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Surface phenotype and antigenic specificity of human interleukin 17–producing T helper memory cells

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Interleukin 17 (IL-17)–producing T helper cells (T_H-17 cells) have been characterized in mice as a distinct subset of effector cells, but their identity and properties in humans remain elusive. We report here that expression of CCR6 and CCR4 together identified human memory CD4$^+$ T cells selectively producing IL-17 and expressing mRNA encoding the human ortholog of mouse RORγt, a transcription factor, whereas CCR6 and CXCR3 identified T_H1 cells producing interferon-γ and T helper cells producing both interferon-γ and IL-17. Memory T cells specific for *Candida albicans* were present mainly in the CCR6$^+$CCR4$^+$ T_H-17 subset, whereas memory T cells specific for *Mycobacterium tuberculosis* were present in CCR6$^+$CXCR3$^+$ T helper type 1 subset. The elicitation of IL-17 responses correlated with the capacity of *C. albicans* hyphae to stimulate antigen-presenting cells for the priming of T_H-17 responses *in vitro* and for the production of IL-23 but not IL-12. Our results demonstrate that human T_H-17 cells have distinct migratory capacity and antigenic specificities and establish a link between microbial products, T helper cell differentiation and homing in response to fungal antigens.

Different types of CD4$^+$ T helper cells develop from naive T cells under the influence of polarizing signals and 'master' transcription factors[1]. T helper type 1 (T_H1) cells require interleukin 12 (IL-12), interferon-γ (IFN-γ) and the transcription factor T-bet and, through the production of IFN-γ and activation of macrophages, mediate protection against intracellular pathogens such as *Mycobacterium tuberculosis*. T_H2 cells require IL-4 and the transcription factor GATA-3 and, through the production of IL-4, IL-5 and IL-13, mediate protection against extracellular parasites.

T helper cells that produce IL-17 (T_H-17 cells) have been described in mice as a distinct subset of effector cells that differentiate from naive T cells in response to IL-6 and transforming growth factor-β (TGF-β)[2,3] and require the transcription factor RORγt[4]. IL-23 also promotes T_H-17 responses *in vivo*, although the mechanism remains to be established[3,5]. IL-23 shares with IL-12 a common p40 chain and is induced together with IL-12 in maturing dendritic cells (DCs) by several microbial stimuli[6,7]. Studies have indicated a functional dichotomy between T_H1 and T_H-17, as the T_H1-associated cytokines IL-12 and IFN-γ strongly inhibit mouse T_H-17 cell differentiation[8,9]. Consequently, it is expected that stimuli that trigger simultaneous production of IL-12 and IL-23 in DCs will favor T_H1 rather than T_H-17 responses.

Mouse and human T_H-17 cells produce IL-17A and IL-17F, two members of the IL-17 family[10] that induce the mobilization, recruitment and activation of neutrophils and trigger the production of proinflammatory cytokines and chemokines by a broad range of cellular targets, including epithelial cells, endothelial cells and macrophages[11]. Reports of infectious mouse models have suggested that T_H-17 cells developed to mediate protection against extracellular bacteria and fungi[12,13]. In addition, subsequent studies have provided convincing evidence for the involvement of T_H-17 cells in the pathogenesis of several autoimmune diseases, including experimental autoimmune encephalitis and collagen-induced arthritis[5,14]. Further studies in humans are needed to understand the function of T_H-17 cells in human diseases and host defense and to assess the possibility of targeting T_H-17 cells in human immune interventions or vaccination.

Chemokine receptors have been instrumental in the characterization of subsets of human memory T cells with distinct migratory capacity and effector functions[15,16]. For example, the chemokine receptor CCR7 discriminates between lymph node–homing central memory T cells and tissue-homing effector memory T cells, whereas expression of the B cell follicle–homing receptor CXCR5 identifies follicular helper T cells. In addition, CXCR3, CXCR6 and CCR5 are 'preferentially' expressed in T_H1 cells, whereas CCR3, CCR4, CCR8 and the prostaglandin D_2 receptor CRTh2 are expressed in T_H2 cells. The ligands for these receptors are inflammatory chemokines and chemoattractants, which are expressed in inflamed tissues and mediate the selective recruitment of different types of effector cells.

Here we report that expression of CCR6 and CCR4 identified in humans a homogeneous population of memory T cells producing IL-17 but not IFN-γ and expressing the human ortholog of mouse RORγt. In contrast, expression of CCR6 and CXCR3 identified a

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