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Editorial

X Inactivation and Immunocompetence in Female Carriers of the X-linked Hyper-IgM Syndrome

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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 predominately 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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References

1. Clark, E. A., and J. A. Ledbetter. 1994. How B and T cells talk to each other. *Nature (Lond.).* 367:425–428.

2. Callard, R. E., R. J. Armitage, W. C. Fanslow, and M. K. Spriggs. 1993. CD40 ligand and its role in X-linked hyper-IgM syndrome. *Immunol. Today* 14:559–564.

3. Notarangelo, L. D., M. Duse, and A. G. Ugazio. 1992. Immunodeficiency with hyper-IgM (HIM). *Immunodefic. Rev.* 3:101–121.

4. Hollenbaugh, D., L. H. Wu, H. D. Ochs, S. Nonoyama, L. S. Grosmaire, J. A. Ledbetter, R. J. Noelle, H. Hill, and A. Aruffo. 1994. The random inactivation of the X chromosome carrying the defective gene responsible for X-linked hyper IgM syndrome in female carriers of *HIGM1. J. Clin. Invest.* 94:616–622.

5. DiSanto, J. P., J. Y. Bonnefoy, J. F. Gauchat, A. Fischer, and G. de Saint Basile. 1993. CD40 ligand mutations in X-linked immunodeficiency with hyper-IgM [see comments]. *Nature (Lond.).* 361:541–543.

6. Cayabyab, M., J. H. Phillips, and L. L. Lanier. 1994. CD40 preferentially costimulates activation of CD4+ T lymphocytes. *J. Immunol.* 152:1523–1531.

7. Notarangelo, L. D., O. Parolini, A. Albertini, M. Duse, E. Mazzolari, A. Plebani, G. Camerino, and A. G. Ugazio. 1991. Analysis of X-chromosome inactivation in X-linked immunodeficiency with hyper-IgM (HIGM1): evidence for involvement of different hematopoietic cell lineages. *Hum. Genet.* 88:130–134.

8. Durie, F. H., R. A. Fava, T. M. Foy, A. Aruffo, J. A. Ledbetter, and R. J. Noelle. 1993. Prevention of collagen-induced arthritis with an antibody to gp39, the ligand for CD40. *Science (Wash. DC).* 261:1328–1330.

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