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Review

Immune monitoring of the body's borders

Ken S. Rosenthal*

Microbiology and Immunology, Roseman University College of Medicine, 10530 Discovery Drive, USA

*** Correspondence:** Email: krosenthal@roseman.edu; Tel: +7028022855.

Abstract: The immune system spends most of its efforts and energy policing rather than attacking, cleaning up the molecular and cellular trash, maintaining the borders of the human body, and quashing minor disturbances rather than responding to pathogenic microbes. The cells that carry out these functions play by rules that are different from those described in the classical immunology textbooks, being triggered by alternative stimulants such as vitamin B analogues, glycolipids and cellular stress molecules and express different cell surface markers. Treg/TR1 cells and Th17 cells shift function depending upon the needs of the situation as directed by the cytokine environment. Better understanding of these "normal" functions for the immune response will also provide greater insights into dysregulation and conditions of excess as occur during autoimmune and inflammatory diseases.

Keywords: GALT; MALT; ILC; MAIT; NKT; γδ T cells; CD8αα cells; Treg; cryptopatches; isolated lymphoid follicles; Peyer's patches

1. Introduction

Cells die, proteins denature and debris, pollutants and microbes from the environment are taken up by the body by breathing and eating. Dealing with this trash is one of the most important normal everyday functions of the innate and immune systems. Many aspects of the immune system are dedicated to these normal processes and ensure that they are undertaken without inflammatory excitement. In addition to dealing with the body's garbage, which was the topic of a previous review [1], the innate and immune systems must also provide constant maintenance of the microbial garden of normal flora, protect the barriers of the body and deal with the sporadic challenges of pathogenic

microbes. This microbial garden is weeded and cultivated by the innate and immune systems. Looking at the innate and immune systems from the point of view of its everyday functions rather than its response to sporadic infections introduces important cellular actors that usually go unmentioned and provides an alternative and insightful way to explain the functions of these systems.

The outside surfaces of the body, including the skin and lumen of the gastrointestinal, genital/urinary and respiratory tracts, are borders that are constantly challenged by bacteria, their metabolites and waste products. We acquire our normal flora early in life and the populations of different bacteria remain relatively stable throughout life unless compromised by antimicrobial or other drug treatments, diarrhea or inflammatory disease or following travel or other change in environment or habits. The innate and immune systems protect these epithelial borders, prevent trespass into the sterile environments of the body by these microbes, and help to select the resident microbial populations with antimicrobial molecules.

Like infection control agents of a city, hospital or a laboratory, sensible protocols have been developed by the innate and immune cells to ensure proper control and cleanup of normal microbial populations without eliciting inflammatory alarm. The borders of the body, especially the GI tract, are maintained by teams of epithelial cells (Box 1), macrophages, dendritic cells (Box 2), neutrophils, various types of B and T cells, and innate lymphoid cells that communicate with each other with cytokines and by direct contact. Although these cells have been working at this job for eons, many of the cells that carry out these functions live in environments and have jobs that are different than the classic textbook descriptions, they have only recently been described or their functions redefined. The lymphocytes include innate lymphoid cells ILC1, ILC2, ILC3, and ILCx (Box 3); T cells such as NKT, γδT, MAIT and CD8αα cells (Box 4), which respond to bacteria differently from classical αβ CD4 and CD8 T cells (Box 5) (The γδ and αβ refer to the subunits of the T cell receptor that define these cells.), and B cells (Box 6). Although these cells can be found in the circulation, they are enriched in the GI and respiratory tracts. The characteristics, role and contributions of the principal members of this cellular maintenance squad will be described for these two mucoepithelial systems.

2. GI tract

The lumen of the GI tract connects the mouth to the anus. Essentially, its contents reside outside the body separated from the rest of the body by a mucous layer and for the intestines, a single cell layer of epithelial cells. These epithelial cells (colonocytes) are constantly bathed with bacteria and exposed to the foreign proteins from the food we eat. Breaks in the barrier occur and luminal proteins and bacteria routinely sneak past the colonocyte barrier. The constant exposure to these elements recruits a resident squad of immune cells to the region who work together within the epithelium and in localized lymphoid tissue, first as cryptopatches (Box 7) and then as isolated lymphoid follicles (ILF) [2]. The more permanent structures, such as Peyer's patches and mesenteric lymph nodes, provide the direction for maintenance of the barriers, manipulation of the microbial population and for restriction of infections and inflammation.

