release [56]. Moreover, the airways harbor hydrophilic surfactant proteins, which are secreted by alveolar epithelial cells and belong to the group of collectins, a type of soluble PRRs. These proteins are able to interact with TLR4 and its co-receptor MD2, thereby preventing the binding of inflammatory agonist TLR ligands [57, 58]. Also, it has been reported that surfactant proteins can induce conformational changes in the TLR4 ligand lipopolysaccharide (LPS, a component of the cell wall of gram-negative bacteria), resulting in a decreased capacity of LPS to activate human macrophages [76]. A recent review by Hussel and Bell provides an updated overview of AMs [77]. Intestinal macrophages, like all tissue macrophages, also serve as antigen-presenting cells in triggering adaptive immune responses at the tissue level, and they also contribute to T cell priming (through the so-called “tissue monocytes” that are able to recirculate to the lymph nodes [78]). In this regard, it is

TABLE I
MAIN CYTOKINES IN MUCOSAL INNATE IMMUNITY

Type	Mediator	Main Sources	Target cells	Major functions
Anti-inflammatory	IL-10	Macrophages and T cells	T and B cells	Inhibits production cytokines and function mononuclear phagocytes [43, 59]
	IL-22	ILC3, NK cells and Th22 cells	Epithelial cells and macrophages	Tissue integrity, enhanced antimicrobial peptide production [60-63]
	TGF- β	Macrophages, various	T and B cells	Inhibit T cell proliferation and promote wound repair [49, 64]
Inflammatory	IL-1 β	Monocytes, macrophages, DCs, neutrophils and B cells	T and B cells and NK cells	Induction of prostaglandins, inflammatory cytokines, ROS, NO and proteolytic enzymes, proliferation and differentiation of lymphocytes [60, 65]
	IL-6	Macrophages, DCs, Th cells and fibroblasts	B cells	Maturation of B lymphocytes to antibody-producing plasma cells [66, 67]
	IL-12	Macrophages and T cells	NK cells and ILC1	Activation of NK cells and ILC1 [68-70]
	IL-17	ILC3, Th17	Neutrophils and macrophages	Recruitment of neutrophils, tissue remodeling [71, 72]
	IL-23	Macrophages and DCs	ILC3 and T cells	Differentiation and activation of ILCs and T lymphocytes [69, 71, 73]
	TNF- α	Macrophages, DCs, mast cells, monocytes and NK cells	Macrophages	Activation of phagocytes and proliferation of normal cells and anti-tumor activity [34, 74]
Others	IFN- α/β	Epithelial cells and fibroblast	Various	Anti-viral and anti-proliferative [75]
	IFN- γ	ILC1, NK cells, T cells	Various	Anti-viral, promotes neutrophil and monocyte function, macrophage and DC activation, increased expression of MHC [75]
	IL-18	Epithelial cells	Epithelial cells	Maintenance of epithelial layer integrity and prevention of dysbioses [24]



now believed that mucosal macrophages are able to transfer luminal antigens to neighboring CD103⁺ DCs through the gap junction channel protein connexin 43 [79]. This interaction supposedly plays a key role in the development of tolerance in the healthy mucosa. It was previously thought that DCs were the cells that could form transepithelial dendrites (TED) *via* expression of tight junction proteins [80, 81]. However, it is now clear that TED originate from CX3CR1⁺ macrophages residing in the *lamina propria*. Thus, macrophages are the main cells involved in sampling luminal content. While intestinal macrophages express high levels of CX3CR1 [34], other tissue macrophages such as AM lack this receptor [32]. A few studies have reported expression of CX3CR1 by mononuclear phagocytes of the human airway mucosa [82-84]. In any case, specific studies are required to determine which are the main macrophage subsets that sample luminal antigens in the airways.

DCs are professional antigen presenting cells (APCs) and link innate and adaptive immunity as a result of their capacity to recirculate from peripheral tissues to the lymph nodes. DCs residing in peripheral tissues have an immature phenotype, i.e., they lack the expression of co-stimulatory molecules (and are therefore unable to present antigens) and are active in antigen capture. Luminal antigens can cross the epithelium after uptake and transcytosis through specialized M cells [85], and Goblet cells [86] and reach underlying DCs. Mucosal DCs are found with macrophages in the *lamina propria* and express CD103. The CD103⁺ DC subset is found in close contact with the epithelium of the human airways and is thought to be primarily involved in the presentation of viral antigens to CD8⁺ T cells [87]. These DCs do not respond to most TLR agonists with the exception of those activating TLR5 [88].

