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Stem cell therapy for Crigler Najjar syndrome type I

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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.

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