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Workshop report

141st ENMC International Workshop Inaugural Meeting of the EURO-Laminopathies Project Nuclear Envelope-linked Rare Human Diseases: From Molecular Pathophysiology towards Clinical Applications 10–12 March 2006, Naarden, The Netherlands

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1. Introduction

EURO-Laminopathies is a European Commission-funded research project, including 13 scientific group leaders in the fields of human genetics, clinical research, structural biology, molecular cell biology, and pharmaceutical industry, and one administrative manager from eight countries (Austria, France, Germany, Italy Israel, Spain, Switzerland and the United Kingdom). The consortium held its kick-off meeting as an International ENMC Workshop in Naarden on the weekend of March 10–12, 2006. The EURO-Laminopathies project aims at understanding the molecular mechanisms of laminopathies, which are rare human diseases linked to mutations in genes encoding nuclear envelope proteins, such as A-type lamins (*LMNA*), proteins involved in the post-translational processing of A-type lamins (*ZMPSTE24*), and lamin-binding proteins (*EMD*, *LBR*, *LAP2*). Laminopathies are clinically manifested after birth, can affect different tissues and progressively develop during childhood or adolescence, often leading to early death. Efficient therapies have been hampered by the lack of understanding the molecular disease mechanisms. The ultimate goal of the project thus is to identify reliable diagnostic markers and drug targets in order to rationally develop new therapeutic interventions and to improve existing therapies for laminopathy patients.

During the workshop, new insights into the clinical and genetic spectrum of laminopathies and into clinical trials on the treatment of lipodystrophy-type laminopathy patients were given and future prospects on novel therapeutic approaches and theranostic tests for the validation of therapies were presented. Furthermore, the consortium discussed clinical and basic research approaches in order to analyze the effects of disease-causing mutations in A-type lamins and in one of their prominent binding partners, Lamina-associated polypeptide 2-alpha (LAP2α) on the atomic structure, interactions, and assembly properties of the proteins and on their potential roles in chromatin organization, gene expression, and differentiation of adult muscle and adipose stem cells.

2. Background

Lamins are major architectural proteins in the nuclei of eukaryotic cells [1,2]. B-type lamins are expressed in all cells and are essential for cell viability, while A-type lamins are expressed primarily in differentiated cells and are involved in tissue homeostasis and function. Mutations in A-type lamins and their binding partners

Abbreviations: ENMC, European Neuromuscular Center; LAP, Lamina-associated polypeptide; pRb, retinoblastoma protein; UMD, Universal mutation database.

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cause a variety of disease phenotypes, collectively called laminopathies [3,4]. These diseases can affect muscle, adipose, nerve, bone, and skin tissues or cause premature ageing. Based on known and proposed functions of lamins, various disease hypotheses have been proposed to explain the molecular basis of laminopathies, but it remains unclear how much a particular disease mechanism can contribute to a given clinical phenotype [2,5,6]. The *mechanical hypothesis* predicts that mutations in lamins and lamin-binding proteins alter their structure and weaken their stability, either by interfering with proper folding of the proteins or by affecting the assembly of lamina protein complexes, thereby predisposing cells and tissues to physical damage. This model seems reasonable particularly for muscle tissue, as lamins provide structural stability to the nucleus and muscle is exposed to physical stress. In line with this hypothesis, laminopathy patient often have structural abnormalities of their cell nuclei. However, the structural disease model cannot explain all clinical pathologies, as un-affected tissues also show deformed nuclei. The *gene expression hypothesis* proposes that mutations in lamins disrupt interactions of lamins with transcriptional regulators, such as the adipocyte-specific transcription factor sterol response element binding protein, and affect tissue-specific patterns of gene expression. Furthermore, lamins are also involved in epigenetic pathways regulating heterochromatin formation through numerous interactions of lamin complexes with DNA and chromatin proteins [7]. Mutations in A-type lamins may cause gross changes in higher order chromatin structure and gene expression. In line with this hypothesis nuclei from patient cells often lack the peripheral heterochromatin. The *cell proliferation/differentiation hypothesis* is mainly based on the *in vivo* interaction between lamins A/C and LAP2α and the tumor suppressor retinoblastoma protein [8,9], which is required for muscle and adipocyte differentiation. It has been suggested that stem cells in laminopathy patients have a defective differentiation potential and cannot effectively regenerate tissues.

3. Genetic and clinical features of laminopathies

Disease-causing mutations are currently reported for 11 genes encoding nuclear envelope components (*LMNA*, *LMNB1*, *LMNB2*, *EMD*, *LAP2*, *LBR*, *LEMD3*, *ZMPSTE24*, *SYNE-1*, *NUP62*, *DYT1*). Among them, the major group of diseases is caused either by mutations in the lamin A/C gene (i.e. primary laminopathies) or by mutations in the *ZMPSTE24* gene affecting the correct post-translational processing of prelamin A and thus considered as secondary laminopathies. Primary laminopathies can be classified into 5 types affecting either specific tissue in isolated fashion, i.e. (1) the striated muscles, (2) the peripheral nerves, and (3) the adipose tissue; or in a systemic way several tissues with (4) the premature ageing syndromes and their related disorders, named also "systemic laminopathies". Finally, numerous heterogeneous clinical situations have been reported and form the fifth group of disorders that comprise overlapping phenotypes characterized by the coexistence of two or more tissue involvements, suggesting a real continuum within the different types of laminopathies [3]. Gisèle Bonne, Jacqueline Capeau, Nicolas Lévy, and Manfred Wehnert reported that up to now, more than 211 mutations of the *LMNA* gene in more than 1037 individuals have been identified, of whom about 60% presented laminopathies affecting the striated muscles (Emery Dreifuss Muscular Dystrophy; Limb Girdle Muscular Dystrophy; Dilated Cardiomyopathy with Conduction Defects), 25% laminopathies affecting the adipose issue (Dunningan type familial partial lipodystrophy), 6% presented with premature aging syndromes (Hutchinson–Gilford Progeria; Atypical Werner Syndrome) and 3% with axonal neuropathies. Faced with this very wide diversity, a Universal mutation database (UMD)-*LMNA* database has been established which brings together all the clinical and genetic data concerning the mutations described by our networks as well as those reported in the literature (http://www.umd.be:2000). Similar UMD mutation databases were also created for the *EMD* (http://www.umd.be:2010) and *ZMPSTE24* gene (soon available on the UMD web site). These mutation databases are useful tools for analyzing phenotype/genotype relation in this complex group of disorders. It was also discussed that in addition to mutations in the lamin A genes, an increasing number of lamin A-interacting proteins, such as emerin, LAP2α, and MAN1 have been linked to similar diseases showing clinically overlapping phenotypes with the lamin-linked laminopathies [3,7]. The number of laminopathy-linked genes is likely to increase, since a growing number of patients with laminopathy-type pathologies do not have mutations in any of the known disease genes. In this context, the human geneticist and clinician partners of the EURO-Laminopathies consortium will mainly focus on: (1) the further description of *LMNA*, *ZMPSTE24*, *EMD* and *LAP2* gene mutations and of the clinical spectrum of associated diseases, (2) the search for new genes responsible for closely related disorders in both a gene and a syndrome candidate approach, (3) the understanding of the clinical variability of these disorders through the analyses of possible phenotype/genotype relations as well as the identification of modifier genes and/or polymorphisms.

4. Molecular disease mechanisms

4.1. Lamin structure and assembly

Lamins represent the principal molecular building blocks of the nuclear lamina, a filamentous meshwork