JCI The Journal of Clinical Investigation

Igα: B all that you can B

Leo D. Wang, Marcus R. Clark

J Clin Invest. 1999;104(8):1011-1012. https://doi.org/10.1172/JCI8510.

Commentary

X-linked agammaglobulinemia, arising from mutation in the hematopoietic-lineage–specific tyrosine kinase Btk, is responsible for most cases of early-onset hypogammaglobulinemia. The mechanisms underlying the remaining portion have remained elusive. In this issue of the JCI, Minegishi et al. describe a novel mechanism responsible for hypogammaglobulinemia in a young female patient (1). Together with their past work (2, 3), this study confirms the applicability of murine studies to human immunodeficiencies. In addition, it highlights the importance of the B-cell receptor as a signaling complex critical for normal B-cell development. B cells generate receptor diversity by undergoing unique, sequential D-J and then V-DJ rearrangements in the genes that code for the antigen-recognition segments of the B-cell receptor complex (BCR). Active signals provided by the BCR or its surrogates regulate progression at discrete stages throughout development. At the pro-B cell stage, this feedback is necessary to enable cells to progress to the pre-B cell stage. The positive signal for further development is only given to cells that have undergone D-J and V-DJ rearrangements that code for intact, full-length receptor chains (4, 5). Studies in mice demonstrate that an intact, membrane-associated, functioning signaling complex containing Igα, Igβ, and μ is essential for mediating this positive signal (6–8). Also, B cells from mice bearing targeted deletions in Igβ may become partially blocked at the transition between […]

Igα: B all that you can B

Commentary

See related article In this issue, pages 1115–1121.

Leo D. Wang and Marcus R. Clark

Section of Rheumatology, Department of Medicine, and Committee on Immunology, University of Chicago, Chicago, Illinois 60637, USA

Address correspondence to: Marcus Clark, Section of Rheumatology, Department of Medicine, University of Chicago, 5841 S. Maryland Avenue, Chicago, Illinois 60637, USA. Phone: (773) 702-0202; Fax: (773) 702-3467; E-mail: mclark@medicine.bsd.uchicago.edu.

X-linked agammaglobulinemia, arising from mutation in the hematopoietic-lineage–specific tyrosine kinase Btk, is responsible for most cases of early-onset hypogammaglobulinemia. The mechanisms underlying the remaining portion have remained elusive. In this issue of the *JCI*, Minegishi et al. describe a novel mechanism responsible for hypogammaglobulinemia in a young female patient (1). Together with their past work (2, 3), this study confirms the applicability of murine studies to human immunodeficiencies. In addition, it highlights the importance of the B-cell receptor as a signaling complex critical for normal B-cell development.

B cells generate receptor diversity by undergoing unique, sequential D-J and then V-DJ rearrangements in the genes that code for the antigen-recognition segments of the B-cell receptor complex (BCR). Active signals provided by the BCR or its surrogates regulate progression at discrete stages throughout development. At the pro-B cell stage, this feedback is necessary to enable cells to progress to the pre-B cell stage. The positive signal for further development is only given to cells that have undergone D-J and V-DJ rearrangements that code for intact, full-length receptor chains (4, 5). Studies in mice demonstrate that an intact, membrane-associated, functioning signaling complex containing Igα, Igβ, and μ is essential for mediating this positive signal (6–8). Also, B cells from mice bearing targeted deletions in Igβ may become partially blocked at the transition between D-J and V-DJ rearrangement. Genes coding for BCR-proximal signaling molecules are also essential for progression past the pro-B cell stage; deletions in Syk and Btk result in B-cell developmental arrest (9–11). These results illustrate that the pro-B–to–pre-B-cell checkpoint marks the transition from intrinsically driven to BCR signal-dependent developmental events. Prior to and during D-J rearrangement, there is little if any requirement for BCR complex molecules or for molecules that act downstream from the BCR. Subsequent to V-DJ rearrangement, signaling through the BCR complex selects for rearrangements capable of encoding for functional heavy chains.

