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The Roles of Interleukin-17 and T Helper 17 Cells in Intestinal Barrier Function

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1. Introduction

Inflammatory bowel diseases (IBD) are caused by chronic inflammation of the gastrointestinal tract, affecting as many as 1.4 million persons in the United States, and 2.2 million persons in Europe (Loftus, 2004). Crohn's disease (CD) and ulcerative colitis (UC), the two major forms of IBD, affect different regions of the intestinal tract and have distinct cytokine profiles. In CD, transmural inflammation can occur over the entire length of the gastrointestinal tract, whereas UC inflammation is restricted to the mucosa of the colon. The T helper (T_h) paradigm was established by Mosmann et al (1986) who observed distinct cytokine patterns were produced by two types of fully differentiated effector T cells which they termed termed T_h1 and T_h2 cells. The initial cytokine profiles observed in IBD helped to classify CD as a T_h1 disease, due to the increased production of the main T_h1 effector cytokine, interferon-gamma (IFN-γ). UC was slightly more difficult to classify because levels of a central T_h2 effector cytokine, IL-4, are not increased; however, other T_h2 effector cytokines, such as IL-5 and IL-13 are produced at higher levels (Fuss et al, 1996). Therefore, UC is not considered fully T_h2, but rather a T_h2-like disease (Fuss et al, 2004).

Conventional IBD therapies, including corticosteroids and anti-tumor necrosis factor-alpha (TNF-α) therapy, are aimed at reducing nonspecific inflammation. TNF-α is a central pro-inflammatory cytokine that contributes to the pathology of many autoimmune disorders. Anti-TNF-α was the first biological therapy introduced for patients with IBD in the late 1990s, and corticosteroid-refractory or fistulizing CD and refractory UC generally respond very well to anti-TNF-α treatment (Hoentjen & van Bodegraven, 2009; Rutgeerts et al., 2006). The initial identification of disease-specific inflammatory mediators in CD and UC, T_h1 and T_h2-associated cytokines respectively, lead to the development of more specific anti-inflammatory treatment options, and the efficacies of these new biological agents have in turn helped evolve our understanding of IBD pathogenesis. Using mouse models of intestinal inflammation that resemble CD, and targeting the main cytokine that drives T_h1 cellular development, IL-12, with an antibody to the IL-12p40 subunit either prevented the development of colitis, or completely cured established colitis (Liu et al., 2001; Neurath et al, 1995). These observations further supported the link between CD and T_h1 responses, in addition to warranting the development of an anti-IL-12p40 antibody for human patients with CD. In clinical trials, anti-IL-12p40 therapy induced clinical responses and remissions in patients with active CD (Mannon et al., 2005; Sandborn et al., 2008), which lead to its acceptance as a new therapy for CD.

Around the same time as anti-IL-12p40 therapy was being tested, discrepancies within the T_h1/T_h2 paradigm observed over the previous two decades were beginning to be resolved (Steinman, 2007). Two models in particular provided the first inconsistencies with the T_h1/T_h2 hypothesis: experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA). EAE is a mouse model of human multiple sclerosis, caused by cell-mediated tissue damage that results in delayed-type hypersensitivity (DTH). DTH reactions are cell-mediated immune reactions to a challenge antigen, leading to swelling, induration, and redness appearing 24 to 72 hours after antigen exposure. Initially, DTH was believed to be mediated by a T_h1 response (Cher & Mosmann, 1987). Therefore, it was hypothesized that EAE would worsen with the addition of the T_h1 effector cytokine, IFN-γ. Interestingly, the results were just the opposite and IFN-γ administration ameliorated EAE damage (Billiau et al., 1988; Voorthuis et al., 1990). Similarly, CIA as a second model of autoimmune tissue destruction was also predicted to worsen with the administration of IFN-γ. Although the disease did worsen when IFN-γ was given before the administration of the adjuvant, it was ameliorated when IFN-γ was given after the adjuvant (Jacob et al., 1989; Nakajima et al., 1991). These puzzling inverse relationships between disease states thought to be controlled by T_h1 responses and the presence of IFN-γ, eventually lead to the discovery of IL-23 and it's role as a master regulator of a new T_h cell subset. IL-23, like IL-12, is a heterodimeric cytokine comprised of two subunits: a unique p19 subunit and a p40 subunit that is also shared by IL-12 (Oppmann et al., 2000). After it was discovered that IL-12 and IL-23 share a common subunit, divergent functions of these cytokines were unraveled, and the autoimmune inflammation in both EAE and CIA was found to result from the actions of IL-23, and not the T_h1 associated cytokine IL-12 (Cua et al., 2003; Murphy et al., 2003). In the same regard, when models of innate and adaptive chronic intestinal inflammation were re-evaluated, IL-23 was found to play a greater role than IL-12 in the induction of inflammation (Hue et al., 2006; Kullberg et al., 2006).

Around the time that IL-23 was found to be a central mediator of autoimmune inflammation, it was also discovered as a master regulator of an emerging T_h cell subset, T_h17 (Aggarwal et al., 2003). This was a significant event, as it shifted the long-standing T_h1/T_h2 paradigm of inflammation to include a novel subset of adaptive T_h cells. Consequently, all inflammatory conditions involving the adaptive immune response have needed re-evaluation. T_h17 cells have high expression of the transcription factors RORα and ROR-γt, produce the cytokines IL-17A, IL-17F and IL-22, have high surface expression of the IL-23R as well as the chemokine receptor CCR6, and can also secrete the CCR6 ligand, CCL20 (O'Connor et al., 2010). Importantly, the CCL20-CCR6 ligand-receptor pair plays an important chemoattractant role at mucosal surfaces (Schutyser et al., 2003). In addition to T_h17 cells, CCR6 is also expressed on T regulatory (T_{reg}) cells that function to maintain homeostatic conditions (Lim et al., 2008). By producing CCL20, T_h17 cells are able to promote the migration of additional T_h17 cells as well as T_{reg} cells (Yamazaki et al., 2008), and both cell types are enriched at mucosal surfaces.

