

At the nucleus of the problem: the nuclear envelope and disease

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Le linkage of some 24 diseases to mutations in proteins of the nuclear envelope has stimulated a major reassessment of the function of the nuclear envelope, and particularly the nuclear lamina, as more than half of these diseases are caused by mutations of the LMNA gene, coding lamin A. As a consequence of these studies, we now envisage the nuclear envelope/lamina functioning not only as a molecular device regulating the transfer of macromolecules between the cytoplasm and the nucleus, but as a key cellular hub in integrating critical functions that include chromatin, organization, modulation of signaling pathways, and transcriptional regulation (1).

A fundamental issue in deciphering the molecular basis of the pathogenic mechanisms of laminopathies has been obtained demonstrating that these diseases are not due to a loss of function of lamin A but to a gain of function of immature forms of the protein, referred to as prelamin A, which are differently modified by posttranslational processes (2).

Here we review the involvement of defects of prelamin A processing in the pathogenesis of different classes of laminopathies, which include muscular, metabolic, and progeric laminopathies. In particular, we will focus on the pathogenic mechanism of the Hutchinson-Gilford progeric syndrome (HGPS), which involve a particular form of prelamin A, the progerin, whose accumulation in the nucleus affects both chromatin arrangement and transcriptional regulation. The identification of the molecular basis of progeric laminopathies contributed to the development of a targeted therapy on the experimental models of the disease (3). In the last three years encouraging results have been also obtained by pharmacological trials on selected groups of progeric patients.

Since low levels of progerin are also accumulated in normal aging, particular attention has been given to differential expression of prelamin A forms in the cells of a particular class of healthy aged subjects, represented by centenarians (4).

References

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