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The Yin and Yang of Signaling in T_{regs} and T_H17 Cells

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Abstract

Substantial advances in our understanding of the developmental and functional relationship between regulatory T cells (T_{regs}) and T helper 17 (T_H17) cells and their potential clinical applications have been made. In response to these break-throughs, the second international conference entitled “China Tregs/Th17 2010 Shanghai Conference,” held in Shanghai, China, was dedicated to this topic. Various types of T_{regs} and T_H17 cells, as well as their relevant cytokines, were discussed. Here, we summarize some of the findings shared at the conference, specifically focusing on the biology of T_H17 cells, including interleukin-17 (IL-17)–producing innate cells, T_{regs}, and the factors that control the critical balance between T_{regs} and cells of the T_H17 lineage.

Helper T cells that have diverse effector functions are differentiated from naïve CD4⁺ T cells upon stimulation with antigen in the presence of different cytokines, which are produced by cells in the microenvironment (1, 2). For example, T helper type 1 (T_H1) cells are induced by interferon- γ (IFN- γ) and propagated by interleukin-12 (IL-12). On the other hand, T_H2 cells require IL-4 for their differentiation. In addition to these well-characterized lineages, there exists a relatively recently characterized subset of T helper cells, T_H17 cells (3–7). It has been well demonstrated that T_H17 cells are involved in the induction of several autoimmune diseases, including collagen-induced arthritis, experimental autoimmune encephalomyelitis (EAE), and inflammatory bowel diseases (8). T_H17 cells also have the ability to clear bacterial infections in the intestine and the airways (8). T_H17 cells require specific cytokines and transcription factors for their development. IL-6 and IL-21 in combination with transforming growth factor β (TGF- β), or IL-6 and IL-23 together with IL-1 β initiate the differentiation of T_H17 cells in vitro through the increased abundance of the transcription factor retinoic acid receptor–related orphan receptor γ t (ROR γ t) (9, 10). In addition, IL-23 synergizes with TGF- β –initiated signals to induce the production of IL-17

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and other T_H17 signature cytokines, such as IL-22 and IL-23, to foster the development of T_H17 cells.

Vijay Kuchroo (USA), the keynote lecturer on T_H17 cells, together with Chen Dong (USA) and Kazuo Okamoto (Japan), provided insights into the molecular basis of the development of T_H17 cells, including the essential role of I κ B α (11). Kuchroo proposed a three-step model for the differentiation of T_H17 cells in which induction is mediated by TGF- β and IL-6, amplification is dependent upon IL-21, and stabilization is achieved by IL-23 (Fig. 1). He also suggested that not only are T_H17 cells highly proinflammatory T cells that are capable of inducing tissue inflammation and autoimmunity but they are also excellent helpers in humoral responses, by inducing the formation of germinal centers and antibody class switching by B cells. Gang Pei (China) reported that microRNA326 (miR-326), a microRNA found in the gene that encodes β -arrestin1, promotes the differentiation of T_H17 cells. He further demonstrated that the extent of expression of miR-326 correlates with disease severity in patients with multiple sclerosis (MS) and in mice with EAE, a model of MS (12). On the other hand, Xuetao Cao (China) discussed how the T_H17-mediated pathology of autoimmune disease could be blocked through the manipulation of the dendritic cell (DC) maturation processes. He described a molecule called rhomboid domain-containing protein (RHBDD3), which is an inhibitor of DC maturation and the production of the proinflammatory cytokines IL-6 and tumor necrosis factor- α (TNF- α) in response to the stimulation of Toll-like receptors (TLRs). He concluded that RHBDD3 contributes to the balance of T_{regs}, T_H1 cells, and T_H17 cells by controlling DC maturation and IL-6 production through the inhibition of nuclear factor κ B (NF- κ B) activation, which subsequently prevents the development of T_H17-mediated autoimmune diseases.

