WHAT'S HOT IN... BIOLOGY , January/February 2009

Help in Understanding New Kinds of Helpers

by Jeremy Cherfas

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A single topic occupying four of the Top Ten places (with a fifth hovering just outside at #12) indicates something rather special afoot. That something is the scramble to understand a relatively recently identified component of the immune system, the T_H17 helper cell, which is specially adapted to fighting bacterial and fungal diseases. It is also implicated in autoimmune disorders such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis.

For the past 35 years or so immunologists have considered two basic kinds of T helper cells in the immune system. T_H1 and T_H2 cells are classes of white blood cell that are not themselves capable of destroying invading pathogens. Instead, they are activated by exposure to antigens and are the core of the immune system's memory. T helper cells recruit and activate the cytotoxic cells, also known as T killer cells, that actively dispatch the pathogens. During their differentiation from naive T cells, T_H1 and T_H2 cells produce cytokine trigger molecules that prod other naive cells down the T_H1 or T_H2 development pathways, an autocrine response that can rapidly boost the number of T helper cells sensitive to a particular antigen. T_H17 cells were first described as having an origin distinct from T_H1 and T_H2 lineages, triggered by the cytokines IL-6 and TGF-ß, but these did not seem to be autocrine messengers that could amplify the production of T_H17 cells.

Biology Top Ten Papers

Rank	Papers	Cites Jul-Aug 08	Rank May-Jun 08
1	K. Takahashi, *et al.*, "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," *Cell*, 131(5): 861-72, 30 November 2007. [Kyoto U., Japan; CREST, Kawaguchi, Japan; Gladstone Inst. Cardio. Dis., San Francisco, CA] *243MG	96	1
2	K. Takahashi, Y. Shinya, "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors," *Cell*, 126(4): 663-76, 25 August 2006. [Kyoto U., Japan; CREST, Kawaguchi, Japan] *080VN	76	†
3	The ENCODE Project Consortium (E. Birney, *et al.*), "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project," *Nature*, 447(7146): 799-816, 14 June 2007. [80 institutions worldwide] *178FV	61	2
4	M. Wernig, *et al.*, "*In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state," *Nature*, 448(7151): 318-24, 19 July 2007. [5 U.S. institutions] *191GC	61	4

5	K. Okita, T. Ichisaka, S. Yamanaka, "Generation of germline-competent induced pluripotent stem cells," *Nature*, 448(7151): 313-7, 19 July 2007. [Kyoto U., Japan; Japan Sci. Tech. Agency, Kawaguchi] *191GC	59	3
6	I.I. Ivanov, *et al.*, "The orphan nuclear receptor ROR?t directs the differentiation program of proinflammatory IL-17+ T helper cells," *Cell*, 126(6): 1121-33, 22 September 2006. [Howard Hughes Med. Inst., New York U., NY; Schering-Plough BioPharma, Palo Alto, CA] *089RF	54	9
7	A. Barski, *et al.*, "High-resolution profiling of histone methylations in the human genome," *Cell*, 129(4): 823-37, 18 May 2007. [NHLBI, NIH, Bethesda, MD; U. Calif., Los Angeles] *172FA	51	†
8	T. Korn, *et al.*, "IL-21 initiates an alternative pathway to induce proinflammatory T_H17 cells," *Nature*, 448(7152): 484-7, 26 July 2007. [Harvard Med. Sch., Boston, MA] *193VG	44	†
9	L. Zhou, *et al.*, "IL-6 programs T_H-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways," *Nature Immunol.*, 8(9): 967-74, September 2007. [NYU Sch. Med., and Howard Hughes Med. Inst., NY; NHLBI, Bethesda, MD] *202QN	38	†
10	R. Nurieva, *et al.*, "Essential autocrine regulation by IL-21 in the generation of inflammatory T cells," *Nature*, 448(7152): 480-3, 26 July 2007. [M.D. Anderson Cancer Ctr., Houston, TX; Inst. Syst. Biol., Seattle, WA; NIH, NIEHS, Research Triangle Park, NC] *193VG	38	†

SOURCE: Thomson Reuter's Hot Papers Database. Read the Legend.

Starting the current ball rolling, and highest in the Top Ten at #6, Dan Littman's group at the Howard Hughes Medical Institute and the New York University School of Medicine showed that a key upstream element is provided by the transcription factor known as ROR?t. This factor switches on the genes that encode IL-17 in naive T cells, and IL-17 is necessary for naive cells to respond to IL-6 and TGF-ß. Mice that lacked the ROR?t gene did not suffer certain autoimmune diseases and lacked fully competent T_H17 cells. Littman's group noted that, given T_H17's role in autoimmune diseases, this new function for ROR?t highlighted "its potential as a therapeutic target in inflammatory diseases."

Next come the two papers at #8 and #10, published back-to-back in *Nature*. Vijay Kuchroo's group at Harvard Medical School (#8) and Chen Dong and Roza Nurieva at the M.D. Anderson Cancer Center and their group (#10) both showed that yet another interleukin, IL-21, was produced by differentiating T_H17 cells and, more importantly, triggered naive T cells to become T_H17 cells. Thus IL-21 was the autocrine cytokine that people had been looking for, both necessary and sufficient to produce T_H17 cells. Sandwiched between those two papers, at #9, is another report from Dan Littman's group that also identified IL-21 as able to cause differentiation of T_H17 cells. IL-21 too was thus a target for therapy.

It therefore seems that IL-6 and TGF-ß cause the expression of ROR?t, which enables T cells to respond to IL-23, a third cytokine associated with T_H17 differentiation. IL-6 also triggers the production of IL-21, and IL-21 is enough to trigger the differentiation of naive cells, even in the absence of IL-6.

Complicating this already complex picture still further are the results reported in the paper at #12. Federica Sallusto and Eva Acosta-Rodriguez and their group at the Institute for Research in Biomedicine in Bellinzona, Switzerland, looked not at mice but at the differentiation of human T_H17 cells (E. V. Acosta-Rodriguez, *et al.*, *Nature Immunology*, 8[9]: 942-9, September 2007; 37 citations this period). Perhaps surprisingly, they found that TGF-ß is not needed for the production of IL-17 in human cells. Indeed, TGF-ß can inhibit IL-17. And while IL-6 alone is not a very good stimulus for T_H17 differentiation, it is much more effective in combination with IL-1. Furthermore, there seems to be a great deal of variation in the amount of IL-17 produced by different donors. If this is linked to the production of T_H17 cells, then the detailed influence of genetic factors on autoimmune diseases is likely to be fertile ground for further investigation.

Why the differences between mice and men? There are no ready answers, but one possibility is that it is

much more difficult for researchers to be certain that they are dealing with truly naive T cells in human subjects. In addition, it may be that T helper cells are not quite so set in their ways as has been presumed. Maybe the various lineages can somehow be converted from one type to another, which might allow more flexibility in the response to an immune challenge. There is also the likelihood that some of the genes involved may be the subject of epigenetic modifications, which would further complicate the picture.

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Keywords: T helper cells, Th-17, IL-6, immune response, TGF-beta, IL-17, Dan Littman, Frederica Sallusto, Eva Acosta-Rogriguez.

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