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Barrier immunity and IL-17

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Abstract

$CD4^+$ T_H17 cells display a featured role in barrier immunity. This effector population of T cells is important for clearance of microorganisms but can also promote autoimmunity at barrier sites. Recent work has indicated that these effector cells share a pathway with $CD4^+$ regulatory T cells (T_R cells) that also have a critical function in barrier protection and immune regulation. The development and function of T_H17 cells, and their relationship with T_R cells are discussed.

Keywords

effector T cells; IL-17; mucosa; regulatory T cells; T_H17 cells

Introduction

Mucosal and epithelial surfaces harbor a significant number of immune cells that are necessary to provide host protection at these susceptible sites for pathogen entry. These surfaces, including the gastrointestinal tract, lungs, skin and reproductive tract, present a particularly difficult and precarious scenario for the cells of the immune system. Unlike the sterile environment of the systemic circulation, the blood and the lymphatics, the epithelial layer is bathed in a sea of microorganisms. The evolution of the immune system has occurred so that a symbiotic relationship exists between the commensal bacteria of the gut and human hosts. Teleologically one may predict that the epithelial barriers are constructed so that microorganisms are sequestered outside of a tight barrier so that immune response to resident bacteria is rare. However, more recent data presents the opposite story and indicates that the gut microflora are a critical component to proper immune function and in their absence, the immune system has inadequate development often leading to immune dysregulation. Thus, the immune system that has co-evolved in the setting of diverse microorganisms that are beneficial and potentially harmful to the host has developed a specialized approach to addressing the complex nature of the barrier layer between host and the outside world.

The phenotype of T cells at the barrier surfaces

Given the unique conditions existing at the body's interface with the external environment, the cells of the immune system at these sites operate differently than those in the lymphoid organs.

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Within the secondary lymphoid organs (SLO), the majority of T cells are naive, identified by the expression of L-selectin (CD62L) and CD45RA (in humans) that upon activation produce IL-2[1]. Naïve cells are primarily recruited to the secondary lymphoid organs such as the lymph node and spleen mediated by L-selectin[2] and the chemokine (C-C motif) receptor 7 (CCR7) [3]. In these locations, naïve cells are continuously surveying available antigen from resident and migrating dendritic cells[4] and awaiting the correct combination of T cell receptor (TCR) signaling in the context of co-stimulation to initiate activation[5]. Following stimulation, T cells differentiate into distinct effector lineages dictated by the activating environment so that the proper immune response occurs[6]. This process requires several days for naïve T cell activation to produce a functional effector T cell exported from the lymph node[7].

In contrast, conventional αβ T cells residing at barrier sites have an effector or memory cell phenotype[8]. These T cells express CD44, a molecule important for their non-specific exit from the systemic circulation and residence within peripheral organs[9,10]. They also express distinct chemokine receptors and integrins that allow recruitment to specific sites. Gastrointestinal tract tropism is determined by CCR9 mediated recruitment via the small intestine's expression of CCL25 (TECK) in combination with α4β7 expressed on effector T cells promoting adhesion to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed by the postcapillary endothelial cells in the small intestine[11,12]. For efficient dermal and epidermal homing, T cells express CCR4 and CCR10 that bind to CCL17 and CCL27, respectively, expressed by the skin during resting and inflammatory conditions [13-16]. In addition, T cells necessary for the protection against inhaled pathogens are directed to the lung by the expression of CCR3 and CCR5. While unique adhesion molecules direct effector T cells to specific barrier locations, other molecules such as α4β1 and CCR6 play a more general but important role in recruitment to mucosa and the skin[17,18].

Another important distinction between the αβ T cells that reside in the epithelial surfaces compared to the compartment within the lymph node or spleen is the reduced threshold for activation and rapid response to pathogens[8]. At barrier surfaces, effector T cell populations are primed for cytokine secretion. These cells are activated much faster at least partially due to altered co-stimulatory molecule expression. Naïve T cells rely on CD28 as their second signal while memory cells located at epithelial layers make use of ICOS as well as others. The cells at these sites are primed and ready to respond rapidly to any sign of infection to help remove the source before it results in infection[19].