IL-17 is produced not only by T_H17 cells. Several speakers reported that cells of the innate immune system can also produce IL-17 and thus provide a link between the IL-17 cytokine family and the innate immune response. Gerard Eberl (France) showed that proinflammatory lymphoid cells that express the T_H17 cell-associated transcription factor ROR γ t and that are enriched in the intestinal lamina propria consist not only of adaptive T_H17 cells, but also of innate lymphoid cells (ILCs), such as lymphoid tissue inducer (LTi) cells and IL-22-producing NKp46⁺ cells. These innate lymphoid cells contribute to the maintenance of a finely tuned equilibrium between intestinal symbionts and the immune system (13). Daniel Cua (USA) further showed that $\gamma\delta$ T cells and LTi cells constitutively express both ROR γ t and the IL-23 receptor (IL-23R) and that they are poised to release IL-17 and IL-22; thus, they serve as sentinels in peripheral mucosal tissues. Kingston Mills (Ireland) demonstrated that not only can IL-1 α and IL-1 β synergize with IL-23 to promote the secretion of IL-17 from memory CD4⁺ T cells, but that these cytokines also induce the production of IL-17 by $\gamma\delta$ T cells, even in the absence of engagement of the T cell receptor (TCR). IL-17-producing $\gamma\delta$ T cells are found at high frequency in the brains and spinal cords of mice with EAE, where they function with T_H17 cells to mediate autoimmune inflammation (14). Furthermore, it appears that $\gamma\delta$ T cells are an important source of innate IL-17 and IL-21, which act in an amplification loop early in the immune response and promote further production of IL-17 by T_H17 cells. Consistent with this observation, Stephen Miller (USA) suggested that IL-17-producing $\gamma\delta$ T cells play a substantial role in the pathogenesis of

EAE. Moreover, Akihiko Yoshimura (Japan) reported that IL-17-producing $\gamma\delta$ T cells induce a delayed phase of brain ischemia (15), and Dale Umetsu (USA) showed that IL-17-producing CD4⁺ natural killer T (NKT) cells are required in ozone-induced airway hyperreactivity (AHR) (16).

T_H17 cells and members of the IL-17 family of cytokines play important roles not only in autoimmune disease but also in infection. Xiaoxia Li (USA) demonstrated the substantial role of IL-17 in the T_H17 response by showing that ablation of the IL-17R-associated adaptor protein and E3 ubiquitin ligase Act1 in the central nervous system ameliorates the symptoms of EAE (17). Allan Lau (Hong Kong) showed that IL-17A can serve as a modulator of cytokines produced as part of the innate immune response during mycobacterial infection. Furthermore, Erik Lubberts (Netherlands) illustrated that vitamin D is effective in suppressing T_H17 cytokines by reducing the abundances of the transcription factors ROR γ t and nuclear factor of activated T cells C2 (NFATC2s) and by inhibiting the pathogenic behavior of primary human T_H17 cells in patients with early rheumatoid arthritis.

A number of signals are required for the survival of T_H17 cells. Jingwu Zang (China) demonstrated that IL-7, a cytokine not previously linked to the T_H17 response, was critically required for the survival and expansion (in number) of pathogenic T_H17 cells in murine EAE and of human T_H17 cells derived from patients with MS. Antagonism of the IL-7R rendered differentiated T_H17 cells susceptible to apoptosis through inhibition of the Janus-activated kinase-signal transducer and activator of transcription 5 (JAK-STAT5) pathway and alterations in the relative abundances of the antiapoptotic Bcl-2 and the proapoptotic Bax, which leads to amelioration of EAE (18).

Another focal point at China Tregs/Th17 2010 Shanghai Conference was the biology of T_{regs}. Thymus-derived natural regulatory T cells (nT_{regs}) represent a subset of CD4⁺ T cells with suppressive activities. T_{regs} are able to suppress all immune responses, including those mediated by T_H1, T_H2, and T_H17 cells (19). T_{regs} are commonly divided into nT_{regs} and induced T_{regs} (iT_{regs}). Both iT_{regs} and nT_{regs} express Foxp3 as a core subset-specific transcription factor, which activates a large array of genes in T_{regs} and also silences many genes required for the functions of effector T cells (including those encoding effector cytokines) through association with a chromatin-silencing complex organized by the Ikaros family protein Eos, among other factors (20).

TGF- β is required for the maintenance of peripheral nT_{regs}, and a deficiency in TGF- β leads to the development of early lethal autoimmunity. Moreover, in the presence of TGF- β , *Foxp3* is induced in naïve T cells in the periphery, and the resulting iT_{regs} exhibit a suppressive phenotype similar to that exhibited by nT_{regs}. Ludger Klein (Germany) discussed the clonal deletion and differentiation of autoreactive thymocytes toward the T_{reg} lineage as mechanisms that induce tolerance. He showed that the nature of the thymic antigen-presenting cell, the avidity of the cognate interaction, and T cell intrinsic “tuning” events are critical parameters for the differentiation of nT_{regs} in the thymus (21). Sankar Ghosh (USA) further showed that the NF- κ B signaling pathway appears to be a key regulator of the expression of *Foxp3* during the development of nT_{regs} (22). Additionally,

TGF- β and its downstream signaling are also required for induced differentiation of Foxp3⁺ T_{regs} in vitro. Wanjun Chen (USA) illustrated the roles of an enhancer and a silencer, the helix-loop-helix proteins E2A and Id3, in TGF- β -induced activation of *Foxp3* expression. Innate immune signaling pathways—such as those involving nucleotide-binding domain, leucine-rich repeat-containing protein, caspase recruitment domain (CARD)-containing 5 (NLRC5)—inhibit the differentiation and function of T_{regs} and T_H17 cells, as was discussed by Rongfu Wang (USA) (23).

