T_H17 Cytokines in Primary Mucosal Immunity

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Abstract T helper type 17 (T_H17) cells are a recently discovered lineage of T cells that produce several effector molecules including IL-17A, IL-17F, IL-21, and IL-22. Scientific evidence to date strongly implicates that this arm of the immune system plays a critical role in mucosal immunity to many extracellular pathogens as well as coordinate adaptive immunity to some intracellular pathogens. In this paper, recent progress in our understanding of these cytokines, their cellular or sources and mechanism of their effector function in the mucosa in various infections is reviewed.

1 Introduction

CD4+ T helper cells are critical mediators of adaptive immune responses. Following interaction with antigen presenting cells, T cells receive signals by engagement of the T cell receptor (signal 1), co-stimulatory molecules (signal 2), and a complex network of cytokine signals (signal 3), then undergo activation and differentiation into effector CD4+ T cells. The critical role these cells play in mucosal immunity was clearly evidenced by the HIV epidemic that leads to the depletion of these cells from the mucosa and periphery (Kader et al. 2009; Mattapallil et al. 2005; Li et al. 2005), leading to the acquired immuno-deficiency syndrome (AIDS).

Five years after the initial clinical description of AIDS in 1981, Mossmann and Coffman described the first two CD4+ T-cells subsets based on discrete cytokine profiles (Mosmann et al. 1986). T_H1 effectors produce Interferon-gamma (IFN-γ) and regulate cellular immunity against intracellular infections, whereas T_H2 cells

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produce Interleukin (IL)-4, IL-5, and IL-13 and mediate humoral immunity against parasite infections.

However, these two T-cell subsets do not completely account for the opportunistic infections seen in congenital or acquired absence of CD4+ T-cells such as mucosal candidiasis, *Pneumocystis carinii* pneumonia, or some bacterial pneumonias. Mice deficient in T_H1 or T_H2 responses (or both) are not permissive for *P. carinii* pneumonia (Garvy et al. 1997a, b), a hallmark infection in AIDS patients with low CD4+ T-cell counts. This data suggests that other CD4+ T-cell lineages are critical for host defenses against opportunistic infections. IL-17 was cloned from CD4+ memory cells in 1993 (Rouvier et al. 1993) and Infante-Duarte demonstrated that IL-17 cells could be produced in response to bacterial lipopeptides (Infante-Duarte et al. 2000). This early study showed that IL-17 producing cells were distinct from T_H1 cells and thus provided the first evidence that T-cell derived IL-17 may have unique effector functions in host resistance against pathogens (Infante-Duarte et al. 2000). Recent evidence has shown that a major subset of cells that produce IL-17 are distinct from T_H1 and T_H2 cells and consist of a third subset of T cells referred to as T_H17 cells (Langrish et al. 2005; Harrington et al. 2005; Park et al. 2005). T_H17 cells produce the cytokines IL-17A (IL-17) (Harrington et al. 2005; Park et al. 2005) and IL-17F (Langrish et al. 2005), as well as the cytokines IL-21 (Nurieva et al. 2007; Korn et al. 2007) and IL-22 (Chung et al. 2006; Liang et al. 2006) (Fig. 1). This new T_H17 cell lineage fills in some of the missing gaps in host immunity not fully explained by the T_H1/T_H2 paradigm.

