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2010 : May 2010 - Fast Moving Fronts : Vijay K. Kuchroo Discusses T(H)17 &amp; Regulatory T Cells

## FAST MOVING FRONTS - 2010

March 2010



Vijay K. Kuchroo talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Fronts paper in the field of Immunology.



**Article: Reciprocal developmental pathways for the generation of pathogenic effector T(H)17 and regulatory T cells**

Authors: Bettelli, E;Carrier, YJ;Gao, WD;Korn, T;Strom, TB;Oukka, M;Weiner, HL;Kuchroo, VK

Journal: NATURE, 441 (7090): 235-238, MAY 11 2006

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### SW: Why do you think your paper is highly cited?

This was one of the first papers which not only reported the identification of differentiation factors for Th17 cells, but also showed that there is a reciprocal relationship between inhibitory iTregs and proinflammatory Th17 cells.

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

It was a new discovery in terms of identifying the differentiation factors for Th17 cells, a methodology to generate them, and it is also a synthesis of knowledge, putting together the relationship between regulatory and effector T cells.

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

Recently, a new group of T cells was identified which predominantly produce a soluble factor called IL-17 and, therefore, the cells were named Th17 cells. These cells play an important role in clearing fungal and bacterial infections but, more importantly, they induce tissue inflammation and mediate autoimmunity.

These cells have been implicated in inducing autoimmune diseases in humans as well, including psoriasis, inflammatory bowel disease, **rheumatoid arthritis**, and **multiple sclerosis**. However, how these

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cells are induced was not clear.

Our studies were the first to describe the factors which are required for the generation of these cells—specifically, a soluble factor, IL-6, produced during an infection or inflammation plays a key role in inducing Th17 cells.

IL-6 plays a dual role, as first it suppresses the generation and functions of protective/inhibitory Treg cells and induces the generation of highly proinflammatory Th17 cells, thus providing a fertile ground for inducing inflammation.

Our studies also showed that there is a reciprocal relationship between proinflammatory Th17 and protective regulatory T cells and that IL-6 plays a key role in regulating this balance.

*"We are in the process of developing a detailed map of Th17 development."*

**SW: How did you become involved in this research and were any particular problems encountered along the way?**

I became involved in this research soon after the discovery of Th17 cells—they are key cells instigating development of tissue inflammation and autoimmunity. Our studies in the lab began with trying to expand these cells *in vitro* so as to study their function.

At that time, IL-23 was described as the key cytokine responsible for induction of these cells. However, when we activated naive T cells *in vitro* with IL-23, we were not able to induce Th17 cells. After repeating this experiment multiple times, we came to the conclusion that other factors besides IL-23 must be differentiation factors for this T cell subset.

Success came to us fortuitously! Mohammed Oukka in our lab had generated a Fox-P3.GFP reporter mouse strain and, while characterizing the mouse strain, he repeated the experiment, showing that the immunosuppressive cytokine TGF- $\beta$  induces Fox-P3 from naive T cells of the reporter mice.

In collaboration with Wenda Gao and Estelle Bettelli, Dr. Oukka systematically added various cytokines to TGF- $\beta$  to see their effect on the induction of Fox-P3. Addition of IL-6 suppressed generation of Fox-P3<sup>+</sup> Tregs and instead induced IL-17 producing Th17 cells. This led us to hypothesize that there is a reciprocal relationship between Fox-P3<sup>+</sup> Tregs and IL-17 producing Th17 cells.

One of the major problems that we encountered was that we could not repeat the observation that IL-23 is the differentiation factor for Th17 cells. However, this also led us to identify the factors that lead to the generation of Th17 cells.

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

We are in the process of developing a detailed map of Th17 development. With this in mind, we should be able to identify nodal points and potential drug targets that regulate the development of Th17 versus Treg cells.

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