Front Physiol. 2018 Oct 15;9:1332. doi: 10.3389/fphys.2018.01332. eCollection 2018.

Modeling Skeletal Muscle Laminopathies Using Human Induced Pluripotent Stem Cells Carrying Pathogenic *LMNA* Mutations.

Steele-Stallard HB[1,2], Pinton L[1,2], Sarcar S[1], Ozdemir T[1,2], Maffioletti SM[1], Zammit PS[2], Tedesco FS[1,3].

Author information

Abstract

Laminopathies are a clinically heterogeneous group of disorders caused by mutations in *LMNA*. The main proteins encoded by *LMNA* are Lamin A and C, which together with Lamin B1 and B2, form the nuclear lamina: a mesh-like structure located underneath the inner nuclear membrane. Laminopathies show striking tissue specificity, with subtypes affecting striated muscle, peripheral nerve, and adipose tissue, while others cause multisystem disease with accelerated aging. Although several pathogenic mechanisms have been proposed, the exact pathophysiology of laminopathies remains unclear, compounded by the rarity of these disorders and lack of easily accessible cell types to study. To overcome this limitation, we used induced pluripotent stem cells (iPSCs) from patients with skeletal muscle laminopathies such as *LMNA*-related congenital muscular dystrophy and limb-girdle muscular dystrophy 1B, to model disease phenotypes *in vitro*. iPSCs can be derived from readily accessible cell types, have unlimited proliferation potential and can be differentiated into cell types that would otherwise be difficult and invasive to obtain. iPSC lines from three skeletal muscle laminopathy patients were differentiated into inducible myogenic cells and myotubes. Disease-associated phenotypes were observed in these cells, including abnormal nuclear shape and mislocalization of nuclear lamina proteins. Nuclear abnormalities were less pronounced in monolayer cultures of terminally differentiated skeletal myotubes than in proliferating myogenic cells. Notably, skeletal myogenic differentiation of *LMNA*-mutant iPSCs in artificial muscle constructs improved detection of myonuclear abnormalities compared to conventional monolayer cultures across multiple pathogenic genotypes, providing a high-fidelity modeling platform for skeletal muscle laminopathies. Our results lay the foundation for future iPSC-based therapy development and screening platforms for skeletal muscle laminopathies.

KEYWORDS: 3D modeling; LMNA; disease modeling; iPSCs; lamin A/C; laminopathies; muscular dystrophy; skeletal muscle

PMID: 30405424 PMCID: PMC6201196 DOI: 10.3389/fphys.2018.01332

Free full text

LinkOut - more resources