Function and development of both macrophage and DC subtypes is greatly influenced by other cells in the mucosa, in primis epithelial cells. Certain factors released by these cells, such as thymic stromal lymphopoietin (TSLP) and TGF- β , have been shown to inhibit IL-12 production by DCs [70, 89]. In addition, the chemokine CCL20 is produced by gut and airway epithelial cells at low basal levels under healthy conditions and plays an important role in regulating the recruitment of immature DCs through the CCR6 receptor [90]. An interesting study investigated how mucin (MUC) 2 can influence the hyporesponsive state of DCs in the mucosa of the small intestine. The study found that MUC2 suppresses inflammatory but not tolerogenic DC responses by upregulating TGF- β 1, retinoic acid (RA) and IL-10 and down-regulating CD83 (a maturation marker) on DCs even in the presence of LPS [91]. Thus, epithelial cells and macrophages of the healthy mucosa play a key role in regulating development and maintenance of DC non-/hyporesponsiveness. More importantly, down-regulatory mechanisms of inflammation are central in preventing DCs from triggering unwanted adaptive immune responses.

ILCs and mast cells have a role in mucosal innate immunity and tissue homeostasis

Other immune cells involved in innate immunity team up with phagocytes in the healthy mucosa to keep potential invaders in

check. ILCs and mast cells are particularly involved in immune surveillance in the mucosa.

ILCs are a heterogeneous group of cells of lymphoid origin, but in contrast to classical lymphocytes lack the expression of specific antigen receptors. ILCs are able to react rapidly and non-specifically to potential dangers by releasing cytokines, and therefore are considered as cells of the innate immune system. ILCs comprise three major subsets: Type 1 ILCs (ILC1), which include the classical cytotoxic natural killer (NK) cells; ROR γ t-independent Type 2 ILCs (ILC2); and IL-22 producing ROR γ t-dependent Type 3 ILCs (ILC3). While ILC1 and ILC3 are major players in mucosal homeostasis and innate defense against bacteria and viruses, ILC2 seem to be more important for innate defense against parasites [68, 92]. Although ILC2s are present in the healthy human gut and airways their function in homeostasis still needs to be determined [93].

The differentiation of mucosal IL-22-producing ILC3s seems to be related to the commensal microbiome [94]. A study on subsets of murine small intestinal ILCs found not only a high production of IL-22 but also of antimicrobial α -defensins in these cells upon co-stimulation with IL-1 β and IL-23, both of which derive from activated mucosal phagocytes [60]. Also, IL-22 is associated with increased production of the antimicrobial proteins RegIII β and RegIII γ in the murine colon [61]. It has been shown that the IL-22 receptor (IL-22R) is expressed in tissues such as the small intestine, colon and lungs [9] and that IL-22 increases lung epithelial cell proliferation [62]. Moreover, very recently a study reported that IL-22 could induce expression of claudin-1, a tight junction protein, in human intestinal epithelial organoids, emphasizing the role of ILC-secreted IL-22 in enhancing mucosal barrier functions [63]. Thus, ILC3-secreted IL-22 seems to prevent epithelial pathogen invasion in the intestine by regulating antimicrobial peptide/protein production and increasing the epithelial integrity. ILC3s are also present in the human lung but their role in maintaining homeostasis has not been well-clarified yet [93].

Mast cells are involved in both innate and adaptive mucosal immunity. They represent up to 3% of cells in the healthy intestinal *lamina propria* and carry out important physiological functions to maintain normal gut and airway tissue function [95]. On the one hand, mast cells that bind IgE on their surface by expressing Fc ϵ RI are able to release histamine and tryptase upon antigen binding to IgE. Dysregulation of this process makes mast cells the main mediators of allergy in the healthy mucosa [96]. On the other hand, they also act as innate effector cells and are able to recognize PAMPs through expression of PRR, such as TLR1-7 and 9 [115, 116], and release cytokines [117]. Similarly to macrophages and epithelial cells, mast cell responsiveness to PRR ligands is tightly regulated in order to avoid exceeding response to commensal products. Interestingly, in homeostasis low amounts of IL-33 are constitutively produced by murine epithelial cells. While during inflammation this cytokine is activating mast cells to release cytokines and chemokines, in homeostasis low IL-33 concentrations (insufficient to trigger mast cell activation) seem to be responsible for mast cell insensitivity to the TLR



