AUTHOR COMMENTARIES - 2010

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Marc Veldhoen

Featured Paper Interview

In December of 2009, the paper "TGF beta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells," (Veldhoen M, et al.*,* Immunity *24(2): 179-89, February 2006) was named a Current Classicin the field of Immunology. At present, the paper ranks among the top 100 Highly Cited Papers in this field in* Essential Science Indicators℠ *from Thomson Reuters, with 766 citations up to October 31, 2009. In the* Web of Science®*, this paper currently shows 837 citations.*

Lead author Dr. Marc Veldhoen is Senior Investigator in the Stockinger Group, Division of Molecular Immunology at the National Institute for Medical Research, London. In March 2010, Dr. Veldhoen will be a Principal Investigator in the Lymphocyte Development and Activation Laboratory at the Babraham Institute, Cambridge. His record in our database includes 12 papers cited a total of 1,272 times.

In this interview, ScienceWatch.com *talks with Dr. Veldhoen about this paper and the impact it had on the research community.*

SW: What factors prompted you and your coauthors to undertake this study?

The start of what ultimately resulted in the highlighted paper was two papers published in 2003, the year I obtained my Ph.D.

This was at a time when many so called co-culture experiments, an *in vitro* culture system consisting of undifferentiated T cells, regulatory T cells (Treg) and dendritic cells (DC), were used to establish the suppressive activity of Treg. Pasare and Medzhitov showed in a 2003 *Science* paper that the suppressive activity of Treg cells was blocked when pathogen recognition receptors were stimulated on

DC. Having performed several of these experiments myself, I certainly agreed with the observations made in this paper, but not with its conclusions. The readout for the suppressive activity of Treg is the failure of the undifferentiated T cells to proliferate, which is overcome when pathogen recognition receptors are stimulated. However, this was not the only readout I was using myself.

Since the mid-1980s, the undifferentiated T cells were known, upon activation followed by proliferation, to be able to differentiate into two effector stages; type I T cells (Th1), principally involved in immunity against intracellular micro-organisms, and identified by their production of interferon (IFN)-?, and type II (Th2) are instrumental in the fight against parasites and identified by their production of interleukin (IL)-4. In the presence of Treg the undifferentiated cells fail to proliferate, and hence do not differentiate to effector cells. Using the production of IFN-? and IL-4 as an additional read-out in my co-culture experiments I was surprised to observe that in the presence of microbial products and despite rapid proliferation of the undifferentiated T cells, these cells failed to produce either IFN-? or IL-4. This was counterintuitive since it would be a metabolic waste to have cells proliferate that have no function to perform.

"Our data that TGF-beta, a cytokine widely thought of as immune suppressive and anti-inflammatory, was involved in driving the differentiation of this T cell came as a surprise."

In a second paper in 2003 published in *Nature*, Cua and colleagues demonstrated that in the mouse model for multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), which had previously been thought to be due to aberrant Th1 responses, it was not a factor (IL-12) involved in Th1 differentiation that was important but another cytokine, IL-23. Interestingly the absence of IL-23 seemed to correlate with the absence of T cells producing yet another cytokine; IL-17.

Although there was no direct relation between cells proliferating in the presence of Treg, microbial products and IL-17 or IL-23, it was tempting to speculate that the proliferating T cells, not belonging to the two known effector subsets, might be producing IL-17 and constitute a third lineage of effector T cells.

SW: How was it conducted, and what were your findings?

The crucial test here was to show that the undifferentiated cells, co-cultured in the presence of DC, Treg, and microbial products, do have an effector function. Prompted by the Cua and colleagues paper, which highlighted the previously underappreciated cytokine IL-17, these cells were first tested for their ability to make this effector molecule. The breakthrough was two-way: these T cells indeed made IL-17, and were distinct from Th1 and Th2.

