Recently Discovered T Cell Subsets Cannot Keep Their Commitments

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ABSTRACT
After activation by antigen/MHC (signal 1) and CD28-dependent co-stimulation (signal 2), resting CD4+ T cells commit to one of a variety of functionally and molecularly defined phenotypes. Two long established CD4 phenotypes, Th1 and Th2 cells, have been regarded as terminally differentiated formats. Recently, two additional phenotypes, tissue-protective regulatory (Tregs) and tissue-destructive Th17 T cells, have also been discovered, and neither represents a terminally differentiated phenotype. Rather, Tregs and Th17+cells respond to cues provided by the inflammatory texture in which these cells reside. We review the important scientific and therapeutic implications of these differences herein.


PARADIGM LOST
Naive CD4+ T cells are activated after interaction of T cell receptors with antigen/MHC (signal 1) and co-stimulation (signal 2). Depending on the fine texture of the inflammatory milieu in which antigen activation takes place, these newly activated T cells commit to one of several CD4+ subset phenotypes (Figure 1). In addition to the classical Th1 and Th2 CD4+ phenotypes, regulatory (Treg) and Th17 phenotypes have been more recently identified and characterized. Whereas effector T cells such as the Th1, Th2, and Th17 phenotypes exert injurious, cytopathic effects on tissues, the Treg phenotype restrains or “regulates” effector T cell–mediated tissue injury.

IL-2–producing Th1 and IL-4–producing Th2 are considered terminally differentiated phenotypes; that is, once they commit, there is no “going back.” Th1 and Th2 cells were once held responsible for diametrically opposing functions in tissue injury. Th1 cells were the most potent mediator and principle architects of CD4-dependent tissue-destructive reactions, whereas Th2 cells were thought to protect antigen-bearing tissues from Th1 cells. This paradigm was supported by data first coming from the work of Mosmann and colleagues and subsequently supported by numerous laboratories showing a prominent Th1 and less potent Th2 response in rejecting allografts harvested from untreated hosts or in tissue undergoing T cell–dependent autoimmune injury. In tissues obtained from tolerant hosts, a diametrically opposing scenario in which a prominent Th2 and diminutive Th1 response is manifest. Although this scenario is easy to remember, Th1 cells attack while Th2 cells protect “foreign” tissues, it is not altogether true. Th1 cells, γ-IFN or IL-2 (Th1 cell products) are not required for rejection. Indeed, anti–IL-12 treatment, used to neutralize the Th1-promoting effects of IL-12, does—as expected—dramatically ablate the antidonor Th1 response and enhance the antidonor Th2 response, but rejection of MHC-mismatched tissues is not delayed. In short, rejection of MHC-mismatched allografts can be conducted by T cells in the Th2 mode.

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TREGS AND IMMUNE TOLERANCE

CD4\(^+\) Tregs, not Th2 cells, are crucially important in restraining the destructive effects of cytotoxic T cells (Figure 2). In keeping with new dogma that CD4\(^+\) T cells take cues from the cytokine environment, a TGF-\(\beta\)–dominant environment leads naive CD4\(^+\) T cells to commit to the regulatory phenotype. Indeed, this commitment is obtained by the TGF-\(\beta\)–triggered expression of the lineage-unique Foxp3 lineage specification factor.\(^8,9\) Whereas newly antigen-activated and TGF-\(\beta\)–stimulated, mature, naive CD4\(^+\) T cells are induced to express the Treg phenotype, a population of Foxp3\(^+\) “natural” Tregs also emerge from the thymus with potent regulatory properties.\(^7\) Hence, two populations, induced and natural Tregs, exist. Unfortunately, a single convenient cell surface marker that discriminates induced from natural Tregs has not been found, thereby creating considerable difficulty in establishing the individual roles of induced and natural Tregs in the induction and maintenance of tolerance.

Humans born with loss-of-function or deletional mutations of Foxp3 rapidly develop devastating forms of autoimmunity.\(^7\) In mice, a similar situation pertains, and destruction of Foxp3 T cells in adult mice also leads to prominent autoimmunity. There can be no doubt that Foxp3\(^+\) Tregs are crucial to the development and maintenance of tolerance, although a role for other immunoregulatory cells is not precluded. In fact, other regulatory cells are well characterized,\(^10\) although their precise role in immune tolerance is less certain. The means by which Tregs restrain effector T cells from destroying antigen-bearing tissue seems multifactorial and includes cell–cell interactions with both effector T cells and dendritic cells as well as release of immunosuppressive cytokines, such as TGF-\(\beta\) and IL-10, and the generation of adenosine catalyzed by subset-specific expression of ectoenzymes.\(^8,9,11\) Indeed, synchronized expression of the CD39 and CD73 enzymes that coordinately catalyze the generation of adenosine may be the most precise cell surface signature for mouse Tregs.\(^11\)