Since their characterization, T_h17 cells have been shown to play an important protective role in infectious immunity where they promote the clearance of extracellular pathogens by enhancing neutrophil recruitment and promoting the expression of antimicrobial factors. Additionally, T_h17 cells have been associated with many autoimmune diseases, such as rheumatoid arthritis, dermatitis, psoriasis, asthma, multiple sclerosis, as well as IBD (Hemdan et al., 2010). Studies of human IBD have shown that the T_h17 effector cytokines IL-17A and IL-17F are both increased in the affected mucosa and sera of CD and UC patients

(Fujino et al., 2003; Rovedatti et al., 2009). Furthermore, polymorphisms in the *IL-17A* and *IL-17F* genes have been linked to UC and animal models indicate that they are fundamentally involved in the etiology of IBD (Arisawa et al., 2008). However, their precise roles in pathogenesis are not entirely clear. This chapter will focus on the cytokines IL-17A and IL-17F, and review what is known about their contributions to mucosal barrier function in the gastrointestinal tract with special emphasis on IBD.

2. The intestinal mucosal barrier

The gastrointestinal tract forms the largest surface in contact with the external environment. The intestinal mucosal barrier separates the internal intestinal tissues from an estimated 10^{14} organisms (Savage, 1977), and is composed of a physical barrier as well as specialized immune cells, primed to react if the physical barrier is breached.

2.1 Anatomy and function of the physical barrier

The physical barrier is comprised of an outer mucus layer less than a millimeter thick, and a single layer of epithelial cells joined together by tight junctions (Figure 1). The main structural component of the outer mucus layer is the heavily O-glycosylated glycoprotein MUC2, which is produced by goblet cells and gives mucus its viscous properties. The outer mucus layer was recently discovered to contain within it two distinct layers: an outer loose mucus layer with high numbers of commensal bacteria, and a dense inner layer that is sterile, containing high concentrations of antimicrobial molecules including nonspecific antimicrobial peptides and specific antimicrobial immunoglobulins (IgA) (Johansson et al., 2008). Commensal bacteria contribute to the function of the mucosal barrier by inducing the production of IgA, recruiting intraepithelial lymphocytes, and providing a physical blockade to prevent the colonization of pathogens (Umesaki et al., 1999).

The second component of the physical mucosal barrier is the single layer of epithelial cells supporting the outer mucus layer. The majority of epithelial cells are transporting enterocytes, but specialized epithelial cell types contribute to mucosal barrier integrity by producing the main constituents of the mucus layer, which minimizes microbial contact with the epithelium. Additionally, epithelial cells have a dense glycocalyx overlaying microvillar projections that prevent microbial attachment (Linden et al., 2008; L. Shen & Turner, 2006). The epithelial barrier needs to be selective to allow the absorption of essential nutrients while preventing the entry of potentially noxious compounds. As depicted in Figure 1, tight junctions that connect the epithelial cells allow the cellular barrier to respond to changes in the environment by regulating the tight junction protein composition, which leads to general or ion-selective changes in paracellular permeability (Arrieta et al., 2006).

In both animal models of IBD and the clinical disease in humans, changes in the physical mucosal barrier have been observed. In patients suffering from UC, MUC2 protein levels are significantly decreased during active phases of the disease, resulting in a thinner protective mucus layer (Hinoda et al., 1998; Tytgat et al., 1996). In animal models of chronic intestinal inflammatory conditions that cycle between active and quiescent phases, paracellular permeability remains increased regardless of the inflammatory state, whereas transcellular permeability is only increased during active inflammation (Porras et al., 2006). Similar observations have been made in humans, where patients with quiescent CD have significantly increased intestinal permeability when compared to controls (Wyatt et al.,

1993). It is believed that the sustained increase in paracellular permeability, indicative of epithelial cell layer dysfunction, contributes to the chronic nature of the disease.

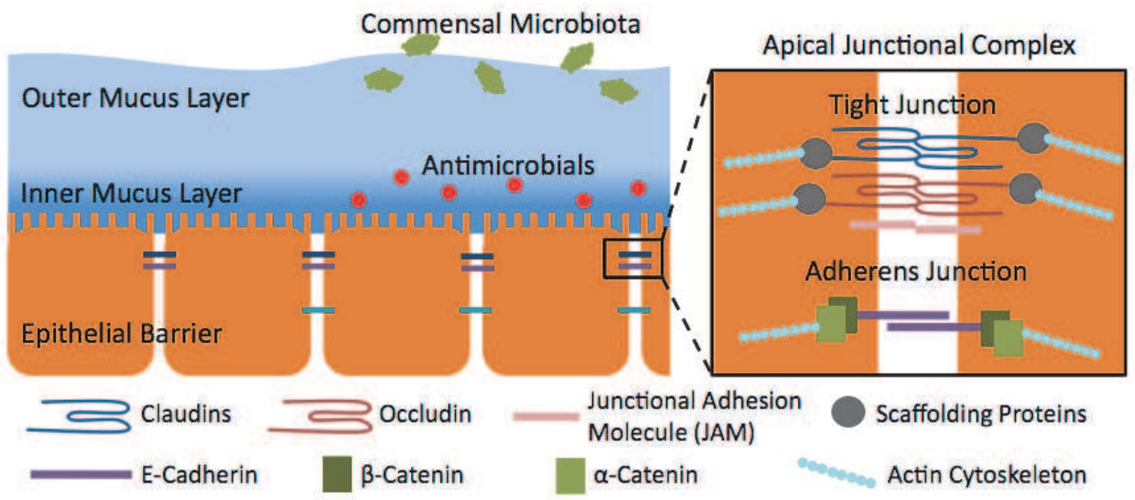

Fig. 1. The physical intestinal mucosal barrier. A single layer of epithelial cells linked together at the apical junctional complex (AJC) and an overlying mucus layer form the physical mucosal barrier. AJCs are comprised of tight junctions and adherens junctions. The protein composition of the tight junction is dynamic, and different claudin-family proteins as well as varying levels of occludin and the junctional adhesion molecule (JAM) allow for specific alterations of paracellular permeability. The foundation of the adherens junction is formed by contacts between epithelial cadherin (E-cadherin)-catenin complexes, which functions to connect neighboring epithelial cells and maintain cell polarity.

