SATELLITE MEETING

EUROPEAN NETWORK FOR LAMINOPATHIES MEETING

September 3-5 2019

Abstract book

September 3 2019	morning	Time
DIAGNOSIS, FOLLOW-UP, NEW THERAPEUTIC TOOLS Chairs: Giulia Ricci and Karima Djabali		**11:30 - 13:00**
Common mechanism: **Does a point mutation alter the structure of a lamin filament?** Ohad Medalia - Switzerland		**11:30 - 11:45**
Muscular Laminopathies: **Deflazacort treatment in *LMNA*-related congenital muscular dystrophy: design of an ongoing Italian cohort pilot study.** Giulia Ricci - Italy		**11:45 - 12:00**
Progeroid Laminopathies: **Autophagic Removal of Farnesylated Carboxy-Terminal Lamin Peptides** Karima Djabali - Germany		**12:00 - 12:15**
Progeroid Laminopathies: **First-in-the-world: TAVI in a patient affected by Hutchinson-Gilford Progeria syndrome** Francesco Musumeci - Italy		**12:15 - 12:30**
Lipodystrophic laminopathies: **Type 2 Familial Partial Lipodystrophy (Dunnigan's Disease): Allelic heterogeneity and variable expressivity** David Araujo-Vilar - Spain		**12:30 - 12:45**
Short talk *Henner Kalden* **AEGERION** ***Novelion***		**12:50 - 13:00**
LUNCH		**13:00 - 14:00**

Does a point mutation alter the structure of a lamin filament?

Oahd Medalia

Zurich, Switzerland

Lamin filaments assemble into 3.5 nm thick fibrous structures that are positioned between the inner nuclear membrane and the peripheral Chromatin. Although we have previously provided a view on lamin organization, we still lacking a high-resolution structure of lamin filaments. This is a fundamental information that is needed in order to understand how point mutations in lamins cause distinct diseases, laminopathies.Taking the advantage of recent advances in cryo-EM, we started to look into the organization of in situ assembled nuclear lamins, in health and disease. Here, I will summarize some of our recent
and ideas on lamin assembly that are fundamental for resolving lamin assemblies at pseudo-atomic resolution.

Deflazacort treatment in LMNA-related congenital muscular dystrophy: designing of an ongoing Italian cohort pilot study.

Giulia Ricci[1], Lorenzo Maggi[2], Adele D'Amico[3], Chiara Fiorillo[4], Erika Schirinzi[1], Antonella Pini[5], Elena Pegoraro[6], Enrico Bertini[3], Pia Bernasconi[2], Giovanna Lattanzi[7], Gabriele Siciliano[1]

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Introduction. LMNA-related congenital muscular dystrophy (L-CMD) and *LMNA*-linked Emery-Dreifuss Muscular Dystrophy (EDMD2) with early onset (<5 years) may be considered a continuum phenotype. There is no cure for patients with these neuromuscular diseases. Literature data and ongoing clinical approaches suggest the use of steroids.
Starting from the collaborative approach and the multidisciplinary effort of the Italian Network for Laminopathies, we are planning an open-label prospective cohort pilot study aimed to: 1) evaluate the effect of the treatment with Deflazacort in a cohort of 20 L-CMD or EDMD2 patients with infantile onset, aged 3-30 years; 2) analyze the secretome profile at basal condition and during steroid treatment, to evaluate variations and establish a correlation between steroid treatment and clinical outcome; 3) validate selected cytokines as biomarkers for L-CMD and EDMD2.
Methods. Study protocol: Patients will be monitored for a period of six months. Then, they will start therapy with Deflazacort for 12 months. After 12 months, the treatment will be stopped and the patients will continue to be clinically followed every 3 months until the end of the study.
Conclusions: Overall, we expect to evaluate whether a 12-month-treatment with deflazacort is effective in improving clinical outcome measures in L-CMD patients. We also expect to identify a panel of cytokines altered in L-CMD that can be considered as biomarkers of disease.

