Université
franco-allemande
Deutsch-Französische
Hochschule

Exon skipping as a therapeutic strategy in dysferlinopathy

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Jakub Malcher

Summary

Dysferlinopathy is a muscular dystrophy that manifests as two major phenotypes: limb-girdle muscular dystrophy type 2B (LGMD2B) or Miyoshi myopathy (MM). It is caused by mutations in the dysferlin gene. Dysferlin is a membrane protein expressed in skeletal muscle. It is responsible for the repair of sarcolemma microlesions produced by muscle contractions. A compromised membrane repair leads to slowly progressing muscle wasting.

This thesis explores the therapeutic potential of an antisense mediated splice switching strategy in LGMD2B caused by the missense mutation c4022T>C in the exon 38 of the dysferlin gene. Antisense oligonucleotides and U7 snRNAs delivered by an adeno-associated viral vector were used as tools to trigger exon skipping in vitro and in vivo. The thesis investigates also if the truncated dysferlin maintains a proper membrane localization and its membrane repair ability.