The effector T cell paradigm

For the past 20 years, the T_H differentiation paradigm consisted of two mutually exclusive pathways, T_H1 and T_H2, defined by distinct cytokine production and immune function[20]. The first, T_H1, is characterized by the production of IFNγ and directs cell-mediated immunity. This subset requires the transcription factor T-bet[21], is induced by IFN-γ and IL-12 from macrophages or DCs[22] and requires STAT1 and STAT4 signaling[23,24]. T_H1 responses are necessary for intracellular pathogen clearance[25] and in mice induce B cells to produce IgG_{2a}[26]. The other subset, T_H2, is characterized by the production of IL-4, IL-5 and IL-13 [27] and in mice, directs B cell secretion of IgE and IgG1[26]. This subset requires the transcription factor GATA3[28], is induced by IL-4 or thymic stromal lymphopoietin from basophils[29], and requires STAT6 signaling[30]. T_H2 responses are necessary for clearance of extracellular parasitic infections and cause allergic disease[25]. The two subsets are distinct lineages in that GATA3 and T-bet negatively regulate each other and the presence of IFNγ prevents T_H2 and IL-4 prevents T_H1[31] differentiation.

More recent work indicates that another subset of effector T_H cells exists. This lineage is defined by the production of IL-17 and has been given the name T_H17. These cells are critical

for protection against extracellular bacteria and fungi and are responsible for several autoimmune conditions[32].

The T_H17 subset

Interleukin 17: structure and function

The T_H17 subset of helper T cells is defined by the production of the IL-17 cytokine. This cytokine was first described 15 years ago and was originally given the name cytotoxic T-lymphocyte-associated antigen 8 (CTLA-8)[33,34], and later renamed IL-17[35]. Subsequent work revealed that it was the first identified in a family of six cytokines, now referred to as IL-17A through F, with IL-17F showing the highest degree of homology with IL-17A followed by B, D, C, and E[36]. The cellular source of IL-17 was originally identified in activated T cells[33,34] but more recently been expanded to include γδ T cells[37], $CD8^+$ memory T cells [38], neutrophils[38] and monocytes[39]. $CD4^+$ T cells are considered the significant producers of this cytokine.

IL-17 is pro-inflammatory and important for the clearance of extracellular pathogens and multiple autoimmune disorders. Experimental models using mice with defective IL-17 signaling or treated with depleting antibodies show increased susceptibility to lung infection by *Klebsiella pneumonia and Mycoplamsa pneumoniae* and a defect in clearance of *Candida albicans* and *Escherichia coli* [40-43]. This effect has been linked to IL-17-mediated neutrophil recruitment as well as induction of anti-microbial proteins from resident cells. IL-17 stimulates a host of inflammatory cytokines and chemokines, including granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein-2 (MIP-2), IL-8, monocyte chemotactic protein-1 (MCP-1), CXCL-8, CXCL-1 and CXCL-10[36,44-47] along with other inflammatory mediators such as prostaglandin E2, nitric oxide, matrix metalloproteases, acute phase proteins and IL-6[45,46,48,49]. Along the same lines, IL-17 can promote unfavorable immune responses indicated by this cytokine's role in multiple autoimmune disorders such as rheumatoid arthritis[50], psoriasis[51], inflammatory bowl disease[52], asthma[53], and multiple sclerosis[54,55].

Given the robust immune response mediated by IL-17, it is not surprising that targets for this cytokine are highly diverse. Studies of mRNA expression indicate that the receptor is present on hematopoetic cells, osteoblasts, fibroblasts, endothelial cells and epithelial cells in the lung, liver, spleen and kidney[35,56]. In fact, this family of receptors is as complex as their ligands. Sequences homology searches have revealed that there are five members, IL-17RA to IL-17RE [36,57]. This group represents a unique family containing domains not observed previously and is structured as a single-pass transmembrane proteins with an extracellular domain and a long intracellular tail[35]. Further analysis indicated that all receptors except IL-17RA have alternative splicing variants that introduce early stop codons allowing for the receptor to be secreted[58,59] and potentially act as a decoy to help reduce IL-17 signaling during an immune response.

To date, functional studies of the IL-17 receptor family are still lacking, with most analyses limited to IL-17RA and more recently IL-17RC. While both of these receptors can bind to IL-17 and IL-17F, IL-17RA has a log fold decreased affinity for IL-17F[60] while IL-17RC binds equally to both[61]. IL-17RA exists as a preformed homodimer[62] or can function as a heterodimer pairing with IL-17RC[63]. In fact, IL-17RA may be a generic receptor for all IL-17 family members given the recent report that both IL-17RA and IL-17RB are necessary for IL-17E (IL-25) signaling, a T_H2 inducing pathway, very different from IL-17[64].