TABLE II
MAIN CHEMOKINES IN MUCOSAL INNATE IMMUNITY

Common name	Receptor	Main sources	Main target cells	References
CCL2/MCP-1	CCR2	Epithelial cells, DCs, macrophages, monocytes and mast cells	Monocytes and eosinophils	[97-99]
CCL3/MIP-1 α	CCR1, CCR5	Monocytes, ILC1	Eosinophils	[72, 100]
CCL11/eotaxin1	CCR3	Monocytes, macrophages and epithelial cells	Eosinophils	[101-103]
CCL5/RANTES	CCR1, CCR3, CCR5	Epithelial cells and macrophages	Eosinophils, NK cells, DCs and monocytes	[104, 105]
CCL20/MIP-3 α	CCR6	Epithelial cells and mast cells	Immature DCs	[99, 106]
CCL28	CCR3, CCR10	Epithelial cells*	Eosinophils and T cells	[107, 108]
CXCL1	CXCR1, CXCR2	Epithelial cells, macrophages	Neutrophils	[109, 110]
CXCL2	CXCR2	Mast cells, monocytes and macrophages	Monocytes, immature DCs and neutrophils	[99, 110]
CXCL5	CXCR1, CXCR2	Eosinophils	Neutrophils	[110, 111]
CXCL6	CXCR1, CXCR2	Macrophages and epithelial cells	Neutrophils	[110, 112]
CXCL8/IL-8	CXCR1, CXCR2	Epithelial cells and monocytes	Neutrophils	[110, 113]
CX3CL1/fractalkine	CX3CR1	Epithelial cells	Monocytes and macrophages	[34, 82, 83, 114]

* Epithelial cells secrete CCL28 apically as an important mucosal antimicrobial factor.

ligands LPS and peptidoglycan. More precisely, IL-33 induces ubiquitination and subsequent degradation of IRAK1, a kinase involved in TLR4 signaling [118]. Moreover, in mice, mast cells and mast cell-derived chymase were reported to be crucial for intestinal epithelial barrier function and orderly turnover of the epithelium, as mice deficient in mast cells or chymase showed a dysregulated expression of the tight junction protein claudin-3 and a decreased intestinal epithelial cell migration [119].

THE MUCOSA IN DANGER: FROM PENETRATION TO INFLAMMATION

Pathogens are able to penetrate the host barrier and provoke cytokine release from epithelial cells

In contrast to commensal bacteria, microbial pathogens are capable to cross the epithelial barrier, thereby triggering an innate inflammatory response (Fig. 2). In order to reach the epithelium, in the first place pathogens have to penetrate the mucus. This can be especially challenging in the colon because of its thick mucus layer. Therefore, some pathogens are equipped with flagella, which facilitate motility, or secrete mucus-degrading enzymes. Furthermore, pathogen-derived toxins that diffuse through the mucus can decrease epithelial mucus production [120]. Toxins, such as the *Clostridium difficile*-derived Toxin B, are also able to disrupt intercellular junctions, increasing the paracellular permeability of the some pathogens [122]. For instance, M cells can be exploited by

Yersinia and *Shigella* to cross the epithelium [123]. Not only paracellular invasion, but also intracellular translocation across epithelial cells can occur with epithelium [121]. A recent review by Doran and colleagues gives an overview of potential strategies in which pathogens are able to pass through host barriers [124].

In order to fight invading pathogens, epithelial cells can recognize PAMPs by means of basolaterally-expressed TLRs and thus initiate the nuclear factor- κ B (NF- κ B)-dependent inflammatory activation pathway that leads to the secretion of cytokines and chemokines, such as IL-1 β , IL-8 and CCL20 [27, 125]. Furthermore, necrotic epithelial cells release ATP, which acts as a danger signal [2].

Inflamed tissue signals recruit effector cells into the reaction site

During the initial stages of inflammation, damaged epithelial cells secrete inflammatory mediators such as IL-6 [66], IL-8 [86] and CCL2 [97]. The first inflammatory cells that enter the inflamed tissue are neutrophils, mainly attracted by tissue-derived IL-8 [113]. Also resident mucosal phagocytes can release large amounts of CCL2. This chemokine attracts blood monocytes, which in the mouse are Ly6C^{hi}, CX3CR^{int} and express CCR2, to the inflamed tissue and it facilitates their transepithelial migration [98]. Other innate immune cells such as eosinophils can also migrate into the mucosa *via* monocyte-derived CCL2, CCL3 and CCL11 [101].