3. Maintaining the relative peace and harmony of the GI tract

Training and recruiting the police force that maintains the peace and harmony of the GI tract is a relatively slow process that develops over the early years of life. Much of the development,

recruitment and maintenance of the policing cells occurs in response to key bacteria in a person's normal flora [3]. In order to keep the peace, the viability and the tight junctions of the epithelial barrier must be maintained, the populations of microbes in the intestine must be controlled, any bacteria that cross the barriers and enter the body must be quickly eliminated; and episodes of infection and inflammation must be controlled in a timely manner with subsequent regulatory and healing responses. The epithelial and immune cells facilitate these functions with mucous, antimicrobial peptides, immunoglobulins, cytokines, and cell-cell interactions.

A single layer of mucoepithelial (intestinal epithelial cells (IEC)) cells joined by tight junctions separates the contents of the intestinal lumen from the internal organs of the body [4]. The intestinal epithelial barrier is constantly being rebuilt from stem cells that are within the layer, as stimulated by IL6, IL22 and other signals. Shedding of infected or damaged cells and rapid replacement, like the infantry, is an important antimicrobial protection. The barrier is protected from the microbial contents of the lumen by a mucous layer. The mucous is produced by goblet cells and its production is promoted by IL4 and IL13 produced by ILC2 and Th2 cells [5].

Antimicrobial peptides produced by epithelial cells, neutrophils, macrophages and other cells are important for weeding and maintaining the bacterial species that reside in the intestine. Paneth cells in the small intestine and IECs are the major producers of these molecules. Antimicrobial peptides include cationic, other peptides and enzymes that have broad spectrum antimicrobial activity but also can have chemotactic and immunomodulatory activities. They include α- and β-defensins, cathelicidins and other peptides that disrupt bacterial membranes or inhibit essential functions. IL1, IL17 and IL22, cytokines produced by Th17, ILC3 and other cells, are critical for the induction of antimicrobial peptide production by epithelial and other cells [6,7]. The antimicrobial peptide response is triggered by pathogen associated molecular pattern (PAMP) receptors that respond to the presence of specific microbial structures. For example, TLR5 senses flagella and is expressed on many different cell types but deletion of the TLR5 on IECs in a mouse model was sufficient to alter the control of intestinal microbiota and cause an increase in inflammation, a type II diabetes-like metabolic syndrome and obesity in these mice [8].

sIgA secreted into the intestine is essential for controlling the microbial population and the toxins that they may produce. sIgA is produced by plasma cells that differentiated from B cells exposed to microbial antigen in mesenteric lymph nodes and then migrated to, and set up residence in the ILF, Peyer's patches and tissue underlying the IEC. Juxtaposition of the plasma cells to the IEC is important for the transepithelial transport of sIgA into the lumen. The IgA response is important for maintaining the microbial herd but IgA is not good for preventing a new microbial challenge since time is required to elicit the new and specific antibody response. For example, a traveler would require a new IgA repertoire to control the regional *E. coli* ingested in food and water during a trip to a foreign country or upon first exposure to a pathogen such as salmonella.

Some microbes can still permeate the mucous or find thin spots in the mucous to reach the outer surface of the epithelium where they can be sensed by IECs and DCs, some of which express CD8αα, and trigger production of antimicrobial peptides without initiating inflammation. The small numbers of bacteria that leak through the barrier can be detained by local macrophages but larger numbers will initiate cytokine alarms and subsequent inflammatory reactions. These responses are disruptive and set up a cycle that can lead to inflammatory disease. TNFα and other inflammatory cytokines initiate responses that disrupt the tight junctions between epithelial cells that will further

compromise the barrier. Inflammatory bowel disease and other problems result from repeated episodes of damage and injury to the barrier.

Resident Th17 cells on the inside surface of the epithelial layer provide the necessary police force that can adjust to the infection needs of the region. When needed, their numbers can be increased by recruitment from the body or conversion of antigen specific TR1 cells into Th17 cells. Production of IL23 to activate Th17 memory cells is very important for maintaining the appropriate police force. Mice lacking IL23 were more prone to dysregulation of gut flora with increases in Bacteroidetes and Firmicute bacteria and development of metabolic syndrome on a high fat diet [9]. The Th17 cytokines activate and heal the epithelium and when necessary, promote a neutrophil response [10]. Unlike Th1 responses, the Th17 cells can revert back to TR1 regulatory cells [11,12] and the neutrophil response is more short lived than that of Th1 activated macrophages (M1).

The regulatory responses from dendritic cells, macrophages, ILCs and T cells are very important for limiting the appropriate and inappropriate inflammatory responses. Dendritic cells that reside under the epithelial cells insert their dendrites into the lumen to taste the surrounding contents. These DCs respond to signals from their environment to maintain the peace [13]. Production of IL10, TGFβ and prostaglandin E2 (PGE2) as well as indoleamine 2,3 deoxygenase (IDO) limit inflammatory responses from T cells and other cells. IDO degrades tryptophan to limit T cell responses. Sufficient TGFβ, produced by ILCreg, Tregs and TR1 cells, will limit the generation of Th17 and Th1 proinflammatory responses and the initiation of inflammation. These DCs are also capable of sending out a cytokine alarm and initiating inflammatory T cell responses to excessive or inappropriate (pathogenic) bacteria that cross the epithelial barrier.