IL-17 is the prototype of T_H17 cytokines and is the best studied of the T_H17 cytokines. The first identified receptor for IL-17, IL-17RA is a Type I transmembrane protein and is ubiquitously expressed on various organs including lung, kidney, and spleen (Yao et al. 1995). This receptor can bind three members of the IL-17 family including IL-17A, the closely related IL-17F, as well as the most distally related IL-17 family member, IL-17E (Gaffen 2009). The best studied examples of cells that express the receptor for IL-17 are leukocytes, epithelial cells, mesothelial cells, vascular endothelial cells, keratinocytes, and fibroblasts. They respond to IL-17R-mediated signaling by production of granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-8 and mediate granulopoiesis, neutrophil recruitment, and inflammatory responses (Ouyang et al. 2008) (Fig. 1). Recently it has been shown that macrophages (Ishigame et al. 2009) and dendritic cells (Bai et al. 2009; Lin et al. 2009) also respond to IL-17 and produce cytokines and chemokines. Overexpression of IL-17 in mice results in massive extra-medullary hematopoiesis (Schwarzenberger et al. 1998) via the induction of G-CSF and stem cell factor (Schwarzenberger et al. 2000). IL-17RA KO mice can develop spontaneous infection with *S. aureus* infection around the eyes and nares (Schwarzenberger and Kolls 2002) and this phenotype is also observed in mice deficient in two of the three ligands for this receptor (Ishigame et al. 2009). Interestingly, this phenotype is not observed in IL-17A or IL-17F single KO mice (Ishigame et al. 2009), suggesting that these two cytokines can compensate for each other in this model. Both IL-17A and IL-17RA KO mice show susceptibility to pulmonary infection with the

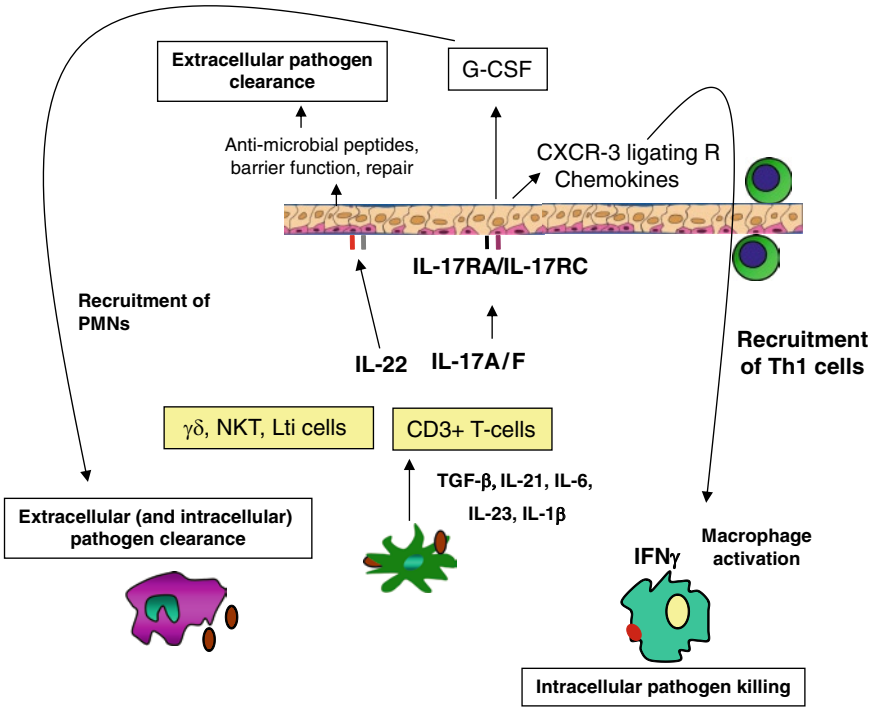

Fig. 1 Overview of Th17 cytokines and immunity at the mucosa. IL-17 and IL-22 can be produced by several immune cells found at mucosal sites in response to a variety of infectious stimuli. IL-17 and IL-22 and signal to the mucosal epithelium, where IL-17 induces G-CSF and CXC chemokine production. These two factors together result in neutrophil recruitment, which is required for bacterial and fungal clearance at mucosal sites. IL-22 and IL-17 can also augment the expression of antimicrobial peptides. IL-22, likely through the activation of STAT3 can also mediate epithelial repair, which is critical to control of extracellular bacterial pathogens. In the setting of vaccine-induced immunity, Th17 cells can induce the production of ligands for CXCR3 and augment the recruitment of IFNγ-producing Th1 cells to control intracellular pathogen growth

extracellular gram negative bacteria *K. pneumoniae,* and again with IL-17RA KO mice showing greater susceptibility than IL-17A KO mice (Aujla et al. 2008). In this model, IL-17RA KO mice fail to recruit neutrophils into the lung, in part due to reduced CXC chemokine production (Ye et al. 2001), but also reduced granulopoiesis through reduced G-CSF production (Ye et al. 2001). Through its effects on dendritic cells, IL-17 has been shown to regulate IL-12p70 production by dendritic cells, thereby regulating T_H1 response to the intracellular pathogen *Francisella tularensis* (Lin et al. 2009) and Chlamydia muridarum (Bai et al. 2009). In contrast, IL-17 appears to be dispensable for T_H1 immunity to *Mycobacterium tuberculosis and Listeria*. Thus, data strongly implicates T_H17 cytokines in host immunity to both extracellular pathogens and certain intracellular pathogens.