Once monocytes enter the mucosa, they up-regulate MHC-II expression and become LyC6⁺ effector inflammatory macrophages. These macrophages are characterized by high phagocytic activity, high expression of CD14 and the ability to produce large amounts of inflammatory cytokines such as IL-1 β , IL-6, IL-12, IL-23 and TNF- α [34, 126]. They can also secrete chemokines (such as CCL2, CCL3 and CCL11) that further increase the recruitment of monocytes and other innate immune cells and, at later stages, also of adaptive immune cells, e.g., T lymphocytes. Activated macrophages have a direct role in taking up and destroying pathogens. Moreover, upon resolution they take the role of anti-inflammatory effectors that dampen the harmful neutrophil activity, and the role of tissue repairing cells that contribute to resolution by promoting the re-establishment of tissue homeostasis [127]. Blood DCs are also recruited to inflamed tissue by means of CCL20. This chemokine can be released by intestinal epithelial cells exposed to flagellin [128] and by lung epithelial cells exposed to allergens and other airborne particles [106, 129], and is recognized by CCR6 on DCs [4]. DCs are moreover able to coordinate the mucosal-protective activity of ILCs during an inflammation. In particular, when CD103⁺ DCs detect the pathogen-derived flagellin by TLR5, they are activated to secrete IL-23. In turn, IL-23 activates ILCs to produce IL-22, which, as described earlier, has a major role in maintaining the integrity of the mucosal epithelial barrier function [73].

ILCs and mast cells participate to the mucosal inflammatory response

As described, activated phagocytes are able to secrete IL-1 β and IL-23 and in this way stimulate ILC3s to produce IL-22 in the human intestine [68]. Similarly, it was found in a murine

model of allergic lung inflammation that ILC3s are able to produce IL-22, ameliorating airway inflammation [130]. While ILC3s and ILC1s are crucial in mucosal inflammation the main role of ILC2s, which account for a very small number of total ILCs in the adult intestine, lies presumably in their antihelminthic properties. Studies on mucosal ILC2 have mainly been focusing on mouse models. In the murine gut ILC2s were found to contribute to nematode removal by producing IL-9 and IL-13. Also, ILC2s in murine lungs seem to be responsible for an immune response against nematodes [93]. Moreover, in response to IL-33, lung ILC2s were found to produce IL-5, a cytokines that is responsible for eosinophil activation [93, 131].

The group of ILC1s comprises not only NK cells but also a subgroup of ILC1 that lacks several NK markers (subsequently called ILC1). NK cells are able to lyse infected or malignant cells by secreting granzymes and perforin that induce apoptosis in these cells. Furthermore, cytotoxic NK cells are able to release cytokines such as IFN- γ and TNF- α , thereby promoting the inflammatory response [132]. The granzyme B- and perforin-lacking ILC1 are likewise able to produce IFN- γ and moreover express the transcription factor T-bet that for instance regulates the gene transcription for the chemokine CCL3 and the chemokine receptor CXCR3. ILC1s were found to accumulate in the inflamed *lamina propria* of patients with inflammatory bowel disease, indicating their role in chronic mucosal inflammation [72].

Mast cells are able to recognize invading pathogens by both innate mechanisms (TLR-mediated recognition of PAMPs) and through antigen-specific antibodies that are bound to their surface *via* Fc receptors. Different innate stimuli can provoke different mast cell reactions. Mast cell activation *via* TLR4 resulted in secretion of TNF- α , while activation of mast cells