Even the normal gut flora contribute to maintaining the calmness [14]. Anaerobic bacteria (like Clostridales, Lachnospiraceae and Ruminococcaceae) and to a much lesser degree, facultative anaerobes (like *E. coli* or *Salmonella*) produce butyrate, a small chain fatty acid, which binds to the PPAR-gamma receptor to promote Treg activity and beta defensin production [15,16]. Different bacterial cell surface structures trigger antimicrobial or regulatory responses from DCs, ILCs and subsequently T cells. For example, segmented filamentous bacteria binding to the IECs induce Th17 responses [17], *Bacteroides fragilis*, expressing polysaccharide A, can convert Th17 cells to TR1 cells through the TLR2 surface receptor [18] and clostridium species can also induce Tregs [17].

4. Rising to the challenge of a pathogen

In addition to policing and maintaining the status quo and guarding our barriers, the immune system must also be able to respond to sporadic microbial challenges that occur upon exposure to new strains of normal flora bacteria (acquired during travel), following trauma to the barrier, or upon invasion by a pathogen. The response to these infections may escalate to an all-out war that activates all the previously described innate cells and their molecular weapons but also requires systemic antigen specific responses.

Entry of normal flora due to leakage or trauma is sensed by IECs, macrophages, DCs, ILCs and innate T cells. PAMPs, especially LPS, glycolipids, vitamin B metabolites, alkylamines, bisphosphonates and organic phosphoantigens from the microbe and stress related small molecules from surrounding cells trigger responses in resident NKT cells, gamma delta T cells, MAIT cells, and ILCs to initiate the response with acute phase and pro-inflammatory cytokines. Neutrophils are recruited and provide antimicrobial activity that is often sufficient to control the incursion. The

process also initiates repair mechanisms [19]. Resident Th17 CD4 helper T cells will also provide a rapid response to the microbial incursion [20]. Additional antigen specific Th17 cells are generated by conversion of TR1 cells triggered by IL6 and IL21. The IL17 that they produce enhances antimicrobial peptide production [6] and neutrophil functions, the TNFα promotes inflammation and the IL22 facilitates epithelial cell growth and repair [21]. Later during recovery, higher concentrations of TGFβ will inhibit IL-23R expression and promote the conversion of some of these cells back to TR1 cells and others to Th17 memory cells.

A continued presence of bacteria and the production of low levels of IFNγ by ILCs and innate T cells validates the conversation of DCs to DC1s which produce IL12p70. These DC1s travel from the infected zone to the mesenteric lymph nodes where they activate, train and mobilize the Th1, as well as Th17, T cell troops which relocate to the site of infection. The larger amounts of IFNγ produced by Th1 cells mobilize and convert macrophages into angry M1 type macrophages required to combat larger and invasive infections. These cells up-regulate the capacity to make reactive oxygen species, acute phase cytokines, IL12 and IL23 [22]. The macrophages are much longer lived than neutrophils and remain as antigen presenting cells to reactivate CD4 T cells. Unfortunately, their longevity and ability to present antigen to CD4 T cells can maintain excessive inflammation. Descriptions of the immune responses that follow an infectious challenge are well described in textbooks and other reviews and will not be pursued herein.

For many people in the world, normal GI flora includes an infestation of parasitic worms. Humans have evolved the ability to respond to the infection, facilitate the elimination of this infectious challenge and limit the potential inflammatory responses. The presence of worms is often noted by increased IL4 levels and eosinophilia characterized, by increased levels of IgE and mast cells. The initial response to the infestation is likely mediated by ILC2 cells resident under the intestinal epithelium and producing IL4. The IL4 that is produced focuses helper T cell responses to Th2. This promotes B cell production of IgE, M2-type macrophages, mucous formation and mast cell activation. Secreted antibody, histamine and other toxic molecules are secreted by the mast cells to damage the worms and the mucous facilitates their expulsion [5,23]. Possibly even more important than induction of antibody, the IL4 produced by the ILC2 and Th2 cells limits the generation of inflammation by limiting Th1 responses [24]. If unchecked, Th1 inflammatory responses to the worm infestation would elicit inflammatory bowel disease. The effect of the parasitic worm infestation can provide systemic tolerance to inflammation and some patients have used this approach as an unsanctioned immunomodulating therapy [25].