2 Regulation of IL-17 and IL-22 in the Lung

The differentiation of T_H17 cells is determined by the exposure to TGF-β, IL-6, and IL-21, while IL-23 further stabilizes the commitment of T_H17 cells to this lineage (reviewed in (Korn et al. 2009)). These polarizing cytokines act on newly primed cells to induce the expression of the transcription factor RORγT and RORα which induces T_H17 differentiation (Ivanov et al. 2006; Yang et al. 2008). RORγT also controls the expression of IL-23-inducible receptors on newly primed T cells, further expanding their responsiveness to IL-23 in order to sustain the T lineage-specific responses. The gp-130-Stat3 pathway is essential for expression of RORγT and T_H17 development. Recently, it has been shown that IL-21 acts downstream of these events to further amplify T_H17 cell generation in an autocrine manner. T_H17 cells also express high levels of IL-R1 (Chung et al. 2009) and TLR2 (Reynolds et al. 2010), and both IL-1β and TLR2 ligands can activate these cells to produce IL-17 and IL-22. Cellular sources of IL-17 in acute primary pulmonary infection with K. pneumoniae (Happel et al. 2003), M. tuberculosis (Lockhart et al. 2006), or Influenza (Crowe et al. 2009) include γδ T-cells, iNKT cells, and possibly LTi cells (Takatori et al. 2009). In many infections, the γδ T-cell response can be the predominant source, plus the cellular production of IL-17 by these cells is critically regulated by both IL-23 and IL-1β (Sutton et al. 2009; Martin et al. 2009). What remains unclear is the cellular sources of IL-23 and IL-1β in vivo and the γδ T-cell subsets that respond to these signals. In a pulmonary model of Aspergillus infection, Vγ1 T-cells are the dominant source of IL-17 (Romani et al. 2008). However, in a model of chronic *Bacillus subtilis* infection, the Vγ6 subset dominates (Simonian et al. 2009), while in a pulmonary model of M.bovis BCG, both Vγ6 and Vγ4 dominate (Umemura et al. 2007).

Since over-induction of T_H17 cells can impact tissue damage due to induction of inflammatory pathways, the generation of T_H17 cells is strictly regulated. For example, cytokines such as IL-27 (Batten et al. 2006; Stumhofer et al. 2006), those belonging to T_H1 (IFNγ) and T_H2 (IL-4) (Harrington et al. 2005; Park et al. 2005), and IL-2 (Laurence et al. 2007) tightly regulate the induction of T_H17 cells. Endogenous lipid mediators like prostaglandin E2 (PGE_2) released under inflammatory conditions promote T_H17 cells differentiation, suggesting that external infection-induced mediators can also influence the decision between a $T_H1/T_H2/T_H17$ and T regulatory cell responses.

Several of these T_H17 polarizing cytokines such as IL-23, TGF-β, IL-6, and IL-1β are induced in dendritic cells activated by components of microbes. Several bacteria and its products such as *Kleibsiella pneumoniae* (Happel et al. 2003, 2005), *Mycobacterium tuberculosis* (Gerosa et al. 2008; Khader et al. 2005), *Helicobacter pylori* (Mitchell et al. 2007), *Francisella tularensis* (Butchar et al. 2007), *Salmonella enterica* (Siegemund et al. 2007), and *Bordetella pertussis* (Fedele et al. 2005) induce these cytokines through TLR signaling. Further bacterial peptidoglycans can induce the generation of T_H17 cells through nucleotide oligomerization domain 2 (NOD2) receptor signaling in dendritic cells (van Beelen et al. 2007). Viruses such as Herpes simplex virus (Kim et al. 2008) and fungus and fungal components such as β-glucans (Gerosa et al. 2008; LeibundGut-Landmann et al. 2007), mannans (Saijo et al. 2010; van de Veerdonk et al. 2009), *Cryptococcus* (Siegemund and

