Structural analysis of the ternary complex between lamin A/C, BAF and emerin identifies an interface disrupted in autosomal recessive progeroid diseases.

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Abstract

Lamins are the main components of the nucleoskeleton. Whereas their 3D organization was recently described using cryoelectron tomography, no structural data highlights how they interact with their partners at the interface between the inner nuclear envelope and chromatin. A large number of mutations causing rare genetic disorders called laminopathies were identified in the C-terminal globular Igfold domain of lamins A and C. We here present a first structural description of the interaction between the lamin A/C immunoglobulin-like domain and emerin, a nuclear envelope protein. We reveal that this lamin A/C domain both directly binds self-assembled emerin and interacts with monomeric emerin LEM domain through the dimeric chromatin-associated Barrier-to-Autointegration Factor (BAF) protein. Mutations causing autosomal recessive progeroid syndromes specifically impair proper binding of lamin A/C domain to BAF, thus destabilizing the link between lamin A/C and BAF in cells. Recent data revealed that, during nuclear assembly, BAF's ability to bridge distant DNA sites is essential for guiding membranes to form a single nucleus around the mitotic chromosome ensemble. Our results suggest that BAF interaction with lamin A/C also plays an essential role, and that mutations associated with progeroid syndromes leads to a dysregulation of BAF-mediated chromatin organization and gene expression.

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