Upon ligand binding, the IL-17 receptor undergoes a conformational change facilitating dissociation of the intracellular region. The IL-17RA has a cytoplasmic tail with motifs similar

to the TLR-IL-1 receptor (TIR)[65] superfamily, now termed SEFIR domain (similar expression to FGF receptor, IL-17 receptor, Toll-IL-1R)[66] but does not require the myeloid differentiation factor 88 (MyD88) for signaling. Upon IL-17RA engagement, signaling via Act1[67] promotes TRAF6 ubiquitination of the receptor[68] and activates the NF-κB transcription factor pathway[67,69-71]. However, even with multiple family members and overlap of IL-17RA and IL-17RC in binding, there is minimal redundancy in the function of IL-17RA given that targeted deletion of this receptor causes profound defects in host defense [47].

T_H17: a new helper subset

As mentioned earlier, $CD4^+$ helper T cells have been divided into two distinct effector lineages, T_H1 and T_H2[20]. These two subsets develop during the course of an infection and are selected by the inflammatory signals provided by the innate immune system so that a particular type of immune response can be carried out. These two effector lineages have somewhat opposing functions[72-74] with T_H1 cells driving cell-mediated immune responses that can cause tissue damage and experimentally characterized as the pathway necessary for delayed type hypersensitivity (DTH)[75], while T_H2 cells promoting antibody-mediated responses and are associated with allergy and the IgE isotype[76].

Although the T_H1/T_H2 paradigm explained many experimental systems and disease models, there were some inconsistencies that provided a framework for the introduction of a new subset [32,77]. These experimental observations related to the IL-12 cytokine family and the discovery of another member, IL-23. IL-12 is a heterodimeric cytokine that is composed of p40 and p35 subunits to make a complete cytokine p70[78,79] that signals via the IL-12 receptor consisting of the IL-12Rβ1 and IL-12Rβ2[80,81]. This signaling pathway is necessary for T_H1 development and genetic deficiency of this cytokine prevents IFNγ production from T cells and mice normally resistant to *Leishmania major* die from the infection[82-84].

However, other experimental models, particular experimental autoimmune encephalitis (EAE) raised questions regarding the simplicity of IL-12 and the IFNγ inducing effect. Initial work using antibodies to block p40 or mice deficient in this subunit showed resistance to EAE, indicating that IL-12 and presumably IFNγ were necessary for disease development[85-87], except that, in the absence of IFNγ, mice were still susceptible to the disease[88]. The data indicated a divergent function between the p40 subunit of IL-12 and IFNγ induction. Support for this notion occurred when p35 deficiency had the same effect on EAE as the IFNγ knockout and opposite effect when p40 was lacking[89]. These observations indicated that the p40 subunit had functions apart from pairing with p35 to induce a T_H1 response.

This issue was resolved when another IL-12 family member, IL-23 was discovered[90] and shown to be critical for the induction of IL-17 from $CD4^+$ T cells[91]. The IL-23 cytokine shares the p40 subunit but pairs with a unique p19 protein that together bind to a receptor composed of the shared IL-12Rβ1 and a unique IL-23 receptor[92] (Table 1). Similar to the IL-12 requirement for IFNγ production, it was shown that the related cytokine IL-23 induces T cells to produce IL-17[91]. Soon after, EAE disease induction was proven to be dependent upon IL-23 derived T_H17 cells and actually protected by the IL-12/IFNγ pathway[55,89]. Thus, very similar IL-12 family member cytokines with a common p40 subunit and IL-12Rβ1 induce distinct effector pathways consisting of T_H1 and T_H17.

T_H17 development

The discovery of IL-23 and the identification of its role in IL-17 mediated disease set the stage for characterization of the new subset, T_H17[55,89], and understanding how these effector cells develop. Similar to T_H1 and T_H2, the T_H17 lineage has a distinct *in vitro* differentiation

pathway. Sorting of naïve T cells and culturing in the presence of TGFβ induces FoxP3 transcription factor and converts the majority of T cells to regulatory T cells (T_R); however, addition of IL-6 to the culture conditions changed the phenotype to IL-17 production[93,94]. In fact, activating T cells with T_R, producers of TGFβ, and DCs stimulated with a Toll like receptor agonist, a source of IL-6, also converted the naïve population to T_H17[95]. In these *in vitro* skewing experiments, the absence of IL-23 had no effect on T_H17 development leading to the conclusion that TGFβ and IL-6 mediate the initial T_H17 differentiation while IL-23 is important for survival and expansion. *In vivo* experiments using genetically altered mice with non-functional TGFβ receptor signaling or impaired T cell production confirmed the role of this cytokine in IL-17 differentiation and subsequent EAE disease development[96,97].