Autophagic Removal of Farnesylated Carboxy-Terminal Lamin Peptides

Karima Djabali

Epigenetik der Hautalterung, Department of Dermatology , TUM School of Medicine, TU Munich, Germany

The mammalian nuclear lamina proteins—prelamin A- and B-type lamins—are post-translationally modified by farnesylation, endoproteolysis, and carboxymethylation at a carboxy-terminal CAAX (C, cysteine; a, aliphatic amino acid; X, any amino acid) motif. However, prelamin A processing into mature lamin A is a unique process because it results in the production of farnesylated and carboxymethylated peptides. In cells from patients with Hutchinson–Gilford progeria syndrome, the mutant prelamin A protein, progerin, cannot release its prenylated carboxyl-terminal moiety and therefore remains permanently associated with the nuclear envelope (NE), causing severe nuclear alterations and a dysmorphic morphology. To obtain a better understanding of the abnormal interaction and retention of progerin in the NE, we analyzed the spatiotemporal distribution of the EGFP fusion proteins with or without a nuclear localization signal (NLS) and a functional CAAX motif in HeLa cells transfected with a series of plasmids that encode the carboxy-terminal ends of progerin and prelamin A. The farnesylated carboxy-terminal fusion peptides bind to the NE and induce the formation of abnormally shaped nuclei. In contrast, the unfarnesylated counterparts exhibit a diffuse localization in the nucleoplasm, without obvious NE deformation. High levels of farnesylated prelamin A and progerin carboxy-terminal peptides induce nucleophagic degradation of the toxic protein, including several nuclear components and chromatin. However, SUN1, a constituent of the linker of nucleoskeleton and cytoskeleton (LINC) complex, is excluded from these autophagic NE protrusions. Thus, nucleophagy requires NE flexibility, as indicated by SUN1 delocalization from the elongated NE–autophagosome complex.

Type 2 Familial Partial Lipodystrophy (Dunnigan's Disease): Allelic heterogeneity and variable expressivity.

David Araújo-Vilar, Fernández-Pombo A, Sánchez-Iglesias S

UETeM. Biomedical Research Institute (CIMUS-IDIS), School of Medicine. University of Santiago de Compostela, Spain

Lipodystrophic laminopathies include both type 2 Familial Partial Lipodystrophy (Dunnigan's disease, FPLD2) and primary and secondary laminopathic progeria syndromes.
Focusing in FPLD2, the majority of pathogenic variants in LMNA gene are missense, and they are located in the C-terminal globular domain of lamin A/C. More than 80% of cases are associated to the missense variants Arg482Trp/Gln/Leu, located in exon 8.
The main phenotypical features of this disorder is the loss of adipose tissue affecting limbs and gluteo-femoral region, and the fat accumulation in face, neck, axillae, interscapular area and labia major. Phlebomegaly and well-defined muscles in extremities, even calf muscular hypertrophy and acanthosis nigricans use to be present in the classical phenotype. This phenotype uses to appear in women around puberty and later in men. These patients have a higher risk for developing insulin-resistant diabetes, hypertriglyceridemia (and acute pancreatitis), non-alcoholic fatty liver, atherosclerotic vascular diseases, heart diseases (dilated/hypertrophic cardiomyopathy, rhythm disturbances), PCOS and other fertility problems. Although this is the classical picture, there are important clinical differences among patients, even in those carrying the same variant. In some cases the clinical diagnosis is very obvious, however in others is a real challenge.
In this talk we analyze two groups of patients with FPLD2, one (n= 51) with patients carrying pathogenetic variants in exon 8 (Arg482Trp, Arg482Leu, Asn466Asp, and Lys486Asn), and the other (n=22) with variants out of exon 8. Physical signs, body composition, analytical parameters and associated metabolic, hepatic, and cardiac complications were compared between both groups.
(*Funding by an intramural grant from the Xunta de Galicia, ED341b 2017/19*)

September 4 2019	morning	Time
PATIENT ASSOCIATIONS, PATIENT CARE, NEW THERAPEUTIC TOOLS Chairs: Lorenzo Maggi and Marjet Stamsnijder		11:30 - 13:15
Muscular Laminopathies: **Natural history and clinical trial readiness in striated muscle laminopathies- the ENMC workshop in 2020** Lorenzo Maggi – Italy		11:30 - 11:45
Muscular Laminopathies: Muscular Laminopathies – **Patients Association speeches A.I.D.M.E.D Onlus and Associazione Alessandra Proietti Onlus** Stefania Fazioli, AIDMED and Irene Proietti, Associazione Alessandra Proietti - Italy		11:45 - 11:55
Muscular Laminopathies: **EDMD patient perspectives** Salomè Mist Kristiansdottir and Eleonora Cugudda - EDMD Facebook Group		11:55 - 12:10
Cardio-laminopathies: **Cardio-laminopathies, recent updates** Andrea Barison and Giovanni Peretto - Italy		12:10 - 12:25
Cardio-laminopathies: **An AAV delivered therapeutic that suppresses Lamin-induced Dilated Cardiomyopathy** Colin Stewart - Singapore		12:25 - 12:40
Lipodystrophic Laminopathies: **AELIP: Multidisciplinary intervention from a socio-sanitary scope, to improve the quality of life of people and relatives affected by lipodystrophy** Naca Eulalia, AELip - Spain		12:40 - 12:50
Progeroid laminopathies: **The importance of Peer Groups** Marjet Stamsnijder, Progeria Family Circle - EU		12:50 - 13:00
Progeroid Laminopathies: **A patient's perspective about the research: from scientific disclosure to the lab** Sammy Basso, AIProSaB - Italy		13:00 - 13:15
LUNCH		13:15 - 14:15