In humans, previous work has determined that mutations in Btk, μ heavy chain, or λ5/14.1 are associated with hypogammaglobulinemia (2, 3, 11, 12). Now, Minegishi et al. describe a patient in whom this disorder results from a point mutation in Igα. They compare her to a previously described individual who is deficient for the μ heavy chain, and they determine that the B cells isolated from the two patients are molecularly and phenotypically similar, arguing that both patients have a block at the same developmental stage. RT-PCR assays demonstrate that gene expression and rearrangement status are also similar in B cells from the two patients. However, the Igα-deficient patient has more pre-B cells than does the μ-deficient patient, and these cells show greater junctional diversity, suggesting that the developmental blockade is less complete in the case of Igα-deficiency. Confirming the molecular results by FACS® analysis, Minegishi et al. find the majority of bone marrow mononuclear cells in this patient to be $CD19^-$ and sIg^- and the few $CD19^+$ cells to be also $CD34^+$ and TdT^+. These results strongly suggest that in humans, this mutation in Igα leads to a block in survival of V-DJ–rearranged pre-B cells.

The apparent "leakiness" of this phenotype may indicate that Igα is not absolutely required for development. Alternatively, an aberrant protein may be expressed. One of the two RNA transcripts detected contains a 13 bp deletion and may encode a truncated Igα protein with some residual activity in pre-B cells. Regardless of this reservation, it is convincing that the patient described suffers from a significant block at the pro-B–to–pre-B-cell transition. This conclusion is consistent with the B-cell deficiency observed in mice lacking wild-type Igα (8).

These studies establish a trend in understanding the pathogenesis of human hypogammaglobulinemias, suggesting that they result from defects in signaling molecules known in mice to cause similar pathologies.

As more light is shed on human B-cell deficiencies parallels to the murine system become more compelling. This has two important implications. First, it confirms that the checkpoint at the transition between the intrinsic and signaling-mediated stages of B-cell development is crucial in both species. The fact that development is arrested at this particular stage when many critical signaling molecules are ablated or made dysfunctional implies that this system is exquisitely regulated at this one step. Second, these studies establish a trend in understanding the pathogenesis of hypogammaglobulinemias, suggesting that the human disorder may result from defects in signaling molecules known in mice to cause similar pathologies. Thus, deficiencies in molecules such as Syk and Igβ, which are known in mice to cause B-cell developmental arrest at the pro-B–to–pre-B-cell transition, would be expected to be a cause of human hypogammaglobulinemia.

1. Minegishi, Y., et al. 1999. Mutations in Igα (CD79a) result in a complete block in B-cell development. *J. Clin. Invest.* 104:1115–1121.
2. Yel, L., et al. 1996. Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. *N. Engl. J. Med.* **335**:1486–1493.
3. Minegishi, Y., et al. 1998. Mutations in the human lambda5/14.1 gene result in B cell deficiency and agammaglobulinemia. *J. Exp. Med.* **187**:71–77.
4. Melchers, F., et al. 1995. Positive and negative selection events during B lymphopoiesis. *Curr. Opin. Immunol.* **7**:214–227.
5. Rolink, A., and Melchers, F. 1996. B-cell development in the mouse. *Immunol. Lett.* **54**:157–161.
6. Kitamura, D., Roes, J., Kuhn, R., and Rajewsky, K. 1991. A B cell-deficient mouse by targeted disruption of the membrane exon of the immunoglobulin mu chain gene. *Nature*. **350**:423–426.
7. Gong, S., and Nussenzweig, M.C. 1996. Regulation of an early developmental checkpoint in the B cell pathway by Ig-beta. *Science*. **272**:411–414.
8. Torres, R.M., Flaswinkel, H., Reth, M., and Rajewsky, K. 1995. Aberrant B cell development and immune response in mice with a compromised BCR complex. *Science*. **272**:1804–1808.
9. Cheng, A.M., et al. 1995. Syk tyrosine kinase required for mouse viability and B-cell development. *Nature*. **378**:303–306.
10. Rawlings, D.J., et al. 1993. Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. *Science*. **261**:358–361.
11. Tsukada, S., et al. 1993. Deficient expression of a B-Cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell*. **72**:279–290.
12. Vetrie, D., et al. 1993. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. *Nature*. **361**:226–233.