T_H17 transcription factors and signaling pathways

Analogous to T-bet, GATA3 and FoxP3 for T_H1, T_H2 and T_{REG}, the transcription factor retinoic acid receptor-related orphan receptor (ROR)γt directs the differentiation of T_H17. Mice that lack RORγt cannot make IL-17 producing T cells and retroviral transduction into naïve cells promotes T_H17 development[98]. In addition, another transcription factor of the same family, RORα, plays a synergistic role with RORγt in T_H17 differentiation[99]. It has recently been shown that Runx1 is an important transcription factor in binding to RORγt and FoxP3 to promote efficient T_H17 development[100]. Interferon-regulatory factor (IRF) 4, a mediator of T_H2 development is also required but not specific for T_H17 induction[101].

The specific sequence of cell signaling events involved in T_H17 development and function has been partially elucidated. IL-23 and IL-6 activate STAT3 signaling, now considered necessary and unique for T_H17 differentiation[102]. As part of activation, the T_H17 cells make IL-21 that provides autocrine signaling and can replace the need for IL-6[103-105]. As part of this process, the suppressor of cytokine signaling (Socs) 3 is turned off as it functions as a negative regulator [106].

T_H17 regulation

Analogous to the inhibitory effects that T_H1 cytokines have on T_H2 development and the reverse, T_H17 function is also influenced by T_H1 and T_H2 cytokines. *In vitro* activation and differentiation of naïve T cells to the T_H17 lineage is enhanced with blocking of IFNγ and IL-4 [94,107]. Mice lacking the T_H1 transcription factor T-bet develop exaggerated T_H17 levels in the setting of autoimmune disease such as myocarditis or during Mycobacterium bacterial infection[108,109]. However, this data does not determine if the presence of these cytokines prevents development of T_H17 cells or regulates the secretion of IL-17 follow lineage commitment. In addition, IL-27, another member of the IL-12 cytokine family, with T_H1 inducing properties, can inhibit T_H17 independent of its T_H1 promoting function[110]. Along the same lines, IL-17E also known as IL-25, has suppressive function and its absence promotes enhanced IL-17 levels that exacerbates EAE[110] and allows for increased T_H17 cell development in the gut[111]. Thus, the IL-17 cytokine contributes to a specific type of inflammatory response and as appropriate is carefully regulated by other cytokines to promote swift resolution of toxic inflammatory conditions to minimize injury to the host.

T_H17: An effector lineage sharing a regulatory T cell pathway

The T_H17 subset is often considered a parallel effector lineage to T_H1 and T_H2[112] with a distinct role in the pathogenesis of specific autoimmune conditions and a mediator of microbial clearance (Table 2). Early work indicating a dependency on IL-23 presented an analogous developmental pathway to T_H1 induction by IL-12[32] and presented the initial idea that the secretion of related factors IL-12 or IL-23 determined the fate of the developing immune response. However, subsequent data established IL-23 as a survival factor and identified

TGFβ in conjunction with IL-6 as the lineage determining cytokines[93-95]. Thus, the comparison to T_H1 development was diminished and a link to T_R cells was introduced.

Activating naïve T cells *in vitro* in the presence of TGFβ alone promotes development of T_R with the addition of IL-6 diverting differentiation to T_H17. This was the first indication that this inflammatory subset shared a common lineage with T_R[93,94]. Further support comes from IL-2, a cytokine necessary for T_R survival[113]. This cytokine constrains the development of T_H17 cells so that TGFβ/IL-6 in the presence of IL-2 had significantly reduced T_H17 development and expanded $FoxP3^+$ T_R cells[114]. However, inflammatory conditions, such as provision of IL-1 with TGFβ/IL-6 in the presence of IL-2 rescued the IL-2 inhibitory effect and restored T_H17 differentiation[115]. Additional reports find that $FoxP3^+$ T_R cells can be converted directly to T_H17 producing cells with the correct inflammatory conditions[116]. The vitamin A metabolite, retinoic acid, produced by DCs within the gut, is responsible for preventing inflammation by diverting T_H17 cells into T_R[117].

