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Th17 Cell Induction and Immune Regulatory Effects

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The T help 1 (Th1) and Th2 cell classification have provided the framework for understanding $CD4^+$ T cell biology and the interplay between innate and adaptive immunity for almost two decades. Recent studies have defined a previously unknown arm of the $CD4^+$ T cell effector response, the Th17 lineage, which promises to change our understanding of immune regulation, immune pathogenesis and host defense. The factors that specify differentiation of IL-17 producing effector T cells from naïve T cell precursors are being rapidly discovered and are providing insights into mechanisms by which signals from cells of the innate immune system guide alternative pathways of Th1, Th2, or Th17 development. In this review, we will focus on recent studies that have identified new subsets of Th cells, new insights regarding the induced generation and differentiation mechanisms of Th17 cells and immune regulatory effects.

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$CD4^+$ T cells can be divided into different subsets with distinct differentiation profiles and functional characteristics (Castellino and Germain, 2006). The best-characterized subsets are T help cell 1 (Th1), Th2, and regulatory T cells (Treg), whose development is specified by the transcription factors T-bet (also known as Tbx-21; a master regulator of Th1 differentiation), A master regulator of Th2 differentiation (GATA-3), and Forkhead box protein 3 (Foxp3), respectively (Wraith et al., 2004; Castellino and Germain, 2006). A unique subset characterized by production of interleukin 17 (IL-17) and crucially involved in the pathogenesis of certain autoimmune diseases such as rheumatoid arthritis and experimental autoimmune encephalomyelitis (EAE) as well as allergen-specific responses was recently identified (Harrington et al., 2006). This promises to change our understanding of immune regulation, immune pathogenesis and host defense. The factors that specify differentiation of IL-17 producing effector T cells (Th17) from naive T cell precursors are being rapidly discovered and are providing insights into mechanisms by which signals from cells of the innate immune system guide alternative pathways of Th1, Th2, or Th17 development (Harrington et al., 2006; Tato et al., 2006).

New $CD4^+$ Effector T Cell: Th17 Cells

Classically, effector $CD4^+$ T cells have been divided into two distinct lineages on the basis of their cytokine production profile: cells of the Th1 lineage, which evolved to enhance eradication of intracellular pathogens (e.g., intracellular bacteria, viruses, and some protozoa), are potent activator of cell-mediated immunity; and cells of the Th2 lineage, which evolved to enhance elimination of parasitic infections (e.g., helminths), are characterized by production of interleukin IL-4, IL-5, and IL-13, which are potent activators of B-cell immunoglobulin IgE production, cosinophil recruitment and mucosal expulsion mechanisms (mucous production and hypermotility) (Harrington et al., 2005; Park et al., 2005). Immune pathogenesis that results from dysregulated Th1 responses to self or commensal floral antigens can promote tissue destruction and chronic inflammation, whereas dysregulated Th2 responses can cause allergy and asthma (Harrington et al., 2005). Recent studies discovered an IL-23-dependent T cell population that produces IL-17 but not IFN-γ or IL-4, which suggested that there is indeed an additional T cell subset (Castellino and Germain, 2006). These findings have indicated a greater diversification of the $CD4^+$ T cell effector repertoire than that encompassed by the Th1 and Th2 lineage (Harrington et al., 2006). This knowledge has forced a

Abbreviations: CTLA-8, cytolytic T-lympnocyte-associated antigen 8; DCs, dendritic cells; EAE, experimental autoimmune encephalomyelitis; Foxp3, forkhead/winged-helix family of transcription factors 3; GATA3, A master regulator of Th2 differentiation; ICOS, inducible costimulator; IL-17, interleukin 17; Ig, immunoglobulin; IFN, interferon; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NFAT, nucleus factor of activating T cell; STAT1, signal transducer and activator of transcription 1; T-bet, encoded by the Tbx21 gene a master regulator of Th1 differentiation; TCR, T cell receptor; TGF-β, transforming growth factor-β; Th1, T help cell 1; Th17, IL-17 producing effector T cells; TNFα, tumor necrosis factor α; TLR2, toll-like receptor 2; Treg, regulatory T cells

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reassessment of the Th1 lineage in autoimmunity. New studies that link the cytokines transforming growth factor (TGF)-β, IL-23 and IL-17 to immune pathogenesis previously attributed to the Th1 lineage have led to the delineation of a new effector $CD4^+$ T cells, referred to as Th17, and IL-17 is its major effect factor that is significantly related to Th17 cell immune regulatory effects (Harrington et al., 2005, 2006; Weaver et al., 2006).

