Emerging topics and new perspectives on regulatory and effector T cells

It is well accepted that the balance of immunity between effector and regulatory T cells determines the outcome of autoimmune and chronic inflammatory diseases. Concerning the topic of ‘Regulatory and Effector T Cells’ as published in this issue of Journal of Molecular Cell Biology, several investigators have provided important new information.

T-helper 1 (Th1) and Th2 cells represent the classical type of Th or effector cells. However, recent studies have also identified several new cell subsets of Th cells, including IL-9-producing T (Th9), IL-17-producing T (Th17), IL-22-producing T (Th22), and T follicular helper (Tfh) cells, extending the Th cell structure. Given their crucial role in the pathogenesis of autoimmune and inflammatory diseases, Th17 cells have received much attention. They mainly express IL-17A, but co-express IL-17B, IL-17E (IL-25), IL-17F, and IL-22. IL-26 is produced by human but not mouse Th17 cells. IL-17A is significantly more potent in initiating signaling and causing autoimmune responses than other cytokines produced by these cells. The differentiation of mouse Th17 cells needs the combination of IL-6 and transforming growth factor-beta (TGF-β) (Bettelli et al., 2006), although IL-6- or TGF-β-independent pathways may also contribute to Th17 cell differentiation. The role of TGF-β in human Th17 cell differentiation is still controversial. Of note, the IL-21 and IL-1 signal pathways seem to be important in initiating Th17 cell development. IL-21 and IL-23 are also known to sustain and expand Th17 cells.

Dr Rychel’s group provides an updated account of the differentiation and function of Th17 cells, particularly during lung injury and inflammatory disease. They demonstrated that lung injury or allergen exposure leads to NLPR3 activation, with formation of the NLPR3 inflammasome complex and caspase-1 activation resulting in mature IL-1β, which may elicit IL-17 production.

Traditionally, asthma is elicited by Th2 cells. It is still unclear whether Th17 cells work independent or together with Th2 cells in the development of asthma. They suggest that Th17 cells promote asthma through modulation of Th2 cells. In fact, IL-17E or IL-25, another IL-17 member, can induce Th2 cytokines and promote allergy. It is also possible that IL-17 regulates allergic responses independent of Th2 cells but Th2 cells promote asthma through Th17 cells since IL-4 does regulate IL-17 levels.

It has been widely accepted that Tregs are critically involved in immune tolerance and homeostasis. Although this concept was suggested in early 1970s, it was resuscitated in 1990s when thymus-derived CD4+CD25+ cells were identified as natural Tregs (nTregs) (Sakaguchi et al., 1995). While Foxp3 has been identified as a unique marker and functional transcription factor for these cells, studies on Tregs have been greatly accelerated. As Treg frequency and functional alterations are associated with many autoimmune diseases, the manipulation of these cells provides a promising treatment possibility for autoimmune diseases. In addition, use of Tregs may be valuable in the prevention of graft rejection of organ transplantation and graft-versus-host disease (GVHD).

Dr Bluestone’s group further provides information on the potential use of these cells in the clinic. They reported that by 2011, three clinical trials have been undertaken to test the safety of Treg therapy in GVHD, and all have demonstrated promising safety and efficacy profiles. Compelling evidence from animal models and human patients demonstrates that tolerance to allogeneic transplant can be achieved by reconditioning the immune system, so that troublesome global immunosuppression can be minimized or completely stopped. They emphasize that a sound trial design should harness the tolerogenic potential of Tregs while minimizing risks. One potential risk with Treg therapy is that these cells can purportedly exhibit some measure of plasticity. Since little is known about the appropriate doses of Tregs in humans, initial trials should be safety-centered evaluating effect of increasing...
dose of Treg therapy on graft rejection, infection, and malignancy. A carefully planned trial will pave the way for future trials evaluating efficacy of Treg therapy in inducing transplant tolerance.

Despite exclusive functional characteristics of nTregs in the controlling of immune responses, it is notable that infusion of nTregs to established autoimmune diseases had poor therapeutic effects (Zhou et al., 2010). nTregs are also less therapeutic to Th17-mediated disease (Huter et al., 2008). Moreover, low frequency of nTregs presents a formidable challenge for cell therapy. Fortunately, induced Tregs provide a potential solution to this vexing problem. IL-10-induced Tr1 cells (Groux et al., 1996) and TGF-β-induced iTregs (Zheng et al., 2002) represent two main forms of induced Tregs.

