HSCsforLSDbrain - HSC-based therapies for LSDs: understanding the modalities of cell replacement in the LSD brain for improving therapeutic efficacy

The recent hypothesis that postnatal microglia are maintained independently of circulating monocytes by local precursors that colonize the brain before birth has relevant implications for the treatment of various neurological diseases, including lysosomal storage disorders (LSDs). LSDs are fatal diseases of childhood occurring in 1:5000-7000 live births; in >50% of the cases, LSD patients experience a severe neurological deterioration. Most LSDs with central nervous system (CNS) involvement lack a curative treatment. Hematopoietic cell transplantation (HCT) form healthy donors is applied to LSD patients in order to repopulate the recipient myeloid compartment, including CNS microglia, with donor-derived cells expressing the defective functional hydrolase. Over the past three decades, about 1000 HCTs have been performed for patients with LSDs with a variable benefit exerted on the CNS. The positive results obtained in Hurler syndrome and few other LSDs and the benefit observed in our on going Phase I/II clinical trial of HSC gene therapy for the demyelinating LSD metachromatic leukodystrophy indicate that migration of the transplanted Hematopoietic Stem Cells (HSCs)/their progeny into the affected human brain occurs. However, timing of resident CNS macrophages and microglia replacement by the transplanted cell progeny is frequently too slow for clinical benefit due to the rapid progression of the primary neurological disease, particularly in the most aggressive LSD variants. Thus, a deep understanding of the modalities, time course and factors that affect this phenomenon might allow enhancing clinical benefit of HSC-based approaches for treating the LSD brain disease. The proposed work, combining basic and innovative preclinical research with the information derived from a pioneering clinical experience, will generate the basis for designing more efficacious and safer transplant approaches for these fatal diseases.

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