Alber 2008), *Candida albicans* (LeibundGut-Landmann et al. 2007) and *Aspergillus fumigatus* (Zelante et al. 2007) can all induce some or all of these polarizing cytokines from dendritic cells and play a role in differentiation of T_H17 cells. These studies suggest that relative amounts of the polarizing cytokines induced by the pathogen will define the final outcome of differentiation of naïve T cells to T_H1, T_H2, T_H17, or T regulatory cells during infection.

3 T_H17 Effector Responses in the Mucosa

Human bronchial lung epithelial (HBE) cells express both IL-17RA, IL-17RC, IL-22R, and IL-10R2 and thus can respond to IL-17A, IL-17F, and IL-22 (McAllister et al. 2005; Kuestner et al. 2007; Aujla et al. 2008; Huang et al. 2007, Fig. 1). The expression of IL-17RA and IL-17RC also appears in a basolateral dominant fashion (McAllister et al. 2005; Huang et al. 2007) such that signaling only occurs in polarized epithelial cells which are exposed to ligands provided by the basolateral surface (Uesugi et al. 2001; Huang et al. 2007). Treatment of HBE cells with IL-17 induces CXC chemokines such as IL-8 (McAllister et al. 2005; Jones and Chan 2002), G-CSF (McAllister et al. 2005), and antimicrobial proteins such as human β-defensin 2 (Kao et al. 2004). IL-17 treatment also induces IL-19 (Huang et al. 2008), which may be important in regulating T_H2 responses in the mucosa. IL-17 also induced the expression of the polymeric immunoglobulin receptor (Aujla et al. 2008) and indeed T_H17 cytokines have been shown to be critical in generating mucosal IgA responses (Jaffar et al. 2009). IL-22 can activate STAT3 (Wolk et al. 2010) in both murine and human lung epithelial cells and synergizes with IL-17 to increases the expression of human antimicrobial genes such as HBD2, lipocalin (Aujla et al. 2008), and the calgranulins (Aujla et al. 2008). An activity that is unique to IL-22 and not shared by IL-17A or IL-17F in human lung epithelial cells is the fact that IL-22 can augment the clonogenic potential of these cells and accelerate wound repair (Aujla et al. 2008). In skin keratinocytes, IL-22 can also cause acanthosis and hyper-proliferation (Zheng et al. 2007). Thus, IL-22 may be important to epithelial repair in infection, as well as augmenting barrier function (Fig. 1). Neutralizing IL-22 in vivo leads to rapid dissemination of bacteria from the lung during *K. pneumoniae* infection (Aujla et al. 2008). Mucosal IL-22 administration can reduce local bacterial growth as well as prevent dissemination in this model (Aujla et al. 2008). The cellular source of IL-22 in the model is unclear, as IL-22 producing cells are present in Rag 2−/− mice but not Rag 2−/−, and γC double KO mice demonstrate that IL-22 producers are γC dependent.

4 T_H17 Cytokines and Bacterial Infections at the Mucosa

As mentioned above, early work in IL-17RA KO mice demonstrates increased sensitivity to cutaneous *S. aureus* (Schwarzenberger and Kolls 2002; Ishigame et al. 2009; Cho et al. 2010) and pulmonary *K. pneumoniae* (Ye et al. 2001) infection

and established a critical role for IL-17 in protective immunity against extracellular bacteria. Further studies show that T_H17 cells play a protective role against extracellular bacterial infections in the gut mucosa. *Citrobacter rodentum*, a naturally occurring mouse pathogen, requires the generation of IL-23-dependent T_H17 cells in the lamina propria for protection (Mangan et al. 2006; Ishigame et al. 2009). Also, IL-22 contributes to the early host defense against *C.rodentium* through the direct induction of the Reg family of antimicrobial proteins in colonic epithelial cells (Zheng et al. 2008). IL-17 signaling also appears to be host-protective in the oral mucosa, as IL-17R-deficient mice are highly susceptible to infection by the gram-negative anaerobic periodontal pathogen, *Porphyromonas gingivalis,* due to reduced neutrophil mobilization and recruitment (Yu et al. 2008).

