The structural and gene expression hypotheses in laminopathic diseases-not so different after all.

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Abstract

Laminopathies are a diverse group of rare diseases with various pathologies in different tissues, which are linked to mutations in the LMNA gene. Historically, the structural disease model proposed mechanical defects of the lamina and nuclear fragility, the gene expression model impairment of spatial chromatin organization and signaling pathways as underlying mechanisms leading to the pathologies. Exciting findings in the past few years showing that mechanical forces are directly transmitted into the nucleus, where they affect chromatin organization and mechanoresponsive signaling molecules, have led to a revised concept of an integrative unified disease model, in which lamin-mediated pathways in mechanotransduction and chromatin regulation are highly interconnected and mutually dependent. In this Perspective we highlight breakthrough findings providing new insight into lamin-linked mechanisms of mechanotransduction and chromatin regulation and discuss how a combined and interrelated impairment of these functions by LMNA mutations may impair the complex mechanosignaling network and cause tissue-specific pathologies in laminopathies.

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