

**X inactivation and immunocompetence in female carriers of the X-linked hyper-IgM syndrome.**

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Editorial

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Immunocompetence requires cognate cell–cell communication that is mediated through cell surface ligand–receptor interactions (1). An important player in such interactions is CD40, a type I membrane glycoprotein that is expressed by a variety of cells, including B cells, monocytes, dendritic cells, and thymic epithelial cells. Crosslinking this surface molecule can induce maturation, activation, and/or proliferation of CD40-bearing cells. This is mediated by the CD40–ligand (otherwise called gp39 or TRAP), a type II membrane glycoprotein that is expressed on the surface of T cells 6–8 h after their immune activation (2).

The importance of the CD40–CD40–ligand interaction is underscored by the X-linked hyper-IgM syndrome. Affected males with this primary immunodeficiency disorder cannot produce IgG and thus cannot mount an effective immune response to antigens (3). As a consequence, these patients have recurrent opportunistic infections. This syndrome results from a mutation(s) in the gene encoding the CD40–ligand on the X chromosome, making it impossible for activated T cells to effect CD40–crosslinking (for review see reference 2).

In this issue of *The Journal*, Hollenbaugh et al. (4) describe their studies on female carriers of the X-linked hyper-IgM syndrome. Because of X-inactivation (5), they find that the activated T cells of such carriers express either the normal gene or an allele encoding a defective CD40–ligand. Importantly, they detect cases of extreme Lyonization. While the activated T cells of some carriers are difficult to distinguish from those of normal donors, most of the activated T cells of other carriers are found to express only the defective CD40–ligand. By all other parameters tested, however, these and other carriers of the X-linked hyper-IgM syndrome have a fully competent immune system.

In many immunologic intercellular interactions, there is a reciprocal dialogue. A recent report indicates that T cells can receive a co-stimulatory signal from CD40–expressing cells via the CD40–ligand (6). However, the physiologic significance of this co-stimulatory signal is not clear. Patients with the X-linked hyper-IgM syndrome have normal numbers of T cells, suggesting that expression of a functional CD40–ligand is not necessary for T cell maturation and survival. The study by Hollenbaugh et al. (4) goes one step further, suggesting that T cells capable of expressing only a defective CD40–ligand can compete effectively with normal T cells for maturation and egress from the thymus. Still unexplained, however, is a prior study, indicating there may in fact be preferential inactivation of the normal paternally derived X chromosome in obligate carriers of this disease (7). While this noted bias may be due to sample variation, if found true, it would suggest that there may be a differentiation and/or proliferation advantage to hematopoietic precursors expressing the X chromosome with the defective allele. In any case, this is very unlike other X-linked immune deficiencies, such as X-linked agammaglobulinemia or X-linked

severe combined immune deficiency, in which carriers predominantly generate mature lymphocytes that express the normal allele.

Cases of extreme Lyonization can result in phenotype expression of an X-linked disease in the female carrier, as has been noted in cases of Wiskott–Aldrich syndrome, hemophilia A, or Duchenne muscular dystrophy. However, with regard to the relative number of T cells that can express a functional CD40–ligand, it seems that a little can go a long way. This may reflect the presence of signaling pathways other than that of the CD40–CD40–ligand, that, once primed by a relatively small number of CD40–ligand–expressing T cells, can perpetuate the cascade of cellular and molecular events required for an effective immune response.

Since all carriers of the X-linked hyper-IgM syndrome are immunocompetent, it may be difficult to treat pathologic autoimmunity or allergy with strategies that only partially block the interaction of CD40 with its ligand. However, collagen-induced arthritis can be inhibited by infusions of antibody to the CD40–ligand (8). It remains to be seen whether such treatments can ameliorate spontaneous autoimmune disease.

Finally, the findings of Hollenbaugh et al. (4) have encouraging implications for patients with the X-linked hyper-IgM syndrome. Indeed, it seems that only a relatively small fraction of the T cells need express a functional CD40–ligand for effective immunity. This implies that children with this immunodeficiency could benefit from even a partial reconstitution with precursor T cells capable of expressing a functional ligand. When the genetic mechanism(s) regulating expression of the CD40–ligand are identified, then this disease should be readily amenable to gene therapy.

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