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Platelet-targeted gene therapy of hemophilia A and B

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Hemophilia A and B are monogenic genetic bleeding disorders, resulting from a FVIII (hemophilia A) or FIX (hemophilia B) deficiency. Protein replacement therapy is available for hemophilia treatment, but it is expensive due to the short half-life of the FVIII and FIX proteins. Furthermore, a subset of patients will develop inhibitory antibody after protein infusion, rendering the routine protein replacement therapy useless. Gene therapy is an attractive alternative for hemophilia treatment. It may provide sustained protein *in vivo* and cure the diseases if gene therapy is successful. Substantial progress has been achieved in the last two decades. We have developed a platelet-targeted gene therapy approach using platelet-specific IIb promoter to drive FVIII or FIX expression for hemophilia A and B gene therapy. Our studies using a transgenic model have demonstrated that platelet-derived FVIII can correct murine hemophilia A phenotype even in the presence of high-titer anti-FVIII inhibitory antibodies (inhibitors). Our further studies have demonstrated that lentiviral gene delivery to hematopoietic stem cells can efficiently introduce sustained therapeutic levels of platelet-FVIII in hemophilia A mice even in the presence of pre-existing immunity, suggesting that platelet gene therapy is a promising approach for gene therapy of hemophilia A patients and the patients with inhibitors. In contrast, platelet-derived FIX can improve hemostasis in hemophilia B mice, but the clinical efficacy is limited in the presence of anti-FIX inhibitors.

Biography

Qizhen Shi graduated from the Fujian Medical University in 1998 and completed her postdoctoral studies from Medical College of Wisconsin, USA. Shi is an Associate Professor of Pediatric Hematology at the Medical College of Wisconsin. She has been the recipient of grants from the National Blood Foundation, the National Hemophilia Foundation, American Heart Association, and the National Institutes of Health to develop gene transfer strategies for the treatment of hemophilia. She has authored or co-authored 36 articles in peer-reviewed scientific journals and serves as an Ad Hoc reviewer for Blood, JTH, TH, et al.

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