2.2 Immune cells of the mucosal barrier: Surveillance and tolerance

In addition to the physical boundary, there are immune cells and gut associated lymphoid tissues (GALT) situated within and below the epithelium. In a healthy intestine these cells and tissues strike a balance between immunity and tolerance, and maintain barrier function. The intestinal tract harbors vast populations of leukocytes. Innate immune cells typically mediate the first line of host defense, and in the intestine these include dendritic cells, macrophages, natural killer (NK) cells, γδ T cells, NKT cells and polymorphonuclear cells (Meresse & Cerf-Bensussan, 2009). Innate immunity evolved to recognize molecular signatures within the products of microbes that are essential to microbial survival. The innate immune system is comprised of pathogen recognition receptors (PRRs), such as toll-like receptors (TLR) and nucleotide-binding and oligomerization domain-like receptors (NLR), which recognize pathogen-associated molecular patterns (PAMPs). Binding of PAMPs to their cognate PRR activates signaling pathways that in turn activate host defense mechanisms. Different cell types have distinct immune functions; they express different combinations and levels of PRRs, and the downstream targets of PRR signaling are cell specific (Wells et al., 2010). Consequently, PAMP-PRR signaling mediates cell specific responses that enable the surrounding tissue to adapt to the dynamic intestinal environment.

Additionally, intestinal tissues are unique in that they harbor large numbers of adaptive immune cells expressing effector or memory phenotypes (Mowat, 2003). These include IgA and IgG secreting plasma B cells and canonical αβ T cells located in the lamina propria.

Adaptive immune responses are antigen specific and typically facilitate expeditious removal of pathogens. In the gut however, adaptive immune tolerance is crucial for maintaining quiescent relationships with the microbial flora and food antigens. In this regard, the intestine is a prime inductive site for large numbers of adaptive T_{reg} cells that home back to the intestinal mucosa, where they help to maintain intestinal tolerance (Belkaid & Oldenhove, 2008; Coombes et al., 2007). Thus, innate and adaptive immune cells in the gut are primed for action so that they can maintain a tolerant immune environment, while still being able to rapidly respond to invading pathogens.

3. Interleukin-17

IL-17 is a central pro-inflammatory cytokine at mucosal surfaces, with important functions in innate and adaptive immunity, as well as host defense against extracellular pathogens. Originally named cytotoxic T-lymphocyte antigen (CTLA)-8, IL-17 was first described in the mid 1990s (prior to the identification of T_h17 cells) as a cytokine produced by activated $CD4^+$ T cells that acts on stromal cells to up regulate inflammatory and hematopoietic processes (Fossiez et al., 1996; Rouvier et al., 1993; Yao et al., 1995a). IL-17 is now best known as the signature cytokine secreted from the recently characterized T_h17 cells, however numerous innate cells can also produce IL-17, including innate-like γδ intraepithelial lymphocytes (IEL), natural killer (NK) T cells, lymphoid tissue inducer (LTi)-like cells, Paneth cells, and neutrophils, as well as other unidentified cell types (Buonocore et al., 2010; Cua & Tato, 2010; Doisne et al., 2011; L. Li et al., 2010; Maele et al., 2010; Michel et al., 2007; Shibata et al., 2007; Takahashi et al., 2006; Takatori et al., 2008). In the context of the intestinal mucosa, γδ IELs are currently the best-characterized innate sources of IL-17. γδ IELs reside at the intestinal mucosal surface between epithelial cells on the basolateral side of tight junctions. They play an essential role in the restitution of epithelial cells following mucosal injury through the production of growth factors, a distinct ability that does not occur in other mucosal T cell populations (Y. Chen et al, 2002). Additionally, γδ IELs play an essential role in controlling bacterial penetration across injured mucosal surfaces, and recruiting neutrophils following *Escherichia coli* infection by acting as the major source of early IL-17 (Ismail et al., 2009; Shibata et al., 2007).

Importantly, since the discovery of IL-17 additional IL-17 family members have been identified. The IL-17 cytokine family consists of six members in mammals: IL-17A (also called IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F (X. Zhang et al., 2011). IL-17F shares 50% sequence homology with IL-17A, is also produced by T_h17 cells, binds the same receptor as IL-17A and in turn shares certain biological activities (Hymowitz et al., 2001). IL-17A and IL-17F are either produced as homodimeric cytokines or as heterodimers composed of IL-17A/F (Wright et al., 2007). When acting on fibroblasts, endothelial cells, or epithelial cells, both IL-17A and IL-17F induce the production of pro-inflammatory cytokines (notably IL-6 and IL-8), chemokines, antimicrobial peptides, and matrix metalloproteinases (Iwakura et al., 2011; Starners et al., 2001). Despite their similar pro-inflammatory actions, IL-17A and IL-17F appear to have distinct roles in mediating inflammatory processes and autoimmune diseases (*discussed later*). IL-17B, IL-17C, and IL-17D are the least well-characterized members of the IL-17 family. IL-17B and IL-17C have 27% homology with IL-17A, but are not produced by activated T cells and do not induce the same pro-inflammatory cytokines as IL-17A and IL-17F (H. Li et al., 2000). IL-17D, which is most similar to IL-17B with 27% sequence identity, is highly expressed in skeletal muscle,

brain, adipose, heart, and lung tissue, but poorly expressed in activated T cells. However, similar to IL-17A and IL-17F, IL-17D can induce the expression of IL-6 and IL-8 from endothelial cells (Starnes et al. 2002). Lastly, IL-17E has the most divergent primary sequence compared to IL-17A with 16% homology, and plays a role in pro-allergic type 2 immune responses (Angkasekwinai et al., 2007; Lee et al., 2001; Pan et al., 2001).