The mechanism of T_{reg}-mediated immune suppression is complex and not fully understood. In his keynote lecture, Shimon Sakaguchi (Japan) summarized several possible mechanisms for T_{reg}-mediated immune suppression, and he observed that suppression dependent on cytotoxic T lymphocyte antigen 4 (CTLA-4) might serve as a core mechanism. Given that anergic T cells and IL-10-secreting Tr1 cells—both of which fail to produce IL-2 but exhibit increased amounts of CTLA-4 upon activation—exert cell contact-dependent suppression of Foxp3⁺ T_{regs} in vitro. Sakaguchi also suggested that T_{regs} that do not express Foxp3 might share a suppressive mechanism with their Foxp3-containing counterparts. The regulation of IL-10 production by T cells and the implications for immune responses to pathogens were elucidated by Anne O'Garra (UK). Ethan Shevach (USA) further illustrated the mechanism of T_{reg}-mediated suppression in vivo, and he concluded that both polyclonal and antigen-specific T_{regs} can inhibit immune responses in vivo, but that they use multiple, distinct mechanisms to modulate the priming of T cells. Furthermore, PTEN (phosphatase and tensin homolog deleted from chromosome 10) plays a critical role in the maintenance of self-tolerance, as was presented by Laurence Turka (USA). Bin Li (China) employed structural, biochemical, and biophysical approaches to examine the function of Foxp3, and he demonstrated that homodimerization of Foxp3, mediated by an antiparallel leucine zipper motif, is dynamically regulated and mediates a defining role in modulating the activity of Foxp3. In addition, Joachim Schultze (Germany) showed that Foxp3-mediated suppression of the abundance of special AT-rich sequence-binding protein-1 (SATB1) is also required for the suppressive functions of T_{regs} in vitro and in vivo.

Compelling evidence that the expression of *Foxp3* might be unstable in both mouse and human iT_{regs} was presented at the meeting. Posttranslational modifications, such as ubiquitination and acetylation, are likely the key mechanisms involved in regulating the stability of Foxp3 protein. Ming Li (USA), Yun-Cai Liu (USA), and Hye-Sook Kwon (USA) demonstrated the molecular mechanisms involved in the expression of *Foxp3* and the modification of Foxp3 protein, including the Forkhead family FOXO transcription factors (24) and the deacetylase SIRT1 (silent mating-type information regulation 2 homolog). These findings further define the mechanisms that underlie immune suppression by various populations of T_{regs}. They also illustrate the concept that T_{regs} represent an unstable, or perhaps even plastic, cell population.

Another area of compelling discussion involved the balance between T_{regs} and T_H17 cells. TGF- β lies at the crossroads of this balance. This cytokine is required for the regulation of the immune response by T_{regs}, and it is also involved in the differentiation of T_H17 cells (Fig. 1) (7). Thus, there is not only functional antagonism between T_H17 cells and T_{regs} in autoimmunity, but there also exists a reciprocal regulation in the generation of these cells

(25). In vivo, many T cells contain both ROR γ t and Foxp3. Ultimately, depending on the interplay between additional environmental cytokines, one or the other transcription factor dominates. A higher abundance of TGF- β induces the expression of *Foxp3* and represses expression of the gene encoding the IL-23R. Foxp3 can in turn bind to ROR γ t and antagonize ROR γ t-dependent, T_H17-like transcriptional programs, which pushes T cell differentiation toward the T_{reg} lineage (26). Proinflammatory cytokines, such as IL-6 and IL-21, which activate STAT3, overcome Foxp3-mediated inhibition of the transcriptional activity of ROR γ t, increase the abundance of IL-23R, and thus push T cell differentiation toward a T_H17-like fate (27). Ultimate T_H17 differentiation is associated with a decrease in the abundance of Foxp3, and the sustained, unopposed transcriptional activity of ROR γ t and STAT3. Although IL-6 inhibits the expression of *Foxp3* at the level of mRNA during T_H17 cell differentiation, it might also be involved in other signal cascades that mediate degradation of Foxp3 protein, because iT_{regs} (Foxp3⁺), upon treatment with IL-6, progressively lose Foxp3 protein. The molecular mechanism involved in the balance between T_{regs} and T_H17 is just beginning to be illustrated, and some of the most recent and interesting findings in this area were discussed at the conference. Fan Pan (USA) demonstrated that hypoxia-inducible factor 1 α (HIF-1 α), the major sensor of hypoxia and a key regulator of transcriptional programs related to metabolism, regulates the balance between T_H17 cells and T_{regs}. In these studies, HIF-1 α promotes the differentiation of T_H17 cells while inhibiting the differentiation of T_{regs} through an active process of Foxp3 degradation. As discussed earlier, the balance between T_{regs} and T_H17 cells is controlled by several factors, and this delicate equilibrium plays a key role in intestinal homeostasis, as illustrated by the presentations of Fiona Powrie (UK) and Yasmine Belkaid (USA). The importance of T_H17 family cytokines in mucosal immunity and chronic inflammation was further demonstrated by the work of Jay Kolls (USA) and Wenjun Ouyang (USA).