IL-17, the prototypic T-cell derived cytokine, belongs to a family containing six members (Infante-Duarte et al., 2000; Li et al., 2000). To date, six IL-17 family ligands (IL-17A-F) and five receptors (IL-17RA-IL-17RD and SEF) have been identified (Moseley et al., 2003). By far the best characterized is IL-17 (cytolytic T-lymphnocyte-associated antigen 8; CTLA-8 or IL-17A), which is secreted primarily by $CD4^+$ T helper cells, Th17 cells (Harrington et al., 2006; Weaver et al., 2006). Although produced by the adaptive arm of the immune system, IL-17 functions as a classic effector of innate immunity, similar to IL-1β, tumor necrosis factor (TNF) α or Toll-like receptor agonists such as lipopolysaccharide (LPS) (Harrington et al., 2005; Schnyder et al., 2005; Guangwei et al., 2006b). Specifically, IL-17 induces expression of many innate inflammatory mediators, including IL-6, acute phase proteins, granulocyte-colony stimulating factor (G-CSF) and prostaglandin E2 (Komiyama et al., 2006). IL-17 also synergizes potently with inflammatory cytokines such as TNFα, amplifying its effects by orders of magnitude (McAllister et al., 2005; Komiyama et al., 2006). Thus, IL-17 is a mean by which the adaptive immune system communicates with the innate immune system to promote inflammation. But, like most inflammatory cytokines, IL-17 plays opposing roles in vivo, depending on disease context (Harrington et al., 2005, 2006).

Th17 Cell Induced Generation and Differentiation

But, how to generate and induce Th17 cells differentiation and to keep Th17 cells survival? Extensive effort has concentrated on IL-23, which seems to be an essential survival factor for Th17 cells, although IL-23 is not required during their differentiation (Khader et al., 2005; Yen et al., 2006). This is an interesting situation that is reminiscent of the dependence of regulatory T cells on IL-2. IL-2-deficient mice have greatly reduced numbers of Foxp3 expressing regulatory T cells in the periphery, but these are generated in normal numbers in the thymus (Bluestone and Tang, 2005; Walther et al., 2005). Similarly, mice lacking IL-23 have almost no Th17 cells, suggesting that even if the cells are generated normally in the absence of IL-23, they do not seem to expand or survive without this cytokine (Iwakura and Ishigame, 2006). Because IL-23 is released in response to inflammatory danger signals and is not constitutively produced like other T cell survival factors, such as IL-7 and IL-15, the prediction is that the long-term survival of Th17 cells could depend on chronic inflammation. Thus, in normal conditions, Th17 cells might be obligatory effector cells that never differentiate to a memory state. This need further experiment to confirm.

