B-lineage ALL cases, those with the *TEL-AML1* had a dramatically lower DNPS than other subtypes. The authors then used gene expression experiments to compare the expression of 82 genes involved in purine metabolism across the B-cell lineage cases. Sixteen genes were found to be significantly associated with the *TEL-AML1* subgroup of ALL, and the expression of several genes (notably *PAICS* and *IMPDH2*) closely correlated with DNPS level. It is not clear mechanistically how the *TEL-AML1* genetic lesion is associated with purine biochemistry, but the association may explain why this subgroup of ALL is especially sensitive to chemotherapy.

ALL is not a common disease, and given that these studies are investigating specific subsets of ALL, the skeptic may claim that the results are unlikely to change the face of cancer therapy. However, as models of clinical investigation, the results are quite interesting and energizing, showing how modern molecular biology can be applied in clever and powerful ways. ■

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GENE THERAPY

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XLA gene therapy turns a corner

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A more clinically relevant mouse model for XLA with severe B-cell developmental and functional defects can be corrected by retroviral-mediated gene transfer into hematopoietic stem cells.

Retroviral-mediated gene therapy has come under intense scrutiny because of safety concerns arising from the incidence of leukemia in 2 severe combined immunodeficiency (SCID) children. Much effort is currently being focused on the safety modification of vectors and efforts to reduce the risk of insertional mutagenesis. It is also important not to lose sight of the fact that gene therapy for SCID has been very effective in 2 separate clinical trials.[1,2] A major reason for this success, and perhaps the problems, is the early block in progenitor development. In cases of SCID resulting from defects in the common gamma chain, Janus kinase 3 (JAK3), adenosine deaminase (ADA), and recombinase-activating gene 2 (rag2) deficiency, a selective advantage exists for normal cells, which have a survival advantage in vivo. This selective advantage increases the proportion of corrected cells following retroviral gene therapy and has proven successful in several animal models for these diseases. However, a major obstacle for translation of gene therapy success in mice to that in humans is that withdrawal of conventional therapy, such as enzyme replacement for ADA deficiency[3] or intravenous immunoglobulin for SCID, is not typically acceptable for most patients, and continued replacement therapy limits the beneficial selective advantage.

X-linked agammaglobulinemia (XLA), although a rare disease, is more common than SCID and is manifested from a deficiency in the B cells and plasma cells but normal numbers of T cells. XLA results in increased susceptibility to recurrent infections. B-cell receptor responsiveness in humans is highly dependent on the Bruton tyrosine kinase (Btk) gene, and defects in Btk activity block B-lymphocyte development and function. Therefore, mouse models for XLA have been of interest for preclinical studies. However, although spontaneous mutant X-linked immunodeficiency (Xid) mice can be corrected with wild-type donor cells with minimal myeloablation,[4] Xid and $Btk^{-/-}$ mice have milder disease manifestation than that in humans. This is because of compensation by Tec, which rescues some of the B-cell function. Therefore, $Btk^{-/-}Tec^{-/-}$ mice were generated to provide a more clinically relevant model for XLA that recapitulates the severe disease phenotype.[5]

In this issue, Yu and colleagues demonstrate that retroviral-mediated targeting of hematopoietic stem cells resulted in sustained correction of B-cell development, rescue of serum immunoglobulin levels, and normalized B-cell receptor–dependent proliferative functions in the $Btk^{-/-}Tec^{-/-}$ model of XLA. This study represents a significant advance toward gene therapy for XLA and presents an ideal model for future preclinical studies to address important issues such as the necessity for myeloablation and the functional immunity following pathogen challenge. The risk-benefit ratio is always an important consideration for any new therapy. For XLA, the selective advantage provides a potentially curative benefit that is unique from SCID, since intravenous gamma globulin therapy may be continued without compromising the selective advantage. ■

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