Ultimately, the response to these warlike challenges must also include an exit strategy to include de-escalation, establishment of memory and a return to peaceful conditions. Inability to do so can lead to a persistent inflammatory response to specific gut microbes and inflammatory bowel disease, including Crohn's disease or ulcerative colitis. This may be due to a genetic predisposition to overreact or under regulate the inflammatory response. Inability to maintain a balance between aggravating bacteria and calming bacteria can also tip the balance in favor of inflammatory responses. For example, the flagella from *Lachnospiraceae* family bacteria of the Clostridiales are sufficient to aggravate both innate and immune responding cells [26]. As mentioned earlier, inability to maintain the epithelial barrier can lead to similar problems.

5. Respiratory system

The respiratory tract uses many of the same protections that are used by the GI tract but also utilizes unique approaches to eliminate the particulate and microbial trash that accompanies each breath [27,28]. Like the GI tract, the lung is bordered by a mucoepithelial barrier. The mucous protects the epithelium from infection and traps unwanted particulate matter and microbes. Unlike the GI tract, the normal flora are squatters, taking up space and provide very limited, if any, function. Microbial exposure of the upper respiratory tract is often problematic and the lower respiratory tract must remain sterile. Whereas gravity facilitates the clearance of unwanted microbes from the GI tract, the respiratory tract must use ciliated epithelium as an escalator to remove the contaminated mucous since gravity tends to pull microbes into the lower lung. The lung does not have the protection afforded by stomach acid and detergent-like bile and is thus susceptible to bacteria and enveloped (surrounded by a membrane) viruses that would otherwise be inactivated. Instead, alveolar macrophages patrol the lumen side of the lung sweeping up particles and microbes, attempting to eliminate them before they cause larger problems. The alveolar macrophages are M2-like macrophages with limited antimicrobial activity.

Under the mucoepithelial layer, the respiratory tract has a similar police force of innate and immune cells as the GI tract. The epithelial cells are heavily decorated by PAMPRs to provide acute phase cytokines and antimicrobial peptide protections. M cells are incorporated with the epithelial cells to provide an antigen portal to an aggregation of DCs and other immune cells. The epithelial barrier lacks Peyer's patch-like structures. These elements remain dispersed but coalesce into bronchus-associated lymphoid tissue (BALT) in answer to infectious or inflammatory challenge. This lymphoid structure composed of lymphocytes and DCs associates with the high endothelial venules and protrude into the bronchi [29].

Unlike the GI tract, which utilizes primarily Treg and Th17 responses to maintain the peace, lung immunity is primarily delivered by Th2, antibody and Treg responses. sIgA is secreted across the mucous epithelium to act on the routine normal flora but its production is often too little and too late to provide protection against other inhaled microbial exposures. The Th2 environment is more likely to promote the production of IgE against inhaled antigens with the potential to initiate allergies, hypersensitivity pneumonitis and asthma. Starting out as Th2 related antibody mediated diseases, repetitive asthmatic episodes can promote progression to chronic Th17 inflammatory disease [30].

Microbes that reach the lower lung are difficult to clear and infections are more apt to be inflammatory. Microbes that reach the lower lung are likely to initiate a pneumonia.

The common microbial exposures are readily controlled by routine innate and immune responses with limited pathology. Annual exposures to specific microbes, such as influenza, trigger establishment of resident memory T cells [31–34], IgA producing B cells and plasma cells [35–37]. Larger or spurious pathogenic microbial exposures will set off cytokine and chemokine alarms that activate inflammatory responses. Monocytes and T cells are recruited. The monocytes become M1 inflammatory macrophages which assist the resident interstitial and alveolar macrophages. Regulatory responses are more likely to be overridden in the lower lung and these infections are more likely to initiate inflammatory disease and pneumonia.

The lung is exposed to many more microbes that initiate intracellular infections of macrophages and epithelial cells than the GI tract, including enveloped viruses, like influenza and parainfluenza, and bacteria such as *M. tuberculosis* and mycoplasma. Some of these viruses, including measles,

mumps, rubella and varicella zoster, use the lung for amplification prior to spread to other organs. The responses to these infections are described elsewhere in detail. Briefly, in the absence of antigen specific responses every cell becomes part of the militia using the type 1 interferon system to provide warning to surrounding cells to activate anti-viral protocols, and activate natural killer and other immune cells of the invasion. The infected cells are either killed by the microbe, call a halt to synthetic machinery and eventually commit apoptotic suicide, are convinced to commit apoptotic suicide by NK or cytotoxic T cells or the infected cells are walled off in a granuloma to prevent spread of the microbe. These everyday protections are usually sufficient. The antigen specific T cell responses are necessary to control measles, varicella, influenza and other infections of the lung and must deal with the extended infection. They tend to be overzealous in the adult and likely to cause more peripheral tissue damage and possibly pneumonia in dealing with the invasion. The mild responses of children are oftentimes sufficient for control or just allow these viruses to continue on to the rest of the body. To limit the spread of intracellular bacteria and fungi, ILC and T cell responses provide TNFα and IFNγ to persistently activate macrophages to differentiate into a wall of epitheliod cells to surround the infected lung macrophages and epithelial cells to form a granuloma.

