Control of regulatory T cells and T helper cells in human diseases: from bench to bedside

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The Third International Conference on Regulatory T cells and Th Subsets and Clinical Application in Human Diseases was held in Shanghai, China during 13–15 October 2012. This conference, organized by Shuiping Jiang, the Conference Founder and President, and Xuetao Cao, the President of Chinese Society for Immunology, brought together many prominent experts in the field of regulatory T cells (Tregs) and T helper cells (Th) subsets immunology and highlighted the cutting-edge advancements on the development, function, homeostasis and interplay of Tregs and Th subsets, especially the latest breakthrough in therapeutic applications in clinical settings.

The balance between effector and regulatory factors in immune system is essential to prevent tissue damage during infection and control excessive or self-destructive responses. It has been proved that Tregs, characterized by the expression of transcription factor FoxP3, as a ‘brake’, play key roles in blocking immune responses, inflammation and tissue destruction by suppressing the functions of multiple cell types (Zhou et al., 2009). In contrast, effector cells mediate the development and pathogenesis of infections, autoimmune diseases, tumors and transplantation rejections. Apart from conventional Th1 and Th2 cells, the newly discovered T helper cell subsets, including Th17, Th9, Th22, T follicular helper cells and innate lymphoid cells, also produce inflammatory cytokines, such as IL-17, IL-9 and IL-22. Regulating the function of these T effector cells may be helpful in developing novel therapeutic strategies.

Given the indispensable role of FoxP3 in Tregs development and function, many groups are trying to explore the molecular mechanism of FoxP3-mediated gene expression. Alexander Rudensky’s group from Memorial Sloan-Kettering Cancer Center showed how FoxP3 cooperated with other regulators to ensure the stability and function of Tregs in basal and inflammatory environments. A high proportion of identified partners of FoxP3 were direct targets of FoxP3, indicating a close-circuit connectivity of reciprocal regulation of expression and cooperation between FoxP3 and several sequence-specific transcription factors. Bin Li’s group from Institut Pasteur of Shanghai found two negative regulators of FoxP3\(^{+}\) Tregs, Stub1 and DBC-1. Stub1 negatively modulates Tregs suppressive activity by promoting proteasome-mediated degradation of FoxP3, while DBC-1 is an essential subunit of the FoxP3 complex and is responsible for attenuating FoxP3 activity by a caspase-dependent mechanism during inflammation. Furthermore, a novel Foxo1-dependent transcription program was reported to control Tregs cell function by Ming O. Li at Memorial Sloan-Kettering Cancer Center. As reported in this meeting, other factors that impinged on the Tregs development and functions included the innate immune components C3aR/C5aR, NF-κB and Nrp1-Sema4a.

To extend the function of Tregs, Diane Mathis from Harvard Medical School reported that different Tregs populations in diverse tissues have distinct characteristics according to their local environment. Tregs further influence non-immune process and mediate the skeletal repair after injury, revealing an exciting possibility to develop new strategies to target disease-specific Tregs, leaving the bulk Tregs population intact.

In addition to Th1 and Th2 cells, recently identified Th17 cells, characteristic of producing cytokines IL-17A, IL-17F, IL-21 and IL-22, have been indicated playing important roles in autoimmunity diseases and cancer. Chen Dong at MD Anderson Cancer Center, who was the first to discover the Th17 subset, reported that Trim33 was required for chromat remodelling in the IL-17 gene locus and Trim33 deficient T cells were defective in Th17 cell differentiation but not Tregs differentiation. Interestingly, high level of sodium chloride intake, a vital ingredient in our daily diet, was reported to be an inflammatory contributor to induce SGK-1 and promote the Th17 cell differentiation, and thus drives autoimmune diseases, as shown by David A. Hafler from Yale School of Medicine and Harvard Medical School. Furthermore, Nicholas P. Restifo from NIH identified a stem cell-like signature of Th17 cells capable of differentiating to Th1-like effect- or cell progeny and self-renewing as IL-17A producing cells. These observations offered a mechanistic basis for the antitumor efficacy of Th17 cells and developing perspective T cell-based immunotherapy. Apart from conventional Th17 cells, Gary A. Koretzky at University of Pennsylvania found a new population of natural Th17 cells (nTh17) with innate immune cell characteristics. Different Akt pathways were involved in the development of these two different populations. Understanding the biology of nTh17 cells may provide novel insight into the role of Th17 cells in normal and abnormal immune responses.

