Nat Mater. 2019 Dec 16. doi: 10.1038/s41563-019-0563-5. [Epub ahead of print]

Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells.

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Abstract

Mutations in the LMNA gene, which encodes the nuclear envelope (NE) proteins lamins A/C, cause Emery-Dreifuss muscular dystrophy, congenital muscular dystrophy and other diseases collectively known as laminopathies. The mechanisms responsible for these diseases remain incompletely understood. Using three mouse models of muscle laminopathies and muscle biopsies from individuals with LMNA-related muscular dystrophy, we found that Lmna mutations reduced nuclear stability and caused transient rupture of the NE in skeletal muscle cells, resulting in DNA damage, DNA damage response activation and reduced cell viability. NE and DNA damage resulted from nuclear migration during skeletal muscle maturation and correlated with disease severity in the mouse models. Reduction of cytoskeletal forces on the myonuclei prevented NE damage and rescued myofibre function and viability in Lmna mutant myofibres, indicating that myofibre dysfunction is the result of mechanically induced NE damage. Taken together, these findings implicate mechanically induced DNA damage as a pathogenic contributor to LMNA skeletal muscle diseases.

PMID: 31844279 DOI: 10.1038/s41563-019-0563-5

Grant support