Do Memory CD4 T Cells Keep Their Cell-Type Programming: Plasticity versus Fate Commitment?

T-Cell Heterogeneity, Plasticity, and Selection in Humans

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The wide range of effector and memory T cells is instrumental for immune regulation and tailored mechanisms of protection against pathogens. Here, we will focus on human CD4 T cells and discuss T-cell plasticity and intraclonal diversification in the context of a progressive and selective model of CD4 T-cell differentiation.

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

Editors: Shane Crotty and Rafi Ahmed

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CD4 T cells are born naïve and upon antigenic stimulation in secondary lymphoid organs differentiate to effector T cells and acquire the capacity to migrate to peripheral tissue and to produce a range of cytokines that mediate effector responses directly and through the activation of innate immune cells. T_H1 cells produce interferon γ (IFN- γ) that activates macrophages to kill intracellular bacteria, whereas T_H2 cells produce interleukin (IL)-4 and IL-5, which activate mast cells, basophils, and eosinophils in response to helminthes, and T_H17 cells produce IL-17 and IL-22, which drive recruitment of neutrophils and production of antimicrobial peptides in response to extracellular bacteria and fungi. T_H cells that migrate to B-cell follicles differentiate to follicular helper T cells (T_{FH}) and provide help to B cells for antibody production. Following antigen-driven expansion, some T cells survive as circulating central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) to provide immune surveillance in lymph nodes and peripheral tissues; others that seed nonlymphoid tissues give rise to a population of tissue-resident memory T cells (T_{RM}) to provide immediate protection at sites of pathogen reentry.

The heterogeneity of effector and memory CD4 T cells raises questions about the nature of differentiation signals, the extent of fate diversity, the lineage relationship between different fates, and the degree of plasticity at different stages of differentiation. Here we will summarize studies performed in the human system that have advanced our understanding of CD4 T-cell heterogeneity and discuss T-cell plasticity and intraclonal diversification in the context of a progressive and selective model of CD4 T-cell differentiation.

HETEROGENEITY OF HUMAN CD4 T CELLS

The extent and nature of naïve T-cell differentiation is determined by signals provided by the pathogen and by the local environment where priming occurs (Medzhitov 2007). By promoting expression of master transcription factors, cytokines produced by dendritic cells and other innate immune cells represent key determinants

of T_H cell differentiation. Classical examples are IFN- γ and IL-12, which induce through STAT1 and STAT4 expression of T-bet that drives the T_H1 program. Similarly, IL-4 through STAT6 induces expression of GATA-3 that drives the T_H2 program, while IL-6 through STAT3 induces ROR γ t that drives the T_H17 program. Importantly, cytokines act in combination with signals from the T-cell antigen receptor (TCR) and costimulatory molecules as well as signals triggered by tissue-specific cues and environmental factors—such as nutrients, vitamins, and even pollutants and salt—to define internal transcriptional landscapes that confer T-cell identity (Bonelli et al. 2014). Some signals trigger internal circuits that enforce, reinforce, or destabilize T-cell polarization through multiple mechanisms, including epigenetic modifications (Wang et al. 2015). MicroRNAs and long noncoding RNAs (lncRNAs) have also been found to control various aspects of CD4 T-cell differentiation and effector function (Baumjohann and Ansel 2013; Panzeri et al. 2015).

Mouse models have been used in a reductionist approach to define the contribution of single elements and signaling pathways involved in CD4 T-cell differentiation and to evaluate the role of different types of polarized T_H cells in protection or immunopathology. Human studies are providing important clues as to the extent of T-cell fate diversity induced by different pathogens in different tissues (Farber et al. 2014; Sallusto 2016). An example is represented by studies analyzing the memory T-cell response induced by extracellular pathogens that elicit two distinct types of T_H17 cells. T cells primed by *Staphylococcus aureus* produce IL-17 and the immune regulatory cytokine IL-10. In contrast, T cells primed by *Candida albicans* have a more inflammatory phenotype, producing IL-17 together with IFN- γ . This difference was found to be dependent on the cytokines elicited by the different pathogens, primarily IL-1 β (Zielinski et al. 2012). Another example is provided by CD4 T cells in the skin of patients with atopic dermatitis or psoriasis that revealed the existence of T cells producing IL-22 but not IL-17 (Eyerich et al. 2009). These T_H22 cells can be also found in the blood, where they express

