A natural choice for hemophilia B

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In this issue of Blood, Crudele et al describe a novel study of adeno-associated virus (AAV) vector-mediated gene therapy that induced immune tolerance to factor IX (FIX) in a hemophilia B (HB) dog with previously formed anti-FIX inhibitor antibodies (IAs). The discovery of a naturally occurring gain-of-function in FIX has prompted the development of highly effective, immune-tolerizing gene therapy for HB. The mutation in question was described in an Italian family with a unique form of X-linked thrombophilia, caused by the substitution of leucine for arginine at position 338 (R338L; R384L including the activation peptide) in FIX, which increased the specific activity of FIX by 5- to 10-fold and was termed FIX-Padua.

TAs complicate replacement therapy in hemophilia generally, although IA formation is much more frequent in hemophilia A than in HB. The fundamental issue remains that no effective treatment is available to eliminate IAs, especially in HB where immune tolerance induction frequently fails and has been complicated by allergic reactions and nephrotic syndrome. A novel development, led by Finn et al, has been the administration of gene therapy to overexpress coagulation factor VIII in dogs with hemophilia A, thereby overwhelming the IA response and establishing immune tolerance. Subsequently, 2 groups showed that overexpression of FIX could similarly induce immune tolerance to FIX through a mechanism dependent on regulatory T-cell activation in HB mice. Given that an AAV vector-mediated FIX-Padua gene therapy was highly effective and nonimmunogenic in HB mice and dogs, it remained for Crudele et al to demonstrate that it would induce immune tolerance in an HB dog with preformed IA.

The AAV vector encoding FIX-Padua was administered at dosages approximately equivalent to a recent successful clinical trial involving patients with HB. Notably, the specific activity of FIX-Padua was 8- to 12-fold higher, in comparison with wild-type FIX, reaching 25% to 40% of normal without provoking anti-FIX antibodies in 2 naive HB dogs. The third HB dog treated (Wiley) had previously formed antibodies that increased after vector administration, signifying a transient anamnestic response, followed by disappearance of anti-FIX by day 70. Remarkably, FIX activity continued to
rise in Wiley’s blood for 800 days while the proinflammatory cytokine interleukin (IL)-6 and anti-FIX antibodies decreased concurrently (see figure). Cytokine profiling suggested that the induction of regulatory T cells occurred both following the initial vector administration and following an immune challenge after day 800, given the rise in both interferon-γ and IL-10 at these times. Importantly, no evidence for thrombosis or nephrotic syndrome was observed during the monitoring of treated HB dogs. An accompanying dose escalation study in mice revealed evidence for thrombosis at the highest levels of FIX activity, a known complication of supraphysiologic FIX activity, which occurred at equivalent FIX activities for either FIX-Padua or wild-type FIX.2–6

Thus, gene therapy with FIX-Padua features safety and efficacy promises success in future clinical trials, with the caveat that supraphysiologic FIX activity presents a risk for thrombosis necessitating careful monitoring.2,7,8 Importantly, FIX-Padua gene therapy could lower the dose requirements for gene therapy in HB, given the high degree of efficacy in the HB dog model at clinically acceptable dosages, which will help to address the well-documented risk for dose-related anti-capsid T-cell responses to AAV vectors in HB clinical trials.9,10 Overall, it seems reasonable to predict a bright future for a “natural choice” for HB gene therapy in FIX-Padua.

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REFERENCES

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Comment on Iacovelli et al, page 1578

Multilevel BCR signals toward CLL

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In this issue of Blood, Iacovelli et al provide the first in vivo experimental evidence on the proleukemogenic relevance of autonomous (exo-antigen–independent) B-cell receptor (BCR) stimulation in conjunction with ligand (autoantigen)-mediated BCR signaling in chronic lymphocytic leukemia (CLL).1

The BCR is a central growth-promoting factor in the pathogenesis of CLL. Prevailing concepts of CLL histogenesis and immunobiology favor particular subsets of normal B lymphocytes1 predestined by reactivity of their BCRs to a restricted set of (auto)antigens for affinity maturation and selection during precursor cell initiation and clonal progression.3 Although mechanistically insufficiently understood, there is mounting data on correlations of disease aggressiveness in CLL with immunoglobulin (Ig) genetics,4,5 BCR signaling capacity,3,5 and receptor reactivity.4,6 BCR pathway components are at the very focus of novel interventional strategies in CLL with great clinical success.

Corroborating the theories of antigen–based selection, the surface membrane Igs (sIgs) (the antigen recognition units) and the third complementary determining region (HCDR3) of the Ig heavy chain variable (IGHV) domain in CLL exhibit remarkable stereotypy.3 Underlying this is a “preferred” constitution of the leukemic BCRs of specific IGHV genes, including their association with certain IGHD-J genes and particular IGLVs/λs. When superimposing these repertoire biases onto a disease categorization based on IGHV somatic mutations (unmutated-CLL [U-CLL] vs mutated-CLL [M-CLL]), CLLs can be clustered into those with sets of stereotyped sIgs (collectively ~1/3 of cases and mostly U-CLL), those using specific IGHVs (U- and M-CLL), and those with heterogeneous or no obvious Ig characteristics (primarily M-CLL). With respect to their cognate antigens, U-CLLs typically carry polyreactive sIgs of low affinity toward processed autologous neo-antigens (eg, myosin chains, vimentin, oxidized lipoproteins, dsDNA, and the lupus-associated ribonuclease Smith [Sm]-antigen), or to microbial (foreign) antigens (eg, pneumococcal polysaccharides and pUL32 of cytomegalovirus).3 The structurally less restricted sIgs of M-CLL react with foreign antigens (eg, yeast-derived β-(1,6)-glucans and Fc-tails of rheumatoid factors) in high-affinity and high-specificity engagements.7 The void of data on the actual leukemogenic contribution of such (auto)antigen-based BCR signaling was one of the issues addressed by Iacovelli et al8 (see below).

At the level of BCR responsiveness, U-CLLs show a higher signaling capacity than M-CLLs, which is in part explained by higher sIgM densities, differential expression of signaling modulators (eg, CD38, ZAP70, and Fc-tails of rheumatoid factors) in high-affinity and high-specificity engagements.1,8 The void of data on the actual leukemogenic contribution of such (auto)antigen-based BCR signaling was one of the issues addressed by Iacovelli et al8 (see below).