JAK2 inhibition, a combinatorial therapeutic approach in need of further study for chronic myeloid malignancies.

As mentioned earlier, the most well-characterized role of the enzymatic activity of mutant CBL is ubiquitinylating receptor tyrosine kinases for proteasome degradation as part of the negative feedback mechanism after cytokine stimulation. This model now provides a platform to identify the effects of CBL mutations on the proteome in specific subsets of primary cells, including rare cell types such as stem cells. This effort, in turn, may identify novel downstream substrates of mutant CBL that mediate its leukemogenic effects and might serve as novel therapeutic targets themselves. Overall, the model generated by Nakata et al represents one of the most faithful genetically engineered murine models of human CMML to date, as well as a valuable reagent to expand our understanding of CMML pathogenesis.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES


Comment on Sun et al, page 2161

Stopping bleeding is not enough to FIX hemarthropathy

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In this issue of Blood, Sun et al demonstrate that replacing factor IX (FIX) for short periods of time does not prevent long-term arthropathy in a mouse model of hemophilia B. Hemophilia B is an X-linked bleeding disorder due to the deficiency of FIX. Recently, new recombinant FIX (rFIX) products with extended half-life (EHL) were approved for both prophylactic and on-demand therapy. In the work here, the authors...
compared a single injection of long-acting glycoPEGylated $r$FIX with the outcomes of multiple injections of unmodified $r$FIX in hemophilia B mice or hemostatically normal mice. In normal mice, the authors successfully demonstrate the limited effect of the induction of hemarthrosis, even when blood was injected into the joint, mimicking the phenotype of hemophilia B mice. EHL–FIX provides a superior effect in minimizing the joint disease in hemophilia B mice compared with single or multiple doses of unmodified FIX by 3 doses daily or 8 doses over 13 days. This was achieved despite comparable FIX levels in plasma and synovial fluid lavage at an early time point. Using a comprehensive histopathology and healing assessment of the synovial and osteochondral wound, they demonstrate that the single dose of EHL–FIX was superior to the multiple replacement strategy of unmodified FIX over time. Moreover, a single dose of EHL–FIX was comparable to the quick joint wound healing observed in hemostatically normal mice. Notably, iron deposition was remarkably reduced by a single dose of EHL–FIX. Interestingly, findings were also noted in the surrounding bone density and structure. The use of noninvasive microcomputed tomography (microCT) (see figure) also confirmed the superior performance of EHL–FIX.

Emerging evidence on the role of severity of intra-articular bleedings and its effect on bone tissue are also supported by these findings. Collectively, these data suggest that the standard clinical strategy of transient factor replacement for only a few days may stop acute bleeding, reduce pain, and improve parameters of joint mobility, but may not be enough to prevent the slow wound-healing process and resulting chronic arthropathy. These findings are supported by data from skin wound-healing studies showing delayed healing in hemophilia B mice compared with hemostatically normal mice. It will be interesting to explore whether replacement with EHL–FIX is superior to unmodified FIX in this wound-healing model. The underlying mechanism of the beneficial effect of EHL–FIX is unclear considering that the plasma half-life of the glycoPEGylated FIX is only ~2.5 hours longer than unmodified FIX in this hemophilia B model. There is a possibility that binding of FIX to extracellular space was the reason for this long-term healing effect. It also may be possible that FIX extracellular binding may explain, at least in part, these effects because collagen IV, the main collagen form that binds to FIX, is present in the synovial intimal layer and meniscus. Interestingly, Stafford’s group suggested that most of the FIX may be located at extravascular sites upon protein infusion, and hemostasis can be achieved at late time points even if FIX is no longer detected in the circulation. These intriguing hypotheses inject some uncertainty regarding the clinical relevance of the typical pharmacokinetics of infused FIX as a marker of biological activity. It will be interesting to know whether the beneficial effects demonstrated here with glycoPEGylated FIX can also be obtained using other forms of long-acting FIX or on long-term expression of FIX by gene therapy. One limitation of the study is the lack of a range of FIX doses tested to identify the minimal dosage with therapeutic effect. Here, they used a rather high fixed dose of FIX (250 IU/kg per injection), which would be economically challenging in a clinical setting.

Moreover, given the large effect on iron deposition demonstrated here, the use of magnetic resonance imaging of the joints could also be incorporated in clinical trials using EHL products to assess a potential protective effect. There are several reports on the use of EHL products in mouse models of hemophilia addressing hemostasis, immune responses, and now hemarthrosis; it will be interesting to see whether these findings have translational potential.

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Comment on Abd Hamid et al, page 2198

Improving transplantation for IL2RG/JAK3 SCID

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In this issue of Blood, Abd Hamid and colleagues describe the long-term follow-up of patients who underwent hematopoietic stem cell transplantation (HSCT) for IL2RG/JAK3 severe combined immunodeficiency (SCID) and demonstrate improved B-cell function and improved quality of life (QoL) in patients who received pretransplantation conditioning.

Since the first successful HSCT for SCID in 1968, HSCT has been the standard, and until recent years, the only, definitive therapy for SCID. However, the best manner of transplantation for classical SCID has remained unclear, with ongoing debate about the risks of preconditioning chemotherapy vs the degree of immune reconstitution necessary for sustained cure. With the widespread use of newborn screening for SCID in the United States and other countries that has permitted rapid diagnosis and increased usage of HSCT in early infancy, the need for long-term, genotype-specific outcomes data is critical.
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