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Cored in the act: the use of models to understand core myopathies.

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Abstract

The core myopathies are a group of congenital myopathies with variable clinical expression - ranging from early-onset skeletal-muscle weakness to later-onset disease of variable severity - that are identified by characteristic 'core-like' lesions in myofibers and the presence of hypothonia and slowly or rather non-progressive muscle weakness. The genetic causes are diverse; central core disease is most often caused by mutations in ryanodine receptor 1 (*RYR1*), whereas multi-minicore disease is linked to pathogenic variants of several genes, including selenoprotein N (*SELENON*), *RYR1* and titin (*TTN*). Understanding the mechanisms that drive core development and muscle weakness remains challenging due to the diversity of the excitation-contraction coupling (ECC) proteins involved and the differential effects of mutations across proteins. Because of this, the use of representative models expressing a mature ECC apparatus is crucial. Animal models have facilitated the identification of disease progression mechanisms for some mutations and have provided evidence to help explain genotype-phenotype correlations. However, many unanswered questions remain about the common and divergent pathological mechanisms that drive disease progression, and these mechanisms need to be understood in order to identify therapeutic targets. Several new transgenic animals have been described recently, expanding the spectrum of core myopathy models, including mice with patient-specific mutations. Furthermore, recent

developments in 3D tissue engineering are expected to enable the study of core myopathy disease progression and the effects of potential therapeutic interventions in the context of human cells. In this Review, we summarize the current landscape of core myopathy models, and assess the hurdles and opportunities of future modeling strategies.

KEYWORDS: Core myopathy; Disease model; Skeletal muscle

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