Induced Pluripotent Stem Cells to Study Mechanisms of Laminopathies: Focus on Epigenetics.

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Abstract

Laminopathies are a group of rare degenerative disorders that manifest with a wide spectrum of clinical phenotypes, including both systemic multi-organ disorders, such as the Hutchinson-Gilford Progeria Syndrome (HGPS), and tissue-restricted diseases, such as Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy and lipodystrophies, often overlapping. Despite their clinical heterogeneity, which remains an open question, laminopathies are commonly caused by mutations in the LMNA gene, encoding the nuclear proteins Lamin A and C. These two proteins are main components of the nuclear lamina and are involved in several biological processes. Besides the well-known structural function in the nucleus, their role in regulating chromatin organization and transcription has emerged in the last decade, supporting the hypothesis that the disruption of this layer of regulation may be mechanism underlying the disease. Indeed, recent studies that show various epigenetic defects in cells carrying LMNA mutations, such as loss of heterochromatin, changes in gene expression and chromatin remodeling, strongly support this view. However, those findings are restricted to few cell types in humans, mainly because of the limited accessibility of primary cells and the difficulties to culture them ex-vivo. On the other hand, animal models might fail to recapitulate phenotypic hallmarks of the disease as of humans. To fill this gap, models based on induced pluripotent stem cell (iPSCs) technology have been recently generated that allowed investigations on diverse cells types, such as mesenchymal stem cells (MSCs), vascular and smooth muscle cells and cardiomyocytes, and provided a platform for investigating mechanisms underlying the pathogenesis of laminopathies in a cell-type specific human context. Nevertheless, studies on iPSC-based models of laminopathy have expanded only in the last few years and, with the advancement of reprogramming and differentiation protocols, their number is expecting to further increase over time. This review will give an overview of models developed thus far, with a focus on the novel insights on epigenetic mechanisms underlying the disease in different human cellular contexts. Perspectives and future directions of the field will be also given, highlighting the
potential of those models for preclinical studies for identifying molecular targets and their translational impact on patients' cure.

**KEYWORDS:** LMNA; Lamin A/C; cell differentiation; chromatin architecture; epigenetic regulation; gene expression regulation; induced pluripotent stem cells (iPSCs); laminopathies