Dr Zheng and colleagues have systemically reviewed the development and function of iTregs. iTregs share many of the phenotypic and functional characteristics with nTregs, but there are notable differences. Infusion of iTregs, particularly antigen-specific iTregs not only prevented, but ameliorated the autoimmune diseases including Th17-mediated diseases in a manner that proved somewhat superior to that of nTregs. However, others have reported that nTregs are superior to iTregs in the prevention of acute GvHD model, and that the instability of iTregs accounted for their inability to prevent disease. Floess et al. (2007) also reported that Foxp3 promoter DNA CpG methylation in iTregs affects their stability. However, recent study observed that DNA CpG methylation in Foxp3 gene locus did not affect Foxp3 expression and maintenance (Lu et al., 2011). In contrast, histone modification of Foxp3 gene locus may indeed contribute to Foxp3 activation and function in iTregs. The stability and functionality of both Tregs under inflammatory conditions need to be further investigated.

The relationship between Tregs and TGF-β is further discussed by Dr Dat Tran. The author presented data supporting the trident of TGF-β in Treg-mediated inhibition of immune activation, conversion of cell differentiation and self-survival. Given the similarities in the phenotype of mice that are deficient in TGF-β pathway and those that lack Tregs due to mutations in Foxp3, the obvious focus has been on the association of TGF-β in Treg functions. Even with the generation of mutant mice that specifically lack TGF-β only in Foxp3+ cells, the data remains inconclusive and controversial. The author’s recent discovery of the function of LRRC32 as a receptor for TGF-β on activated Tregs will allow a novel opportunity to understand the necessity of expressing TGF-β on their surface. Targeting LRRC32 will selectively affect just one of TGF-β’s pathways and therefore offer a unique opportunity to manipulate Tregs without global disruption of the myriad pathways affected by this pleiotropic cytokine. Moreover, since Tregs are comprised of a heterogeneous population of subsets, some of which have been shown to demonstrate instability and are potentially pathologic, the author suggests that bona fide Tregs are those with the ability to express membrane TGF-β.

Drs Li and Brandley discuss the difficulties in transplanting nTregs, particularly for treatment of type 1 diabetes (T1D). In addition to the generalized concerns as described above, the clinical use of nTregs in T1D poses a more specific problem. Because nTregs are highly dependent upon IL-2 for homeostasis, IL-2/IL-2R expression defects in T1D present a critical drawback for nTreg treatment. The authors propose that in vitro differentiated iTregs, which have been shown to reverse hyperglycemia and/or prevent diabetes onset, make an obvious alternative choice. iTregs could be an ideal translatable candidate for T1D therapy because these cells can be easily generated and more stable. Importantly, they found that iTregs developed into memory cells that were long-lived in adoptive recipients and maintain active protection. Because of their memory characteristics, these cells utilize distinctive mechanisms of homeostatic regulation, in particular, reliance on IL-7 for maintenance instead of IL-2. This allows for circumvention of the IL-2 dependence associated with nTregs, offering a remarkable advantage for therapeutic use of iTregs and is particularly promising cell-based therapy for T1D.

Double negative (DN) Tregs, a rare cell population in mice and humans that express an αβ T cell receptor (TCR) but do not express CD4, CD8, or NK cell markers, are another subset of Tregs. DN Tregs are unique antigen-specific Tregs that can prevent allograft rejection and inhibit autoimmune responses. In their review, Drs Juvet and Zhang discuss recent progress in the DN Treg field, with a particular focus on the mechanisms by which they prevent allograft injury by T cells of the same antigen specificity. This process involves the binding of DN Treg TCR with a peptide—major histocompatibility complex (MHC) complex on an antigen-presenting cell. DN Tregs can acquire the peptide—MHC complex via trogocytosis and then present it to responder T cells sharing the same antigen specificity. When this occurs, specific killing of the responder T cells via Fas–Fas ligand interaction is the result. The authors also discussed new evidence showing that DN Tregs can prevent the development of autoimmune diabetes in a variety of mouse models. A significant challenge faced by those working in this field is the need to identify a marker specific to DN Tregs with regulatory properties.

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References