To further explore the clinical efficacy of targeting the IL-23 immune pathway, researchers generated anti-IL-23p19-specific antibodies and tested to determine whether blocking IL-23 function can inhibit EAE, a preclinical animal model of human multiple sclerosis (Hofstetter et al., 2005; Vaknin-Dembinsky et al., 2006). Anti-IL-23p19 treatment reduced the serum level of IL-17 as well as central nervous system expression of interferon (IFN)-γ, IL-17, IL-6, and TNFmRNA (Zhang et al., 2003; Chen et al., 2006). In addition, therapeutic treatment with anti-IL-23p19 during active disease inhibited proteolipid protein (PLP) epitope spreading and prevented subsequent disease relapse (Chen et al., 2006). Thus, therapeutic targeting of IL-23 effectively inhibited multiple inflammatory pathways that are critical for driving central nervous system autoimmune inflammation. It is now clear that IL-23 has key roles in autoimmune destruction in experimental allergic encephalomyelitis, collagen-induced arthritis and inflammatory bowel disease (Aggarwal et al., 2003; Komiyama et al., 2006). IL-23 drives the development of autoreactive IL-17-producing T cells and promotes chronic inflammation dominated by IL-17, IL-6, IL-8 and tumor necrosis factor as well as neutrophils and monocytes (Aggarwal et al., 2003; Vaknin-Dembinsky et al., 2006). It is unlikely that IL-23 and its downstream effects evolved just to cause autoimmunity, but its real benefit to the host and the lineage relationship between IL-17-producing cells and T helper 1 cells remain unclear.

Otherwise, researchers found that the presence of either IFN-γ or IL-4 in primary cultures potently inhibited Th17 development (Lubberts et al., 2000; Harrington et al., 2005; Park et al., 2005). Thus, TCR stimulation of naive CD4 T cells in the presence of IL-23 alone did not result in a significant fraction of IL-17-producing cells (Cruz et al., 2006). However, activation of CD4 T cells under these same conditions with concurrent IFN-γ and IL-4 neutralization induced development of a discrete population of IL-17 $CD4^+$ T cells, which were negative for IFN-γ and IL-4 (Iwakura and Ishigame, 2006). Additionally, the ability of IFN-γ-deficient CD4 T cells to secrete IL-17 was impeded when cultures were supplemented with exogenous IFN-γ or IL-4 (Cruz et al., 2006). Thus, Th1 and Th2 cells were both resistant to IL-23-induced IL-17 expression and were potently inhibitory of Th17 development. These results strongly suggested that the development of IL-17-producing effectors was by way of a lineage distinct from Th1 and Th2. To further explore this, the key signaling pathways for Th1 and Th2 differentiation were examined. $CD4^+$ T cells deficient in either signal transducer and activator of transcription (STAT) 1 or STAT6, the principal signaling molecules downstream of IFN-γ and IL-4, respectively exhibited augmented IL-17 production (Aggarwal et al., 2003). This provided a potential explanation for the observed segregation of IFN-γ and IL-17 producing CD4 T cells in EAE: IFN-γ acts autonomously to enhance IFN-γ expression and to repress IL-17 production. Interestingly, the addition of exogenous IL-17 did not similarly suppress Th1 or Th2 polarization (Iwakura and Ishigame, 2006). This suggests that IL-17 cannot directly potentiate its own differentiation by extinguishing Th1 or Th2 differentiation by way of IL-17, although it is possible that other factors that promote the development of, and/or are secreted by, IL-17-positive CD4 T cells are capable of suppressing Th1 and Th2 development in favor of Th17 development.

In further recent studies, researchers have examined factors that might directly or indirectly block the inhibitory actions of IFN-γ to determine their possible actions on Th17 development. It has been reported that TGF-β inhibits Th1 and Th2 development, at least in part through blockade of effector cytokine production, although it also inhibits the Th1 developmental program by way of the T cell intrinsic effects (Veldhoen and Stockinger, 2006). Researchers have examined the effects of TGF-β on Th17 development, and, remarkably, have found that this cytokine induces IL-17 expression in the absence of IL-23 (Veldhoen et al., 2006). Importantly, the effect of TGF-β on Th17 induction is independent of simple inhibition of IFN-γ, as it induces much stronger IL-17 responses than deficiency of IFN-γ alone (Mangan et al., 2006). Furthermore, under the conditions used for Th17 induction, TGF-β did not induce strong Treg development (Starnes et al., 2001). So, this result suggests that TGF-β probably have some effects on Th17 induction under some conditions. Meanwhile, these results also support a model in which competing effects of antagonistic cytokines act early to establish Th17 lineage commitment, similar to the competitive effects of IFN-γ and IL-4 for Th1 and Th2. TGF-β1 inhibits the differentiation of Th1 and Th2 cells,