A convincing piece of work proving a common lineage between T_H17 and T_R cells comes from a study using reporter mice to track the expression of FoxP3 and RORγt in T cells. The authors showed that TGFβ signaled in a concentration dependent manner to promote the expression of both FoxP3 and RORγt. FoxP3 directly bound to RORγt preventing T_H17 differentiation an effect relieved by IL-6, IL-21 and IL-23[118]. An additional report confirms the suppressive function of FoxP3 on RORγt and adds that Runx1 is critical in binding both transcriptions factors to promote T_H17 development[100].

Additional support for a T_H17/T_R shared developmental pathway was provided by identification of T cells fated to become T_R but unable to express FoxP3 due to an insertion of GFP in place of this gene. In so doing, the T_R fated cells in the absence of FoxP3 converted to RORγt expressing cells and produced IL-17[119]. Thus, in the absence of FoxP3, natural mechanisms selecting for T_R development default to T_H17, suggesting that altering thymic conditions such as IL-6 or IL-1 may select for T_H17 cells from the T_R compartment.

T_H17 associated cytokines

The T_H17 subset is associated with several other cytokines that contribute to this subset's unique function. The IL-17 family member, IL-17F, the closest related cytokine to IL-17 within this family, is also secreted by this lineage[55]. IL-17F can function similar to IL-17 by inducing production of IL-6, IL-8 and CXCL1 from *in vitro* cultured cells and administration of exogenous IL-17F during asthma induction promotes neutrophil recruitment[120,121]. However, despite similarities in protein sequence and function, IL-17F does not have complete redundancy with IL-17. For example, IL-17 knock out mice exhibit reduced arithritis[122], EAE[123] and allergic responses[124]. In fact, recent data indicates a distinct role during gut inflammation given that IL-17 knockout mice have reduced survival during DSS-induced colitis while IL-17F deficient mice are protected[125].

The IL-10 family member, IL-22, is also an established T_H17 associated cytokine. *In vitro* activation of naïve T cells in the presence of T_H17 skewing conditions, *i.e.* TGFβ and IL-6, promotes IL-22 production[126,127]. The source of IL-22 is limited to T cells, NK cells and NK T cells[128]. The receptor for IL-22 consists of the IL-10 receptor (IL-10R) β and IL-22 receptor (IL-22R)[129]. While the IL-10Rβ has broad expression, the IL-22R is limited to the skin, liver, lung and pancreas but not detected in T cells[128,130]. Thus, IL-22 promotes signaling to peripheral organs and does not directly influence T cell responses.

IL-22 is an important factor during inflammation. This cytokine in cooperation with IL-17 induces anti-microbial peptide activation to enhance clearance of bacterial infections[126]. IL-22 knockout mice indicate that this cytokine has an important role in psoriasis and hepatitis.

In the setting of dermal inflammation, IL-22 plays a pathologic role in promoting acanthosis [127]. Conversely, during acute inflammation of the liver, IL-22 is protective and reduces liver enzyme elevation[131].

IL-17: an important cytokine in immune barrier function

The IL-17 cytokine is a major player in the immune responses at epithelial surfaces. This factor is important for efficient clearance of pathogenic infections and responsible for significant autoimmune pathology.

Lung

IL-17 is critical for protecting the host from lung-associated pathogens. Studies using IL-17RA and IL-23 knockout mice highlight the importance of this cytokine in the clearance of the pathogen *Klebsiella pneumonia*[41,132]. Other bacterial infections such as *Mycobacterium tuberculosis*[133] and *Mycobacterium bovis*[134] can induce an IL-17 response that is important for preventing lethal disease. A role for IL17 has been suggested in viral infections such as in synergistic recruitment of neutrophils in human rhinovirus infection[135]. This cytokine has also been linked to opportunistic fungal infections such as the HIV related *Pneumocystis carinii*[136] and *Candida albicans*[40].

While IL-17 is considered beneficial for protecting the lungs from the constant exposure to potential pathogens, this cytokine is responsible for directing inflammation during allergic asthma. This cytokine is increased in the airways of people with asthma consistent with its inflammatory role in promoting inflammation[137]. However, its function in allergic lung inflammation is not clear. While IL-17 contributes to the recruitment of neutrophils and eosinophils to the lungs, IL-17RA knockout mice have worse T_H2 disease indicating an inhibitory/protective role in mediating T_H2 type disease[138]. Additional studies in mice indicate that the IL-17 cytokine promotes a distinct type of inflammatory lung disease. Mice that receive T_H2 skewed T cells were responsive to treatment with dexamethasone while T_H17 skewed cells induced significant airway inflammation but unresponsive to steroid treatement[139]. Thus, this subset can direct unwanted lung inflammation and may help to explain why some people are resistant to conventional asthma therapy.