Table 1. Atypical T cell receptor ligands and activators.

Receptors	Ligands	
Alpha beta TCR		
CD1	glycolipids	
MR1	Riboflavin (vitamin B) analogues and metabolites	
Gamma delta TCR		
	cellular stress molecules	Alkylamines
		Bisphosphonates
		Organic phosphoantigens (e.g., hydroxy-methyl-butyl-pyrophosphate)
Other Receptors		
	Butyrate	
	Vitamin A and retinoic acid	
	Vitamin D	
	AhR ligands	Tryptophan metabolites: indole-3-lactic acid

6. Box 1. Intestinal epithelial cells

Like the wall in Shakespeare's Midsummer Night's Dream, the intestinal epithelial cell layer provides barrier function but also communicates with its ILC, lymphocyte and dendritic cell neighbors [4]. IECs in the layer also participate in the antimicrobial host response. Within the layer are specialized epithelial cells, such as secretory goblet cells and Paneth cells, that secrete mucus and antimicrobial peptides and M cells, which are windows into the intestine for the Peyer's patches. The IECs also provide the means for delivery of secretory IgA into the lumen (described later). IECs express pathogen associated molecular pattern receptors (PAMPR) for molecules such as endotoxin, peptidoglycan, teichoic acid, and flagellin. PAMPRs include Toll like receptors (TLR) that sense and respond to microbes and produce mucins, cytokines and antimicrobial peptides as part of the protective response. IEC TLR5 recognition of flagellated bacteria are critical for maintaining a

healthy microbial flora and their deletion in the mouse leads to inflammation, metabolic syndrome and obesity [9].

IECs are also polarized responding differently to a microbial challenge at the basolateral and apical surfaces [38]. This facilitates the IECs ability to elicit a regulatory response to a microbe in the lumen (basolateral) and an inflammatory response to a microbe within tissue (apical).

7. Box 2. Dendritic cells

The guidance for dealing with proteins, microbes and other molecular trash is initially provided by dendritic cells (DC) and subsequently by ILCs and T cells. DCs and Langerhans cells of the skin are garbage pickers that phagocytize, process and evaluate the garbage to determine the appropriate response [16]. They use pattern recognition to distinguish normal trash, consisting of dead human cells and denatured proteins, from microbial trash using their PAMPRs and other receptors. Dead cells and denatured proteins are decorated with "eat me" signals but also immunosuppressive signals [39–41] to regulate subsequent responses in a process termed efferocytosis. Certain microbes also present inhibitory signals to promote the development of tolerance inducing DCs. The DCs, designated as DC1, DC2 or DCreg, generate different sets of cell-cell interactions and cytokines to direct different responses from T and other cells [13,42].

Binding of bacterial PAMPs to PAMPRs [43] triggers activation cascades that promote maturation of the dendritic cells. Once activated, the DC directs the local cell response to deal with the microbial presence using cytokines, matures and then travels to the lymph node to present antigen and instruct naive CD4 and CD8 T cells regarding the appropriate response to deal with the microbial presence. The directions may differ depending upon the microbe and the location of the challenge. DC1 dendritic cells promote antimicrobial inflammatory responses with acute phase cytokines, IL1, TNFα and IL6, and also IL23 and IL12 to promote proinflammatory Th17 and Th1 cell responses whereas a regulatory response would include IL10 and TGFβ.

8. Box 3. Innate lymphoid cells

Resident innate lymphoid cells (ILC) help to maintain the peace but can still provide rapid responses to infection. ILCs are defined by the cytokines that they produce as ILC1, ILC2 and ILC3. ILCs mimic the functions of T cells but utilize PAMPRs and other receptors to detect infected and stressed human cells and microbes rather than antigen specific T cell receptors (TCR) [44,45]. The cytokines produced by resident ILCs can maintain a tolerant attitude and support the status quo or a different set of these cells can react rapidly to kick-start a response to a microbial challenge by producing the appropriate cytokines.

