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Microbial-induced Th17: Superhero or Supervillain?

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Abstract

Th17 cells are an effector lineage of CD4 T cells that can contribute to protection against microbial pathogens and to the development of harmful autoimmune and inflammatory conditions. An increasing number of studies suggest that Th17 cells play an important protective role in mobilizing host immunity to extracellular and intracellular microbial pathogens such as *Candida* and *Salmonella*. Furthermore, the generation of Th17 cells is heavily influenced by the normal microbial flora highlighting the complex interplay between harmless microbes, pathogens, and host immunity in the regulation of pathogen-specific Th17 responses. Here, we review current understanding of microbe-induced Th17 cells in the context of infectious and inflammatory disease.

Introduction

Naïve CD4 T cells exit the thymus and, in the absence of cognate antigen, repeatedly travel through peripheral blood and lymphatic vessels (1). Initial activation of CD4 T cells occurs within secondary lymphoid organs and requires recognition of antigenic peptides presented by MHC class-II molecules on the surface of migrating or resident dendritic cells (2). Throughout the period of activation, CD4 T cells integrate signals from the T cell receptor, co-stimulatory molecules, and cytokine receptors to ultimately determine which effector capabilities will be acquired (3). Thus, antigen presenting cells and the local stimulating environment can shape the development of the effector T cell pool in an appropriate manner. In infectious disease models this plasticity allows the development of pathogen-specific effector T cells that are tailored to combat different types of microbial pathogen.

Heterogeneity within the CD4 T cell compartment was initially reported by investigators studying antibody or delayed-type hypersensitivity responses after immunization with protein or bacterial products (4–6). This led to the discovery of CD4 Th1 and Th2 populations, which represent distinct T effector lineages with differential ability to produce anti-microbial cytokines (7, 8). Th1 cells are defined by the expression of the transcription factor T-bet and secretion of IFN-γ, a cytokine that can activate macrophages to kill intracellular pathogens (9). Th2 cells are characterized by the expression of GATA-3 and production of IL-4, IL-5, and IL-13, cytokines that are critical for eradication of many extracellular parasites (10, 11). Although the definition of Th1 and Th2 provided an important conceptual framework for understanding effector CD4 T cell development, a much wider range of effector lineages is now appreciated (12). In this review we focus on the development of Th17 and how they interact with the microbes that colonize or infect the mammalian host.

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Discovery and importance of Th17 cells

Th1 and Th2 differentiation can be examined by in vitro stimulation of naïve antigen-specific CD4 T cells in the presence of IL-12 and IL-4, cytokines that are normally induced by the innate immune response to microbial ligands (13). In one particular study, it was observed that if IL-12 was replaced by *Borrelia burgdorferi* lysate, mycobacterial lysate, or IL-6, this caused the development of effector CD4 T cells that produced IL-17 (14). Furthermore, these IL-17-producing CD4 T cells co-expressed TNF-α and GM-CSF but did not express IFN-γ or IL-4, suggesting the development of an effector subset distinct from Th1 or Th2. Further evidence that IL-17-producing cells represented a novel subset came from the observation that IL-23 could promote the development of these cells (15). IL-23 is a member of the four-chain long helix bundle family of cytokines, which includes IL-6 and IL-12. IL-23 shares the p40 subunit with IL-12 but has a unique p19 subunit (16), and the discovery that models of autoimmunity were dependent on IL-23p19 rather than IL-12p35 initiated a re-evaluation of prior studies using p40-deficient animals (17, 18). The real notoriety of Th17 cells came with the discovery that IL-17-producing T cells, driven by IL-23, are the major contributors to pathogenesis of autoimmune inflammatory diseases (19). Previously Th1 cells were thought to drive autoimmunity, but many subsequent studies in mouse models and human disease brought the realization that Th17 cells represent a new and important target for therapy of psoriasis, inflammatory bowel disease, uveitis, multiple sclerosis and arthritis (20, 21). Genetic polymorphisms or deficiencies that modulate the IL-23/Th17 axis, including IL-23R, CARD9, STAT3, and AIRE result in enhanced susceptibility to inflammatory disease, and the importance of Th17-related targets in human autoimmunity is now being validated in clinical trials targeting p40, IL-17, IL-17RA and IL-23(p19).

