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IL-17 and anti-bacterial immunity: protection versus tissue damage

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1 Introduction

IL-17 can impact health in a variety of ways. It is protective for some pathogens but it is also associated with tissue damaging inflammation. By examining the role of IL-17 in a variety of bacterial infections the mechanisms by which this cytokine mediates both protection and damage can be dissected. A key element in understanding the role of this cytokine is determining where and when it is acting. Dissecting its essential protective role from its immunopathologic role will allow for improved intervention in both acute and chronic disease.

The interaction between IL-17 and bacteria occurs most often at a mucosal surface. In the simplest example: an extracellular bacteria invades the host, triggers expression of IL-23 via pathogen pattern recognition receptors and this cytokine drives release of IL-17 from rapidly responding cells such as γδ T cells expressing IL-23R. This IL-17 then acts upon tissue cells to release IL-8, which in turn recruits neutrophils that then control bacteria. A more complex interaction between the host and its bacterial colonists is that seen between the gut flora and the mucosal immune system of this tissue. In this case there are extensive and varied populations of bacteria in the gut the presence and composition of which have a profound impact on the population of IL-17 producing cells. In addition to both protective and homeostatic responses to bacteria, IL-17 and the cells that produce it appear to be involved in priming and exacerbating inflammatory immune responses in lungs, brain, peritoneum and gut. Thus IL-17 producing cells can be found in normal non-inflamed tissue, they can promote tissue inflammation and an increase in the frequency of IL-17 producing cells is associated with increased pathologic consequences. While these effects appear counter to the health of the host they are probably based in the importance of limiting the dissemination of extracellular bacteria as abscesses and granuloma formation can be functionally altered in the absence of IL-17.

By dissecting the pathways by which IL-17 mediates its protective and pathologic effects and by integrating this into the impact of the gut flora on the establishment of IL-17-producing populations we will be better able to modulate this cytokine to our benefit. The expression of either acute effector function or as a mediator of chronic tissue damage by IL-17 is illustrated both in bacterial infections and by fungal infections.

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2. Acute effector function

IL-17 can be produced rapidly in response to bacterial challenge. Indeed, it appears to be one of the more basic responses as oysters rapidly produce an IL-17 homologue from their hemocytes in response to bacterial challenge [1]. NKT cells are also potent producers of IL-17 [2] as are γδ T cells [3]. In an animal model wherein *Escherichia coli* is administered intraperitoneally IL-17 is rapidly induced, this cytokine is derived from γδ T cells and results in neutrophil recruitment. When IL-17 is blocked there is reduced neutrophil recruitment and reduced bacterial clearance [4]. In this model, the absence of the Toll-like receptor (TLR) 4 results in reduced IL-23 expression and reduced IL-17 production by γδ T cells [4, 5]. Interestingly, the γδ T cells that respond are resident within the peritoneum and respond very rapidly in an IL-23, tyk2 dependent manner [5]. Similarly, systemic infection with *Listeria monocytogenes* induces rapid expression of IL-17A in the liver and in the absence of this response (IL-17A deficient mice) there is a loss of protection. In this model again the major producers of IL-17 are γδ T cells [6]. In an interesting recent paper the ability of antigen-naive γδ T cells to produce IL-17 upon direct stimulation of the T cell receptor was demonstrated, the authors took this to suggest a critical role for these cells in acute inflammatory responses to novel antigens [2].

Even while IL-17 may be essential to controlling rapidly growing bacteria it can have a pathologic role in this type of infection. For example, when *Staphylococcus aureus* or *Bacteroides fragilis* are injected intraperitoneally into mice they generate abscesses that contribute to morbidity. These abscesses have IL-17-producing CD4 T cells in their periphery and anti-IL-17 ablates formation of these abscesses [7]. While these abscesses are detrimental to health it is also the case that individuals with a STAT3 mutation that impacts induction of the transcriptional regulator RORγt are less able to generate IL-17 producing cells and have an increased susceptibility to *Staph. aureus* [8]. These data suggest that while IL-17 must act rapidly to generate acute inflammation it must be controlled in order to ensure tissue viability.

