Gene therapy targets XLP

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Studying a murine model of X-linked lymphoproliferative syndrome (XLP), Rivat et al report in this issue of Blood that the immune function defects of the disorder are improved or corrected by lentiviral vector–mediated gene transfer of SH2D1A into autologous hematopoietic stem cells.

X-linked lymphoproliferative syndrome (XLP) caused by genetic defects in SH2D1A encoding SAP (Slam-associated protein), described in the 1970s and molecularly defined in 1998, is a prematurely lethal immunodeficiency resulting from developmental and functional defects in NK cells, T cells, and NKT cells. The most severe complications, hemophagocytic lymphohistiocytosis (HLH), lymphoproliferative disorders, and vasculitis, have all been closely associated with EBV infection that is not adequately controlled in affected males due to weakened humoral and cellular responses.

Rivat and colleagues demonstrate that NK cytotoxicity appears to be fully reconstituted while the proportion of thymic NKT cells, although improved compared with SAP-deficient mice, remain decreased at the time point assessed. Gene-corrected animals are also more capable of generating immunoglobulins and specific T-dependent antibodies, presumably through improvement in CD4 T-cell function supporting the development of germinal centers. Importantly, the authors indicate that the immunologic outcomes after gene transfer into SAP-deficient mice are equivalent to those seen with hematopoietic cell transplantation from normal mice.

The advent of gene therapy treatment is a welcome addition to the future management of patients with XLP. Historically, supportive...
care with chronic IV IgG supplementation, surveillance for EBV exposure and reactivation, and treatment of autoimmune manifestations have been mainstays of management.

The development of HLH or lymphoma has often prompted allogeneic hematopoietic cell transplantation (HCT). A recently published international survey of transplant outcomes in the current era showed that 81.4% of patients with genetically defined XLP are surviving after allogeneic HCT with evidence of immunologic improvement in most. However, post-HCT survival in patients who had developed HLH was shown to be substantially worse at 50%, while all patients without prior HLH survived the HCT procedures. What’s worse at 50%, while all patients without prior HLH survived the HCT procedures. What’s

Thus the time has come to develop clinical vector(s) and plan future clinical trials for XLP in patients lacking suitably matched HCT donors. Lentiviral vector constructs, as used in the current report, have been shown to be highly effective in terms of transduction because of their ability to infect both replicating and nonreplicating cells, including hematopoietic stem cells. Current data from experimental systems indicate that lentiviruses have significantly lower genotoxicity compared with the long terminal repeat–driven γ-retroviral retroviruses used in earlier trials of gene therapy in other immunodeficiencies that resulted in cases of leukemogenesis directly linked to the therapy: X-linked severe combined immunodeficiency (SCID), Wiskott–Aldrich syndrome, and X-linked chronic granulomatous disease.

In addition to selection of the safest effective vector, the time frame and intensity of patient conditioning after stem cell harvest but before infusion of gene–corrected autologous stem cells requires thoughtful planning and discussion. 

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REFERENCES


Comment on Gruber et al, page 1175

UGT2B17 as a disease accelerator in CLL

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In this issue of Blood, Gruber and colleagues provide a new potential enzyme involved in chronic lymphocytic leukemia (CLL) progression by identifying uridine diphospho (UDP) glucuronosyltransferase 2B17 (UGT2B17) as both a prognostic marker and therapeutic target. 

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LL is characterized by accumulation of malignant B cells in the blood, bone marrow, and lymphoid tissues and it has a very heterogeneous outcome. Multiple prognostic factors have been identified in CLL that predict poor outcome with the biggest drivers being immunoglobulin heavy chain (IgVH) unmutated status, ZAP-70 protein overexpression, and the presence of select genomic abnormalities [del(17p13.1) and del(11q22.3) or mutations (NOTCH1, SF3B1, and p53)]. Here, Gruber and colleagues identify for the first time that uridine diphospho (UDP) glucuronosyltransferase 2B17 (UGT2B17) is both overexpressed in CLL tumor cells and that high levels of UGT2B17 mRNA correlate with shorter treatment–free survival and overall survival (see figure). UGT2B17 mRNA levels were effective in further discriminating outcome of patients with of IgVH mutated but not unmuted patients. In addition, increasing UGT2B17 expression change from baseline to day 3 of treatment after fludarabine and cyclophosphamide (FC) or FC with rituximab identified patients with low response rate to this treatment. Collectively, the findings of this article strongly indicate the role of UGT2B17 as a new prognostic marker and a potential therapeutic target for patients with high-risk CLL.

Notably, the story does not stop here but extends to biology of this important enzyme. UGT2B17 is a member of the uridine diphosphoglucuronosyltransferase (UGT) protein family and catalyzes the glucuronidation of a diverse range of substrates including steroid hormones and lipid-soluble drugs. Thera-
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