and abrogating TGFβ in T cells results in the spontaneous uncontrolled differentiation to Th1 and Th2 effector cells. It is currently unclear which physiological conditions promote the differentiation of Th17 cells through TGFβ but, clearly, both IFN-γ and IL-4 strongly interfere with this process (McKarns and Schwartz, 2005; Li et al., 2006). IFN-γ inhibits Smad3 phosphorylation downstream of TGFβ and induces inhibitory Smad7 that prevents Smad3 interacting with the TGFβ receptor (McKarns and Schwartz, 2005). Th1 cells upregulate Smad7 following activation, whereas Th17 cells are still negative for Smad7 expression (Fantini et al., 2004). However, the involvement of TGFβ in promoting the differentiation of Th17 cells exceeds the inhibition of Th1 and Th2 cell development (Veldhoen et al., 2006). Although Th17 cell differentiation occurs when both these pathways are blocked, this totally depends on the presence of endogenously produced TGFβ (Mangan et al., 2006; Weaver et al., 2006).

A key regulator of Th1 lineage commitment is T-bet (encoded by the Tbx21 gene), and it is likely that a common Th1/Th17 precursor cell would differentiate via a T-bet dependent pathway (Mathur et al., 2006). T-bet is a member of the extensive T-box family of transcription factors that is upregulated in developing Th1 cells, but not Th2 cells, and it is crucial for optimal expression of IFN-γ and IL-12 by Th1 cells (Veldhoen et al., 2006). T-bet expression can be stimulated in $CD4^+$ T cells by IFN-γ or IL-27 signal through STAT1 (Harrington et al., 2005). However, it is possible that other pathways are utilized for T-bet upregulation, because Stat1 and Tbx21 knockout mice display distinct phenotypes following EAE induction (Lord et al., 2005; Park et al., 2005; Ylikoski et al., 2005). Notably, T-bet deficient mice do not succumb to EAE. This has been attributed to the inability of these mice to generate Th1 effector cells (Kamiya et al., 2004; Guangwei et al., 2006a). However, given the finding that Th17 cells, not Th1 cells, are crucial for EAE induction, it was conceivable that T-bet might be an important transcription factor in Th17 differentiation and that Th1 and Th17 cells might indeed develop from a common progenitor cell (Eaton et al., 2006). Nevertheless, it was found that Th17 development was unimpaired in T-bet deficient CD4 T cells (Kamiya et al., 2004). Furthermore, immunization of T-bet deficient mice with myelin oligodendrocyte glycoprotein (a protein antigen used to induce EAE) resulted in the development of a discrete population of IL-17-producing CD4 T cells, suggesting that the resistance of T-bet deficient mice to development of EAE is not attributable to a defect in Th17 development (Mathur et al., 2006). Thus, although a role for T-bet in Th17 biology cannot be excluded at this time, it is unlikely to have intrinsic effects on Th17 development. By contrast, it is worth noting that molecules known to induce T-bet (e.g., IFN-γ and STAT1) potently suppress Th17 differentiation in vitro, which suggests that T-bet might, in fact, have a role in inhibiting IL-17 secretion from CD4 T cells. In this regard, researchers examined the development of IL-17-producing cells in immunized mice deficient in IFN-γ and T-bet (Ravindran et al., 2005; Mathur et al., 2006). Irrespective of the targeted deficiency examined, IL-17-positive cells developed normally, which supports the in vitro data of our group that show that these factors are dispensable for Th17 differentiation. Therefore, although the precise role of T-bet in autoimmune inflammation remains elusive, these data show clearly that T-bet is not required for IL-17 production from CD4 T cells, reiterating the notion that Th17 effector cells develop independently of Th1 and Th2 cells. Consistent with this, STAT4-deficient mice are resistant to the chronic inflammatory disorders in which the IL-23–IL-17 pathway drives autoimmune disease, EAE, suggesting that STAT4 is required for development of pathogenic Th17 cells (Persky et al., 2005). Indeed, signaling through the IL-23R complex has been shown to phosphorylate STAT1, STAT3, and STAT4, as well as to induce the formation of STAT3/STAT4 heterodimers, suggesting that both STAT3 and STAT4 might be important for IL-17 production from CD4 T cells (Lin et al., 2005). However, STAT4-deficient CD4 T cells were unimpaired in their ability to produce IL-17 in vitro and in vivo, indicating that this transcription factor is dispensable for commitment to the Th17 lineage and IL-17 production (Sanchez-Guajardo et al., 2005). Whether STAT4 is required for IL-23-dependent effects on developing Th17 cells that are unrelated to IL-17 production remains to be determined, as does a possible role for STAT3 (Sawa et al., 2006). Collectively, however, these data support a divergent model for Th1 and Th17 effector differentiation, and emphasize the counter regulatory features of these two lineages. Meanwhile, these experimental results also suggest Th17 cell induced generation and differentiation is related to many cytokines and cell signal pathways (Fig. 1).