The impaired balance between T_{reg} and T_H17 cell populations has been linked with autoimmune disease in many animal models, such as EAE and type I diabetes, as well as in MS and tumors in patients. In humans, however, CD4⁺ T cells have more heterogeneity and flexibility than do their murine counterparts. David Hafler (USA) reported the identification of a population of “T_H1-type” Foxp3⁺ T_{regs} in patients with MS. Antonio Lanzavecchia (Switzerland) discussed the differentiation of “T_H22 cells” from human CD4⁺ T cells, and he proposed an organization of effector and memory T cells based on their distinct functions.

Despite this heterogeneity of T_{regs} and the complexity of T_H17 cells in humans, the therapeutic potential of manipulating T_{regs} and T_H17 cells is nevertheless appealing. Yong-Jun Liu (USA) demonstrated that the blockade of T_{regs} by an antibody against the T cell costimulatory molecule OX40 could improve antitumor immune responses. Dale Umetsu (USA), Tyler Curiel (USA), Rachel Caspi (USA), and Weiping Zou (USA) summarized the roles of T_{regs}, NKT cells, and T_H17 cells in asthma, human autoimmunity, immune tolerance in the eye, and cancer—all diseases for which the manipulation of T_{regs} could provide new or improved therapies. On the other hand, the functions of T_{regs} can be enhanced to prevent autoimmune diseases, including diabetes, as demonstrated by Matthias von Herrath (USA), and EAE, as presented by Roland Liblau (France). Furthermore,

harnessing T_{regs} in adoptive cell therapy is promising for the promotion of transplantation tolerance. The presentations of Herman Waldmann (UK), Petra Reinke (Germany), and Hans-Dieter Volk (Germany) provided compelling evidence to support such a notion. Bruce Blazar (USA) presented data from preclinical testing of ex vivo expanded T_{regs} to control graft-versus-host disease. He showed that a brief treatment with a small molecule inhibitor of protein kinase C θ (PKC- θ) improved the in vitro suppressor function of human umbilical cord blood (UCB)–derived T_{regs}. He also demonstrated the safety and efficacy of human UCB T_{regs} in transplant recipients and suggested a pathway to clinical approaches that target signaling molecules that influence the function of T_{regs}. These investigations are important steps to bring the potential benefits of T_{reg} manipulation therapy to the patient.

Together, the 40 plenary lectures given over the intense 4-day meeting highlighted several substantial advances in our understanding of the development, function, and potential clinical applications of T_{regs} and T_H17 cells and provided a worthy successor to the “China T_{regs} 2008” conference, which was held in Beijing, China, in 2008 (28, 29). In addition to these lectures, numerous short talks and 160 posters were also presented. We apologize to those speakers and presenters whose work has been insufficiently discussed or not covered here due to space restraints (30).

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Fig. 1.

A scheme for the reciprocal differentiation of T_{regs} and T_H17 cells. Upon encountering their cognate antigens, naïve CD4⁺ T lymphocytes (defined as CD44^{low}, CD25^{negative}, and CD62L^{high}) differentiate into different effector subsets. Although several “master” transcriptional regulators responsible for specifically guiding differentiation toward distinct lineages can be induced in naïve T cells upon activation, the local microenvironment provides the main driving force that determines the outcome of the differentiation process. The presence of TGF-β and active IL-2 signaling through STAT5 is known, at least in vitro, to generate iT_{regs}, which like those generated in the thymus, express Foxp3. On the other hand, IL-6 in combination with TGF-β or IL-1β, signaling through STAT3, which drives the expression of RORγt, result in the differentiation of T_H17 cells. As indicated, several additional factors may be required for subsequent functional maturation or may be responsible for the fine-tuning of effector functions. IL-21 feeds back on developing T_H17 cells. IL-23 might be required to induce further effector molecules in committed T_H17 cells to establish their terminally differentiated effector phenotype. The characteristic cytokine profiles of each subset are shown. AhR, arylhydrocarbon receptor.