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CCR6 and the skin-homing receptors CLA and CCR10, and can differentiate from naïve T cells in a process that requires the transcription factor AHR and signals from vitamin D3 (Duhon et al. 2009; Trifari et al. 2009). Yet other examples include IL-9-producing T_H9 cells, initially defined in mice (Veldhoen et al. 2008) that are also increased in the skin lesions of psoriasis (Schlapbach et al. 2014) and granulocyte macrophage colony-stimulating factor (GM-CSF)-only-producing T_H cells (Noster et al. 2014).

Studies on the human T-cell response induced by *Mycobacterium tuberculosis* led to the discovery of a distinct type of IFN- γ -producing T_H1 cells (that we defined as T_{H1}^*) that can be distinguished from virus-induced T_H1 cells based on the expression of chemokine receptors and transcription factors (Acosta-Rodriguez et al. 2007; Lindestam Arlehamn et al. 2013). T_{H1}^* cells express CXCR3 and T-bet, as classic T_H1 cells, but also CCR6 and ROR γ t, which are characteristic of T_H17 cells (Fig. 1). Interestingly, T_{H1}^* development, but not T_H1 development, is impaired in patients with RORC loss-

of-function mutations (Okada et al. 2015), a finding that supports the existence of distinct pathways of T_H1 cell differentiation. The signals present in the context of bacterial infections that induce T_{H1}^* cells remain to be defined. These cells may derive directly from naïve T cells in a ROR γ t-dependent fashion or from T_H17 cells that convert to T_{H1}^* under the influence of IL-12, TNF- α , and/or IL-1 β . The latter possibility is consistent with the finding that in T_{H1}^* cells, like in T_H17 cells, *RORC2* and *IL17A* are demethylated (Mazzoni et al. 2015).

A regulated cytokine production is required for the proper elimination of microbial pathogens, for instance IFN- γ production by T_H1 cells for intracellular microbes and IL-17 by T_H17 cells for *C. albicans*. However, when analyzed in more detail, microbe-specific memory T cells are found not only in the expected subset but also, at lower frequencies, in other subsets that have different, and even divergent, functions (Becattini et al. 2015). For instance, *C. albicans*-specific T cells are mainly T_H17 , but some are T_H1 , T_{H1}^* , or T_H2 . Similarly,

Figure 1. Two types of human T_H1 cells. $CXCR3^+CCR6^-$ T_H1 cells expressing T-bet are preferentially elicited by viruses, whereas $CXCR3^+CCR6^+$ T_{H1}^* cells expressing T-bet and ROR γ t are preferentially elicited by bacteria, possibly by different polarizing cytokines present at sites of induction. IFN, Interferon; IL, interleukin.

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Mycobacteria-specific T cells are primarily T_H1^* , but a few are T_H1 or T_H17 . The heterogeneity of T-cell fates revealed by human studies is not surprising considering the continuous environmental exposure to commensal and pathogenic microbes and the accumulation of memory T cells that have undergone repeated encounters with antigen over several years. Although it is possible that these heterogeneous fates are the result of differential priming, it is also possible that they represent distinct stages of differentiation, owing to the property of T cells to acquire additional functions or to be reprogrammed to alternative fates if exposed to appropriate stimuli, a property that has been defined as T-cell plasticity.

