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Mechanisms underlying helper T-cell plasticity: Implications for immune-mediated disease

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CD4 helper T cells are critical for proper immune cell homeostasis and host defense but are also major contributors to immune and inflammatory disease. Arising from a simple biphasic model of differentiation (ie, T_H1 and T_H2 cells). A bewildering number of fates seem possible for helper T cells. To what extent different helper cell subsets maintain their characteristic gene expression profiles or exhibit functional plasticity is a hotly debated topic. In this review we will discuss how the expression of "signature cytokines" and "master regulator" transcription factors do not neatly conform to a simple helper T-cell paradigm. Although this might seem confusing, the good news is that the newly recognized complexity fits better with our understanding of immunopathogenesis. Finally, we will discuss factors, including epigenetic regulation and metabolic alterations, that contribute to helper cell specificity and plasticity. (J Allergy Clin Immunol 2013;131:1276-87.)

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Abbreviations used

Bcl6:	B-cell lymphoma 6
Foxp3:	Forkhead box protein 3
HIF:	Hypoxia-inducible factor
H3K4me3:	Histone 3 lysine 4 trimethylation
H3K27me3:	Histone 3 lysine 27 trimethylation
IRF:	Interferon regulatory factor
mTOR:	Mammalian target of rapamycin
mTORC:	Mammalian target of rapamycin complex
PU.1:	SFFV proviral integration 1
Rorγt:	Retinoic acid receptor–related orphan receptor γt
T-bet:	T-box transcription factor
T_{FH}:	Follicular helper T
Treg:	Regulatory T

CD4 T cells are critical for host defense, but in addition to their key role as helper cells, they can also be troublemakers, driving autoimmune diseases, asthma, and allergies.[1,2] Classically, we viewed helper T cells as having 2 major fates, T_H1 and T_H2 cells (Fig 1, *A*), but we now know that the opportunities for helper diversity are far greater than just these 2 outcomes. The new diversity includes T_H17, T_H9, and T_H22 cells; follicular helper T (T_{FH}) cells; and different types of regulatory T (Treg) cells (Fig 1, *B*).[2-6] In addition, the emerging data point to the increased flexibility of these subsets. Fortunately, we are also beginning to understand the molecular basis of this complexity. This newer appreciation is not just pertinent for understanding the basic aspects of T-cell biology; on the contrary, the new insights provide a more sophisticated understanding of immune-mediated disease and new opportunities for therapy. In this review we discuss helper cell differentiation decisions and how the regulation of helper cell specificity pertains to susceptibility to immune and inflammatory disease. We will consider the intrinsic and extrinsic factors that drive specification and the mechanisms that influence flexibility. Of particular interest with respect to the issue of plasticity are advances in epigenetic technologies as they pertain to T-cell biology. The insights provided are especially relevant for immunologically mediated diseases, in which both genetic and environmental factors play key roles in susceptibility.

COMPLEXITY OF HELPER CELL FATE DETERMINATION

For more than 2 decades, it has been recognized that CD4 T cells specialize in response to microbial challenges. The first subsets recognized were denoted T_H1 and T_H2 cells based on the selective production of 2 cytokines, IFN-γ and IL-4, respectively.[7] This T_H1/T_H2 paradigm was reasonably useful for initial categorization of mechanisms involving elimination of microbial pathogens. For instance, T_H1 cells are critical for the clearance of many intracellular pathogens, such as *Leishmania major* and

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Terms in boldface and italics are defined in the glossary on page 1277.

Mycobacterium tuberculosis.[8,9] Similarly, T_H2 cells were found to be important for elimination of helminthic parasites, such as *Nippostrongylus brasiliensis* and *Schistosoma mansoni*.[10]

At first, the pathogenesis of immune-mediated disease also seemed to fit within this paradigm. Human asthma, as well as animal models of allergic airway inflammation, revealed the importance of cytokines produced by T_H2 cells, namely IL-4, IL-5, and IL-13[11-14]; the contribution of these various cytokines to the pathophysiology of airway inflammation, eosinophilia, fibrosis, and other responses is well recognized.[15-17] Moreover, ***genome-wide association studies*** of asthmatic patients have revealed the association of DNA variants in the T_H2 cytokine ***locus*** and the *IL4R* gene with susceptibility to asthma.[18-20] Equally important has been the successful use of therapeutic mAbs directed against IL-5 (mepolizumab) and IL-13 (lebrikizumab).[21-24] Such discoveries clearly point to the pathophysiologic role of these cytokines, although it is also clear that not all patients respond to these agents. Such findings clearly point to the additional complexity of these diseases.

Initially viewed as one of the products of T_H2 cells, IL-9 is an important factor that promotes mucus production; its expression is increased in the airways of asthmatic patients.[25-27] Recently, however, IL-9 has been found to be produced in a subset of cells that is distinct from classical T_H2 cells.[5,28] These cells are dubbed T_H9 cells, but precisely how they relate to other subsets and the extent to which they constitute a stable subset remain to be determined.

