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Emerin Is Required for Proper Nucleus Reassembly after Mitosis: Implications for New Pathogenetic Mechanisms for Laminopathies Detected in EDMD1 Patients.

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Abstract

Emerin is an essential LEM (LAP2, Emerin, MAN1) domain protein in metazoans and an integral membrane protein associated with inner and outer nuclear membranes. Mutations in the human *EMD* gene coding for emerin result in the rare genetic disorder: Emery-Dreifuss muscular dystrophy type 1 (EDMD1). This disease belongs to a broader group called laminopathies-a heterogeneous group of rare genetic disorders affecting tissues of mesodermal origin. EDMD1 phenotype is characterized by progressive muscle wasting, contractures of the elbow and Achilles tendons, and cardiac conduction defects. Emerin is involved in many cellular and intranuclear processes through interactions with several partners: lamins; barrier-to-autointegration factor (BAF), β-catenin, actin, and tubulin. Our study demonstrates the presence of the emerin fraction which associates with mitotic spindle microtubules and centrosomes during mitosis and colocalizes during early mitosis with lamin A/C, BAF, and membranes at the mitotic spindle. Transfection studies with cells expressing EGFP-emerin protein demonstrate that the emerin fusion protein fraction also localizes to centrosomes and mitotic spindle microtubules during mitosis. Transient expression of emerin deletion mutants revealed that the resulting phenotypes vary and are mutant dependent. The most frequent phenotypes include aberrant nuclear shape, tubulin network mislocalization, aberrant mitosis, and mislocalization of centrosomes. Emerin deletion mutants demonstrated different chromatin binding capacities in an in vitro nuclear assembly assay and chromatin-binding properties correlated with the strength of phenotypic alteration in transfected cells. Aberrant tubulin staining and microtubule network phenotype appearance depended on the presence of the tubulin binding region in the expressed deletion mutants. We believe that the association with tubulin might help to "deliver" emerin and associated membranes to decondensing chromatin. Preliminary analyses of cells from Polish patients with EDMD1 revealed that for several mutations thought to be null for emerin protein, a truncated emerin protein was present. We infer that the EDMD1

phenotype may be strengthened by the toxicity of truncated emerin expressed in patients with certain nonsense mutations in *EMD*.

KEYWORDS: EDMD1; LAP2β; emerin; lamin; lamin A/C; laminopathy; mitotic spindle; tubulin

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