Other immunologists had been trying to find out how IL-17 production was initiated in T cells, largely focusing on IL-23. IL-23 was unable to generate IL-17-producing T cells from undifferentiated precursors. It would be a very hard job to try and find out how these cells are generated, since there are a multitude of factors. However, we now had a culture condition that provided us with IL-17-producing cells from an undifferentiated starting population, providing possible clues on how these cells are generated.

The Pasare and Medzhitov paper had shown that in order to overcome the suppression of Treg on undifferentiated T cells, IL-6 is required. Indeed, neutralizing IL-6 in our co-cultures blocked the generation of IL-17-producing T cells. However, IL-6 alone was not sufficient to generate them. Since these cultures crucially depend on the presence of Treg, I focused on factors these cells could

contribute. At the time these would primarily be two: IL-10 and transforming growth factor (TGF)-beta. The neutralization of TGF-beta, but not IL-10, prevented the generation of IL-17-producing T cells. Importantly, we could show that only the combined presence of IL-6 and TGF-beta was required for the development of IL-17-producing T cells.

Obtaining these cells from undifferentiated precursors also allowed us to establish that these cells were generated independently from Th1 and Th2 cells, and did not depend on specific transcription factors from either lineage.

SW: How was the paper received by the community?

IL-17-producing T cells, now known as Th17, were associated early on with autoimmune disorders. Our data that TGF-beta, a cytokine widely thought of as immune suppressive and anti-inflammatory, was involved in driving the differentiation of this T cell came as a surprise. Indeed, during the lengthy reviewing process, concern was expressed regarding our interpretation of the role of TGF-beta. However, our data reconciled previously unexplained findings of a paradoxical pro-inflammatory role of TGF-beta in an experimental arthritis model that predated the discovery of IL-17-producing T cells, yet shows typical hallmarks of this T cell subset.

The apparent absence of a role of IL-23, so crucial in Th17 biology, in the development of this subset also came under initial criticism. However, IL-23 never was suggested to be a differentiation factor for T cells in the published papers, but it certainly had been ambiguously phrased in some papers, giving the perception of IL-23 as a differentiation factor, which became widespread.

"The crucial test here was to show that the undifferentiated cells, co-cultured in the presence of DC, Treg, and microbial products, do have an effector function."

Upon publication the paper was highlighted in other immunology journals. Together with two papers that came out during our reviewing process, it stood at the basis of breaking a 20-year dichotomous paradigm in adaptive immunology, and it was the first to provide the "recipe" for the generation of this subset. Th17 were already associated with autoimmune disorders and infectious diseases, the ability to culture these cells *in vitro* and the improved understanding of their development greatly accelerated this research. The latter has been evident with an exponential growth in publications relating to Th17 and the high number of quotations our paper received.

SW: Where have you taken this research since this paper's publication?

Soon afterwards we were able to show the important role this subset plays in the initiation of EAE. Interestingly, using detailed gene-expression analysis comparing the new Th17 subset with other T cell subsets allowed us to identify a Th17-specific transcription factor that could offer a possible link between autoimmune disorders and environmental pollutants: the aryl hydrocarbon receptor.

The opening up of the two-effector type T cells response has furthermore contributed to more detailed analysis of T helper cell biology. This has put more focus on greater flexibility of these cells after their initial initiation, and has allowed us to contribute an additional subset, termed Th9.

SW: Does this work have, or is it expected to have, any clinical applications?

It certainly has offered new insights in both auto-immune disorders as well as infectious diseases. Genetic mutations have been identified impairing the development of human Th17 and have been associated with increased susceptibility to certain infections. Furthermore, genome-wide association

studies have identified genes associated with Th17 biology, most notably the IL-23 receptor, which in addition to IL-17, is also targeted in numeral clinical trials.

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Marc Veldhoen's current most-cited paper in *Essential Science Indicators*, with 766 cites:

Veldhoen M, *et al*., "TGF beta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells," *Immunity* 24(2): 179-89, February 2006. Source: *Essential Science Indicators* from Thomson Reuters.

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