ICGEB International Centre for Genetic Engineering and Biotechnology | Developing Knowledge

ICGEB International SEMINAR PROGRAMME 2017

Wednesday, 15 March 2017 | 12:00 noon | ICGEB Seminar Room, W building | Padriciano, 99, Trieste, ITALY

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LAMA2-related muscular dystrophy (LAMA2 MD or MDC1A) is the most frequent form of early-onset, fatal congenital muscular dystrophies. It is caused by mutations in LAMA2, the gene encoding laminin-α2, the long arm of the heterotrimeric (α2, β1, γ1) basement membrane protein laminin-211 (Lm-211). Here we establish that despite compensatory expression of laminin-α4 muscle basement membrane is labile in LAMA2 MD biopsies. Consistent with this deficit, recombinant Lm-411 polymerized and bound to cultured myotubes only weakly. Both functions were restored to levels similar to Lm-211 by addition of two specifically designed linker proteins. One, called αLNNd, consists of the N-terminal part of laminin-α1 and the laminin-binding site of nidogen-1. The second, called mini-agrin (mag), contains binding sites for laminins and α-dystroglycan. Transgenic expression of mag and αLNNd in a mouse model for LAMA2 MD fully restored basement membrane stability, recovered muscle force and size, increased overall body weight and extended life span from weeks to more than 2 years. These findings thus provide a mechanistic understanding of LAMA2 MD and lay a strong basis for a possible treatment.

"Designed linker proteins restore basement membrane and correct LAMA2-related muscular dystrophy"

Host: F. Pagani

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