Th17 Cell Immune Regulatory Effects

Emerging evidence indicates that Th17 probably plays a central role in inflammation and autoimmunity (Mangan et al., 2006). IL-17 has been associated with many inflammatory diseases such as rheumatoid arthritis (Komiyama et al., 2006), asthma (Chen et al., 2003), lupus (Wong et al., 2000) and allograft rejection (Yoshida et al., 2006). IL-17 is also important in contact, delayed-type and airway hypersensitivities, as shown in a study using IL-17 deficient mice (Ferretti et al., 2003). In related studies, IL-17 deficient mice as well as wild-type mice that received an IL-17R antagonist, have shown resistance to an arthritis like disease (Nakae et al., 2003; Tan et al., 2006b). Although the role of Th17 cells in the pathophysiology of autoimmunity is conspicuous, this is unlikely to be their primary function. IL-17 mediates the stimulation of neutrophil mobilization, placing it at the interface between adaptive and innate immune responses (Stark et al., 2005; Cruz et al., 2006). It has been suggested that Th17 cells are an important early response to catastrophic injuries that require immediate neutrophil recruitment to prevent tissue necrosis or sepsis (Witowski et al., 2000). IL-17 has been linked to tissue neutrophil recruitment through the induction of granulocyte colony-stimulating factor and IL-8, and IL-17R deficient mice have impaired host defense against microbacterial infection because of a substantial reduction in granulocyte colony-stimulating factor and macrophage inflammatory protein 2 in the lung (Miyamoto et al., 2003). IL-17 and neutrophils also have a role in the host defence against Gram-negative bacteria, such as Klebsiella pneumoniae or Bacteroides fragilis (Ferretti et al., 2003). The preferential expression of IL-17 in human and murine T cells also occurred in the presence of Borrelia burgdorferi and Mycobacterium tuberculosis (Khader et al., 2005). Certain microbial products from, for example, Bordetella pertussis, preferentially stimulate IL-23, and the activation of toll-like receptor (TLR)2 instead of TLR4 by microbial products such as peptidoglycan, a cell wall component of Gram-positive and Gram-negative bacteria, likewise results in higher levels of IL-23 rather than IL-12 from DCs (Wozniak et al., 2006). Thus, it is possible that these infections promote the expansion and survival of Th17 cells (Khader et al., 2005). What is currently unknown is whether TGFβ is differentially expressed in certain infections and, thus, might preferentially stimulate the differentiation of Th17 cells at the expense of Th1 and Th2 cells.

