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Stem cell therapy for Crigler Najjar syndrome type I- Sharmila Fagoonee, Institute of Biostructure and Bioimaging, Italy

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The Crigler Najjar syndrome type I (CNSI) is a rare recessive disorder caused by mutations in the Ugt1a1 gene. There is no permanent cure except for liver transplantation, and current therapies present several shortcomings. Since stem cell-based therapy offers a promising alternative for the treatment of this disorder, we evaluated the therapeutic potential of a population of stem cells isolated from cryopreserved hepatocytes known as human liver stem cells (HLSC) in immune-compromised NOD SCID Gamma (NSG)/Ugt1-/- mice, which closely mimic the pathological manifestations in CNSI patients. In order to assess whether HLSC expressed UGT1A1, decellularised mouse liver scaffolds were repopulated with these cells. After 15 days' culture in this 3D setting ex vivo, HLSC differentiated into hepatocyte-like cells expressing markers such as albumin and cytochrome 1a1. For the in vivo human cell engraftment and recovery experiments in the Crigler-Najjar mouse model, NSG/Ugt1-/- mice were generated. A single dose of HLSC was injected in the liver parenchyma of 5 days old phototherapy-treated NSG/Ugt1-/- pups and HLSC functionality and phenotype rescue were assessed in vivo at post-natal Day 21. HLSC expressed UGT1A1 in vivo, induced a decrease in serum unconjugated bilirubin, and improved phenotype and survival compared to untreated controls. A significant reduction in eosinophilic neurons was also observed in HLSC-injected mutant mice hippocampus and cerebellum reflecting recovery from brain damage versus controls. Our results show that HLSC express UGT1A1 in vivo and improve the phenotype and survival of NSG/Ugt1-/- mice, and show promises for the treatment of CNSI.

Crigler-Najjar syndrome is a rare autosomal recessive inherited disorder characterized by the absence or decreased activity of UDP-glucuronosyl transferase, an enzyme required for glucuronidation of unconjugated bilirubin in the liver. It is one of the major causes of congenital non-hemolytic jaundice. The increased concentration of unconjugated bilirubin is the sole cause of disease manifestation. The disease severity depends upon the number of enzymes produced required for the glucuronidation of bilirubin. Newborns may present with hyperbilirubinemia, but other signs progressively develop later in life.

Crigler-Najjar syndrome is of two types based on the clinical criteria such as molecular and functional features, the severity of clinical presentation, and phenobarbitol response. Type I is the most severe form with an almost complete absence of UDP-glucuronosyltransferase enzyme activity, whereas type II is less severe with a reduced level of enzyme activity. Central nervous system involvement complicated by kernicterus is seen mainly in Crigler-Najjar type I.

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