Nuclear state alterations in centronuclear myopathy

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Résumé

Centronuclear myopathies (CNMs) are severe muscle disorders characterized by the abnormal accumulation of myonuclei in central or internal positions, rather than at the fiber periphery. Although this nuclear mispositioning is a defining feature of the disease, the mechanisms connecting altered nuclear organization to muscle dysfunction remain poorly understood.

Using the myotubularin 1 (*Mtm1*) knockout mouse model of X-linked myotubular myopathy, this work examines how centrally positioned myonuclei differ from normally positioned peripheral nuclei. Transcriptomic analyses reveal disease-associated nuclear populations and candidate molecular regulators, including the long non-coding RNA *Lincmd1*. These molecular changes are accompanied by pronounced nuclear remodeling, with imaging and ultrastructural analyses showing altered nuclear morphology and changes in chromatin organization.

The linker of nucleoskeleton and cytoskeleton (LINC) complex, which connects the cytoskeleton to the nuclear envelope, represents a potential interface between cytoskeletal forces, nuclear positioning, nuclear architecture, and gene regulation. Analysis of LINC-complex and nuclear-envelope components, both *in vivo* and in an *Mtm1* knockdown C2C12 model, supports the possibility that disrupted nucleo-cytoskeletal coupling contributes to disease-associated nuclear phenotypes.

Together, these findings suggest that nuclear mispositioning in centronuclear myopathy is not only a structural hallmark but is also associated with broader changes in nuclear identity, chromatin state, and nuclear envelope organization. This work highlights LINC-associated nuclear remodeling as a potential contributor to CNM pathogenesis.

Mots-Clés: Centronuclear myopathy, MTM1, myonuclear positioning, LINC complex, nuclear envelope, Lamin A/C, Nesprin1, chromatin remodelling.

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