Although these studies strongly suggest that T_H17 cytokine responses are protective against most extracellular pathogens, in some cases, T_H17 responses contribute to tissue pathology. This was first shown in response to chronic biofilm infection with *Pseudomonas aeruginosa* where IL-23 deficient mice had markedly reduced IL-17 responses and less tissue pathology in response to chronic mucoid *P. aeruginosa* infection. Furthermore, in whooping cough, an infection caused by *B. pertussis*, a gram negative extracellular bacterial infection in the respiratory tract resulted in persistent cough as one of the hallmarks of the clinical disease. Accumulating evidence suggests that the *B. pertussis* infection may bias the host response towards the production of T_H17 cytokines (Siciliano et al. 2006; Fedele et al. 2008) by preferentially inhibiting IL-12 and inducing IL-23 (Fedele et al. 2008). *B. pertussis* causes severe respiratory pathology including bronchiectasis, while *B. parapertussis* causes less severe disease pathology (Carbonetti 2007). Interestingly, *B. pertussis* lipooligosaccharide induces potent production of IL-23, IL-1β, and IL-6 from DCs and drives a more robust differentiation of naïve CD4 T cells to T_H17 cells when compared to DCs activated with LPS from *B. parapertussis* (Fedele et al. 2008). The current emerging hypothesis is that host bias towards T_H17 following *B. pertussis* infection results in inflammation and destruction of the airways, leading to bronchiectasis and persistent cough. This hypothesis is further supported by another cause of bronchiectasis, cystic fibrosis, which is highly associated with bronchiectasis due to chronic biofilm infection with *P. aeruginosa* and elevated IL-17 and IL-22 responses in draining lung lymph node cells (Aujla et al. 2008). Following *M. tuberculosis* infection, the lung inflammation was caused by repeated vaccinations with BCG and resulted in pathological consequences that were IL-17 dependent (Cruz et al. 2010). These disease models may serve as an example for the role of IL-17 in mediating pathology while conferring protection against extracellular bacterial infections in the respiratory mucosa. These findings are not confined to the lung. In *H.pylori* infection in the gastrointestinal tract, the T_H17 response may culminate in a pathogenic inflammatory response in the gut mucosa (Luzza et al. 2000; Caruso et al. 2008). In contrast, certain intracellular pathogens that may require both T_H1 cells and neutrophils for protection at mucosal sites may be dependent on IL-23/IL-17 for pathogen control. For example, the induction of IL-17 and IL-17F production following acute *Mycoplasma pneumonia*

pulmonary infection is IL-23-dependent and contributes to neutrophil recruitment and mediates protection against the infection (Wu et al. 2007). Also, infection with *Salmonella typhimurium,* which can exist as an intracellular pathogen, results in induction of IL-17 and IL-22 in the ileal mucosa. The absence of IL-17R signaling results in increased translocation of the bacteria to the mesenteric lymph nodes, reduced induction of chemokines, anti-microbials, and reduced neutrophilic recruitment to the ileal mucosa (Raffatellu et al. 2008). Using a macaque model of *Simian Immuno-deficiency Virus* (SIV) to study HIV human disease and related complications arising due to bacterial co-infections such as *S.typhimurium*, it was found that SIV co-infection selectively inhibits T_H17 responses elicited by *S. typhimurium,* probably due to depletion of $CD4^+$ T cells in the ileal mucosa (Raffatellu et al. 2008). This results in an inability of SIV-infected macaques to mount normal mucosal inflammatory response to *S. typhimurium* infection and allows dissemination of bacteria into the mesenteric lymph node. This data may provides a basis for the observation that people with HIV are at a increased risk of developing bacteremia due to dissemination of bacteria resulting from reduced CD4 T_H17 responses. HIV-infected individuals that receive anti-retroviral therapy undergo effective CD4 T-cell restoration and this is usually associated with enhanced CD4 T_H17-cell accumulation (Macal et al. 2008).