Despite the varying degrees of sequence homology and varying functions, the C-terminal region of each IL-17 family member is quite conserved, containing 4 cysteine and 2 serine residues. Three IL-17 crystal structures have been resolved thus far: IL-17A with its neutralizing antibody, IL-17F, and IL-17F with its receptor IL-17RA. These structures have demonstrated the 6 conserved residues adopt a cysteine knot fold, which differs from the canonical cysteine knot found in TGF-β and neurotrophin proteins due to the absence of two cysteine residues (Ely et al., 2009; Gerhardt et al., 2009; Hymowitz et al, 2001).

3.1 IL-17 receptor and signaling

Cytokine receptors are generally classified into six main categories: IL-1 receptors, class I cytokine receptors, class II cytokine receptors, TNF receptors, tyrosine kinase receptors and chemokine receptors (Wang et al., 2009). The IL-17 receptors do not belong to any of these categories based on their unique structure and cytokine interaction (X. Zhang et al., 2011).

The IL-17 receptor family contains 5 members: IL-17RA (or IL-17R), IL-17RB, IL-17RC, IL-17RD, and IL-17RE. IL-17B is known to signal through IL-17RB, IL-17C through IL-17RE, and IL-17E through IL-17RA/IL-17RB (Iwakura et al., 2011; Wright et al., 2008). The receptor for IL-17D remains unknown. IL-17RA and IL-17RC are normally required for IL-17A, IL-17F, and IL-17A/F signaling (Iwakura et al., 2011). However, the IL-17RA is highly expressed on mouse T cells, while IL-17RC is undetectable, and only IL-17A but not IL-17F can induce signaling (Ishigame et al., 2009). Thus, it appears in some cell types IL-17RC is dispensable for IL-17RA signaling. This has lead to the hypotheses that IL-17RA forms either a homodimeric signaling complex or that other subunits can pair with IL-17RA in some cell types that do not express IL-17RC (Gaffen, 2009). Clarification of the receptor complexes for IL-17A and IL-17F is important for understanding how a cell or tissue responds to IL-17A versus IL-17F and will undoubtedly reveal crucial aspects of tissue specific T_h17 responses.

Signaling through IL-17 receptors triggers pathways that are usually associated with innate immune signaling (F. Shen et al., 2005; Park et al., 2005). Classical T_h1 and T_h2 cytokines activate JAK/STAT signaling, however IL-17A and IL-17F mediate signaling through nuclear factor (NF)-κB, NF-κB activator 1 (Act1) and tumor necrosis factor (TNF) receptor associated factor 6 (TRAF6) (Chang et al., 2006; Schwandner et al., 2000; Yao et al., 1995b). This mode of signaling is similar to those used by TLRs and the IL-1 receptor family, which function in innate immunity. Furthermore, IL-17A and IL-17F generally induce events that are typical of early inflammation (Gaffen, 2009). Upon receptor binding, IL-17A and IL-17F induce expression of many pro-inflammatory genes including: the cytokines TNF, IL-1, IL-6, granulocye-colony stimulating factor (G-CSF) and granulocyte-macrophage (GM)-CSF; the chemokines CXCL1, CXCL5, IL-8, CCL2, and CCL7; antimicrobial defensins, and S100 proteins; as well as matrix metalloproteinases (MMP)-1, -3, and -13 (Iwakura et al., 2011). In this regard, signaling by IL-17A and IL-17F through an IL-17 receptor complex is considered to mediate innate-like inflammatory events.

3.2 Interleukin-17 and the mucosal barrier

Although the majority of the defined roles played by IL-17 in mucosal barrier function are related to innate and adaptive immune functions, IL-17 has also been found to directly regulate components of the physical mucosal barrier. In colonic epithelial monolayers IL-17A enhances tight junction formation by increasing claudins 1 and 2 association with the membrane (Kinugasa et al., 2000). Direct application of IL-17A to T84 monolayers increased transepithelial resistance and decreased manitol flux through monolayers. Thus, IL-17A may have an important role in maintaining tight junctions and epithelial restitution during repair processes. In airway epithelial cells IL-17A induces mucin gene expression, and it may have similar inductive effects in the intestine on goblet cells (Chen et al., 2003). IL-17A also induces expression of β-defensins in the colon (Ishigame et al., 2009). Furthermore, in subepithelial myofibroblasts, which sit just below the epithelium, IL-17A reduced TNF-α-induced secretion of pro-inflammatory cytokines, demonstrating that IL-17 is not implicitly a pro-inflammatory cytokine. Additionally, IL-17 receptor-deficient mice show increased dissemination of *S. typhimurium* from the gut (Raffatellu et al., 2008). Taken together, it appears IL-17 can dynamically regulate components of the physical intestinal epithelial barrier, and the barrier is dysfunctional when IL-17 signaling is impaired.

4. Adaptive immunity and T_h17 cell development

4.1 Induction of adaptive immunity

There are numerous locations in the gut where adaptive immune responses are initiated. These include organized lymphoid tissue such as Peyer's patches and isolated lymphoid follicles (ILF) that are embedded directly in the epithelial wall, and mesenteric lymph nodes (MLN), which are connected to the intestinal mucosa by draining lymphatic vessels (Figure 2, Mowat, 2003). Furthermore, there is evidence that adaptive responses occur directly in the lamina propria via dendritic cell and epithelial cell signaling (He et al., 2007).

