Meeting Report

Frontiers in Clinical Immunology and Immunoregulation 2010: The Highlight

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The 10th meeting of the Federation of Clinical Immunology Societies (FOCIS) was held in Boston during 23–27 June 2010. As usual, this conference highlights the greatest advancements in the field of clinical immunology over the previous year. It is especially remarkable since this is the 10th meeting and many programs were set up to celebrate this decade of FOCIS meetings. Two of the FOCIS founders, Drs Garrison Fathman and David Hafler, made special lectures in FOCIS Founder Symposium and both speakers emphasized that FOCIS provides a platform for clinicians and scientists to meet to discuss the commonalities of immune-based diseases. They expressed their belief that advances in immune-based pathophysiology can be encompassed by the five pillars of FOCIS: immunoregulation, immunogenetic/genomics, immunotherapy, immunodiagnosis/immune monitoring and host defense. More than 450 participants attended the meeting, which comprised 4 keynote addresses, 60 plenary lectures and 94 selected oral presentations. In addition, 344 posters were presented to an interested audience.

The development of regulatory T cell therapy seems to be one of quickest steps moving forward to clinical trial in autoimmune diseases, organ transplantation allograft protection and the prevention of severe side effect of acute graft-versus-host disease (GVHD) in stem cell transplantation.

Bruce Blazar at University of Minnesota reported the safety of his natural Treg cells (nTregs) ex vivo expanded from umbilical cord blood (UCB) in patients with hematopoietic malignancies who had received bone marrow stem cell therapy. His data revealed that the side effects of nTreg cell expanded from complete and partial MHC-matched UCB were minor when nTreg cell product was used with the dose up to 3 × 10⁶ cells/kg. This group also observed that injection of nTreg cells could significantly decrease the incidence of I–II GVHD to 39% (n = 18) versus control groups (61%, n = 115) in patients who received bone marrow stem cell therapy. However, it is noted that there were 39% of patients who received stem cells and nTreg cell therapy will still develop GVHD, suggesting that improvement for this nTreg therapy protocol is desirable. Amy Putnam of Jeffrey Bluestone’s group at UCSF also provided a safety data in the use of CD4⁺CD127low/−CD25⁺ polyclonal Tregs. They found the use of these cells that had been expanded ex vivo were safe for the treatment of recent onset type I diabetes in their phase I clinical trial. Maria Grazia Roncarolo in San Raffaele Telethon Institute for Gene Therapy demonstrated that antigen-specific human IL-10-producing Treg (Tr1) cells not only were safe, but also displayed a potential efficacy in the protection of islet transplantation and prevention of GVHD in bone marrow stem cell therapy.

Recent studies have demonstrated that nTreg cells have a plasticity feature when stimulated with pro-inflammatory cytokines (Xu et al., 2007; Wan and Flavell, 2007; Zheng et al., 2008; Lu et al., 2010). Previous studies have revealed that adoptive transfer of nTreg cells was able to prevent but unable to treat the established autoimmune diseases such as collagen-induced arthritis (Bardos et al., 2003; Morgan et al., 2005). Song Guo Zheng’s group at University of Southern California has discovered that addition of all-trans-retinoic acid (atRA) now can overcome the plasticity and restore the functionality of nTreg cells in the inflammatory milieu. More importantly, this group has also found that nTreg cells pre-treated with atRA were completely resistant to Th17 cell conversion when stimulated with IL-6, and restored the suppressive effects in vitro in the presence of IL-6 and on established autoimmune arthritis in vivo. These data implicate that atRA-treated nTreg cells may have an important therapeutic role in the treatment of patients with autoimmune diseases.

It is still unclear whether increased responder T cell resistance or impaired Treg cell suppressive activity mainly contribute to the pathogenesis and development of autoimmune diseases. Clare Baecher-Allan’s group in Brigham & Women’s Hospital now provided new evidence that increased expression of Granzyme B in CD4⁺ T response cells may contribute to their resistance to Treg cells. However, Granzyme B expression seems to be critically important for the suppressive activities for Tr1 cells, according to Mario Graza Rocorolo’s presentation. Previous studies have reported that Granzyme B plays an important role in suppressing B cell responses by nTregs.
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Although it has been well defined that TGF-β can trigger the development of iTreg cells in animal cells, it is also reported that TGF-β lacks the ability to induce human CD4+ cells to become iTregs. They found atRA not only enhances Foxp3+ cells to become bona fide iTregs. They found atRA not only enhances Foxp3 expression of TGF-β-treated CD4+ cells, but also promotes the maturation of these cells. Their data revealed that injection of these cells in a xeno GVHD model can significantly prolonged the survival of mice.