IL-17 does have important positive roles in the regulation of intestinal barrier functions through the induction of tight junction formation (Zhang et al., 2006). The inflamed mucosa of inflammatory bowel disease patients was shown to contain increased numbers of Th17 cells but it is unclear whether these cells have a pathophysiological role in the disease (Wang et al.,

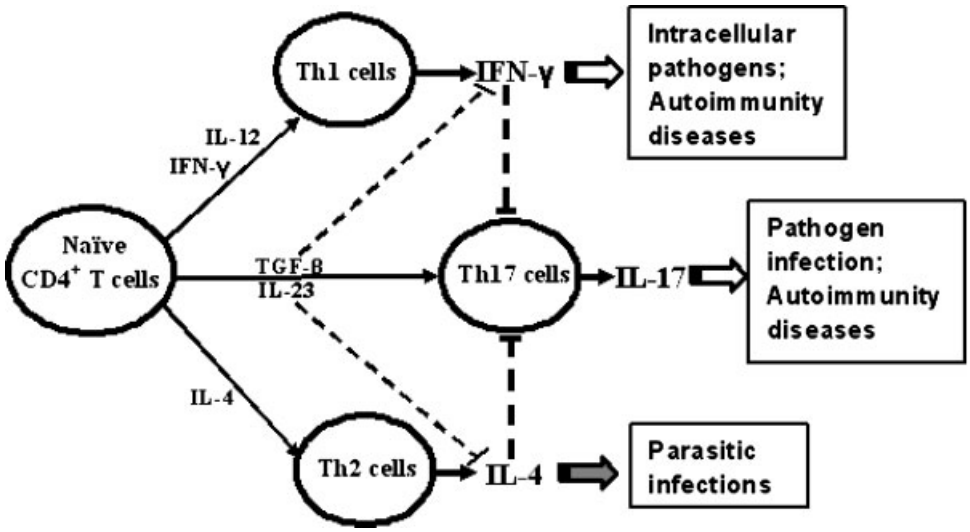

Fig. 1. Cytokine networks control CD4 effector T cell differentiation and immune response. Recent studies have established that Th1 and Th2 effector cytokines, IFN-γ and IL-4, respectively, potently inhibit Th17 development. Furthermore, TGF-β, a cytokine previously implicated in regulatory T cell development and function, appears to be required for Th17 cell development, both through indirect effects (blockade of IFN-γ and IL-4 production by cells of the innate immune system) and through direct effects on naïve CD4 T cell precursors. Otherwise, IL-12 can promote Th1 cell development and function, and IL-23 can promote Th17 cell development and function, respectively. Th1 cells evolved to enhance eradication of intracellular pathogens (e.g., intracellular bacteria, viruses, and some protozoa) and autoimmune diseases, are potent activator of cell-mediated immunity; and Th2 cells were evolved to enhance elimination of parasitic infections (e.g., helminths); and Th17 cells all can be evolved to intracellular pathogens and parasitic infection and autoimmune diseases.

2004). Experimental studies using anti-IL-17 treatment in dextran sulfate sodium (DSS)-induced colitis showed an exacerbation of the disease in antibody-treated mice, suggesting a positive role for Th17 cells (Yen et al., 2006; Zhang et al., 2006). Interestingly, a recent study described defective acute inflammation in Crohn's disease, characterized by abnormally low neutrophil accumulation in response to rectal, ileal or dermal trauma (Awane et al., 1999). Although this study did not investigate IL-17 or TGFβ, the defect in the acute inflammatory response, which might result in damage to the mucosal barrier, could indicate a possible deficiency in the IL-17 response, a supposition that has yet to be tested.