Under homeostatic conditions, intestinal luminal contents are constitutively sampled and processed by professional antigen presenting cells (pAPC). pAPC present processed antigen to the naive T cell population, which has an infinite repertoire of antigen-specific receptors. Upon presentation of antigen to a T cell bearing a cognate receptor, the pAPC drives an antigen specific T cell response. Depending on the accompanying signals from the pAPC and surrounding environment, the T cell may become activated into an effector cell, anergic (unresponsive to antigen) or apoptotic. Classically there are three types of cells that act as pAPC: B cells, macrophages and dendritic cells. Arguably, antigen acquisition by dendritic cells is most critical for priming adaptive immune responses, as dendritic cells are the most efficient class of pAPC.

In Peyer's patches and ILF, antigen is transported from the lumen by microfold (M) cells to dendritic cells located in the follicle associated epithelium or the underlying subepithelial dome. From there, dendritic cells move into local T cell/follicular areas or drain to the MLN to initiate adaptive responses (Artis, 2008; Kelsall, 2008; Mowat, 2003). The other site for antigen entry is the non-follicular associated epithelium overlying the lamina propria. Under normal conditions antigen is moved across the non-follicular associated epithelium by receptor-mediated transport (Kelsall, 2008) and by dendritic cells located in the lamina propria, which project dendrites through the tight junctions into the lumen (Figure 2, Chieppa et al., 2006; Rescigno et al., 2001). When the epithelium is damaged, as occurs in IBD and pathogenic infections, antigens also enter directly.

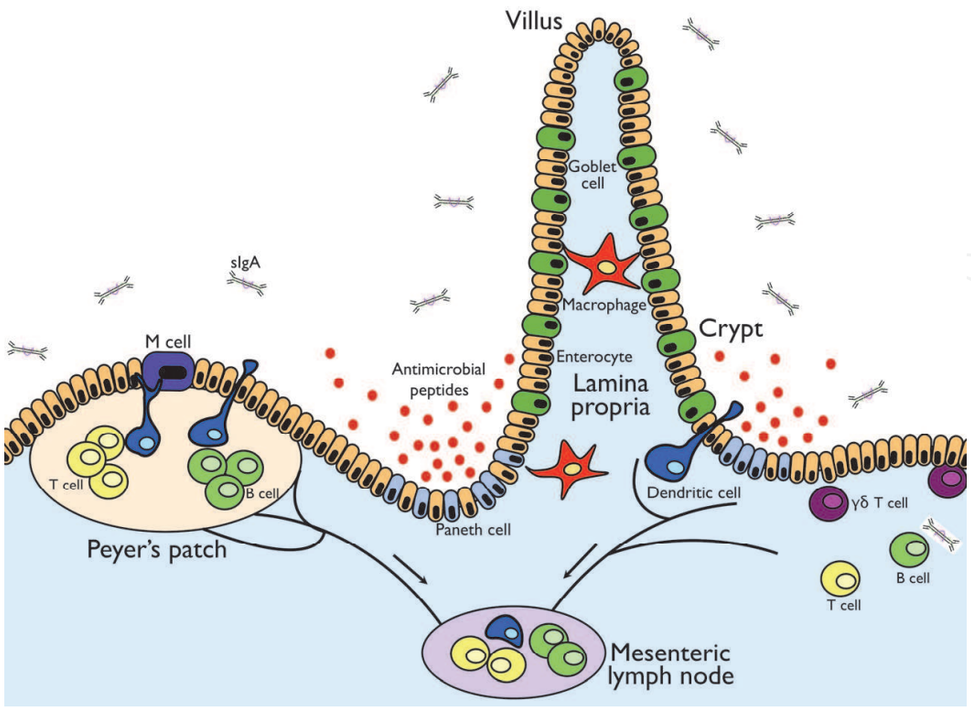

Fig. 2. Schematic of organized gastrointestinal lymphoid tissues. Antigens can be transported from the lumen to antigen presenting cells, such as dendritic cells (DC), by the specialized M cells of Peyer's patches where adaptive immune responses can be generated. Additionally, DCs are able to directly sample luminal antigens by projecting dendrites through the intestinal barrier. DCs can then migrate to local T cell areas, or drain to mesenteric lymph nodes (MLN) through lymphatic vessels. Other immune cells in the lamina propria include: mucosal macrophages, γδ T cells, αβ T cells and IgA-secreting B cells.

Dendritic cells are equipped to recognize microbial products with an array of PRR and in doing so, undergo a process of maturation in order to become proficient antigen presenters for naive T cells. In addition to down-regulating their phagocytic machinery and up-regulating antigen processing pathways, dendritic cells secrete an array of immuno-modulatory cytokines. At first, they express a mixed cytokine profile. However, a dominant cytokine profile emerges and this dictates the type of adaptive immunity that develops (Wilson et al., 2009). The specific constellation of PRRs that are engaged on a dendritic cell is what determines their cytokine profile.

4.2 Adaptive immune cells

The defining feature of an adaptive immune system is antigen-specific immunity. The first encounter with antigen leads to clonal expansion of a few antigen-specific lymphocytes, which target immune responses towards their cognate antigens. Some of these cells become long-lived memory cells and they enable the immune system to remember antigen that has already been encountered, so that upon re-exposure a tailored immune response is quickly recalled. The cells of the adaptive immune system are T and B-lymphocytes. Each lymphocyte bears a surface receptor of a single specificity that binds antigen in a highly specific manner. T and B cell development generates an infinitely diverse repertoire of T and B cell receptors, so that in

theory any possible antigen can be recognized. Classical naive T cells express an αβ T cell receptor and a co-receptor, which comes in two flavors: CD4 or CD8. Accordingly, CD4 expressing T cells are called $CD4^+$ T cells and CD8 expressing T cells are called $CD8^+$ T cells. $CD4^+$ T cells are also called T helper cells because following establishment of the adaptive phase by innate defenses, $CD4^+$ T cells become the central coordinators of the adaptive immune response. The primary effector function of $CD4^+$ T cells is to help and regulate other immune cells. Upon encountering their cognate antigen on mature pAPCs, $CD4^+$ T cells proliferate and differentiate into antigen-specific effector cells.