Gastrointestinal tract

At this mucosal surface of the gastrointestinal tract, the body is exposed to an abundance of microorganisms, most of which are important for preventing overgrowth of pathogenic bacteria and necessary for immune homeostasis. As such, the immune system has developed mechanisms to distinguish between the harmful and the helpful residents of our gut. One indication that the T_H17 subset plays an important role at this site comes from the study that initially identified RORγt as the lineage specific transcription factor. In this study, the authors found the highest concentration of T_H17 cells were within the lamina propria of the small intestine, almost 10% of αβ T cells[98]. This finding is quite striking when considering that it was later shown that mucosal DCs were poor inducers of T_H17 cells, secondarily to the production of retinoic acid, compared to their lymph node counterparts that were much more T_H17 permissive[117]. These findings appear to be contradictory unless one considers that the T_H17 cells located in the lamina propria originate somewhere else and the retinoic acid from the mucosal DCs control these imported potentially pathogenic T cells.

There is a dynamic interaction between the commensal bacteria and the immune cells of the gut. Toll-like receptors are responsible for mediating this cross talk and instructing the immune system appropriately[140]. For example, toll-like receptor 9 detects gut flora DNA to regulate the balance between T_R and T_H17 cells of the gut. In the absence of this signaling pathway,

the T cells of the gut are overwhelmed with regulatory cells and prevent productive immune function[141]. Similarly, the native gut flora provides a balance between related IL-17 cytokines, IL-17 and IL-17E (IL-25). Pathogen-free conditions promote T_H17 overgrowth and elevated IL-23 while restoration of microorganisms signals for IL-17E to re-establish the proper balance and promote healthy intestinal homeostasis[111].

The IL-17/IL-23 axis is a critical player in the promotion of inflammatory bowl disease. Mouse models of gut inflammation were originally attributed to T_H1 effector subsets based on the observation that antibodies directed at the p40 subunit of IL-12 proved to be an effective treatment[142]. However, the identification of p40 as a shared subunit between IL-12 and IL-23 has prompted a re-examination of gut inflammation. It is now established that the IL-17 pathway is an important cytokine involved in autoimmune disease of the gut[143,144]. In human studies, it was observed that IL-23 and IL-17 are elevated in patients with IBD[145] and that treatment with anti-p40 antibodies is very effective in preventing the disease symptoms [146], most likely due to reduction in IL-23 and subsequently IL-17. The IL-23/IL-17 pathway has also been implicated in the promotion of unwanted gut inflammation with the identification of genetic variations of IL-23, STAT3 and other T_H17 associated genes linked to Crohn's disease and ulcerative colitis[147].

Skin

The dermis/epidermis is another very large barrier organ housing a distinct immune cell population. At this site, similar to the gut, microorganisms are ubiquitous along the outside border. Here too, T_H17 cells are present and help to protect this potential danger zone from pathogen entry. People with an inability to clear the opportunistic fungal infection *Candida* suffer from mucocutaneous candidiasis. A recent report indicates that peripheral blood mononuclear cells from these patients have reduced IL-17 and IL-22 mRNA and that their $CCR6^+$ $IL\text{-}17^+$ T cells are significantly reduced[148]. Mouse studies confirm the role of IL-17 in preventing this cutaneous yeast infection[40].

In addition, the T_H17 associated cytokine IL-22 has been at the forefront of autoimmune pathology of the dermis. Mouse models of psoriasis indicate that IL-22 production promotes keratinocyte survival and drives acanthosis[127]. Furthermore, it has been reported that human psoriatic lesions have increased IL-23 mRNA compared to healthy skin[149]. As one might expect, IL-17 expression from psoriatic plaques correlated with disease severity and cytokine levels normalized following treatment with cyclosporine[150].