PLASTICITY AND FATE COMMITMENT: HUMAN STUDIES

Soon after the seminal discovery of T_H1 and T_H2 cells (Mosmann et al. 1986), some studies both in mice and humans reported the existence of CD4 T-cell clones with a mixed cytokine secretion pattern (Maggi et al. 1988; Umetsu et al. 1988; Street et al. 1990; Openshaw et al. 1995). These T_H0 clones producing IFN- γ and IL-4 cells were suggested to be the precursors of T_H1 and T_H2 cells (Street et al. 1990). This phenomenon was later analyzed by studying epigenetic modifications at cytokine gene loci in naturally occurring human memory T_H1 and T_H2 cells (Messi et al. 2003). It was found that memory T_H1 cells display acetylated histones at the *IFNG* promoter, but not at the *IL4* promoter, whereas reciprocally memory T_H2 cells display acetylated histones at the *IL4* but not *IFNG* promoter. However, the hypoacetylation of the nonexpressed cytokine gene did not lead to its irreversible silencing because, on stimulation under T_H2 conditions, T_H1 cells up-regulated GATA-3 and acquired *IL4* acetylation and expression while continuing to produce IFN- γ , thus becoming T_H0 cells. Reciprocally, when stimulated in the presence of IL-12, most T_H2 cells up-regulated T-bet and acquired *IFNG* acetylation and expression while continuing to produce IL-4. These findings indicate that most in vivo-primed human T_H1 and T_H2 cells

maintain both memory and flexibility of cytokine gene expression.

Several studies have now provided convincing evidence that most T_H cells, in particular T_H17 cells, have a great degree of flexibility. For instance, T_H17 cells from the synovial fluid of oligoarticular-onset juvenile idiopathic arthritic patients can shift in vitro from the T_H17 to the T_H17/T_H1 or T_H1^* phenotype (Cosmi et al. 2011). In patients with allergic asthma, T_H17 cells also produce IL-4, suggesting a shift from T_H17 to T_H17/T_H2 mixed phenotype. Finally, IL-1 β can induce conversion of IL-10 $^+$ T_H17 into more inflammatory IFN- γ^+ T_H17 cells (Zielinski et al. 2012). These examples of flexibility in cytokine gene expression underline the robust and adaptive behavior of effector T cells in the immune response.

There is growing evidence that plasticity is maximal at early stages of differentiation. Consistent with this notion, circulating CCR7 $^+$ T_{CM} cells and CXCR5 $^+$ T_{FH} -like cells, which represent subsets of less differentiated T cells characterized by hypoacetylated cytokine genes, have the potential to differentiate to either T_H1 or T_H2 when appropriately stimulated (Messi et al. 2003; Rivino et al. 2004). Plasticity in T_{FH} cells is consistent with the finding of subsets of CXCR5 $^+$ T cells that have characteristics of T_H1 , T_H2 , or T_H17 cells (Morita et al. 2011). Plasticity can be progressively lost as cells reach terminal differentiation stages. For instance, T_{EM} cells expressing CRT $_{H2}$ and producing high levels of IL-4 are unable to up-regulate T-bet and to acquire IFN- γ -producing capacity (Messi et al. 2003). Although irreversible commitment appears to be the exception rather than the rule, these findings suggest that certain conditions of stimulations in vivo exist that lead to irreversible commitment. These conditions may be found at special sites in the body or may develop in particular pathologic situations. Sites of chronic inflammation may represent antigen and cytokine rich environments in which effector T cells are continuously stimulated. Indeed, repeated stimulations of mouse CD4 T cells in the presence of IL-12 or IL-4 enhance cytokine production and lead to strongly polarized T_H1 or T_H2 cells (Murphy

et al. 1996). It would be interesting to determine whether reduced plasticity is a characteristic of tissue-resident memory T cells, which in humans also represent a prominent subset of differentiated T cells (Thome and Farber 2015). Further studies are required to assess the plasticity of T cells at different stages of differentiation and in different anatomical compartments.