ILC1 cells resemble Th1 T cells to promote proinflammatory responses to microbial infections, and like them, they produce interferon γ (IFN γ) and TNFα. IFN γ activates inflammatory responses by promoting and directing DC1 and macrophage (M1) activation, cytolytic T cell responses and B cell differentiation to produce IgG. Activated M1 macrophages upregulate the production of reactive oxygen species and other antimicrobial functions. NK cells, which resemble CD8 cytolytic T cells in their ability to kill cells using perforin and granzyme, are included within ILC1s. Like some CD8 T cells, some NK cells can also make IFN γ.

ILC3 cells mimic Th17 cells by producing IL17A and IL22. IL17A promotes neutrophil function and inflammatory responses. IL22 promotes the growth of epithelial cells and is especially important in the GI tract to facilitate the health and regeneration of the one cell thick layer of the intestinal epithelial cell barrier. Like Th17 cells, differentiation of ILC3 cells is driven by the RORγt transcription factor.

ILC2 cells mimic Th2 cells by producing IL4, IL5, IL9, and IL13. Some ILC2 cells also produce IL10. These cytokines maintain the status quo to promote mucous production and antibody production. Parasitic worm infestations of the colon trigger ILC2 cells to produce these cytokines which focus the helper T cell response to favor Th2 responses and promote IgE production, mucous production and activation of mast cells to promote expulsion of the worm. Like CD4 Th2 cells, differentiation of the ILC2 cells is driven by RORα and GATA3 transcription factors.

ILCregs play a large role in maintaining the harmony within the intestinal tract. These cells, like Tregs, secrete TGFβ and IL10, cytokines that suppress inflammation [42]. ILCregs gradually increase in number after a microbial challenge to facilitate the return to normalcy after the challenge. Interestingly, the presence of pro-inflammatory cytokines TNFα, IL1 and IL6 in response to infection combines with TGFβ to change the ILC and T cell responses from a regulatory to a proinflammatory Th17 response.

9. Box 4. MAIT, NKT, γδ T cells and CD8αα cells

T cells remain resident in areas of constant microbial exposure, like the GI tract. Many of these resident T cells respond to a different drummer than conventional T cells recognizing and responding to small molecules and glycolipids from bacteria or stressed epithelial cells instead of short peptides. These alternative T cells are very important as immune sentries capable of a rapid and continual response to microbes but also important for recruiting more conventional T cell responses.

9.1. Mucosal Associated Invariant T (MAIT)

MAIT cells can detect many different bacteria and some fungi by their molecular odor, which consists of secreted metabolites of vitamin B (riboflavin) [47–51]. Large numbers of MAIT cells are found in the mucosa of the GI and respiratory tracts as well as in the liver but represent only a small percentage of circulating T cells (1–10%). A major histocompatibility complex (MHC)-like molecule, MR1, expressed on many types of cells of the body, captures the vitamin B metabolites and this complex is recognized by an invariant αβ TCR on the MAIT cells. These cells lack CD4 and CD8 co-receptors. MAIT cells are put on high alert by IL12 and IL18, which may be produced by DCs or other cells in response to PAMPS. Activation of MAIT cells results in release of IFN γ and TNFα as well as the cytolytic molecules, perforin and granzyme.

9.2. γδ T cells

γδ T cells are another major component of the resident T cell squad in the GI tract (at least 35%) [52–57]. These cells express the invariant γδ TCR instead of one of many different αβ TCRs. Like the ILCs, the γδ T cells can generate different cytokine or even cytotoxic responses depending upon the nature of the stimuli. Similar to the ILCs, these cells can kickstart other T cell responses by rapid production

of cytokines, including IL17, IFNγ and TNFα, and chemokines. Like the MAIT, the γδ T cells are activated by small molecules, including cellular stress molecules, from a wide array of bacteria, parasites and even stressed human cells. These molecules include alkylamines, bisphosphonates, and organic phosphoantigens, such as hydroxy-methyl-butyl-pyrophosphate, a microbial metabolite from the isoprenoid pathway. The stress of an intracellular infection of intestinal epithelial cells, as with salmonella, would promote the expression of these molecules. The γδ T cells would then make IL17 to facilitate anti-bacterial responses and IL22 to facilitate epithelial regeneration [58]. IL17, IL22, IFN γ and chemokines can recruit and activate other protective cells to deliver the appropriate response. Interestingly, γδ T cells can also promote regulatory functions to maintain the status quo within the intestine.

9.3. NKT cells

NKT cells have NK and T cell characteristics and respond to ligands of NK receptors as well as a limited range of ligands for its αβ TCRs [59,60]. Some NKT cells express an invariant TCR that recognizes glycolipids bound to a MHC I -like molecule called CD1 [61]. The glycolipids may be from the cell wall of mycobacteria, fungi or parasites or even glycolipid molecules from human cells. LPS from invading gram negative bacteria can stimulate NKT cells directly through Toll Like Receptor 4. Alternatively, LPS can stimulate DCs and promote production of IL12 which increases the sensitivity of the NKT cells to the CD1: glycolipid complex, including to self-glycolipids, to promote activation of the NKT cell to produce IL17 or interferon gamma. These cytokines focus and activate the subsequent conventional helper T cell responses to Th17 and Th1.

