CDB SEMINAR

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16:00-17:00 Seminar Room A7F

Antisense therapy for Fukuyama type congenital muscular dystrophy

Summary

Fukuyama type congenital muscular dystrophy (FCMD) is a second common, severe childhood muscular dystrophy in Japan. All patients have ancestral insertion of a SINE-VNTR-Alu retrotransposal element (SVA) into a causative gene fukutin. We show that aberrant mRNA splicing, induced by SVA exon-trapping caused FCMD. Introduction of three cocktailed antisense oligonucleotides (AONs) targeting around these splice sites prevented pathogenic splicing in FCMD patient cells and model mice, and normalized protein production and functions of Fukutin as well as /O/-glycosylation of α-dystroglycan. Here we show the results of an optimization of the best, single AON for clinical trial. We re-designed AONs precisely around the splice sites and assessed the efficacy for exon trap inhibition of these AONs in FCMD patient cells and model mice. By testing on normal Fukutin production and functional analysis, we finally selected one best candidate AON termed AON-F. Then we also performed /in silico/ analysis if AON-F has off-target or on-target effect on other sites in human genome. We also succeeded in improvement on production efficacy for AON-F. We show the promise of splicing modulation therapy as the first radical clinical treatment for FCMD in the near future.

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