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Plasticity of Th17 cells and therapeutic conundrum

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CD4$^+$ T cells are highly heterogeneous with respect to their phenotype, secretion of effector molecules, transcription factors and functions. In the periphery, CD4$^+$ T cells can be polarized into distinct subsets under the influence of antigen presenting cells and cytokine milieu. Recently, Th17 cells that express lineage-specific transcription factor RORC (RORγt in mice) and produce cytokines IL-17A and IL-17F were identified as distinct lineage of CD4$^+$ T cells [1]. Th17 cells are important to clear extracellular bacteria and fungi. However, when tolerance mechanisms breach, these Th17 cells can also mediate inflammation and can play critical role in the pathogenesis of several autoimmune diseases. In fact, a large number of autoimmune and inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, asthma, lupus, psoriasis and others are characterized by an aberrant activation of Th17 cells and hyper-expression of Th17 inflammatory mediators such as IL-17, IL-21, IL-22, CCL20 and GM-CSF [2-3]. Therefore, Th17 cells are one of the potential targets to treat these diseases.

Th17 cells provide several opportunities to target them. These targets could be both direct and indirect. The indirect targets are those factors that mediate Th17 differentiation/expansion. Th17 cells are dependent on IL-21 for their differentiation and IL-6, IL-1β and IL-23 for expansion and stabilization [4-5]. Therefore, interference with these cytokines either by neutralizing monoclonal antibodies or by soluble receptors can inhibit Th17 generation. Important point is that such strategies are already explored in autoimmune patients. A human monoclonal antibody ustekinumab that targets p40 subunit of IL-12/IL-23 is a promising therapeutic candidate for psoriasis and Crohn's disease [6-7].

Direct therapeutic targets are those that are intrinsic to Th17 cells such as Th17-protoype cytokine IL-17 and Th17-specific transcription factors RORC and STAT-3. Although, Th17 cells also secrete other inflammatory mediators such as IL-21, IL-22, CCL20 and GM-CSF, they are not specific for Th17 cells as other immune or non-immune cells also produce these cytokines/chemokines. For the moment, two independent approaches have been explored to target IL-17: to inhibit IL-17 transcription or to neutralize this cytokine by monoclonal antibodies. Experimental models show that 1,25-dihydroxyvitamin D3 can inhibit transcription of IL-17 with a concomitant amelioration of experimental autoimmune encephalomyelitis (EAE) [8]. Of interest, two anti-IL-17 neutralizing humanized monoclonal antibodies AIN457 and LY2439821 have shown promise in patients with rheumatoid arthritis, psoriasis and uveitis [9-10]. Pioglitazone, a nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) agonist; simvastatin, a cholesterol-lowering agent; and cardiac glycoside digoxin inhibit Th17 generation by interfering with RORγt/RORC [11-13]. Moreover, molecules such as zinc, platelet-activating factor receptor antagonist PCA-4248 and leukemia inhibitory factor block phosphorylation of STAT3 and hence are effective inhibitors of Th17 cells *in vitro* and *in vivo* [14-16].

All these reports point out that identification of Th17 targeting therapies is an active area of research and of intense clinical investigation. However, do we need therapies that specifically target Th17 cells for all the pathological conditions? As per current understandings of Th17 biology, we may not need Th17-specific therapies for most of the diseases that are associated with an aberrant activation of Th17 cells. Importantly, plasticity of Th17 cells and their instability pose dilemma of to target these cells specifically or to use broad-spectrum therapies. The experimental models and analysis of T cells from patients with inflammatory conditions have demonstrated that under acute inflammatory conditions, Th17 cells are stable while under chronic inflammatory conditions, they tend to acquire the characteristics of other effector cells such as Th1, Th2 or even regulatory T cells (Tregs) [17-20]. Thus, in EAE, Th17 cells that migrate to central nervous system tend to loose IL-17 expression and acquire IFN-γ [20]. This report although confirms previous notion that IFN-γ-producing CD4$^+$ T cells are pathogenic in EAE, these IFN-γ-producing T cells were not generated because of differentiation of naïve CD4$^+$ T populations into Th1 cells. Rather, IFN-γ-producing T cells were originated from Th17 cells that have previously produced IL-17. In humans, CD4$^+$ T cells that are double positive for IFN-γ and IL-17 is a common feature during *in vitro* differentiation or expansion of Th17 cells [21-22]. In asthma patients, distinct populations of circulating memory CD4$^+$ T cells that co-express IL-17 and IL-4 have been identified [23]. Therefore, for chronic inflammatory conditions, therapies that specifically target Th17 cells may not provide expected benefits.

In addition to plasticity that is inherent to Th17 cells, it is still unclear whether human autoimmune disorders including rheumatoid arthritis and psoriasis are universally Th1-mediated or Th17-mediated. Several reports suggest that both Th1 and Th17 cells are involved in the pathogenesis of rheumatoid arthritis while, skin lesions in psoriasis are characterized by the infiltration of distinct populations of highly differentiated Th1 and Th17 cells [17,24,25]. Similarly, all three major CD4$^+$ T subsets Th1, Th2 and Th17 cells are implicated in the pathogenesis of lupus [26,27]. However, in view of plasticity of Th17 cells, it remains to be determined if mixed phenotype of CD4$^+$ T cells in these conditions is due to discrete T cell subsets that are polarized

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independently or due to acquisition of phenotype of other T cells by the infiltrating Th17 cells.

In view of the instability of Th17 cells that can acquire phenotype of either Th1/Th2 cells under chronic inflammatory conditions, and mixed phenotype of $CD4^+$ T cells in many autoimmune and inflammatory conditions, Th17-specific targeting may not provide much benefit. Therefore, therapies that have broad specificities (Th17-Th1 or Th17-Th2 for example) would be ideal. In fact, several therapeutic molecules that are explored for inhibition of Th17 cells also inhibit other pathogenic cells and can be associated with reciprocal up-regulation or expansion of Tregs. These therapies include ustekinumab that inhibit both Th1 and Th17 cell populations by inhibiting IL-12 and IL-23 [6,7]; intravenous immunoglobulin (a therapeutic preparation of pooled normal IgG obtained from the plasma pool of several thousand healthy donors) that suppresses Th17 and Th1 while reciprocally enhancing Treg expansion [22,28-29]; N-acetylglucosamine [30]; and platelet-activating factor receptor antagonist PCA-4248 [15]. Among them, it is noteworthy to mention that IVIg is a proven therapeutic molecule in a wide-range of autoimmune diseases while ustekinumab has already shown promise in initial clinical trials. Remaining two molecules have provided encouraging results in experimental models and hence are possible candidates to test in the patients.

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