9.4. CD8αα T cells

An additional set of unconventional T cells in the intestine express a variant of CD8 which has two alpha subunits (CD8αα) instead of α and β subunits with or without the classic αβTCR [62]. The CD8αα may be expressed on CD4, CD8 αβ T cells and γδ T cells. The CD8αα molecule seems to regulate the extent of response of these cells, especially to common microbial antigens.

10. Box 5. Conventional T cells and memory T cells

Conventional T cells with αβTCRs are defined by the cytokines that they produce and the transcription factors that control their expression. These include Th2 cells which produce IL4, IL5, IL10 and IL13. These cytokines promote T and B cell growth, and B cell differentiation to produce IgG, IgE and IgA. IL4 reinforces the Th2 response and also stimulates mucin production [23]. Th2 cytokines limit inflammation by restricting the development of Th1 responses.

The Th17 and Th1 proinflammatory responses are primarily induced in response to microbial challenge. Th17 responses can be induced by infections that trigger IL6 production and acute phase alarmist responses in the presence of the normal low levels of TGFβ. Memory Th17 cells are activated by IL23 produced by DC and other cells. Th17 cells produce IL17, IL21 and IL22 to stimulate neutrophil activation, antimicrobial peptide production and epithelial cell growth and repair. As with neutrophils, Th17 responses are readily activated and are much more short lived than the macrophage associated Th1 responses. Th17 cells are very important for routine intestinal

protections but also are key elements in the immunopathogenesis of autoimmune diseases [63]. Th1 responses are activated by IL12 produced primarily by activated DCs or macrophages. Th1 cells produce IL2, IFNγ and TNF [64]. These cytokines promote T cell growth, activation of cytolytic T cells, NK cells and macrophages, as well as IgG production.

CD4 Treg cells can be generated in the thymus or as TR1 cells in the peripheral tissues. The constant presence of bacterial antigen draws them to set up residency under the intestine wall. CD4 Treg cells are conventional T cells characterized by the expression of CD25 and the Foxp3 transcription factor. They are attracted by chemokine ligands for the CCR9 receptor [65] and produce the immunoregulatory cytokines TGFβ and IL10. These cytokines suppress inflammatory responses from lymphocytes as well as activated macrophages. Tregs are generated in the thymus and induced Treg cells (TR1) can be derived in the colon from naïve T cells or by conversion of Th17 cells.

The plasticity of Th17 cells and TR1 cells allows these cells to adjust to conditions and deliver the needed response. IL6 or IL22 produced in response to infection provide a warning signal that combines with the maintenance levels of TGFβ to generate Th17 cells from naïve or TR1 cells [11,14]. When the infection has dissipated and TGFβ levels increase, the Th17 cells revert to TR1 cells to maintain the peace. Vitamin A, vitamin D and ligands of the arylhydrocarbon receptor also promote Treg activity [12].

11. Box 6. B cells, plasma cells, IgA, and IgG

B cells and plasma cells are factories for producing antibody. These cells are found in blood and specialized sections of lymph nodes, the spleen, and in Peyer's patches of the GI tract. B cells and plasma cells can also set up temporary housing in sites of recurrent antigen stimulation. IgM, IgG, IgE and IgA antibody is produced by classical immunogenetic recombination and mechanisms influenced by the cytokines and cell-cell interactions of CD4 T helper cells promote class switch and somatic mutation which serves to improve the IgG, IgE and IgA response.

In addition to producing antibody, the B cell is also a very potent antigen presenting cell for CD4 T cells, each cell presenting a focused repertoire of antigenic peptides originating from the antigenic protein as determined by the antibody produced by the individual B cell. This activity of the B cell plays a major role in maintaining and localizing the proinflammatory T cell activity of autoimmune diseases.

Secretory IgA (sIgA), sIgM and to a lesser extent, IgM and IgG, are major tools for weeding and controlling the microbial livestock within the GI and respiratory tracts. sIgM and sIgA are produced by B cells and plasma cells adjacent to mucoepithelial cells. IgM is produced as a monomer (two light and two heavy chains connected by disulfide bonds) and pentamer while IgA is produced as a monomer or dimer. The components of the pentamer and dimer are connected with the J chain which also promotes binding and transcytosis of the immunoglobulin across epithelial cells. The J chain is cleaved enroute through the epithelial cell to become the secretory component as the immunoglobulin is secreted into the lumen. Like IgM, there are natural low affinity polyreactive IgAs [1,66] produced by IgA plasma cells [67]. Although stimulated by cytokines, the polyreactive IgA producing plasma cells do not require the classical type of T cell help. These IgA proteins can recognize molecules from multiple species of intestinal bacteria.