Initiating autoimmune disease is clearly not the *raison d'etre* of IL-17-producing CD4 T cells, and a more complete picture is now emerging of how Th17 cells can contribute to host defense against microbial pathogens. (22, 23). Several studies have detected IL-17-producing CD4 T cells in diverse infectious disease models and a theme that has emerged is that this lineage contributes to host defense against extracellular microbes (24, 25). The cytokines produced by Th17 cells are well suited to this role: IL-17 and TNFα can synergize to activate epithelial cell production of anti-microbial peptides, monocyte-recruiting chemokines, while G-CSF additionally drives granulopoeisis (26). IL-22 produced by Th17 cells promotes the production of anti-microbial peptides and the proliferation of epithelial cells, which can be important for repairing damage inflicted by microbial invasion (27). GM-CSF and IL-17 also activate monocytes and neutrophils to promote phagocytosis of microbes and clearance of the infection. However, it should be emphasized that Th17 cell development is not limited to extracellular infections and these cells have been observed in numerous intracellular bacterial, viral, and extracellular parasite infection models (28–30). The potent ability of Th17 cells to elicit chemokine production in tissue sites, including Th1-recruiting chemokines such as CXCL13 makes them ideally suited as first responders during re-infection (31). In addition, IL-17 can promote IL-12 production through regulation of IL-10 in dendritic cells during infection with *Mycobacterium tuberculosis* (32) and *Francisella tularensis* (33), two intracellular infections that require both IL-17A and Th1 responses for optimal pathogen control. Thus, while Th17 cells are often associated with extracellular infection, they are a CD4 lineage that is commonly elicited in response to a wide variety of pathogens. In the latter half of this review we will focus on Th17 immunity to examples of extracellular and intracellular pathogens: *Candida* and *Salmonella*.

Th17 cell differentiation

Th17 cells were officially recognized as a distinct subset of helper T cells following seminal studies demonstrating that differentiation of IL-17 producing CD4+ T cells is dependent on STAT3 and RORγt expression, but independent of putative Th1 or Th2 transcription factors (34–36). TGFβ, IL-6, and IL-21 drive the activation of STAT3, which can subsequently activate RORγt (37, 38). TGFβ together with IL-6 and IL-1 promote expression of RORγt, and IL-6 drives the expression of IL-23R (39). IL-23 subsequently acts on these early developing Th17 cells to drive effector cell differentiation and expansion (40). Some controversy persists over the precise role of TGFβ in Th17 cell differentiation in mice and humans. TGFβ and its receptor are both required for T cell intrinsic Th17 development in mouse models of colitis and encephalomyelitis (41–43). However, high concentrations of TGFβ and IL-6 stimulate production of IL-10 and inhibit the pathogenic functions of murine Th17 cells activated in vitro (44, 45). In addition, human Th17 cell differentiation does not seem to require the addition of TGFβ, which may even suppress their development (46, 47).

Classical Toll-like receptor (TLR) activation drives production of a variety of inflammatory cytokines, but the triggering of receptors of the C-type lectin family (CLRs) seems to provide a more specific Th17-inducing signal (Figure 1). Fungal components bind to Dectin1, Dectin2, and Mincle leading to recruitment of the tyrosine kinase Syk, activation of the adaptor CARD9 and downstream signaling via NF-KB, resulting in upregulation of IL-23, IL-1, IL-6 and TNF (48–51). Humans with loss-of-function mutations in CARD9 develop chronic mucocutaneous candidiasis and have reduced Th17 cells (52). Microbial ligands that induce Th17 responses via TLRs and CLRs have primarily been defined for *Candida*, but similar ligands likely exist for bacteria and viral pathogens. Mycobacterial cord factor was recently shown to bind to Mincle and activate Syk/CARD9 signaling to promote Th17 responses in a BCG vaccine model (53), and this may explain the efficacy of heat-killed *Mycobacterium bovis* as a Th17-inducing adjuvant. Furthermore, yeast, *Mycobacterium*, and heat-killed *Streptococcus pneuomoniae* activate TLR2 to promote Th17 development (54, 55), and flagellin expression by segmented filamentous bacteria also induces intestinal Th17 responses (56). Although CLR signaling can occur independently of TLRs, collaboration between TLRs and Dectin-1 signaling enhances the production of IL-6 and IL-23 (51, 57) and conversely it has been proposed that CLR signaling modulates TLR signaling to downregulate the production of IL-12 and favor Th17-inducing cytokines such as IL-23 (49, 57, 58).