4.2.1 T Helper cell differentiation

There are currently four well characterized lineages of T_h cells: T_h1, T_h2, T_{reg}, and T_h17 (Figure 3). Naïve $CD4^+$ T cells differentiate into T_h1 cells in the presence of IFNγ and IL-12, which enhances the expression of the principal T_h1 transcription factors, T-box family of transcription factors (T-bet) and the signal transducers and activators of transcription protein 4 (STAT4). Effector cytokines produced by T_h1 cells include IFNγ, TNFα and IL-2, which help to clear intracellular pathogens. T_h2 cells differentiate in the presence of IL-4, which activates STAT6 and leads to the expression of the transcription factor GATA binding protein 3 (GATA3). T_h2-derived cytokines, including IL-4, IL-5 and IL-13, are important in mediating asthma and allergic responses (Zhu & Paul, 2010).

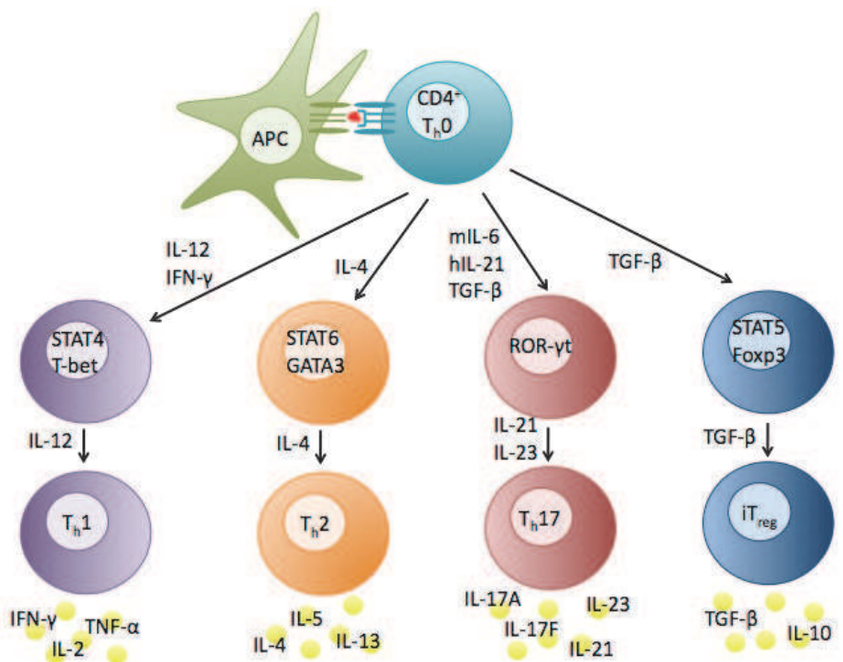

Fig. 3. T helper cell differentiation. After encountering an antigen-presenting cell (APC) within the periphery, naïve T helper (T_h0) cells are able to differentiate into one of four T_h subsets based on the cytokine milieu present. In the presence of interleukin (IL)-12, the activation of transcription factors STAT4 and T-bet lead to T_h1 development, whereas IL-4 results in the activation of STAT6 and GATA3, leading to T_h2 development. In the presence of TGF-β, T_h0 cells will differentiate into inducible T regulatory (iT_{reg}) cells following transcription of STAT5 and Foxp3, unless IL-6 (in mouse) or IL-21 (in human) is present in addition to TGF-β, in which case T_h17 cells will develop following ROR-γt transcription.

Most T_{reg} cells, termed natural T_{reg} (nT_{reg}) cells, are fully differentiated before leaving the thymus, upon TCR stimulation and encountering IL-2 or IL-15. This results in the activation of STAT5 and leads to forkhead box (Fox)p3 expression, the characteristic transcription factor of T_{reg} cells (Burchill et al., 2008). Once these cells leave the thymus, they can home to mucosal surfaces, including the GI tract where the presence of TGF-β helps them to maintain their regulatory phenotype (Barnes & Powrie, 2009). TGF-β is also able to induce the expression of Foxp3 in naïve T cells within the periphery, resulting in inducible T_{reg} (iT_{reg}) cells. Primarily through the production of IL-10, nT_{reg} and iT_{reg} cells share the same suppressive phenotype and function to maintain peripheral tolerance and prevent autoimmunity (Maloy et al., 2003; Read et al., 2000; Zheng & Rudensky, 2007).

T_h17 cellular differentiation also depends on TGF-β, however with the additional presence of IL-6 in mice (Veldhoen et al., 2006), or IL-21 in humans (L. Yang et al., 2008), Foxp3 expression is inhibited and STAT3 activation leads to expression of the transcriptional regulator retinoic acid receptor-related orphan receptor-γt (RORγt), which drives T_h17 differentiation (Ivanov et al., 2006). Once differentiated, T_h17 cells are highly responsive to IL-21 and IL-23, cytokines that function to maintain the T_h17 phenotype. The principle effector cytokines produced by T_h17 cells include IL-17A, IL-17F, IL-21, and IL-22.

5. Role of IL-17 in enteric infections

Several murine models of infectious disease highlight the presence and importance of IL-17 in intestinal inflammation: *Helicobacter hepaticus, Salmonella enterica* serotype *typhimurium*, and *Citrobacter rodentium*. In *H. hepaticus*-induced typhlocolitis, a model of T-cell independent innate inflammation, local increases in IL-23 induced the secretion of IL-17 from non-T cell sources (Hue et al., 2006). A similar study using the same *H. hepaticus* model of bacteria-driven innate colitis confirmed the IL-23-dependent increases in IL-17, and went on to characterize the IL-17-producing cells. This led to the identification of a novel innate lymphoid cell population that accumulates in the inflamed colon, and is able to mediate acute and chronic innate colitis in response to IL-23 stimulation (Buonocore et al., 2010).

