GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Phenotypic correction and stable expression of factor VIII in hemophilia A mice by embryonic stem cell therapy

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Genet. Mol. Res. 12 (2): 1511-1521 (2013)
Received March 28, 2012
Accepted November 23, 2012
Published May 13, 2013
DOI http://dx.doi.org/10.4238/2013.May.13.4

ABSTRACT. Hereditary deficiency of factor VIII (FVIII) leads to hemophilia A, a severe X-linked bleeding disorder. Current therapies include fixed-dose FVIII prophylaxis, factor replacement therapy, and most recently, gene therapy. Prophylaxis and FVIII replacement therapies are limited by incomplete efficacy, high cost, restricted availability, and development of neutralizing antibodies in chronically

treated individuals. Limited success has been obtained in preclinical trials using gene therapy for the treatment of hemophilia. Therefore, new options for therapy for hemophilia A are needed. We evaluated the potential of embryonic stem cells for correcting hemophilia A in mice. FVIII-deficient mouse blastocysts were collected and injected with mouse embryonic stem cells stably expressing green-fluorescent protein (GFP) and transferred to pseudopregnant recipient mice. Expression of FVIII was measured in the liver and plasma of the 5 chimeric mice that were produced. Three of these mice were GFP-positive at the age of 6 months. The plasma FVIII activity levels were equal to those of wild-type mice. These data demonstrate that embryonic stem cell transplantation at an early embryonic stage has potential as therapy for this progressively debilitating, life-threatening bleeding disorder.

Key words: Hemophilia A; FVIII; Embryonic stem cells; Blastocysts; Chimeric mice