It is also well appreciated that IgE is a central player in the pathophysiology of allergies and asthma.[24,29] Although the generation of IgE-producing B cells is a well-accepted action of IL-4, it is also becoming clear that a specific population of CD4 T cells are important for providing B-cell help. These cells are designated as T_{FH} cells and are identified based on their location in ***germinal centers*** and surface expression of the molecules CXCR5 and programmed cell death 1 *(PD-1)*.[4,30-32] IL-21 has been referred to as the signature cytokine for T_{FH} cells, but IL-21 is also produced by T_H1 and T_H17 cells.[33,34] In addition, T_{FH} cells can produce cytokines made by other subsets, including IFN-γ, IL-4, IL-17, and IL-10.[4,35,36] Therefore T_{FH} cells might have both overlapping and distinct contributions to disease because they can make T_H1 and T_H2 cytokines but also contribute specifically to antibody formation. Because they do not localize to tissues, the direct effects of their cytokine production are unlikely to be with regard to tissue inflammation but rather with regard to isotype-specific antibody production. Accordingly, genetic mutations in ***inducible costimulator (ICOS)*** or SLAM-associated protein *(SAP)*, genes expressed by T_{FH} cells that are necessary for interaction with B cells, result in a loss of T_{FH} cell development and thus antibody production.[37-39] In addition, patients with mutations in ***signal transducer and activator of transcription (STAT)*** 3 have reduced T_{FH} cell numbers, which might contribute to the altered antibody repertoire they display.[40]

The attempt to link common autoimmune diseases with a simple T_H1/T_H2 paradigm has been even more problematic.[41] Certainly, there is evidence that excessive activation of T_H1 cells contributes to organ-specific autoimmune diseases.[42] However, a number of lines of evidence suggest that autoimmune mechanisms cannot be reduced to the action of T_H1 cells alone. In particular, the discovery of a new cytokine, IL-23, led to the recognition of a new subset of helper T cells and their importance in autoimmunity.[43]

GLOSSARY

BLIMP1: A key transcription factor for the differentiation of B cells into antibody-secreting plasma cells within lymphoid organs.

EPIGENETICS: The term was coined by Waddington before the era of modern molecular biology. It has come to denote hereditable changes in phenotype or gene expression without changes in DNA sequence.

EPIGENOME: The term indicates the status of the genome-wide chemical changes to the DNA and histone proteins.

GENOME-WIDE ASSOCIATION STUDIES: Cohorts of patients with and without a given disease are examined across the entire genome for single nucleotide polymorphisms that are overrepresented in patients with the disease. This identifies regions of the genome that contain a variant gene or genes that confer disease susceptibility. Candidate genes are then selected based on how closely they are associated with the disease and whether their biologic function correlates with the disease under study.

GERMINAL CENTER: An area within a lymphoid follicle where affinity maturation occurs. B cells activated by antigen and helper T cells migrate into germinal centers. Somatic mutation of V region genes in these B cells generates antibodies with different affinity for antigen. Binding of B cells to antigen presented on follicular dendritic cells rescues these B cells from apoptosis. B cells with the highest affinity for antigen will have a survival advantage, which results in an average increase in the affinity of antibodies for antigen during the immune response.

INDUCIBLE COSTIMULATOR (ICOS): ICOS is a member of the CD28 family of costimulatory receptors on T cells. ICOS binds to ICOS ligand on antigen-presenting cells and promotes effector responses. Mutations in the ICOS gene have been reported in patients with common variable immunodeficiency.

IMMUNE DYSREGULATION–POLYENDOCRINOPATHY–ENTEROPATHY–X-LINKED SYNDROME: *FOXP3* mutations lead to immune system dysregulation in this disorder. Features include early-onset diabetes, diarrhea, and failure to thrive. Newborns have an eczematous rash. Serious infections can occur. Laboratory abnormalities include high IgE, normal IgG, normal IgM, and normal IgA levels. T and B subsets are also normal. Autoimmune hemolytic anemia, neutropenia, and thrombocytopenia can occur. Female carriers are usually healthy.

LOCUS: The position in a chromosome of a particular gene or allele.

MUCOCUTANEOUS CANDIDIASIS: Persistent superficial candidal infections of the mucous membranes, skin, and nails. Other defects that are associated with mucocutaneous candidiasis include CARD9/Dectin-1 deficiency and *AIRE* gene defects. Patients have selective anergy to *Candida* species on delayed-type hypersensitivity testing.

NAIVE CD4 T CELLS: T cells that have completed maturation in the thymus but have not yet encountered foreign antigen. They are characterized by no effector function, no cell cycling, and high expression of CCR7 and CD62 ligand (L-selectin and peripheral lymph node homing receptor). Their major CD45 isoform is CD45RA.

RAPAMYCIN: An immunosuppressant drug used in renal transplantation as prophylaxis against organ rejection.

SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION (STAT): Transcription factors that are a part of the Janus kinase (Jak)–STAT pathway. Many cytokines use Jak-STAT pathways for signaling. There are 7 STATs (1-4, 5a, 5b, and 6). The discovery of the Jak-STAT pathway came from analyses of interferon signaling.

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