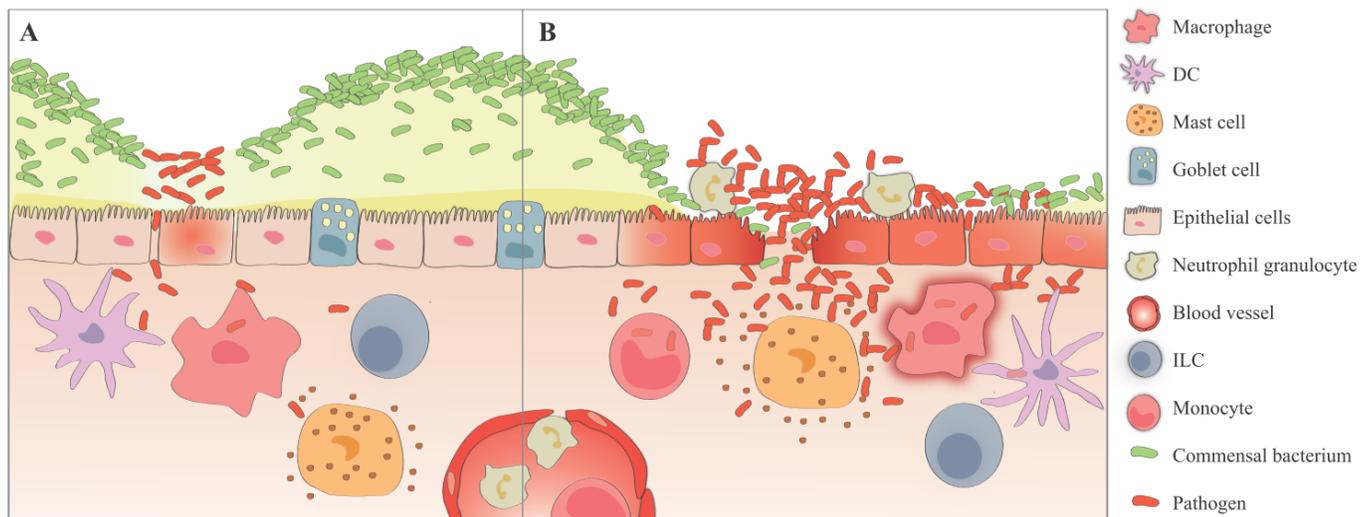


Fig. 2. Inflammation arising in the intestine. Pathogens can bypass the mucus barrier, e.g., by secretion of mucus degrading enzymes (A). Furthermore, released toxins act on epithelial cells and their intercellular junctions leading to gaps, which pathogens exploit to cross the epithelial layer and enter the subepithelial tissue. By crossing the epithelium, pathogenic bacteria come in contact and activate the epithelial basolaterally-expressed TLRs and the subepithelial innate cells, and trigger the release of various mediators, such as cytokines and chemokines. These factors activate and attract other immune cells towards the tissue in order to take part in the inflammatory reaction (B). Monocytes and neutrophils are abundantly recruited to the inflamed mucosa from the blood. Tissue macrophages, as well as blood monocytes, are highly phagocytic. Neutrophils are able to attach to the apical side of the epithelium and release proteases and reactive oxygen species (ROS) in order to harm surrounding pathogens. They however also damage epithelial cells that, in turn, release danger signals such as ATP, which also contributes to the inflammatory activation of surrounding immune cells (e.g., by cooperating with ROS in the activation of the NLRP3 inflammasome).



through TLR2 also triggered histamine release [133]. Extracellular ATP, a danger signal released from injured or dying epithelial cells, is also able to evoke mast cell activation [134]. Thus, depending on the stimuli, mast cells can produce cytokines such as TNF- α and IL-1 β , chemokines such as CCL2, CCL20 and CXCL2, and lipid mediators such as eicosanoids [99], besides preformed histamine, serotonin, heparin, proteoglycans and serine proteases. These mediators play important roles in the progression of mucosal inflammation. For instance, histamine, is able to activate resident immature DCs [135], while chemokines recruit monocytes, DCs and neutrophils from the blood [136]. In addition, mast cells also play a role in inhibiting and resolving inflammation, as histamine can induce IL-10 production in AMs [137].

Neutrophils have an early effector role in mucosal inflammation

Several tissue-derived chemokines, including CXCL1, CXCL2, CXCL5, CXCL6, and IL-8, are involved in the recruitment of neutrophils to the inflamed mucosa. These chemokines bind to the two IL-8 receptors on neutrophils and drive their entry into the site of inflammation [110]. Once in the *lamina propria*, neutrophils can further migrate through the epithelium of gut and airways into the luminal space. This chemotactic process is mediated by a gradient of heptoxilin A3, an eicosanoid secreted apically from epithelial cells at inflammatory conditions [113, 138]. In response to contact with microorganisms, neutrophils degranulate at the site of infection, and release oxygen species (ROS) and several proteases, such as proteinase-3 or cathepsin G, that are competent in killing microbes. Moreover, neutrophils produce matrix metalloproteases (MMPs), which are able to cleave chemokine precursors. For instance, MMP-8 cleaves CXCL5 and CXCL8 improving their activity. MMP-9 is likewise able to activate CXCL1 and CXCL8 and in this way attract more neutrophils to the site of inflammation [139]. On the other hand excessive protease activity can lead to significant tissue damage, and also accounts for neutrophils being central in several human inflammatory diseases such as necrotizing enterocolitis, idiopathic inflammatory bowel disease or bronchitis [140].

