WHAT'S HOT IN... BIOLOGY , November/December 2009

Sorting out the Triggers, Differentiation, and Roles of T_H-17 Cells

by Jeremy Cherfas

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Oh, the drama that hides behind *Science Watch*'s inexorable grinding of data. Making its first Top Ten appearance at #8—the only newcomer in fact—is a paper from Federica Sallusto's group at the Institute for Research in Biomedicine in Switzerland. This occasion is its last opportunity to appear, because the Hot Papers lists are based on citations over the preceding two years, and this paper, dating back to June 2007, will henceforth become too "old" for further eligibility. So why now? Why the sudden late spurt?

Probably because just outside the Top 10 are a couple of papers, including another from Sallusto and colleagues, that depend on, and cite, #8. The big problem is that while these papers delve deeper into the story, they actually make it more complicated. All are about T helper cells. When a "naive" T cell is exposed to antigens (usually from an infection) it differentiates into T helper cells, which secrete various compounds that fight the infection directly and summon other cells of the immune system to help.

For a long time, there were believed to be only two kinds of T helper cell. In the January/February 2009 issue of *Science Watch* from Thomson Reuters, this column discussed a set of papers that had crashed the Biology Top Ten and that dealt with a new kind of immune memory cell, the T_H-17 cell. It is called T_H-17 because it produces interleukin-17 (IL-17), and had been linked to immune defense and autoimmune diseases. Complicating that account was the Sallusto paper, then at #12, now reappearing at #13 (E.V. Acosta-Rodriguez, *et al.*, *Nature Immunol.*, 8[9]: 942-9, September 2007; 31 citations this period, 206 overall). This report showed that the essential triggers and pathways leading to the differentiation of T_H-17 cells in humans are in many respects different from those in mice. A neighboring paper, from a team led by Rene de Waal Malefeyt, of Schering-Plough Biopharma in Palo Alto, California, showed likewise that the development of T_H-17 cells is fundamentally different in humans and mice. That paper was originally not as highly cited, but now shows up just above Sallusto at #12 (N.J. Wilson, *et al.*, *Nature Immunol.*, 8[9]: 965-7, 2007; 31 citations this period, 224 overall).

Federica Sallusto

Institute for Research in Biomedicine

To deal first with the Sallusto paper at #8, one of the crucial points was that infection with the fungus *Candida albicans* specifically triggered T_H-17 cells, rather than either of the two previously known kinds of T helper cells. Why this should be so remains a mystery, although the authors speculate that it could have something to do with the tissue in which the infection occurs. This gets a boost from de Waal Malefyt's team. They looked at psoriasis sufferers, and discovered that cells from psoriasis lesions were enriched in T_H-17 cells. From this and other evidence it seems possible that T_H-17 cells exist largely to deal with infections affecting the skin.

As for the differentiation of T_H-17 cells, one of the crucial differences between mice and men is that in mice, transforming growth factor ß (TGF-ß) is absolutely crucial for the development of T_H-17 cells, while in men (and women) it is not needed. In fact, Sallusto and de Waal Malefyt agree that TGF-ß inhibits the production of IL-17. They also agree that IL-1, especially in combination with IL-6, is a potent trigger for the production of T_H-17 cells. They disagree, however, on some of the other triggers–for example, IL-23. Sallusto *et al.* find that IL-23 is not very effective at inducing T_H-17 cells. By contrast, de Waal Malefyt's group find that IL-23 is a potent inducer of T_H-17 cells. For Sallusto, IL-23 in combination with IL-1 is a better trigger than IL-1 alone. For de Waal Malefyt, IL-1 is as potent alone as it is in combination with IL-23.

What might eventually help to make sense of these disagreements is the observation that cells from different donors vary markedly—up to 50-fold—in the amount of IL-17 they produce. There is some evidence that genetic and epigenetic factors can influence IL-17 production, and it could be that the differences between the two teams are the result of different donor populations. Another possibility is that the human T cells being studied are not, in fact, completely naive. Mice can be subjected to a variety of experimental procedures to ensure that their T cells have not been exposed to any antigens. Cells isolated from human donors might already have been triggered to start differentiating.

These mysteries will doubtless be solved eventually. And as more and more becomes known about T_H-17 cells, their role is

being investigated in everything from the bone loss associated with severe periodontal disease to the inflammations of the gut that characterize Crohn's disease. It is fitting, therefore, that some of the pioneering papers had their moment in the limelight before they grew too old.

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Biology Top 10 Papers

Rank	Paper	Citations This Period (May-Jun 09)	Rank Last Period (Mar-Apr 09)
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	91	1
2	Intl. HapMap Consortium (K.A. Frazer, *et al.*), "A second generation human haplotype map of over 3.1 million SNPs," *Nature*, 449(7164): 854-61, 18 October 2007. [72 institutions worldwide] *221LY	72	2
3	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	55	4
4	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	51	†
5	P. Landgraf, *et al.*, "A mammalian microRNA expression atlas based on small RNA library sequencing," *Cell*, 129(7): 1401-14, 29 June 2007. [27 institutions worldwide] *188HQ	51	†
6	V. Cherezov, *et al.*, "High-resolution crystal structure of an engineered human $beta_2$-adrenergic G protein-coupled receptor," *Science*, 318(5854): 1258-65, 23 November 2007. [Scripps Res. Inst., La Jolla, CA; Stanford U., CA] *233JG	48	5
7	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	40	9
8	E.V. Acosta-Rodriguez, *et al.*, "Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells," *Nature Immunology*, 8(6): 639-46, June 2007. [Inst. Res. Biomedicine, Bellinzona, Switzerland] *170YY	38	†
9	E. Zeggini, *et al.*, " Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes," *Nature Genetics*, 40(5): 638-45, May 2008. [5 U.S. and U.K. institutions] *293WS	36	6
10	D.F. Easton, *et al.*, " Genome-wide association study identifies novel breast cancer susceptibility loci," *Nature*, 447(7148): 1087-93, 28 June 2007. [87 institutions worldwide] *183HT	35	†

SOURCE: Thomson Reuters Hot Papers Database. Read the Legend.

KEYWORDS: T HELPER CELLS, T CELLS, TH-17 CELLS, IMMUNE SYSTEM, FEDERICA SALLUSTO, RENE DE WAAL MALEFEYT.

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