Intestinal Th17 cells – the microbiome as regulator of tolerance verse autoimmunity

It has become increasingly clear that the resident bacterial population (the ‘microbiome’) in any given individual can profoundly impact their overall health and susceptibility to inflammatory and infectious disease (59). The microbiome is comprised of bacterial, viral, and eukaryote species that continuously colonize host mucosal and epithelial surfaces. While these microbes can be found associated with the skin, lung, genital, and oral cavity, we will focus our discussion here on the intestinal tract (60). It has long been considered that tolerance is induced to these constituent microbes, allowing them to reside in these various tissue sites without inducing inflammation (61). In fact, Inflammatory Bowel Disease (IBD) most likely arises as a consequence of developing an inappropriate immune response against host commensal flora (62). However, it is becoming increasingly clear that sub-clinical responses induced against microbes residing in the gut may also have far-reaching consequences throughout the body.

Endogenous microbial flora play a major role in the differentiation of Th17 cells and regulatory T cells in the small intestine under steady-state conditions, and antibiotic-treatment or the complete absence of bacterial flora reduces the number of Th17 cells in the gut (63). Indeed, re-colonization of the intestine with *Clostridia*-related commensal species, and segmented filamentous bacteria (SFB) in particular, is sufficient to induce CD4 T cells that produce IL-17 and IL-22, as well as other CD4 T helper lineages (64, 65). SFB are gram-positive anaerobes that are normally tightly attached to epithelial cells and are highly dependent on the host for many essential nutrients (66, 67). It is now apparent that intestinal flora, and especially SFB, can strongly modulate the induction of Th17 responses throughout the body, and thereby regulate the susceptibility of mice to arthritis (68), colitis (69, 70), diabetes (71), and EAE (72).

The specific bacterial products that drive homeostatic intestinal Th17 differentiation have not been well defined, however, flagellins are attractive candidates since they are expressed by SFB, recognized by TLR5-expressing intestinal phagocytes, induce IL-23 from $CD103^+$ dendritic cells, and drive Th17 responses to enteric pathogens (56, 66, 67, 73, 74). Recent data suggest that IL-1β production by intestinal macrophages is induced by TLR recognition of microbial flora and that IL-1R signaling on intestinal T cells is required for homeostatic differentiation of intestinal Th17 cells (75). It remains to be determined how local production of IL-1β in the lamina propria directly affects naïve T cell differentiation within secondary lymphoid tissues, but it seems possible that Peyer's patches could play a major role, since naïve CD4 T cells in this location are closely associated with SFB and lamina propria macrophages (64).

It is possible that the development of inflammatory Th17 responses to enteric pathogens differs substantially from the homeostatic development of Th17 cells in response to microbial flora. While IL-6 is reported to play a key role in Th17 development, this cytokine does not seem to be required for intestinal Th17 development under steady state conditions (75–77). Th17 cells generated in the presence of IL-23 or IL-6/TGF-beta develop different functional and pathogenic potential in autoimmune models (40, 45). Furthermore, recent data show that human Th17 cells induced by *Candida albicans* or *Staphylococcus aureus* have differential capacity to produce IFN-γ or IL-10 (78). Therefore, a degree of functional heterogeneity may exist between steady state Th17 and pathogen-specific Th17 cells, between Th17 cells induced by different classes of microbial pathogens, or between Th17 cells that are elicited at different anatomical sites. To complicate matters further, enteric pathogens such as *Salmonella* and *Citrobacter* can also modify the composition of the microbial flora (79, 80), and as a result may indirectly modulate steady state development of Th17 cells.