3. Gut mucosa

The balance between protection and pathologic consequences can be seen in the association between *Helicobacter pylori*, IL-17 and damage to gastric mucosa that leads to ulceration. In this interaction IL-17A mRNA and protein are associated with *H. pylori* lesional sites from human gastric biopsies [9–11]. When biopsies are cultured in vitro and IL-17 activity is blocked there is a reduction in IL-8 gene expression and this suggests that IL-17 may be driving this inflammatory mediator [9]. In these biopsies both CD4 and CD8 T cell are the source of IL-17 and IL-23 is present at high levels in the lesional tissue compared to the surrounding tissue; when IL-23 is blocked STAT3 and IL-17 expression are reduced [12]. These observations mirror those showing that IL-17 is associated with inflammatory bowel disease (IBD). Thus, in IBD patients there is a higher level of IL-17 in the mucosa and serum that is not seen in controls [13] and there is reduced colitis in animal models where IL-17 activity is reduced [14, 15]. In human genome wide screens, polymorphisms in the IL23 gene are strongly associated with IBD [16] however IL-17 polymorphisms associated auto-immunity in the gut may yet be identified. Further, these cytokines may be acting independently. In a recent insightful paper using a murine model of IBD it appears that IL-23 rather than acting through induction of IL-17, acts to overcome the natural regulation of inflammatory responses [17].

In an acute model of gut infection, *Citrobacter rodentium* induces an acute but self-limiting diarrheal disease wherein both B and T cells mediate protection [18]. Following a high oral dose of this pathogen, the colon becomes inflamed and a high frequency of IL-17-producing

CD4 T cells occurs in the lamina propria [19]. In a re-challenge model, previously infected mice are able to clear bacteria rapidly and this is associated with increased IgG, IFNγ IL-2 and IL-17 [20]. Finally, in a model where prolonged diarrheal disease occurs there is increased IL-17 [21]. As for IBD however, a causative role for IL-17 in either protection or pathogenesis has not been established in this model. In particular, while the absence of IL-23 results in reduced inflammation and reduced bacterial clearance, the IL-17 CD4 population remains identical to the wild type mice [19]. These data suggest that either IL-23 is required at the lesional site to drive IL-17 production (thus IL-17 producing cells may be detected but may not be active at the site due to lack of IL-23) or there is a need for IL-23 to release the regulatory activity to allow the immune response to inflame the tissue but at the same time limit bacterial growth. One mucosal site where IL-17 is known to be protective is the buccal cavity during *Porphyromonas gingivalis* infection as in the absence of IL-17RA there is reduced neutrophil recruitment and increased bone loss [22, 23]. Finally, IL-17-producing CD4 T cells appear to be required to retain bacteria within the gut; thus *Salmonella typhimurium* is normally localized in the cecum, however in the absence of CD4 T cells making IL-17 there is a greater propensity to disseminate from this tissue [24, 25]. Determining the role of IL-17 and IL-22 in IL-23-dependent disease development is key to identifying targets for intervention.

The impact of the commensal gut flora on Th17 populations in the gut has been the subject of much recent literature and is fascinating. It seems as if the population composition of the flora and the Th17 population in the lamina propria are inextricably linked. In the ileum and the colon there is a high number of IL-17 producing cells [26] and it appears that bacterial products can drive both induction and regulate this population. Thus, ATP from bacterial sources drives expansion of the Th17 population and can induce colitis [27] while polysaccharide A derived from *Bacteroides fragilis* promotes IL-10 production which limits this population and *Helicobacter hepaticus* induced colitis [28]. In contrast, the absence of commensal bacteria (as seen in germ-free mice) results in an increased Th17 population compared to normally colonized mice, as it appears that commensal induction of IL-25 by intestinal epithelial cells limits Th17 expansion by limiting IL-23 [29]. Finally, the bacterial species within the commensal population also impact the Th17 population as ablation of populations by antibiotic treatment or the delivery of specific populations to the naive host results in loss or gain of the Th17 population; cytophaga-flaobacter-bacteroidetes bacteria are the defining population [30]. Importantly, TLR signaling, IL-23 and IL-21 were not required but TGFβ activation was [30]. It will be very important to determine how different commensal population dynamics influence inflammatory disease development.

