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Stability of T-cell lineages in autoimmune diseases

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Life is about change and instability – so should we be surprised that our favorite T-cell lineages are not as stable as we desperately hoped they would be? Probably not, and as much as this complicates our scientific lives, we need to understand this and learn to interpret our data accordingly, no matter how little we like it. But let's start at the beginning.

In the mid 1980s Mosmann *et al.* made the fundamental observation that T-helper (Th) cells could be distinguished into two subsets with fundamentally different functional properties: Th1 cells, which produce IFN- γ , granulocyte macrophage-colony stimulating factor (GM-CSF) and IL-2, and Th2 cells, which produce IL-4 [1]. Shortly thereafter, the concept evolved that IFN- γ -producing Th1 cells are the cells that promote pathology in a number of autoimmune diseases, including autoimmune Type 1 diabetes and multiple sclerosis, and that Th2 cells are 'good' and provide protection, or at least, are neutral [2–4]. Not surprisingly, however, evidence soon appeared suggesting that Th2 cells had pathogenic potential in some autoimmune disease models such as experimental autoimmune encephalomyelitis (EAE) and autoimmune gastritis [5,6]. However, even before that realization the discussion had begun as to how stable T-cell lineages are [7–9].

The dawn of the 21st century brought with it the rise of the Th17 cell. Cua and colleagues first showed that IL-23 was indispensable for induction of EAE [10], and then IL-23-promoted IL-17-producing cells and Th17 cells were established as a Th1/Th2-independent T-cell lineage [11,12]. Subsequently, a number of papers established Th17 cells as being critical for tissue inflammation in animal models of rheumatoid arthritis and EAE [11,13].

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However, the debate continued as to which cytokines were the true harbingers of disease pathology. For example, IFN- γ was shown to be important for disease pathology, but so was TNF, IL-17 and IL-23 [10,11,14]. Shortly thereafter, it was questioned whether the signature Th17 cytokines, IL-17A and IL-17F, were as critical for the pathogenesis of autoimmune diseases as initially thought, since deficiency of GM-CSF, a cytokine that these cells also produce, completely abolished disease, whereas genetic deficiency of Th17 signature cytokines did not [15–17]. Interestingly, GM-CSF had been reported to be critical for EAE almost a decade earlier [18]. Thus, why was IL-23 critical for disease, but not other Th17 signature cytokines? As it turned out, IL-23 is linked to the production of GM-CSF by Th17 cells [19].

Since the initial description of Th17 cells, additional T-cell lineages have emerged, each with a particular role in immunity and autoimmune disease pathology: Tregs, follicular helper T (Tfh) cells, and most recently, Th9 and Th22 cells [3]. To make matters more complicated, the different T-cell lineages may not be as stable as we would like to assume, and they can change their phenotype (cytokine secretion, transcription factor [TF] and surface receptor expression) in response to different environmental stimuli [20]. Furthermore, T cells can affect each other's differentiation, viability and stability and their role in immunity (i.e., their function in disease). Interestingly, it appears that highly proinflammatory Th17 cells may go hand-in-hand with anti-inflammatory Tregs [20].

An important conceptual issue is to separate the stability of a T-cell lineage, with regard to producing certain pro- or anti-inflammatory cytokines, from its changing functional role in disease pathogenesis, in terms of promoting pathology, being protective or switching from one role to the other. A prime example of the latter is T cells producing IFN- γ or TNF. Initially, both of these cytokines were thought to be pathogenic and therefore cells producing them were assumed to promote disease. However, subsequently a protective role was shown for both IFN- γ (conceivably via induction of T-cell apoptosis) and TNF (by promoting remyelination via TNF receptor 2). Thus, the question must be asked; at what time point during the course of autoimmune disease does a cell stop being pathogenic and possibly even become protective (or the other way around), even if it maintains its cytokine profile and lineage integrity? Currently this is an understudied area, particularly in terms of the timing and kinetics under which these cells and related cytokines exert pathogenic or protective function.