Th17 cells in defense against *Candida*

A requirement for IL-17 has been demonstrated in host resistance to extracellular pathogens such as *Candida albicans* (81). Mice with a deficiency in IL-17A or IL-17RA are more susceptible to intravenous *Candida* infection (82, 83), and IL-17RA- and IL-17RC-deficient mice are unable to clear oral infection with *C. albicans* (84, 85). In contrast, neither IL-17F or IL-22 are essential for host resistance to *Candida* infection (83, 84, 86). In the oral infection model, mice lacking IL-17RA signaling have decreased neutrophil infiltration (84), confirming a key role for IL-17A in recruiting phagocytes to the local site of infection. *Candida*-infected IL-23-, or IL-17RA-deficient mice also have reduced production of anti-microbial proteins, and saliva from these mice show reduced bactericidal activity (84). Thus, IL-17 plays an indirect role in defense against extracellular pathogens by recruiting phagocytes and inducing anti-microbial peptides at the site of infection. A key role for IL-17 in fungal defense has also been documented by genetic analysis of patients with increased

susceptibility to chronic mucocutaneous candidiasis (CMC) (87). Patients with autosomal recessive IL-17RA or autosomal dominant IL-17F deficiency experience recurrent candida infections of the oral and genital mucosa (88). Similarly, patients with a gain of function mutation in STAT1 have increased responses to cytokines that impair the development of Th17 cells, and as a result are highly susceptible to CMC (89). Interestingly, patients with IL-17F deficiency produce a mutant IL-17F that can still form a heterodimer with IL-17A or wild-type IL-17F but with reduced functional activity (88), thus IL-17A rather than IL-17F may be critical for defense against *Candida* in humans. Together, these murine and human studies demonstrate that production of IL-17 at the site of fungal infection plays a key role in the resolution or susceptibility to disease. Studies with other many other microbes have established the paradigm that Th17 cytokines play a major role in mobilizing local host defense against infection with extracellular pathogens (23, 90).

Th17 cells in defense against *Salmonella*

Salmonella is a facultative intracellular pathogen that causes serious gastrointestinal and systemic infections (91). Like other intra-macrophage pathogens, Th1 cells are essential for protective immunity and mice with a genetic deficiency in T-bet or IFN-γ are unable to resolve *Salmonella* infection (92, 93). However, recent data demonstrate that Th17 cells develop during *Salmonella* infection and play an important role in host defense in the intestine.

Th17 cells can be induced when mice are infected with *Salmonella* via non-physiological routes, however, the population is typically small, and mice lacking IL-23R p19 or IL-17A experience only a minor delay in resolving primary infection (94, 95). In contrast, there is accumulating evidence that Th17 cells and associated cytokines play an important role in resistance to mucosal *Salmonella* infections (91, 96). Using a ligated loop model in rhesus macaques, it was noted that IL-22, IL-17, and IL-17 responsive genes were rapidly transcribed after *Salmonella* infection and prior depletion of CD4 T cells by SIV infection reduced this response considerably (97). SIV infection also reduced IL-17-producing CD4 T cells in the lamina propria and correlated with enhanced dissemination of *Salmonella* to mesenteric lymph nodes (97). This is an important finding since patients with HIV are highly susceptible to disseminated *Salmonella* infections and the loss of protective Th17 cells in the intestine may explain this susceptibility (96, 98). Consistent with this idea, patients with a primary genetic deficiency in Th17 development are also highly susceptible to disseminated *Salmonella* infections (96).

Given the rapid induction of Th17 cytokines in the ligated-loop model it is due to *Salmonella*-specific Th17 cells. It is more likely that intestinal Th17 cells are activated in a non-specific fashion in response to IL-1 or other inflammatory cytokines. Indeed, the early Th17 response to intestinal *Salmonella* infection requires expression of Myd88 and IL-1R (99). However, Nod1, Nod2, and the production of IL-6 can also cause rapid innate activation of Th17 cells (100), although IL-6 was dispensable in a different infection model (101). Non-cognate induction of effector T cells blurs the lines between innate and adaptive immunity to infection but is a common feature of immunity to *Salmonella*. Indeed, effector Th1 CD4 and CD8 T cells in *Salmonella*-infected mice rapidly secrete IFN-γ in response to innate stimuli (102, 103).