Natural history and clinical trial readiness in striated muscle laminopathies - the ENMC workshop in 2020

Lorenzo Maggi[1], Susana Quijano-Roy[2], Carsten Bönnemann[3], Gisèle Bonne[4].

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To date, there is no effective treatment for Striated muscle laminopathies (SMLs), although there is an increasing interest in these diseases and some experimental drugs seem to be promising in the next future. To this purpose, sensitive and clinically meaningful outcome measures to evaluate patients affected by *SMLs* are not available for possible future clinical trials and natural history of these diseases is still unclear. In addition, outcome measures are also needed in clinical practice to evaluate clinical progression, facilitating patient management. On the other hand, biochemical, molecular and imaging biomarkers have been proposed as possible alternative outcome measures, considering they may show earlier response to treatment and provide very objective data. Hence, a multidisciplinary approach to the identification of outcome measures in SMLs is strongly suggested, including clinical and basic research experts.

A specific workshop focused on natural history studies and clinical trial readiness for the whole spectrum of SML has been recently approved by the European Neuromuscular Centre (ENMC) and planned for March 2020. All the participants involved are recognized European and non-European experts in the SMLs field, in particular in basic research or in different clinical aspects which should be covered in the context of a multidisciplinary approach to such complex diseases. In addition, patient representatives have been also involved, in particular in relation to the creation of patients' reported outcomes.

Muscular Laminopathies – Patients Association speeches A.I.D.M.E.D Onlus and Associazione Alessandra Proietti Onlus

Stefania Fazioli and Irene Proietti
AIDMED and Associazione Alessandra Proietti, Italy

Description of the association A.I.D.M.E.D Onlus
A.I.D.M.E.D Onlus was founded in 2012 by patients suffering from Emery-Dreifuss Muscular Dystrophy, and is also supported by their families.
The association has two specific objectives:

- Build a network of solidarity among all people affected by this disease
- Financially support specific research projects on the disease, with the aim of finding a cure, through the cooperation with Research Institutes of recognized competence

Description of the Alessandra Proietti Onlus Association:
Alessandra Proietti Onlus Association was founded in November 2012 by parents and family members in the name of Alessandra Proietti, a young girl who died at the age of only 19, due to a severe form of Laminopathy.
The Association was born with the purpose of:

- Spread the knowledge on the muscular pathology of which Alessandra was suffering, and Laminopathies in general
- Improve patients' quality of life by offering them material and technical support
- Support research that allows the understanding of these diseases in order to reach a cure
- Build a network of solidarity among patients, doctors and researchers in a synergy of intent

The presentations will highlight the activities carried out to carry out the objectives of the Associations.

EDMD patient perspectives

Salomè Mist Kristiansdottir and Eleonora Cugudda

EDMD Facebook Group

A Facebook group was established in 2014 to provide a platform for EDMD patients to connect, share experiences and ask questions. The group currently has 415 members from more than 20 countries with representatives for 6 of the 7 types of EDMD. The topics in the group have been wide ranging but a few common themes have emerged. Most patients face a long road to receiving the correct diagnosis, with some patients dealing with symptoms for decades before their formal designation as an EDMD patient. After receiving their diagnosis, the next challenge facing patients is the uncertainty/fear of what this means for their life. EDMD patients, especially those far from MD centers, often have serious difficulties in finding knowledgeable caregivers. Guidelines for standards of best practice for providing care to EDMD patients are not available and difficulties are frequently found in designing an appropriate care plan because of the difficulty in finding published guidance. Having a diagnosis does not mean that a patient will necessarily get good care.