Recent studies revealed that innate lymphoid cells (ILCs) lacking linage markers (Lin\(^{-}\)) can produce a variety of...
effector cytokines, similar to that of cor-
responding Th subsets (Spits and Cupedo,
2012). The newly defined ILCs include
Type 1 ILCs (ILC1), Type 17 ILC (ILC17)
and/or Type 22 ILC (ILC22), and Type 2 ILC
(ILC2). In this meeting, Hergen Spits from
Tytgat Institute for Liver and Intestinal
Research, University of Amsterdam
showed that ectopic expression of GATA-3
by retroviral gene transfer in Lin~ CD117+ CD127~ CRTH2~ cells resulted in CRTH2 in-
duction and acquisition of the capacity to
produce high amounts of IL-5 and IL-13 as
well as IL-4 in response to TSLP plus IL-33,
indicating the critical role of GATA-3 in the
function of ILC2s. Ror-γt+ ILCs involved in
lymphoid tissue genesis were also reported
to express Ror-γt, an important transcrip-
tional factor of Th17 cell differentiation,
and produce IL-17 and IL-22. These ILC
populations probably represent distinct
lymphocyte lineages that have unique effect-
or pathways in various immune responses.
Follicular helper cells have emerged as a
new immune regulatory population that
drive and maintain germinal center B cell
responses. Carola G. Vinuesa from Australian
National University demonstrated that
decreased IFN-γ mRNA decay caused exces-
sive IFN-γ signaling in T cells and led to the
accumulation of T helper cells, spontane-
ous GC, autoantibody formation and neph-
ritis. Michael G. McHeyzer-Williams at the
Script Research Institute discussed follicu-
lar helper T cells and B cells programs. In
this session, multiple subclasses of
antigen-specific T follicular helper (Tfh)
cells were found to exert different roles in
controlling the facets of high-affinity class-
specific B cell memory.
As plenty of studies have demonstrated
the therapeutic efficacy of Tregs in animal
disease models, adoptive transfer of
human Tregs may represent a promising
clonal therapy for the treatment of auto-
immune diseases, transplantation rejec-
tions and inflammatory diseases. Three
trials of Tregs therapy for graft-versus-host
disease (GVHD) in patients have revealed
its efficacy in transplantation (Tang et al.,
2012). Qi Zhi Tang from University of
California at San Francisco emphasized
three key points in transplantation toler-
ance, including the reduction of donor-
specific T cells, induction of more effective
donor-reactive Tregs than polyclone Tregs,
and aborting CTL effector responses in allo-
graft. Bruce Blazar at University of
Minnesota presented the potential efficacy
of using ex vivo expanded natural and indu-
cible Tregs for the prevention of GVHD.
In addition, new signaling targets for
modulating Tregs or effector T cell function
can be employed for developing novel
therapeutic strategies by either increasing
suppressive function of Tregs in transplant-
ation and autoimmune diseases, or block-
ing Tregs and boosting T effector cells in
tumors. For example, low dose of IL-2 has
been reported to lead to Tregs recovery
and concomitant clinical improvement in
patients with HCV-induced vasculitis
(Saadoun et al., 2011). In this meeting,
Yong-Jun Liu (University of Texas M.D. and
Baylor Research Institute) and colleagues
demonstrated that HDACi-induced OX40L
inhibited the generation of IL-10-producing
type 1 Tregs, providing an anti-tumor re-
sponse in patients. Yong-Jun Liu further illu-
strated that humanized agonist m Ab to
human OX40 prompted effector T cell func-
tion and blocked the function of both iTregs
and nTregs.
Two scientists Jun Yan (University of
Louisville) and Yuping Lai (East China
University Normal University) presented the role of
IL-17 in regulating psoriasis pathogenesis.
Therefore, targeting and modulating cellu-
lar responses to IL-17 could be benefi-
cial in certain types of IL-17 mediated diseases.
In two recent Phases 2 clinical trials,
anti-IL-17 and anti-IL-17 receptor anti-
bodies indicated significant improvement
of the clinical symptoms of psoriasis
Leonardi et al., 2012; Papp et al., 2012),
which further illustrated the role of IL-17
in human autoimmune and inflammatory
diseases. These findings substantiate the
therapeutic strategy for immune diseases
by using antibodies that target or block ef-

cactor molecules. Indeed, Yajun Guo at
Chinese Military General Hospital pre-
sented the clinical application of targeted
immunotherapy for cancer by antibody.
Given the promising results from recent
clinical trials, targeting on Tregs and other
T effectors will become an important trend
in clinic application of immunotherapy in
treating human diseases. We look forward
to hearing more exciting progress in next
conference that will be held in 2 years.
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