This rapid innate response does not mean that *Salmonella*-specific Th17 cells cannot also contribute to immunity at mucosal surfaces. A recent report documented simultaneous development of *Salmonella*-specific Th17 and Th1 cells in the intestine and spleen respectively after oral infection (74). These anatomically segregated Th17 and Th1 responses targeted different *Salmonella* antigens that were highly expressed in each tissue.

The factors responsible for driving *Salmonella*-specific Th17 cell development in the intestine have not yet been clearly defined but previous reports show that dendritic cells conditioned with *Salmonella* direct Th17 and Th1 development in vitro (104, 105), and recent data show an intriguing role for B cell-derived IL-6 in the generation of Th17 cells (106). Interestingly, *Salmonella*-specific Th17 cells recognize *Salmonella* flagellin (74), an antigen that has intrinsic stimulatory capabilities and induces IL-1 and IL-6 production (107, 108). It is therefore possible that innate recognition of flagellin via TLR5 and/or NLRC4 is responsible for driving *Salmonella*-specific Th17 development in the intestine during infection.

As noted above, intestinal Th17 cells play a key role in early protective immunity by limiting dissemination of *Salmonella* to the mesenteric lymph node (97). However, it should be emphasized that there is yet no evidence for Th17 cells playing a protective role after *Salmonella* have spread to systemic tissues. Instead, intestinal Th17 cells prevent *Salmonella* dissemination using similar mechanisms implicated in immunity to extracellular bacteria. Intestinal epithelial cells can respond to local IL-17 and IL-22 in vitro by increasing production of anti-microbial proteins and chemokines during *Salmonella* infection (97, 109). These include anti-bacterial proteins such as, iNOS, mucin, calprotectin, RegIIIγ, and lipocalin-2, which can directly or indirectly limit bacterial growth (110). The chemokine CCL20 is also prominently produced in response to IL-17 and IL-22 and can recruit immature $CCR6^+$ dendritic cells and presumably initiate adaptive responses (109, 111). The production of G-CSF and CXC chemokines also recruits neutrophils to the intestine and these engulf bacteria that have crossed the epithelial barrier (112).

Thus, the mechanism of Th17 defense against *Salmonella* penetration is similar to defense against extracellular bacteria. Indeed, while it is can be conceptually appealing to think of Th17 cells protecting against extracellular organisms and Th1 cells combating intracellular organisms, data from the *Salmonella* model suggest that Th17 cells can be highly active against intracellular organisms during the initial phase of trans-epithelial entry. Since most other microbial pathogens also have some degree of variation in life cycle stage or tissue tropism, a heterogenous T effector response is probably the norm rather than the exception.

Conclusions

We have discussed the role of microbes in the differentiation of Th17 cells in both autoimmune and infectious disease models and have focused on *Candida* and *Salmonella* as two examples of pathogens that induce Th17 responses. It is apparent that the differentiation of Th17 cells is surprisingly complex, involving the elicitation of multiple cytokines, most likely as a result of several microbial ligands activating receptors on DCs or other innate cells. There is also a degree of functional heterogeneity within the Th17 lineage that may mean that this lineage is adapted to fit the immune response to different pathogens or immunity at different anatomical sites. Greater understanding of how this complexity and functional heterogeneity can impact the specific effector response against different classes of pathogen is now required. Furthermore, the tripartite interactions that occur between host, microbiome, and microbial pathogen, have not been examined in any depth, and much greater understanding of how communication flows between each of these players in the regulation of Th17 cell development should be forthcoming. However, this may be challenging technically since it will likely require the definition of endogenous flora as a variable within many current experimental systems. Furthermore, the specific crosstalk that has evolved between pathogenic and non-pathogen organisms in the induction of human Th17 cells may be difficult to replicate in animal models unless greater attention is paid to the use of natural animal pathogens and routes of infection. However, greater understanding

of these issues may lead to the development of vaccines and therapeutics for important infectious and inflammatory disease.