In the second infectious model with *S. typhimurium*, initial inflammatory responses are important to contain the infection as localized gastroenteritis, and prevent the systemic spread of bacteria. Macrophages and dendritic cells infected with *S. typhimurium* are a major source of IL-23, and five hours post- *S. typhimurium* infection, IL-17 expression is markedly up regulated (Raffetulla et al., 2008, 2009). The increased IL-17 production resulted in IL-17-dependent intestinal epithelial induction of antimicrobial peptides (Raffatellu et al. 2009). In IL-23p19-deficient mice, the increased expression of IL-17 during *S. typhimurim* infection was abrogated. Although αβ T cells were found to be the predominant cell type expressing the IL-23R, there was a marked increase in γδ T cells expressing the IL-23R during *S. typimurium* infection. γδ T cell-deficient mice demonstrated a blunted expression of IL-17, suggesting that γδ T cells are a significant source, but not the only source of IL-17 during an acute bacterial infection (Godinez et al., 2009).

Lastly, *C. rodentium* is a non-invasive bacterium that transiently colonizes the large intestine of mice. In addition to serving as a model for attaching/effacing bacteria, *C. rodentium* infection can be used a model of IBD, as the infection-associated pathology shares many features with IBD (Mundy et al., 2005). The first evidence of IL-17 involvement in *C. rodentium* infection implicated its importance during the peak and late stages of infection, demonstrating a role for adaptive T_h17 cells in clearing the infection (Symonds et al., 2009;

Zheng et al., 2008). More recent evidence also suggests there is an early T_h17-like response during *C. rodentium* infection that is dependent on the activation of the innate immune receptors Nod1 and Nod2 (Geddes et al., 2011). Whether or not this will directly relate to the *NOD2* coding variants identified as risk factors for IBD (Hugot & Cho, 2002) remains to be explored.

6. Role of IL-17 in IBD pathogenesis

Since the discovery of IL-23 as a critical regulator of T_h17 responses and that there are increased numbers of T_h17 cells in IBD patients (Kleinschek et al., 2009), the importance of T_h17 cells and their effector cytokines has been an active area of IBD research. To help elucidate the precise role of the T_h17 subset, three principle animal models of intestinal inflammation resembling CD have been employed: T cell transfer models of colitis, trinitobenzene sulfonic acid (TNBS)-induced colitis, and dextran sulfate sodium (DSS)-induced colitis. With the T cell-transfer model, the initiation of colitis via an adaptive immune response is modeled through the transfer of naïve $CD4^+$ T cells ($CD45RB^{high}$) to immune-deficient mice that lack T cells and B cells, such as recombination activating gene (RAG)-deficient mice, or severe combined immune-deficient (SCID) mice. The naïve cells introduced develop into pro-inflammatory effector T cells in the absence of a mature immune cell population ($CD45RB^{low}$) containing T_{reg} cells, and spontaneous intestinal inflammation develops (Powrie et al., 1994a). TNBS-induced colitis is also dependent on the adaptive immune system, where mucosal inflammation following the administration of the haptenizing agent TNBS is mediated by T_h1 and T_h17 responses (Alex et al, 2009). In contrast to the latter two models, DSS-induced colitis does not require T cells to initiate inflammation. DSS is thought to disrupt the epithelial barrier, resulting in the activation of lamina propria cells by the normal microflora. In the acute DSS model both T_h1 and T_h17 cells accumulate; however, if the DSS is given in several cycles to establish chronic inflammation, the cytokine profile shifts towards T_h2 (Alex et al., 2009). Therefore, acute DSS can be used as a model for CD whereas chronic DSS is more representative of UC.

6.1 The IL-23/T_h17 axis and IBD

IL-23 has been found to critically mediate intestinal inflammation through both adaptive and innate immune pathways. Interestingly, an uncommon coding variant of the *IL23R* gene, which encodes a subunit of the IL-23 receptor, was found to confer strong protection against both CD and UC (Duerr et al., 2006). T cell transfer models show that IL-23 is required for spontaneous development of colitis by activated $CD4^+$ T cells (Elson et al., 2007; Hue et al., 2006). Similarly, RAG deficient mice that are also IL-23p19 or IL-12p40 deficient (do not produce IL-23) do not develop spontaneous intestinal inflammation, whereas RAG deficient mice that lack IL-12p35 (do not produce IL-12) still develop colitis (Hue et al., 2006). In these experimental systems IL-23 and not IL-12 drives intestinal inflammation. Interestingly, though IL-23p19 deficient mice fail to develop intestinal inflammation, they still develop a systemic inflammatory response (Hue et al., 2006). This demonstrates that IL-23 driven inflammation by $CD4^+$ T cells is localized to the gut. A transfer model with bacteria-reactive $CD4^+$ T cells showed that neutralization of IL-23p19 with a monoclonal antibody attenuates intestinal inflammation and that individually, bacteria-reactive T_h17 cells induce more inflammation than bacteria-reactive T_h1 cells (Elson et al., 2007). The latter study also highlights that T_h1 and T_h17 cells have an overlapping ability to promote

pathologic responses. Although IL-12 as a T_h1 inducing cytokine is dispensable for initiating colitis, T_h1 responses should not be considered insignificant in inflammatory bowel disease. Previous studies have shown that neutralization of IFN-γ (signature T_h1 cytokine) prevents intestinal inflammation and severe wasting, and transfer of IFN-γ deficient T cells into RAG deficient mice fails to induce colitis (Ito & Fathman, 1997; O'Connor et al., 2009; Powrie et al., 1994b). Taken together, these results suggest that although IFN-γ still appears to be the main effector cytokine driving the cell-transfer colitis model, IL-23 and T_h17 responses are essential to support the development of chronic inflammation.