It is important to consider that plasticity is influenced by the expression of cytokine receptors and transcription factors in the responding T cells and by the availability of polarizing signals in the tissue where antigen reencounter occurs. For instance, T_H17 cells that express IL-12R and IL-1R can acquire a T_H1^* phenotype in response to microbes that elicit production of IL-12 or IL-1, a situation that may be found in the course of coinfections. It can be speculated that, in the context of challenge by a related pathogen in a different tissue, the property of plasticity may confer an evolutionary advantage.

T-CELL PLASTICITY AND INTRACLONAL DIVERSIFICATION

The finding that the human T-cell response, even to a single microbial pathogen, is heterogeneous could be explained by priming of multiple clonotypes, each undergoing a distinct differentiation pathway determined by the nature and strength of antigen, costimulatory, and cytokine signals. Alternatively, it is possible that within an expanding T-cell clone the proliferating cells might acquire different fates as the consequence of stochastic stimulation and plasticity. The “one cell—one fate” and “one cell—multiple fates” models were tested in humans by analyzing the distribution of clonotypes within memory T-cell subsets (Becattini et al. 2015).

By combining antigenic stimulation and TCR deep sequencing on isolated subsets of T_H1 , T_H2 , T_H1^* , and T_H17 memory T cells, it was shown that the same clonotype could be found in different subsets. *C. albicans*-specific clonotypes present in the T_H17 subset were also found in the T_H1^* and T_H2 subsets (Fig. 2A). This finding was strengthened by the isolation of T-cell clones with identical TCR $\alpha\beta$, but different surface marker and effector function, and

by in vitro priming experiments showing that a single naïve T cell could generate multiple fates in one round of stimulation with *C. albicans* (Becattini et al. 2015). The intraclonal differentiation toward multiple fates was even more striking in the case of memory T cells induced by the tetanus toxoid vaccine with several TCR V β sequences being found in T_H1 , T_H2 , T_H1^* , and T_H17 subsets (Fig. 2B).

Given the overwhelming evidence for intraclonal diversification, how can we explain highly polarized responses to pathogens? Interestingly, the dominant T_H17 response induced in vivo by *C. albicans* was because the clones within this subset were more expanded, rather than more numerous, as compared to the clones in the other subsets. This finding would be consistent with the initial priming of multiple types of T cells, followed by the selective expansion of T_H17 cells, which may be determined by the prevailing cytokines at the site of priming or in the tissue where the pathogen is encountered. Interestingly, this was not the case for T cells primed by a weak vaccine such as tetanus toxoid that failed to select for a particular type of polarized cells. The generation of a range of effector and memory T cells within the same clone may be consistent with an early diversification or with the priming of uncommitted CD4 T-cell clones that subsequently progress along multiple differentiation pathways (Lanzavecchia and Sallusto 2000).

In the context of heterogeneous T-cell responses, an important question that needs to be addressed is whether the generation of functionally diverse T-cell subsets is advantageous for the host. Although failure to generate the right class of T_H cell response may lead to susceptibility to infections, it is possible that the induction of a spectrum of effector and memory T cells endowed with different migratory capacities would provide the host with a range of differentiated precursors to be recruited and expanded where necessary.

Moving ahead, the challenge is to dissect in terms of time and space the events that determine the functional heterogeneity of T-cell responses in humans. Improved technologies for obtaining information on antigen specific-

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Figure 2. Graphical representation of the extent of sharing among T-cell antigen receptor (TCR) clonotypes of memory T_H1 (red), T_H2 (yellow), T_H1^* (blue), and T_H17 (green) cells primed by *Candida albicans* (A), or tetanus toxoid (B). Outer rings and connecting lines identify clonotypes shared between two or more T-cell subsets. Data are representative of single donors. (From Becattini et al. 2015; modified, with permission.)

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ity, TCR sequence, and phenotype from single T cells will likely unravel even further degrees of interclonal and intraclonal heterogeneity in the T-cell response to microbial pathogens and vaccines (Han et al. 2014). Resolving the behavior of T-cell populations at the level of individual cells and in the context of protective or pathological immune responses is a major challenge that holds promise for a better understanding of the immune system and for immune interventions.

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