TH17 CELLS: A NEW POTENT EFFECTOR T CELL POPULATION

Remarkably, TGF-\(\beta\), in the presence of IL-6\(^12\) or IL-21\(^12\), promotes commitment of naive murine and human CD4\(^+\) T cells to the highly cytotoxic Th17 phenotype (Figure 1). In humans, other proinflammatory cytokines, including TNF-\(\alpha\) and IL-1\(\beta\) in addition to IL-6, elicit a similar effect.\(^13\) Indeed, the presence of these proinflammatory cytokines precludes commitment of naive CD4\(^+\) T cells to the regulatory phenotype.\(^2,12,14,15\) Regulation of the commitment of naive CD4\(^+\) T cells to the Th17 phenotype is governed by unique lineage specification factors within the retinoic acid receptor–related orphan nuclear receptor family.\(^16\) In this case, two specification factors,
RORγt and to a lesser extent RORα, conspire to direct commitment to the Th17 phenotype. Th17 cells express a variety of potent proinflammatory cytokines including but not limited to IL-17A, IL-17F, and osteopontin. IL-23, although not necessary for the commitment to the Th17 phenotype, is essential to stabilize this commitment. Th17 cells are potent effector cells, perhaps more potent than Th1 cells, in several but not all autoimmune states. A vicious cycle in respect to Th17-dependent tissue destruction is formed through the ability of Th17 cells to stimulate antigen-presenting cells to express IL-6 and by the ability of IL-6 to stimulate commitment of naïve T cells to the Th17 phenotype.

Th17 cells participate in extremely inflamed forms of T cell–dependent tissue injury. Within these toxic environments, the ability of Foxp3+ T cells to restrain effector T cells from executing tissue injury is severely compromised. Owing to the violence of Th17-dependent tissue injury, a means to target Th17 selectively for therapy is a potentially important unmet need. The precise role of Th17 cells in rejection is under study by our and other laboratories. Preliminary experiments suggest, as is the case in autoimmune diseases, that Th17 cells participate in rejection.

CAN T CELLS KEEP THEIR COMMITMENTS?

The pivotal role of particular cytokines in dictating the precise nature of the commitments of naive T cells undergoing antigen activation is now clear for the Th17 as well as for the Treg, Th1, and Th2 phenotypes (Figure 1). Thus, the role of cytokines in directing differentiation or commitment to the Th17 and Treg phenotypes is new but also classical in the sense that cytokines are widely known to influence the expression of lineage-determining specification-type transcription factors.

Unprecedented is the recent discovery that the cytokine and inflammatory milieu in which Tregs and Th17 cell function alters the molecular and functional phenotype of these committed, presumably terminally differentiated T cells. For example, IL-27 stimulates Th17 cells to express IL-10, an immunosuppressive cytokine, and thereby negates the ability of these cells to act as tissue-destructive effector cells. Moreover, Th17 cells require IL-23 to expand and maintain viability. Thus, maintenance of the Th17 viability of the tissue-injuring effector phenotype is not immutable, because Th17 cells take all important cues from the state of innate immunity in the microenvironment in which they reside. In a parallel manner, stimulation of Foxp3+ regulatory T cells with an agonist type anti–T cell Ig mucin domain 1 mAb triggers loss of immunoregulatory function and downregulation of Foxp3 and TGF-β by Tregs.

In short, a detailed knowledge of the molecular and functional phenotype of previously unknown T cell subsets has emerged from recent work. Moreover, the fine texture of inflammation within the milieu of antigen-driven CD4+ T cell responses in triggering commitment to and destabilization from tissue-destructive and tissue-protective CD4 subset phenotypes shapes the intensity of CD4-dependent immunity. This new information suggests shortcomings in many time-honored strategies to gain T cell tolerance and new strategies to achieve this elusive goal in transplant recipients and patients with autoimmune diseases.

Immunologists, with good reason, have directly targeted T cells in attempts to subdue autoimmunity and allograft rejection or stimulate cancer immunity. Although these strategies are well founded and have spurred major advances in treatment, the opportunity to use parallel strategies to modify the state of innate immunity in which T cell activation or re-activation has not received equal attention. The road untaken may be laden with opportunity. For example, we tested the hypothesis that inflammatory mechanisms directly trigger the loss of immune tolerance to islets and β cell–destructive insulinitis in the NOD mouse. Treatment with α1 antitrypsin, an agent that dampens inflammation but does not inhibit T cell activation directly, ablates invasive insulitis and restores euglycemia, immune tolerance to β cells, normal insulin signaling, and insulin responsiveness in NOD mice with recent-onset type 1 diabetes by favorable changes in the inflammation milieu. Indeed, the functional mass of β cells expands in α1 antitrypsin–treated diabetic NOD mice.

DISCLOSURES

None.

REFERENCES

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