6.2 Contributions of IL-17A and IL-17F to IBD

There are multiple lines of evidence to suggest that blocking IL-17A and IL-17F would prevent intestinal inflammation as both cytokines robustly induce neutrophil recruitment and pro-inflammatory cytokines, blocking IL-23 prevents development of pathogenic T_h17 cells and colitis in animal models, and blocking IL-23 signaling is beneficial for treating CD. Along these same lines, IL-17R-deficient mice are significantly protected from TNBS-induced colitis, despite no change in the levels of IL-23 or IL-12 and IFN-γ (Z. Zhang et al., 2006). Thus, it was unexpected that neutralization of IL-17A exacerbated intestinal inflammation in the dextran sodium sulfate (DSS) colitis model (Ogawa et al., 2004). Animals treated with an IL-17A monoclonal antibody had enhanced inflammatory cell infiltrates into the mucosa and submucosa, more severe mucosal injury and drastically increased weight loss. Moreover, addition of IL-17A attenuated the response (Ogawa et al, 2004). These results were confirmed in IL-17A knockout mice, which also developed more severe DSS-induced colitis (X. Yang et al., 2008). Interestingly, this same study showed that IL-17F knockout mice, unlike IL-17A knockouts, were protected from DSS-induced colitis. Colons of IL-17F deficient mice showed little pathology and extremely low levels of pro-inflammatory cytokines (Yang et al, 2008). Using a T cell transfer model, IL-17A secretion by T_h17 cells was also protective against the development of intestinal inflammation, as IL-17A deficient T cells transferred into RAG deficient mice caused more severe disease than transferred wildtype T cells (O'Connor et al, 2009). Additionally, IL-17A has been shown to directly inhibit T_h1 cells and suppress T_h1 mediated intestinal inflammation (Awasthi & Kuchroo, 2009). Taken together, these data suggest that IL-17A has protective roles in acute tissue inflammation and that IL-17F has pathogenic functions. However, there has also been some evidence that IL-17A is not protective. T cells deficient in ROR-γt, and therefore unable to differentiate into T_h17 effector cells, were unable to induce colitis when transferred to RAG-deficient mice, but treatment with IL-17A caused colitis after the transfer of ROR-γt-deficient cells (Leppkes et al., 2009). Therefore, additional work on the mechanisms, function, and regulation of IL-17A/F in the context of intestinal inflammation is required before confident and definitive conclusions can be drawn.

7. Conclusion

Knowledge of T_h17 cells and their characteristic cytokines IL-17A and IL-17F has rapidly progressed. Likewise, significant progress has been made towards understanding their role in regulating the gut environment. However, there are numerous outstanding questions.
The T_h17 subset is unequivocally associated with chronic inflammatory bowel diseases, and the current belief is that they are instigated by a loss of tolerance to the intestinal microflora.

In addition to T_h17 cells, dysregulated T_h1 and Foxp3$^+$ iTreg responses are also involved. Yet, the precise nature of the relationship between T_h17 cells and T_h1 *as well as* T_h17 cells and Foxp3$^+$ iTregs is unclear. Furthermore, in the gut there appears to be multiple cellular sources of IL-17A and IL-17F, in addition to heterogeneous expression of their receptors, IL-17RA and IL-17RC. Our understanding of how IL-17A and IL-17F mediate their cell specific effects and how this plays out during steady states, infectious disease and chronic inflammation in the intestinal tract is currently in progress. Beneficial results have been obtained using antibodies to neutralize IL-12p40 in Crohn's disease and genome wide association studies implicate the IL-23-T_h17 axis in both Crohn's disease and ulcerative colitis. Together these data suggest therapies specifically targeting T_h17 responses might provide better treatments. However, animal models have also shown IL-17A and IL-17F to critically mediate host protection and components of normal barrier function. Thus given these roles, targeted interventions of IL-17A and IL-17F will need careful consideration.

Inflammatory bowel diseases are a complex set of diseases involving pre-disposing genetic factors and environmental triggers. The emerging IL-23-T_h17 axis represents one significant component of these diseases among several. Though progress has been made, a substantial amount of work remains to identify pathways and mechanisms that connect T_h17 cells, IL-17A and IL-17F to the etiology of inflammatory bowel diseases. In particular, genome wide association studies have established a key role for innate immunity in these diseases. Most well known are *NOD2* and autophagy genes *ATG16L* and *IRGM* involved in bacterial detection and processing. In this regard, much less is known about IL-23, IL-17A and IL-17F in aberrant innate immune responses. For now we can ascertain that both innate and adaptive immunity coordinate an imbalanced relationship between host and microflora that leads to chronic intestinal inflammation, and that T_h17 cells and the IL-17A/F cytokine network participate in both arms of the immune system that has gone awry.

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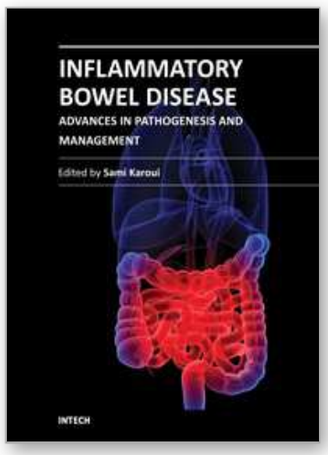

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This book is dedicated to inflammatory bowel disease, and the authors discuss the advances in the pathogenesis of inflammatory bowel disease, as well as several new parameters involved in the etiopathogeny of Crohn's disease and ulcerative colitis, such as intestinal barrier dysfunction and the roles of TH 17 cells and IL 17 in the immune response in inflammatory bowel disease. The book also focuses on several relevant clinical points, such as pregnancy during inflammatory bowel disease and the health-related quality of life as an end point of the different treatments of the diseases. Finally, advances in management of patients with inflammatory bowel disease are discussed, especially in a complete review of the recent literature.

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