

This Week's Citation Classic

Waldmann T A, Broder S, Blaese R M, Dunn M, Blackman M & Strober W.

Role of suppressor T cells in pathogenesis of common variable hypogammaglobulinaemia. *Lancet* 2:609-13, 1974.

[Metabolism Branch, Natl. Cancer Inst., Natl. Insts. Health, Bethesda, MD]

In some cases, common variable hypogammaglobulinemia was shown to be caused by abnormalities of regulatory T cells which suppressed B cell maturation and antibody synthesis. This was the first demonstration of suppressor T cells in humans and the first description of a disease caused by suppressor T cell abnormalities. [The SCⁱ® indicates that this paper has been cited in over 665 publications since 1974.]

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January 11, 1983

"The project on common variable immunodeficiency disease was part of a program of studies performed at the Metabolism Branch, National Cancer Institute (NCI), on immunoregulatory disorders in patients with immunodeficiency diseases. The intramural National Institutes of Health (NIH) environment was especially favorable for the study of these rare yet extremely instructive diseases. Common variable immunodeficiency is a heterogeneous group of diseases characterized by hypogammaglobulinemia due to different causes. Prior to the studies in this report it was assumed that these diseases were caused by intrinsic defects of the B lymphocytes and plasma cells. I was stimulated to consider an alternative pathogenetic mechanism by the seminal discovery made by Richard Gershon¹ of a new type of lymphocyte in mice, the suppressor T cell, that acts as a negative regulator of many immunological responses. We considered the possibility that certain patients with hypogammaglobulinemia might have excessive suppressor T cell activity as the cause of their hypogammaglobulinemia. To examine this hypothesis we developed an *in vitro*

technique to study the terminal maturation of human B lymphocytes and described a new co-culture procedure to study suppressor T cell function. When we applied these techniques to the study of the pathogenesis of common variable immunodeficiency, we demonstrated that some patients had normal B cells but had an excessive number of activated suppressor T cells that inhibited B cell maturation and antibody synthesis. We suggested that in this subset of patients the hypogammaglobulinemia might be caused by these suppressor T cells. The basic observations were rapidly confirmed, but many questions were raised concerning their biological significance. These questions have largely been answered. However, the most critical issue, that is, whether the activation of suppressor cells is a primary pathogenetic mechanism causing the hypogammaglobulinemia or is a secondary event, will only be answered definitively when therapeutic techniques are developed that enable one to eliminate the suppressor T cells *in vivo* without affecting human B cell function.

"In the years since the publication of this study, we and others have demonstrated excessive suppressor T cell activity in association with an array of diseases including thy-moma and hypogammaglobulinemia, selective IgA deficiency, and certain neoplasms including leukemias of suppressor T cells.²

"I believe that this paper is a *Citation Classic* for two reasons. It described the first method for the study of suppressor T cells in humans and was the first demonstration that a disorder of suppressor T cell activity can cause a human disease. Honors received as a result of these studies include the Stratton Medal from the American Society of Hematology; the Michael Heidelberger Lecture, Columbia University, and the G. Burroughs Mider Lectureship, NIH. Fredrickson, then director of NIH, introduced the Mider Lecture by stating, 'Dr. Waldmann's landmark discovery of active suppression of antibody synthesis by human suppressor T cells has revolutionized thinking about the pathogenesis of immunodeficiency disease and has generated a whole new field of research demonstrating the delicate balance of cell interactions in the homeostatic immune network.' "

1. Gerhon R K. T cell control of antibody production. (Cooper M D & Warner N L, eds.) *Contemporary topics in immunobiology*. New York: Plenum Press, 1974. Vol. .3. p. 1-40.
2. Waldmann T A & Broder S. Suppressor cells in the regulation of the immune response. *Prog. Clin Immunol.* 3:155-99, 1977.