FAST MOVING FRONTS - 2009

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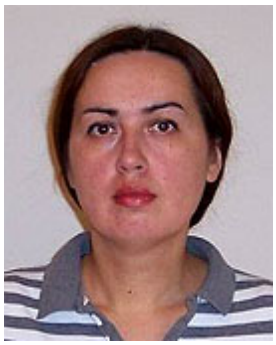
Roza I. Nurieva & Chen Dong talk with *ScienceWatch.com* and answer a few questions about this month's Fast Moving Front in the field of Immunology.



Article: Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages
Authors: Nurieva, RI;Chung, Y;Hwang, D;Yang, XO;Kang, HS;Ma, L;Wang, YH;Watowich, SS;Jetten, AM;Tian, Q;Dong, C
Journal: IMMUNITY, 29 (1): 138-149 JUL 18 2008
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SW: Why do you think your paper is highly cited?

Upon activation, CD4+ T cells differentiate into distinct effector lineages that regulate different types of immune responses. Germinal center structures where activated B cells undergo tremendous proliferation have been associated with autoimmune diseases and B cell lymphomas.

Follicular helper T (Tfh) cells have been recently found to be localized in germinal centers and are specialized in providing help for B cells. Although Tfh cells are important in humoral immunity, their developmental regulation has been unclear.

In this article, we extensively characterized the developmental regulation of Tfh cells. We demonstrated that Tfh cells are distinct in their gene expression and immune function and develop via a pathway that is dependent on IL-21 or IL-6 but independent of T helper (Th)1, Th2, or Th17 lineages. Thus, this study significantly advances our understanding of the biology of Tfh cells.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Yes, it describes for the first time the developmental regulation of Tfh cells. In addition, we developed a method to generate Tfh cells *in vitro*.

SW: Would you summarize the significance of your paper in layman's terms?

This paper provides the evidence that defines Tfh cells as a distinct T-cell subset, and shows that interleukin-21 plays a critical role in their

differentiation. This knowledge may help us to find ways to treat antibody-mediated autoimmune diseases and B lymphoma.

Coauthor
Chen Dong

SW: How did you become involved in this research, and were there any problems along the way?

Our previous work has indicated an important role of inducible costimulatory receptor (ICOS) and its ligand, B7h, in regulation of humoral immunity, especially germinal center reactions.

We also studied the role of IL-21 in Th17 cell differentiation. Since Tfh cells are regulated by ICOS and they also express IL-21, we decided to carry out an extensive analysis of Tfh cell development and their relationships with other types of T cells, especially Th17 cells.

To determine the factors involved in Tfh cell development, we utilized many gene knockout animals, including those provided by Dr. Anton M. Jetten's group in the National Institute of Environmental Health Sciences (NIEHS) at the National Institutes of Health (NIH).

SW: Where do you see your research leading in the future?

Although our paper described Tfh cells as a distinct lineage of T cells, it did not provide any genetic mechanism whereby Tfh cell development is programmed, especially by lineage-specific transcription factor.

In August, our group and several others published reports that illustrate Bcl6 as a transcription factor that is selectively expressed by Tfh cells and is necessary for Tfh cell development and germinal center reactions.

These studies support our ideas that Tfh cells represent a unique subset of T cells. At the moment, we do not know very much about mechanistically how Bcl6 works. In addition, we would like to address the stability and plasticity of Tfh cell genetic program.

SW: Do you foresee any social or political implications for your research?

Yes. Antibody-producing B cells need to be tightly controlled. Any dysregulation of T-cell function can have a significant effect on the antibody-producing B cells. For example, excessive function of Tfh cells has been attributed to the pathogenesis of antibody-mediated autoimmune diseases such as lupus.

B lymphomas often arise from germinal centers. In this regard, specific targeting of the Tfh pathway will help to prevent or treat these diseases.

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KEYWORDS: CXC CHEMOKINE RECEPTOR-5; B-CELLS; GENE-EXPRESSION; ROR-GAMMA; DIFFERENTIATION; RESPONSES; AUTOIMMUNITY; IL-21; BETA; T(H)17.

PDF

back to top

2009 : November 2009 - Fast Moving Fronts : Roza I. Nurieva & Chen Dong Talk ABout of T Follicular Helper Cells