

In 1993, the published reports of four different laboratories (for review see reference 1) characterized one form of hyper IgM (HIM) syndrome as resulting from a defect in the ligand for CD40 ligand (CD40L) on T cells. In this issue of *The Journal*, Conley et al. (2) describe an additional cellular deficiency which results in HIM, caused by a defect in the B cell which does not allow normal signal transduction via CD40 despite the fact that CD40 is expressed on the patient B cells. Unlike the prominent form of HIM, the T cells from those patients described by Conley et al. (2) express normal levels of CD40L upon activation. Based on these distinctions, individuals with HIM can be classified into those that are CD40L+ and CD40L-.

Molecular interactions between a number of cell surface proteins on T and B cells have been shown to be necessary for B cell activation. CD40, a mitogenic receptor on B cells, and its ligand CD40L, (also known as gp39, TBAM) expressed on activated CD4+ T cells, is one such receptor-ligand pair involved in T cell-dependent humoral immunity. The propensity of HIM patients to suffer from recurrent bacterial infections, the inability to mount secondary immune responses (memory) to antigens, and the abnormally low levels of circulating IgG and IgA are clinical characteristics of the syndrome. Given the data presented by Conley and co-workers (2), we now know that mutations in either CD40 or its ligand manifest as HIM syndrome.

Mice deficient in CD40 (3) or its ligand (4) have been constructed by genetic targeting. As observed in both forms of HIM in humans, both CD40- and CD40L-deficient mice have reduced levels of downstream serum immunoglobulins. Although less is known about the CD40L+ form of HIM, the CD40L- form and the two types of knockout mice show impaired T-dependent humoral immune responses, germinal center formation, and development of immunological memory. Humans lacking a functional CD40L molecule, in addition to a complete failure to produce secondary antibody responses (5), also fail to mount IgM antibody responses to at least some T-dependent antigens including the bacteriophage ϕ X 174 (6). Mice which are treated with an antibody to CD40L (7, 8) can be rendered unresponsive to challenge with a T-dependent antigen, are incapable of germinal center formation, and are unable to produce memory B cells. These latter studies show that blockade of CD40L function is similar to the genetic loss of CD40L function and underscore the use of anti-CD40L as a potential therapeutic in the control of T-dependent humoral immune responses in humans. HIM patients, the CD40- and CD40L-deficient mice, and mice treated with anti-CD40L show impaired responses to T cell-dependent antigens, but not to T-independent antigens. Both the CD40- and CD40L- mice give normal responses to T-independent antigens, including the ability to switch from IgM to IgG. Collectively, these data prove

that T-dependent responses require CD40 interactions while T-independent responses do not.

The interesting feature of the CD40L+ HIM syndrome is that the B cells from these patients are unable to upregulate CD23 and CD25 in response to CD40 signalling, yet do respond to other forms of stimulation (IL-4) (2). The data suggest that these patients have a selective defect in the CD40 signalling pathway. Further support for this hypothesis was provided by the observation that B cells from CD40L+ HIM patients activated in vitro with anti-CD40 and IL-4 produce 5% of the IgE observed from CD40L- HIM-derived B cells or normal controls. These data provide conclusive evidence of a defect in the B cell population in the CD40L+ form of HIM, and it is predicted that these individuals will be unable to mount anemestic responses or form germinal centers.

Germinal centers in lymph nodes and spleens are sites of somatic mutation and affinity maturation of B cells. Though the molecular events required to drive proliferation, differentiation, and memory B cell formation within the germinal center are not completely known, evidence from HIM patients suggests that CD40 plays a major role in these events. HIM patients have demonstrated that signalling through CD40 via anti-CD40 mAbs results in extensive B cell proliferation, a primary event in the germinal center reaction. Furthermore, anti-CD40 prevents the apoptosis of germinal center B cells (for review see reference 1). Finally, mice treatment of mice with anti-CD40L mAb prevents B cells from differentiating into memory B cells. Therefore, mutations in this ligand-receptor pair interfere with a multitude of events during the course of B cell growth and differentiation.

The report by Conley and co-workers (2) establishes that mutations which affect CD40 signalling in B cells mirror mutations in the CD40 ligand on T cells and cause severe immunodeficiency. The concordant data provided by HIM as well as the CD40- and CD40L-deficient mice provide conclusive evidence of the essential role of this receptor-ligand pair in T-dependent humoral immune responses. The extensive redundancy in the immune system is such that the existence of a single receptor-ligand pair absolutely required for T cell-dependent humoral immunity is indeed remarkable. As such, the unique nonredundant feature of the CD40-CD40L interaction makes it a singularly attractive candidate for therapeutic intervention in autoimmune disease.

Teresa M. Foy, Sally R. Masters, and Randolph J. Noelle
Department of Microbiology
Dartmouth Medical School

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