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Efficient engraftment of pluripotent stem cell-derived myogenic progenitors in a novel immunodeficient mouse model of limb girdle muscular dystrophy 2I.

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Abstract

BACKGROUND: Defects in α-dystroglycan (DG) glycosylation characterize a group of muscular dystrophies known as dystroglycanopathies. One of the key effectors in the α-DG glycosylation pathway is the glycosyltransferase fukutin-related protein (FKRP). Mutations in FKRP lead to a large spectrum of muscular dystrophies, including limb girdle muscular dystrophy 2I (LGMD2I). It remains unknown whether stem cell transplantation can promote muscle regeneration and ameliorate the muscle wasting phenotype associated with FKRP mutations.

RESULTS:
Here we transplanted murine and human pluripotent stem cell-derived myogenic progenitors into a novel immunodeficient FKR-P-mutant mouse model by intra-muscular injection. Upon both mouse and human cell transplantation, we observe the presence of donor-derived myofibers even in absence of pre-injury, and the rescue of α-DG functional glycosylation, as shown by IIF6 immunoreactivity. The presence of donor-derived cells expressing Pax7 under the basal lamina is indicative of satellite cell engraftment, and therefore, long-term repopulation potential. Functional assays performed in the mouse-to-mouse cohort revealed enhanced specific force in transplanted muscles compared to PBS-injected controls.

CONCLUSIONS: Altogether, our data demonstrate for the first time the suitability of a cell-based therapeutic approach to improve the muscle phenotype of dystrophic FKR-mutant mice.

KEYWORDS: FKR; LGD21; Muscle regeneration; Muscular dystrophy; Pluripotent stem cells; Transplantation

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