γδ T cells as a source of IL-17 at epithelial surfaces

The γδ T cell subset makes up a small fraction of the total T cell compartment but serves a distinct conserved function. These T cells develop in the thymus, require random recombination events similar to αβ T cells but are produced in waves of subsets defined by the individual γ and δ receptors that they express. The different subsets of γδ T cells vary in function and location[151], [152]. Thus, this group of immune cells has the potential to generate great diversity in antigen recognition but somehow targets specific T cell subsets to reside in distinct locations to provide a protective function unique to the individual site. γδ T cells are not restricted to classical MHC class I or II molecules like their $CD8^+$ or $CD4^+$ αβ counterparts. A small population of γδ T cells has been shown to recognize MHC class IB antigens T10 and T22 inmice[153] and other “stress markers” such as MICA in humans through their TCR [154] or by expression of NKG2D[155,156]. Thus, γδ T cells do not require foreign antigen to induce activation and promote inflammation but rather respond to endogenous signals that indicate pathogen entry into protected sites. It may be this unconventional activation mechanism that has selected for their niche within the immune system.

γδ T cells have several mechanisms in which they contribute to immune responses. These T cells have been noted to provide common T cell cytokines such as IFNγ and IL-17 during the innate phase of inflammation. γδ T cells produce IL-17 and depending on the timing, can represent a majority of cells producing this cytokine[157]. This subset is unique in that these T cells do not require priming to allow effector function causing a delay in IL-17 production but rather can secrete this cytokine immediately upon activation. This ability to produce IL-17 is part of the thymic developmental pathway that selects the individual γδ subsets given the observation that Vγ4 thymocytes in mice can produce IL-17 while the Vγ1 cells have minimal production[158] which may be related to the affinity for ligand binding taking place within the thymus[159]. As such, γδ T cells may be an important source of the IL-17 cytokine. Given the role of IL-17 in neutrophil recruitment and other early inflammatory responses, this population of T cells being instructed in the thymus to populate host organs, especially the barrier surfaces, and having an ability to produce IL-17 immediately upon activation presents a unique model for T cell production of IL-17 and helps fine tune the immune response.

Conclusions

T cells are critical in the complex regulation of barrier immunity. These unique sites require dynamic interactions between the cells of the immune system and the surrounding environment. The immune system has evolved not only to prevent unwanted activation in response to microorganisms residing at these sites but makes use of these species to shape the mature compartment guarding the epithelial lining. A newly described helper T cell subset, T_H17, has proven to be a major player in protecting the host barrier surfaces. IL-17 has been implicated in clearance of bacterial, viral and fungal infections occurring in the lung, gut and skin as well as the pathogenic mediator of multiple mucosal and cutaneous autoimmune diseases.

The T_H17 subset, while often described as a third effector lineage, parallel to the T_H1 and T_H2 subsets, has certain characteristics that may place these cells in a class of their own. One of the most striking findings is the direct lineage relationship with T_R cells. These two subsets require a common cytokine TFGβ for lineage commitment and recent work has observed direct interactions between the lineage specific transcription factor FoxP3 and RORγt. While T_H1 and T_H2 cells function as late contributors to pathogen clearance, the T_H17 subset is implicated in neutrophil recruitment, a function that is necessary during early inflammation, before the conventional adaptive phase of the immune response. Thus, one may speculate that this subset is already pre-formed waiting for the correct signal to promote inflammation and direct efficient immune clearance and host protection. We are still adding pieces to the puzzle defining the T_H17 subset to reveal the true role of this unique and critical helper T cell subset.

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Table 1

IL-12 and IL-23 cytokines and receptors

	cytokine structure		receptor structure		T helper pathway
	unique	**common**	**unique**	**common**	
IL-12	p35	p40	IL-12Rβ2	IL-12Rβ1	T_H1 (STAT4)
IL-23	p19	p40	IL-23R	IL-12Rβ1	T_H17 (STAT3)

Table 2

Description of Helper T cell subsets

	cytokines	TF*	signaling	in vitro skewing	pathogen clearance	disease
TH1	IFNγ	T-bet eomes	STAT1 STAT4	IL-12 anti-IL4	intracellular	delayed type hypersensitivity
TH2	IL-4, IL-5, IL-13	GATA3	STAT6	IL-4 anti-IFNγ	parasites	asthma, allergy
TH17	IL-17, IL-17F, IL-22	RORγt RORα	STAT3	TGFβ/IL-6/IL-23/IL-21 anti-IL-2	extracellular	EAE, RA, IBD, psoriasis
Treg	TGFβ, IL-10	FoxP3	STAT5	TGFβ/IL-2		tumor

* transcription factors