The EDMD Facebook group has therefore been an important source of information for many patients through the years. We all strive to support each other and provide good advice. In July we created a questionnaire based on things that we have found relevant. We will share the results of that questionnaire in our presentation and hopefully that will give you some realistic insight into the challenges EDMD patients face.

Cardiolaminopathies, recent updates

Andrea Barison[1] and Giovanni Peretto[2]

1. Fondazione Toscana G. Monasterio, Pisa, Italy
2. IRCCS San Raffaele Hospital and University, Milan, Italy

Cardiac laminopathies, associated with mutations in the LMNA gene, encompass a wide spectrum of clinical manifestations, involving electrical and mechanical alterations of cardiomyocytes: bradyarrhythmias (sinus node disease or atrioventricular blocks), atrial arrhythmias (atrial fibrillation and flutter), ventricular tachyarrhythmias, dilated cardiomyopathy and heart failure. Several clinical, electrophysiological and imaging parameters have been demonstrated to predict life-threatening complications of LMNA-associated heart disease, in particular sudden cardiac death and end-stage heart failure. In our recent Italian multicenter study on 164 LMNA mutation carriers, non-sustained VT, left ventricular ejection fraction <50% and tendon retractions were associated with major cardiovascular events (cardiovascular death, heart transplantation, malignant ventricular arrhythmias) during a median 10-year follow-up. Moreover, in a subset of patients (n=41) undergoing cardiac magnetic resonance, late gadolinium enhancement was significantly associated with major ventricular arrhythmias. Further multicentric studies are needed to refine risk stratification in mutation carriers, in order to tailor an early treatment with a combined pharmacological and device approach.

An AAV delivered therapeutic that suppresses Lamin induced Dilated Cardiomyopathy

Chai RJ[1], Burke B[1], Foo SYR2 and Colin L. Stewart[1].

[1]Institute of Medical Biology, A*STAR, Singapore and [2]Cardiovascular Research Institute, Yong Loo Lin School of Medicine, National University of Singapore and Genome Institute A*STAR

Mutations in the lamin A/C (LMNA) gene are the 2nd most common genetic cause of Dilated Cardiomyopathy (DCM). It affects as many as 1/12,500 and is curable only by a heart transplant. We identified a protein (S1) that when suppressed extends lifespan of mouse models that develop LMNA DCM from less than 1 month to >1 year. Based on these findings we developed an adeno-associated virus (AAV)-based gene therapy approach to introduce into diseased hearts, a modified version of the protein that suppresses and prevents the progression of DCM. Our initial findings show that this extends the lifespan of LMNA DCM mice from ~30 days to at least 100+days. For the first time this offers a realistic route to treating LMNA induced DCM that is the biggest cause of heart transplants.

AELIP: “Multidisciplinary intervention from a socio-sanitary scope, to improve the quality of life of people and relatives affected by lipodystrophy"

Naca Eulalia, AELip - Spain

AELIP is an Association of Families and People Affected by Lipodystrophy, created on 19 April 2012. It is composed of parents, relatives, and professionals of all areas, with the aim of creating spaces for the exchange and coexistence among people diagnosed with lipodystrophies and their relatives. It also aims at raising awareness about the public health issue represented by lipodystrophies, which are rare due to their low prevalence. Our actions target children, young people, and adults who suffer from lipodystrophies, and the issues derived from this condition.

Through this powerpoint presentation, AELIP emphasizes the importance of a multidisciplinary intervention and of the different axes of priority action, which guarantee an integral attention that helps to improve the quality of life of people affected by lipodystrophy and their relatives.

The importance of Peer Groups

Marjet Stamsnijder

Progeria Family Circle,The Netherlands and EU

The significance of a peer group varies of course, and it is different for toddlers, children, adolescents or adults. They (as we do) all have to cope with limitations, grief and loss, each in their own way.. but being able to share is gold. After meeting others,they do not feel different, but special. And knowing there are just about as many devoted researchers as progeria patients who are working towards better understanding and -maybe even acure, means the world to them all.

A patient’s perspective about the research: from scientific disclosure to the lab

Sammy Basso

AIProSaB, Italy

A patient's perspective about the research: from scientific disclosure to the labA patient's perspective about the research: from scientific disclosure to the labThe purpose of my talk is to tell about my role inside the Sammy Basso Italian Association for Progeria and about a new strategy for a possible treatment of HGPS. So, starting from my own life and experience, and from the A.I.Pro.Sa.B. activities, I will explain the argument of my graduation thesis findable in the paper titled “Development of a CRISPR/Cas9-based therapy for Hutchinson–Gilford progeria syndrome”, in which the major authors are Olaya Santiago Fernandez and Carlos Lopez Otin (2019).
So, I will focus on the use of the CRISPR-Cas9 system from a cellular point of view and especially on the progeroid mice experiments done.
Then I would offer a new view also about HGPS self, for example analyzing the importance of organs that usually are not considered too important to treat for contrasting the disease.

