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Characterization of mesoangioblasts and modulation of their engraftment capacity for Duchenne muscular dystrophy gene therapy

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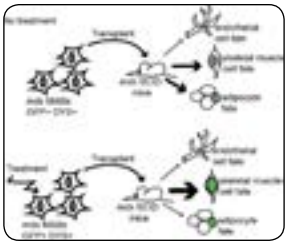
Duchenne muscular dystrophy (DMD) is a lethal monogenic pathology characterized by progressive muscle degeneration. We designed a potential autologous gene therapy protocol based on the intra-muscular transplantation of dystrophic mdx mesoangioblasts (MABs) transfected with full length dystrophin using the piggyBac transposon system into mdx SCID mice. This approach allowed us to detect transplanted MAB-derived dystrophin expression in myofibers and a functional amelioration of the muscle function. Transplanted muscle analysis revealed different fates for MABs. Some fused with myofibers, while the fate of other cells remained unclear. In order to characterize these cell populations, a mass cytometry analysis was performed before and after MABs transplant. This revealed that a subpopulation deriving from the MABs, that we named MAB-SAT, express satellite cell markers. A transcriptome analysis of this MAB-SAT subpopulation revealed an identity intermediate to MABs and endogenous satellite cells. The characterization of other MAB fates revealed a diverse spectrum of differentiation paths after transplant which allows quantifying the proportion of MABs for each particular differentiation lineage. In parallel, we screened signaling pathways affecting satellite cell markers expression in MABs, allowing the identification of several signaling pathways that favor the expression of satellite cell markers in MABs before transplant, in attempts to enhance the MABs potential to engraft and differentiate into myogenic lineage when used in autologous cell therapy.



Recent Publications

1. Iyer P S, Mavoungou L O, Ronzoni F, Zemla J, Schmid-Siegert E, Antonini S, et al. (2018) Autologous cell therapy approach for Duchenne muscular dystrophy using piggybac transposons and mesoangioblasts. Molecular Therapy 26(4):1093-1108.
2. Ley D, Van Zwieten R, Puttini S, Iyer P, Cochard A and Mermod N (2014) A PiggyBac-mediated approach for muscle gene transfer or cell therapy. Stem Cell Research 13(3 Pt A):390-403.
3. Van Zwieten R W, Puttini S, Lekka M, Witz G, Gicquel-Zouida E, et al. (2014) Assessing dystrophies and other muscle diseases at the nanometer scale by atomic force microscopy. Nanomedicine 9(4):393-406.
4. Puttini S, van Zwieten R W, Saugy D, Lekka M, Hogger F, Ley D, Kulik A J and Mermod N (2013) MAR-mediated integration of plasmid vectors for *in vivo* gene transfer and regulation. BMC Mol Biol 14:26.
5. Ley D, Harraghy N, Le fourn V, Bire S, Girod PA, Regamey A, Rouleux-Bonnin F, Bigot Y and Mermod N(2013) MAR elements and transposons for improved transgene integration and expression. PLOS ONE 8(4):e62784.

Biography

Lionel O Mavoungou is a First Assistant in Prof Nicolas Mermod's laboratory at the University of Lausanne. After completing his PhD at the University of Montreal, he specialized in Stem Cell Biology and their interactions with their environment via signaling pathways. He joined Nicolas Mermod's laboratory in order to work on a gene therapy model focused on Duchenne muscular dystrophy. This project integrates gene therapy aspects with stem cell engineering as well as metabolomic and genomic approaches, aiming to enhance stem cells capacity to restore diseased muscle function.

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