5 T_H17 Cytokines and Fungal Infections at the Mucosa

The role of T_H17 cytokines in fungal infection has been controversial, but emerging evidence in both animal and human models shows that these cytokines play a critical role in mucosal infections. Initial observations suggested that T_H17 cytokines, particularly IL-17, contribute to tissue pathology in invasive aspergillus infections in the lung, predominantly in the setting of NADPH oxidase deficiency (Romani et al. 2008). However, IL-17 and IL-17RA signaling are critical for host resistance to oro-pharyngeal candidiasis and for the expression of mouse β-defensin 3 that has anti-Candicidal activity (Conti et al. 2009). Patients with Hyper IgE syndrome (HIES) that frequently suffer from oro-pharyngeal candidiasis have mutations in STAT3 (Holland et al. 2007; Minegishi et al. 2007). They fail to generate Candida specific T_H17 cells, adding further evidence that this phenotype is tightly linked to T_H17 immunity (Milner et al. 2008; de et al. 2008). Treatment of skin keratinocytes with T_H17 cytokines markedly increases anti-Candicidal activity in vitro, while activated T-cells from HIES patients are unable to induce this anti-Candicidal activity. It has recently been shown that patients with chronic mucocutaneous candidiasis also have antibodies that can block IL-17 and/or IL-22 which may also explain the susceptibility of these patients to mucosal Candida infection (Puel et al. 2010). In respiratory tract models of fungal infections using *Pneumocytis carnii* (Rudner et al. 2007) and Aspergillus fumigatus (Werner et al. 2009), induction of IL-23 and IL-17 following pathogen challenge is protective,

since IL-23KO mice or neutralization of the IL-23/IL-17 axis resulted in impaired clearance of the pathogen.

6 T_H17 Cytokines and Viral Infection

The role of T_H17 cytokines in viral infection is a rapidly emerging area of research. *Herpes simplex virus* (HSV-1) infection of the cornea results in early induction of both IL-23 (Kim et al. 2008) and IL-17 (Molesworth-Kenyon et al. 2008). IL-17RA KO mice have also reduced early infiltration of neutrophils and corneal opacity following HSV infection (Molesworth-Kenyon et al. 2008). In contrast, IL-23KO mice have exacerbated disease and pathology possibly due to HSV increased IL-12 responses and increased IFNγ producing cells (Kim et al. 2008). In pulmonary influenza infection, IL-17R KO mice had record tissue pathology and weight loss suggesting that in this model, IL-17 contributes to tissue pathology as well (Crowe et al. 2009). In a heterotypic influenza model, CD8+ cells that produce IL-17 can mediate protection against influenza challenge (Hamada et al. 2009). Thus, the role of the IL-17 response to primary influenza infection versus heterotypic infection appears to differ. Human *rhinovirus* (HRV) infections are associated with exacerbations of asthma and chronic obstructive pulmonary infiltration. IL-17 was shown to function synergistically with HRV to induce IL-8 from epithelial cells and may contribute to the recruitment of neutrophils, immature DCs, and memory T cells to the lung; contributing to severe inflammatory profiles seen during viral exacerbations of airway disease (Wiehler and Proud 2007).

7 Conclusions

We specifically did not address the role of T_H17 cytokines vaccine-induced immunity as this has been recently reviewed (Khader et al. 2009). Current data suggests that T_H17 cells have evolved to mediate protective immunity against a variety of pathogens at different mucosal sites. Moreover, deficient T_H17 responses explain in part, the increased susceptibility to certain infections such as mucocutaneous in HIES patients and the depletion of T_H17 cells by HIV. Taken together, strategies to augment these cells or recover these cell populations will be important for improved vaccine or therapeutic efficacy in these patients. It is important to remember that IL-17 is evolutionary conserved and that the gene exists in mollusks and *Ciona intestinalis.* This predates the development of adaptive T-cell immunity, and this cytokine likely bridged innate and adaptive immunity. What remains unclear is how evolutionary pressure forced this gene to be expressed in memory CD4+ T-cells in mammals. This will be an important area of future investigation.

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