In order to have a greater understanding of the role of Tregs in disease, crucial biomarkers and methods are needed to identify their subsets, particularly the peripheral induced and the thymic-derived populations. The evidence thus far indicates that Tregs in the peripheral blood of humans contain a mixture of both thymic- and peripheral-derived Tregs. Dat Tran at University of Texas Medical School of Houston, collaborating with Ethan Shevach in NIH, identified Helios as a biomarker for the thymic-derived Tregs. Their data revealed that in healthy adults, around 75% of the Foxp3+ Tregs in peripheral blood are Helios+. In age-matched controls, adults with HIV infection have significantly lower percentage of Helios+ Tregs, suggesting an increase in induced Tregs. Lastly, they showed that the Helios-Foxp3+ Tregs have lower level of Foxp3 and are the cytokine producing subset that might account for the plasticity of Tregs. Ultimately, it is critical to separate these two subsets to analyze for their plasticity and function.

CD8+ Treg cells have emerged as a new subset of Tregs cells. Although natural CD8+Foxp3+ cells likely appear to exist in normal homeostasis, it is rare population compared with natural CD4+ Treg cells (Cosmi et al., 2003). Several studies have previously reported that administration of tolerogenic peptides can induce CD8+ Treg cells, and these CD8+ Tregs are responsible for the induction of immune tolerance in vivo (Kang et al., 2007; Skaggs et al., 2008). In this meeting, Kevan Herold at Yale University provided another line of evidence that CD8+ Treg cells are also crucial for the induction of immune tolerance administrated by anti-CD3 antibody. His data demonstrated anti-CD3 antibody administration did not down-regulate CD4+ cell frequency; conversely, this antibody up-regulated CD8+ cell frequency and these CD8+ cells can suppress SEB-stimulated PMBC proliferation. He also found that TNF-α is essential for the induction of CD8+ Treg cells following anti-CD3 treatment.

Only recently has a better understanding of the cellular and molecular mechanisms for T cell help for antibody production emerged. A subset of T cells, termed follicular helper cells (Tfh cells), provides a helper function to the production of antibodies by B cells in lymphoid tissues (Vinuesa et al., 2005; King, 2009). Unlike Th1 and Th2 helper cells, Tfh cells express chemokine receptor expression (CXCR5) and ICOS. Salah-Eddine Bentebibel in Baylor Institute for Immunology Research identified two subsets of Tfh cells, ICOS(high)CXCR5(high) and ICOS(low)CXCR5(low). While ICOS(high)CXCR5(high) cells promote germ center (GC) B cells to produce IgA and IgM, ICOS(low)CXCR5(low) cells help helper function for naïve B cells and induce GC B cell apoptosis, suggesting a balance mechanism to control B cell activation.

Th17 cells have been considered as one of the important pathogenic cells associated with pathogenesis and development of many autoimmune and inflammatory diseases (Annunziato et al., 2009; Pernis, 2009). In some cases, the combination of Th1 and Th17 cells is necessary for the disease development. Rachel Caspi’s group at the NIH reported an interesting finding where they demonstrated that even a combined defect of Th1 and Th17 cells did not affect the development of ocular autoimmunity. They further found that IL-17F is elevated in IFN- and IL-17A double KO mice.

The laboratories of Huimin Fan and Zhongmin Liu at the Shanghai East Hospital at Tongji University reported that TGF-β is able to induce naïve rat CD4+CD25hi iTregs and that addition of atRA can enhance the differentiation and maintenance of Foxp3+ cells induced by TGF-β. Moreover, they observed that injection of iTregs can markedly suppress Th17 cell production and prevent bronchiolitis obliterans syndrome, one of the most common complications related to lung transplantation failure. The laboratory of Xuan Zhang in Beijing reported that CD4+CD25 Foxp3+CD127– cells do not function like a real Treg cell subset in new-onset SLE patients, indicating that CD127(high)/– may not represent an appropriate marker for the identification of Treg cells in patients with SLE.

References


Zhongmin Liu at the Shanghai East