In general, cytokine-mediated cross-activation between innate immune leukocytes and epithelial cells emphasizes the importance of a coordinated and tightly regulated chain of events in the development of protective inflammatory responses. Such networks of cellular interactions in the intestinal mucosa are extensively described in Rescigno's recent review [141].

A successful inflammatory reaction aims at re-establishing homeostasis, and it resolves after elimination of the danger

Upon elimination of inflammatory agents (pathogenic microbes, infected cells, *etc.*), the inflammatory reaction that was triggered by such stimuli gradually subsides. Resolution of inflammation is an active process, involving several biochemical mechanisms, that enables inflamed tissues to

return to homeostasis (reviewed in [142]). As described in the first section of this review, the innate immune mechanisms that maintain a healthy human gut and airway mucosa are also required during inflammatory resolution and restoration of normal tissue function.

A main molecular mechanisms by which the resolution phase occurs, is through the TGF- β - TGF- β R axis [64] and by an increased release of IL-10. Macrophages, such as those present in the gut, have a major role in restoring tissue homeostasis after an inflammatory reaction. As mentioned before, mononuclear phagocytes clear contaminants and apoptotic neutrophils in damaged tissue. Entry of neutrophils from the subepithelial space to the airway lumen can also contribute to the resolution of inflammation by effectively removing infected/damaged cells [143]. In addition, neutrophils are able to generate several neutrophil-derived lipid mediators, such as resolvins, protectins, and lipoxins. These mediators diminish neutrophil and eosinophil infiltration, enhance phagocytic activity of macrophages and attenuate inflammatory mechanisms, such as IL-8 expression and NF- κ B activation, as well as enhancing production of antimicrobial peptides [142, 144]. The release of antimicrobial peptides *via* action of specialized neutrophil-derived resolvins accelerates the return to homeostasis, a process initiated by cyclooxygenase (COX)-2 [145]. COX-2 is fundamentally involved in generating active lipid mediators. In particular, lipoxin A4 [146, 147], resolvin E1 [148, 149] and protectin D1 [148] have been identified as key mediators of inflammatory resolution by blocking neutrophil chemotaxis and transmigration, blocking IL-12 release from DCs and stimulating monocytes and macrophages through different G-protein coupled receptor (GPCR) pathways [142]. Moreover, the chemokine receptor CCR5, which is down-regulated on late apoptotic neutrophils during inflammation, is up-regulated on these cells in resolution by lipid mediators such as lipoxin A4 and resolvin E1. CCR5 is responsible for sequestration and clearance of the innate leukocytes attracting chemokines CCL3, CCL4 and CCL5 and therefore, CCR5 is involved in terminating inflammatory chemokine signaling [150]. Another mechanism by which inflammation is resolved occurs as neutrophils normalize oxygen levels in the tissue microenvironment (known as physiological hypoxia). This condition triggers the stabilization of hypoxia inducible factor (HIF), a gene, which then activates multiple key target genes that promote the active resolution of inflammation and re-establishment of barrier function within the mucosae [151]. If the cross-regulating interaction between the microbiome, the epithelium and immune cells fail at any stage, a pathogenic or chronic inflammation can take place. Deregulated immune responses can for example result in inflammatory bowel disease [45] and chronic obstructive pulmonary disease [140, 152].

CONCLUSIONS

This review highlights how complex and vital mucosal innate immunity is in coordinating an effective physiological inflammatory response and how this mucosal system has adapted to their particular organ function. Furthermore, the gut



and airway mucosae consist of a specialized tissue that rely on the co-existence with commensal microbes as well as the constant interaction of mononuclear phagocytes and structural cells to prevent colonization of pathogens. The tightly regulated innate mechanisms that permit normal mucosal function and coordinate physiological inflammation are only effective if inflammation can be resolved. Considering the diversity of mucosal physiology between humans and mice, more studies should focus precisely on characterizing and distinguishing human innate immune cells and their phenotypes in different sites of the body.

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