Nuclear Envelope-linked Rare Human Diseases: From Molecular Pathophysiology towards Clinical Applications

Objective

Laminopathies are inherited human disorders, including muscular dystrophy, cardiomyopathy, lipodystrophy, insulin-resistance, diabetes, and premature aging, which are linked to mutations in genes encoding nuclear envelope proteins, such as A-type lamins (LMNA) and lamin-binding proteins (EMD, LBR, LAP2). Laminopathies are clinically manifested after birth, progressively develop during childhood, and often lead to early death. Efficient therapies have been hampered by the lack of understanding the molecular mechanisms causing the disorders. We will test various disease hypotheses, identify drug targets, and screen drugs for therapeutic interventions. Structural biologists will investigate how disease-causing mutations in A-type lamins or in one of their prominent binding partners LAP2alpha affect atomic structure, interactions, and assembly properties of lamins, which may reduce stress resistance in patient cells. Using patient cells and animal models (mouse, C. elegans) that either lack A-type lamins or LAP2alpha, or express disease variants, we will test how mutations or loss of these proteins affect chromatin organization, gene expression, and differentiation of adult muscle- and adipose stem cells. Differentiation will be studied ex vivo in cell culture, focusing on the molecular functions of A-type lamins and LAP2alpha in differentiation-linked pathways, and in vivo in animal models analyzing muscle regeneration after stress, injury, or aging. Data obtained in these systems as well as chemical compound screening using the zebrafish model system will identify potential drug targets and drugs for testing in animal disease models and for potential therapeutic intervention. Furthermore, we will extend and evaluate clinical trials on the treatment of lipodystrophy-type laminopathy patients with drugs that target
the adipocyte differentiation pathway, and develop theranostic tests for the validation of therapies.

Programme(s)

FP6-LIFESCIHEALTH - Life sciences, genomics and biotechnology for health: Thematic Priority 1 under the Focusing and Integrating Community Research programme 2002-2006.

Topic(s)

LSH-2004-2.1.1-9 - Rare disorders of nuclear organisation

Call for proposal

FP6-2004-LIFESCIHEALTH-5

See other projects for this call

Funding Scheme

STREP - Specific Targeted Research Project

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