4. Lung mucosa

The lung is a major mucosal organ where bacteria interact with the host immune system. In this organ *Bordetella pertussis* and *Bordetella bronchiseptica* induce strong IL-17 responses [31, 32] and the IL-17 response is protective in mice that have been previously exposed to the pathogen [33]. *Mycoplasma pneumoniae* also induces both IL-23 in alveolar macrophages and IL-17 production in CD4 T cells; blocking IL-23 in this model leads to reduced IL-17, and a trend toward reduced neutrophil influx and bacterial clearance [34]. *Pseudomonas aeruginosa* induces IL-17 and patients with cystic fibrosis have higher serum levels of IL-17 when experiencing an infection with this pathogen [35]. In a murine model of *P. aeruginosa*, absence of IL-23 results in reduced IL-17 and lower inflammation but is not required to control dissemination [36, 37]. In mycobacterial infection a high dose of bacteria delivered to the lung results in an IL-17 response derived from γδ T cells and when this response is blocked by antibody there is a reduction in neutrophil recruitment [38]. During a low dose challenge a later γδ and antigen-specific IAb-restricted IL-17 response can be detected [39, 40] and both mice and humans infected with mycobacteria have IL-17

producing T cells [41–43]. The majority of the IL-17 response in the lung following mycobacterial infection is IL-23 dependent as in the absence of this cytokine, IL-17 mRNA expression and the IAb-restricted response is severely curtailed [40]. There is however an IL-17 response in IL-12p40 deficient mice [44]. In the absence of IL-23, and thereby much of the IL-17 response, initial control of bacterial growth is not impacted however, modest changes in the nature of the granulomatous response are seen [40]. This is in keeping with the altered granulomatous response seen in mycobacterially infected γδ T cell deficient mice [45]. As antigen exposure increases in mycobacterially infected hosts, there is an additional role for IL-23 and IL-17 in the generation of tissue damage as in the absence of either of these cytokines damaging immunopathologic consequences are reduced (A. Cruz et al pers. comm.). In addition, in a subunit vaccine model of protection against *Mycobacterium tuberculosis*, expression of IL-17 in vaccinated mice correlates with expression of chemokines in the lung; in the absence of this response accelerated accumulation of protective memory cells does not occur [43]. Also, in mice that are protected against infection in a whole cell wall pertussis vaccine model, anti-IL-17 treatment reduces protection [33]. Thus, while IL-17 is associated with pathogenicity it may also be important for vaccine-induced protection.

The role of IL-17 in the response of mice infected with the extracellular bacteria *Klebsiella pneumoniae* has been most extensively studied and it is in this model wherein IL-17 is clearly protective. Infection with this pathogen results in IL-17 induction and in the absence of the IL-17R mice are more susceptible in that they have a delayed recruitment of neutrophils and greater dissemination of bacteria [46]. Over-expression of IL-17 in this model results in improved neutrophil recruitment and protection [47]. It appears that ligation of TLR4 is required for IL-23 induction and subsequent IL-17 production in both CD4 and CD8 T cells following *K. pneumoniae* infection [48]. *K. pneumoniae* provides an interesting model as both IFNγ and IL-17 are protective. Interestingly, when IL-12p40 deficient mice are infected they are extremely susceptible as they lack both IFNγ and IL-17, however when IL-12p35 deficient (i.e. lack IL-12p70) or IL-23 p19 deficient mice are infected, the mice remain susceptible but to a lesser degree than the IL-12p40 deficient mice [49]. This is in contrast to the mycobacterial model wherein loss of IL-12p40 does not completely ablate IL-17 production [50] but absence of IL-23 results in a substantial drop in IL-17 without major consequences [40]. In the absence of IL-12p35, mice are less susceptible to mycobacterial infection than IL-12p40 but the protection and IFNγ production seen in these mice is due to IL-23 [40]. The relative impact of IL-23 on IL-17 induction in different bacterial models is of interest and determining the importance of both cytokines will be of importance when delivering anti-IL-23 treatments.

5. Conclusion

IL-17 has likely been retained as a key element in our defense mechanisms as an acute effector molecule capable of bringing in neutrophils to limit rapid bacterial expansion. It also acts to generate cellular foci to contain both acute and chronically infective bacteria. It has a critical role in defense against several pathogens although it plays subtle and less critical roles in others. Although associated with many chronic inflammatory diseases it is not the proven mediator whereas the role of IL-23 in these diseases is more clearly defined. In order to intervene in chronic inflammatory diseases and avoid inadvertent reactivation of infectious disease we need to define when and if IL-17 is the critical agent in both protection and pathogenesis and whether it or IL-23 is the primary mediator.

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