Otherwise, Th17 cell probably have some relationship with regulatory T cells (Veldhoen et al., 2006). During co-cultures of $CD25^+$ $CD4^+$ T cells with naive T cells and DCs. Researchers noticed that in the presence of IL-6, these naive T cells differentiated efficiently to Th17 cells, an effect that depended on TGFβ1 (Reddy et al., 2005). A recent study described a dichotomy in the generation of regulatory and Th17 T cells, with TGFβ alone promoting the generation of anti-inflammatory regulatory T cells from naive $CD4^+$ T cells, whereas TGFβ in the presence of IL-6 promoted Th17 cells. TGFβ has previously been reported to support the maintenance of Foxp3 expression in addition to regulatory function in $CD25^+$ $CD4^+$ T cells (Zheng et al., 2006). However, it is still debatable whether the differentiation of $CD25^+$ $CD4^+$ T cells from mature $CD4^+$ T cells is a mechanism that occurs in physiological conditions in vivo, because T cell activation is much more likely to occur in the context of an inflammatory stimulus that activates the innate system. Although the in vitro generation of $CD25^+$ $CD4^+$ T cells from naive $CD4^+$ T cells was confirmed in Foxp3 reporter mice, there is no evidence for these events in conditions of pathogen-induced immune responses in vivo. Given that regulatory T cells are generally seen as regulators of effector responses that can downmodulate immune pathology and are, therefore, proposed as therapeutic agents in a number of disease situations, it is particularly ironic that this cell population might, in certain conditions, induce further immune pathology. Although only limited extrapolation is possible from an in vitro finding, because spatial and temporal aspects of regulatory T cell recruitment and activation in vivo will be crucial, it is nevertheless worth considering that the adoptive transfer of regulatory T cells into an inflammatory milieu might exacerbate, and not ameliorate, disease.

It is not clearly known about how IL-17 expression is regulated (Liu et al., 2005). But some studies may be give our some implies. Researchers examined the requirements and mechanisms for IL-17 expression in primary mouse lymphocytes. Like many cytokines, IL-17 is induced rapidly in primary T cells after stimulation of the T cell receptor (TCR) through CD3 crosslinking. Surprisingly, however, the pattern of regulation of IL-17 is different in mice than in humans, because "costimulation" of T cells through CD28 only mildly enhanced IL-17 expression, whereas levels of IL-2 were dramatically enhanced (Tan et al., 2006a). Similarly, several other costimulatory molecules such as inducible costimulator (ICOS; Park et al., 2005), 4-1BB(a kind of costimulator molecules; Liu et al., 2005) and CD40 ligand (CD40L; Schnurr et al., 2005) exerted only very weak enhancing effects on IL-17 production. In agreement with other reports, IL-23 enhanced CD3 induced IL-17 expression. However, IL-17 production can occur autonomously in T cells, as neither DCs nor IL-23 were necessary for promoting short term production of IL-17 (Harrington et al., 2005; Vaknin-Dembinsky et al., 2006; Yen et al., 2006). Finally, to begin to characterize the TCR-mediated signaling pathway(s) required for IL-17 production, researchers showed that IL-17 expression is sensitive to cyclosporine A and mitogen activated protein kinase (MAPK) inhibitors, suggesting the involvement of the calcineurin/nucleus factor of activating T cell (NFAT) and MAPK signaling pathways (Liu et al., 2005).

Closing Remark and Prospective

The rapid emergence of the TGFβ, IL-23 and IL-17 cytokine network as a central player in immune pathogenesis has been followed by studies that have linked these cytokines to a new $CD4^+$ T effector lineage, Th17, which has strong pathogenic potential. Although not addressed in this brief review, it is certain that the Th17 lineage evolved to control certain classes of pathogens, analogous to the specialized functions of Th1 and Th2 for handing intracellular pathogens and parasitic infections, respectively. Given the prominent association of TGFβ, IL-23, and IL-17 with host protection in a growing number of bacterial infection models, it is not unlikely that the Th17 lineage evolved to cope with a range of extracellular bacterial pathogens, although more studies will be needed to define the range of pathogens linked to Th17. Irrespective of the focus on autoimmunity or host defense, a number of crucial questions remain to be answered. How are IL-23 and IL-12 differentially regulated by pathogens and their products, and how might inappropriate Th17 responses be induced and lead to immune pathogenesis? What role does IL-23 play in amplifying or maintaining Th17 responses in vivo? Are there complementary or antagonistic roles for Th17 and Th1 responses in chronic inflammatory disease? Clearly, a great deal is yet to be learned in this field of research, but with the discovery of this novel pathway in immune regulation, the foundation for a new era in treatment of diseases of immunity has been laid.

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