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Consequences of *Lmna* Exon 4 Mutations in Myoblast Function

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Abstract

Laminopathies are causally associated with mutations on the Lamin A/C gene (œ´ fi !). To date, more than 400 mutations in œ´ fi ! have been reported in patients. These mutations are widely distributed throughout the entire gene and are associated with a wide range of phenotypes. Unfortunately, little is known about the mechanisms underlying the effect of the majority of these mutations. This is the case of more than 40 mutations that are located at exon 4. Using CRISPR/Cas9 technology, we generated a collection of œNÖÏ exon 4 mutants in mouse C2C12 myoblasts. These cell models included different types of exon 4 deletions and the presence of R249W mutation, one of the human variants associated with a severe type of laminopathy, œ´ fi ! -associated congenital muscular dystrophy (L-CMD). We characterized these clones by measuring their nuclear circularity, myogenic differentiation capacity in 2D and 3D conditions, DNA damage, and levels of p-ERK and p-AKT (phosphorylated Mitogen-Activated Protein Kinase 1/3 and AKT serine/threonine kinase 1). Our results indicated that œNÖÏ exon 4 mutants showed abnormal nuclear morphology. In addition, levels and/or subcellular localization of different members of the lamin and LINC (LInker of Nucleoskeleton and Cytoskeleton) complex were altered in all these mutants. Whereas no significant differences were observed for ERK and AKT activities, the accumulation of DNA damage was associated to the œNÖÏ p.R249W mutant myoblasts. Finally, significant myogenic differentiation defects were detected in the œNÖÏ exon 4 mutants. These results have key implications in the development of future therapeutic strategies for the treatment of laminopathies.

Keywords: CRISPR; LMNA; laminopathy; nuclear envelope.

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