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Phenotypic correction of murine hemophilia A by bone marrow-derived liver cells

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Hemophilia A is caused by mutations within the Factor VIII (FVIII) gene that lead to depleted protein production and inefficient blood clotting. Current therapies include fixed-dose FVIII prophylaxis, factor replacement therapies, and most recently, gene therapy. Liver is the primary site of FVIII synthesis; however, the specific cell type(s) responsible for its synthesis remain controversial. We hypothesize that the partial replacement of mutated liver cells by healthy cells in hemophilia A (HA) mice could ameliorate the severity of the bleeding disorder. The aim of this investigation was to study the cellular origin of FVIII by examining bone marrow cell (BMCs) therapy for treatment of HA in mice. Recipient liver was perturbed with either acetaminophen or monocrotaline (MCT) to facilitate the engraftment and differentiation of lineage-depleted (Lin-) enhanced green fluorescent protein (eGFP)-expressing BMCs. Immunohistochemistry experiments with the liver tissue showed that the donor-derived cells expressed the markers of both hepatocytes (albumin and cytokeratin-18) and endothelial cells (von Willbrand factor). Both cell types expressed FVIII light chain mRNA and protein, which was further confirmed by transmission electron microscopy. The transplanted HA mice showed FVIII activity in plasma ($P < 0.01$) and survived tail-clip challenge ($P < 0.001$). The results of fluorescent in situ hybridization and immunocytochemistry experiments suggested that differentiation was direct in this model. Overall, this report demonstrates that phenotypic correction in HA mice with conditioned liver is possible by transplantation of BMCs. Thus, BMC therapy is a potential alternative approach to managing HA.

Biography

Dr. Neelam Yadav has completed her Ph.D from Industrial Toxicology Research Centre, Lucknow and postdoctoral studies from Stem Cell Biology Laboratory of National Institute of Immunology (NII) New Delhi, India. She is Assistant Professor in Department of Biochemistry, at Dr. R.M.L. Avadh University, Faizabad, India. Dr. Neelam has published many papers in reputed international journals and filed one patent.