Although IgG is not usually considered a secretory antibody, considerable amounts are transported across the placenta and across epithelial cells into the lumen of the GI, respiratory and vaginal tracts [68,69] by the neonatal Fc receptor (FcRn) [70].

12. Box 7. Immune outposts: Cryptopatches, isolated lymphoid follicles and Peyer's patches

Local outposts, some more permanent than others, arise in hot spots of infection and inflammation in addition to the established Peyer's patch and lymph node forts [71]. Cryptopatches, visualized in the mouse, are clusters of DCs, T and B cells which may even contain follicles of B cells, while isolated lymphoid follicles (ILF) and Peyer's patches are more like mini-lymph nodes. The cryptopatches can initiate the development of ILFs [72,73], neither of which are permanent immune outposts.

ILFs in the mouse are generated in the intestine soon after birth in response to IL-7 and other cytokines, [74,75], chemokines (e.g., CXCL13, CCL19 and CCL21) and adhesion molecules (e.g., VCAM1 and ICAM1) produced by ILC3 cells, DCs and stimulated intestinal epithelial cells reacting to intestinal flora. The epithelial cells are converted into scaffolds that recruit and capture lymphocytes.

Chronic infection, including the constant microbial exposure of intestinal and other epithelial surfaces, or inflammation, attracts and encourages specialized T cells and antigen specific memory CD4 and CD8 T cells to set up residence in the region. Constant activation of these lymphocytes enhances production of their molecular anchors and binding to the epithelium and down regulates the chemotactic receptors for the lymph node or for wandering through the body. CD4 memory cells specific for bacterial antigens reside under the mucosal epithelium and cycle through the body but home back to the GI tract during inflammation [76,77]. Kick started by the cytokines produced by the other resident T cells and ILCs, the memory T cells rapidly amplify specific protections against reinfection [35,36]. In the lung, resident memory CD8 T cells (T_{RM}) supplement antibody to provide protections against viral reinfections [34]. Sites of HSV recurrence in the skin and elsewhere are also populated by resident memory T cells (T_{RM}) to help limit the consequence of recurrences [78]. In addition, B cells and plasma cells are drawn to areas of chronic infection or inflammation and can provide immune regulation in addition to antibody [79].

The Peyer's patches are part of the gut associated lymphoid tissue (GALT) and represent a permanent immune outpost in the GI tract. The Peyer's patches are mini-lymph nodes that provide observation posts for the intestinal lumen and local surroundings. The Peyer's patch is capped by a M cell that acts as a window to the contents of the GI lumen. The M cell transports molecules from the lumen into this mini lymph node. The Peyer's patch consists of the full complement of cells found in a lymph node providing barracks to organize the cells. Intestinal challenges from lumen contents stimulate the Peyer's Patches to respond with local regulatory or inflammatory actions and tehn communicate with mesenteric lymph nodes to take appropriate systemic action. Tonsils, part of the mucosal associated lymphoid tissue (MALT), do a similar job with challenges to the mouth, throat and respiratory system. Tonsils have a large B cell population and capacity to initiate antibody production but also restricts inflammation [80,81].

Bronchus-associated lymphoid tissue (BALT) are inducible structures that assemble under the bronchial epithelium only when needed as a temporary outpost during sizeable infectious or

inflammatory challenges [29]. These immuno-bivouacs contain B cell follicles with follicular DCs and T cell zones with conventional DCs. The structures may remain for months after the challenge.

13. Conclusion

Immunologists have expended a great deal of effort in understanding and developing how the immune system prepares for a microbial invasion and the military attack that ensues. Only recently, has the ability and interest developed to appreciate the normal, everyday functions of the immune system. Much of the relevant biology has been uncovered by recent interest in the interplay between the microbiome and the immune response. The immune system spends most of its efforts and energy policing rather than attacking, cleaning up the molecular and cellular trash [1], maintaining the borders of the human body, and quashing minor disturbances. The cells that carry out these functions play by rules that are different from those described in the classical immunology textbooks, being triggered by alternative stimulants such as vitamin B analogues, expressing different cell surface markers, such as CD8αα, and being capable of shifting function depending upon the needs of the situation, such as Treg/TR1 cells and Th17 cells. Better understanding of these "normal" functions for the immune response will also provide greater insights into dysregulation and conditions of excess as occur during autoimmune and inflammatory diseases.

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Conflict of interest

The author has no financial conflicts of interest in this paper.

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