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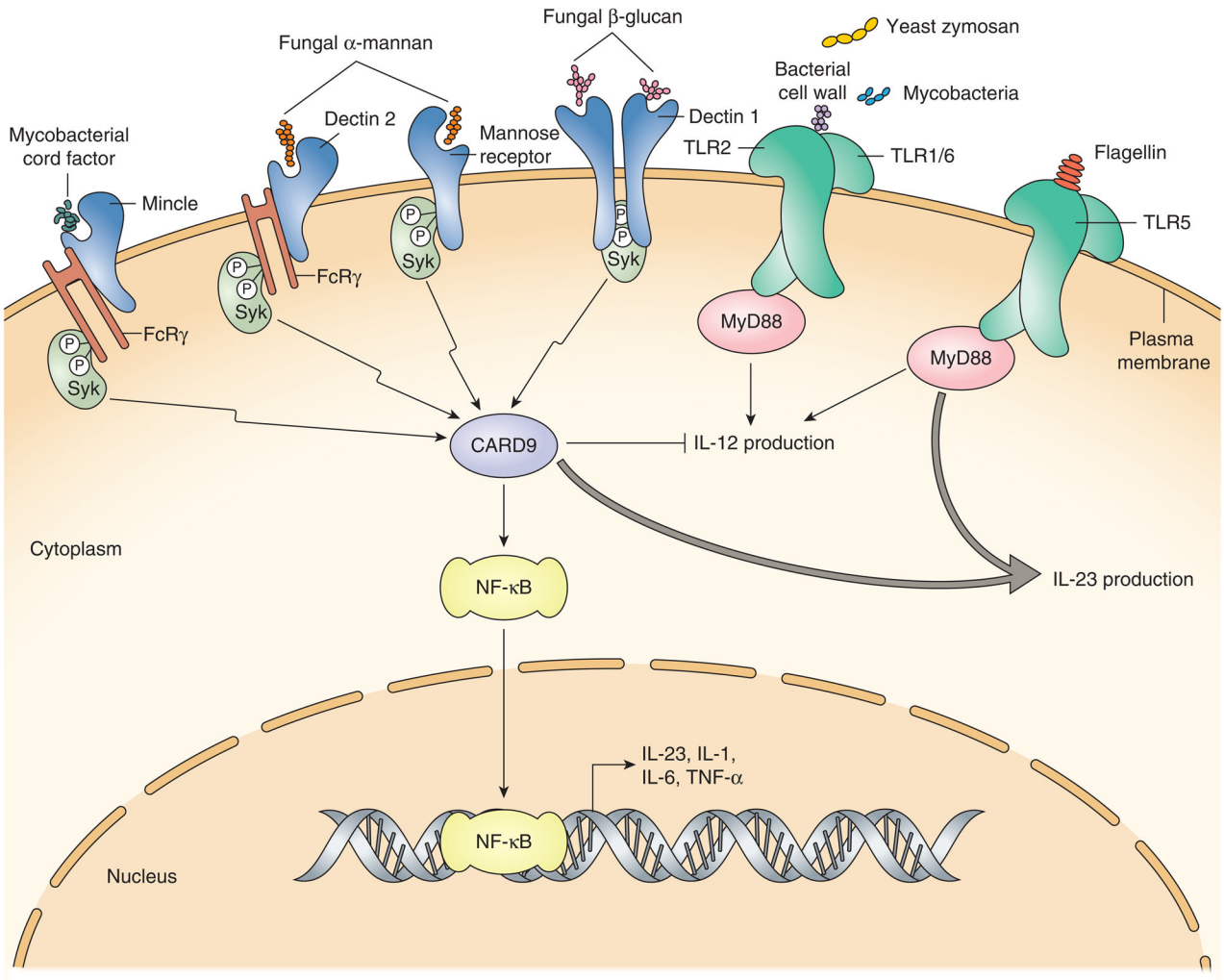

Figure 1. Induction of Th17-promoting cytokines by microbial products

C-type lectins Mincle, Dectin 1 and Dectin 2 as well as Mannose receptor are expressed on dendritic cells and macrophages and recognize fungal and mycobacterial components to activate Syk kinase and the CARD9 adaptor, leading to production of inflammatory cytokines that promote Th17 development in naïve T cells. Toll-like receptors (TLR) also recognize microbial products and induce production of both Th17 and Th1-promoting cytokines including IL-23 and IL-12. CLEC signaling modulates TLR signaling to downregulate Th1-promoting and favor Th17-promoting conditions, thus CLECs and TLRs co-operate to provide fine-tuning in the type of T helper response elicited.