Closing the circle, the changing role of T cells in promoting or inhibiting disease pathology may be closely linked to the stability or 'plasticity' of a T-cell lineage. Along these lines, Bending *et al.* pointed out that Th17 cells can often produce IFN- γ and become double-producing cells, and hence the Th1/Th17 cell paradigm may be too simplistic [21]. They, as well as Hirota and colleagues, investigated the fate of Th17 cells and found that under chronic inflammatory conditions during EAE, Th17 cells rapidly switched to the production of IFN- γ and represented the main source of this cytokine in the CNS [21,22]. As a result, they have coined the term 'ex-Th17 cells', which in itself, implies lineage stability that yet remains to be proven (e.g., do ex-Th17 cells ever revert back to Th17 cells?). However, the plasticity of the Th17 lineage is not only linked to cytokine secretion, but also to the expression of different TFs and receptors, such as the aryl hydrocarbon receptor, a TF that is

prominently linked to the Th17 response and enhanced autoimmunity, and whose expression is regulated by environmental factors [23]. Environmental factor-regulated TFs may maintain effector T cells in a particular functional state until the respective external signals wane, at which point these cells become open to different environmental cues reflective of a new situation, which may require a different type of T-cell response. Along these lines, Th17 plasticity seems to be a rapid and dynamic process, and numerous factors may play a role in Th17 formation, function and plasticity during autoimmunity, and eventually lead them to express a Th1 phenotype.

Last but not least, T-cell lineage stability may not only be an issue for classical Th cells, but may also affect other T-cell lineages such as Tregs. The Treg lineage is important to establish and maintain peripheral self-tolerance by modulating autoreactive CD4⁺ and CD8⁺ T cells through a variety of mechanisms [24,25]. Recently, Zhou *et al.* revisited Foxp3 expression in CD4⁺CD25⁺ T cells using an elegant mouse model with yellow fluorescent protein expressed under the control of the Foxp3 promoter [26]. Interestingly, they found that Foxp3⁺ T cells can either downregulate or completely abolish Foxp3 expression and become 'ex-Foxp3' Tregs [26]. Importantly, these ex-Tregs can produce proinflammatory cytokines, maintain a memory phenotype, and can transfer self-reactivity and promote autoimmunity. These observations raise the question of how stable the Treg lineage is, and how their functional integrity is maintained in order to sustain self-tolerance. This brings us to commonalities between Th17 cells and Tregs:

- TGF- β is important for initiation and differentiation of both lineages;
- There is evidence that some T cells coexpress Foxp3⁺ROR γ t⁺ and that this 'intermediate' lineage produces IL-17 and can differentiate to either Th17 or Tregs;
- And there is a direct relationship between the transcription factors Foxp3 (Tregs) and ROR γ t (Th17) and the levels of IL-17 expression [20].

Thought-provokingly, Tregs can also change to a Th1 phenotype by expressing T-bet and producing IFN- γ [26–28].

Finally, there is evidence that certain T-cell lineages are more likely to convert to a different and specific lineage, such as Tregs to Th17 or Tfh [20], Th17 to Th1 [21] and Th9 to Th2 [29], although these changes do not appear to be reciprocal, and Th1 and Th2 lineages are believed to be particularly stable [30,31]. The question of what makes some T-cell lineages more stable than others, and how stabilizing 'preferable' T-cell lineages (e.g., Th1 cells in case of intracellular pathogens) could be exploited to provide protection from infectious or autoimmune diseases, would therefore be a relevant area for research.

The immune system intrinsically seems to favor balance and flexibility as indicated by Tregs and Th17 cells sharing many similar properties, for example [20], or the ability of proinflammatory Th1 cells to produce anti-inflammatory cytokines such as IL-10 [32]. Th17 converting into IFN- γ -producing ex-Th17 cells, and Tregs converting into Foxp3⁺Tbet⁺ IFN- γ -producing cells, provide further evidence supporting this view.

Thus, in the final analysis; do we really need to chase the elusive ‘overlord’ of pathogenic T cells, the ‘one’ pathogenic cytokine? Or rather, should we take advantage of the existing instability and potential for change and exploit the flexibility and loopholes of the immune system for the treatment of autoimmune diseases and protection from invading microorganisms? We favor the latter view, and suggest embracing instability and plasticity within T-cell lineages in particular and the immune system in general. However, to do so means to accept it and not to turn a blind eye to it, even if it gets in the way of our favorite hypotheses.

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Biographies

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