September 4 2019	afternoon	Time
European Network for Laminopathies management Chairs: Gisèle Bonne and Giovanna Lattanzi		18:15 - 19:15
Network organization **The European Network for Laminopathies as a legal entity** Giovanna Lattanzi - Italy		18:15 - 18:30
Network activities Gisèle Bonne		18:30 - 18:45
Network relationship with ECLip and other consortia **The European Consortium of Lipodystrophies (ECLip)** David Araujo-Vilar - Spain		18:45 - 19:00
Proposals and discussion All partners		19:00 - 19:15

The European Consortium of Lipodystrophies (ECLip)

David Araujo-Vilar[1], Giovanni Ceccarini[2], Giovanna Lattanzi[3], Ferruccio Santini[2], David B Savage[4], Julia von Schnurbein[5], Ekaterina Sorkina[6], Marie-Christine Vantyghem[7], Camille Vatier[8], Corinne Vigouroux[8], Martin Wabitsch[5]

1. Universidade de Santiago de Compostela, Spain. 2. University Hospital of Pisa, Italy. 3. CNR Institute of Molecular Genetics, Unit of Bologna, Italy. 4. University of Cambridge. 5. Ulm University Medical Centre, Germany. 6. Endocrinology Research Centre, Moscow, Russia. 7. University of Lille, France. 8. Sorbonne University, Paris, France.

In 2014 a group of European physicians and scientists founded in Bologna (Italy) the European Consortium of Lipodystrophies (ECLip, www.eclip-web.org) with the aim to join efforts, knowledge and skills to going deep in the study of both clinical and molecular aspects of rare lipodystrophy syndromes but also to contribute to the disseminate information about these disorders not only in Europe but worldwide.

In order to reach out these objetives ECLip members have annual meetings (2015 Paris, 2016 Santiago de Compostela, 2017 Rome, 2018 Münster, 2019 Burgos) in which different teams present ~~its~~ results, discussing different topics about molecular basis, new lipodystrophy subtypes, clinical studies and new therapeutic advances. We are also very involved in helping European national lipodystrophy advocacy groups, encouraging the creation of new ones.

At present 48 groups from 20 countries are part of ECLip, some of them out of Europe, as Egypt, United Arab Emirates or USA. We work in a collegiate way with a governing board. All the decisions are taken on a basis of consensus. Due that in European Union there is not legislation about scientific societies, we are in the process to provide a legal frame to ECLip, in this case, setting up in Spain.

So far, ECLip activities have been funded by its own members, trying to be independent of private companies. Several actions have been promoted in order to search financial support from EU, and at present we are in the process to applying for a COST action.

A very important achievement of ECLip is the European Lipodystrophy Registry (http://134.60.15.143:8080/login.xhtml), at present fully functional (ClinicalTrials.gov, ID: NCT03553420). ECLip registry will allow to build a basis for sound research in the area of lipodystrophy and thereby to enable an improved estimate of the prevalence of lipodystrophy in Europe, provide a study base for patient-centred Europe-wide lipodystrophy research and to provide a platform for nested investigations on specific topics.

In summary, ECLip is an example of international scientific cooperation, without *big economic expenses*. The key of ECLip success is probably settled on two points: 1. The absence of a single leader, all of us are important, and 2. a high level of commitment wth science and altruism.

September 5 2019	morning	Time
PATHOMECHANISMS AND THERAPIES Chairs: Pavel Hozak and Nolwenn Briand		11:30 - 13:00
Common mechanisms: **Inositol phosphates functions in regulation of gene transcription** Pavel Hozak - Czech Republic		11:30 - 11:45
Progeroid Laminopathies: **Endothelial progerin expression causes cardio-vascular pathology through a paracrine profibrotic signaling** Roland Foisner - Austria		11:45 - 12:00
Muscular and Progeroid Laminopathies: **Laminopathy discoveries in Sweden** Einar Hallberg - Sweden		12:00 - 12:15
Lipodystrophic laminopathies: **Lipodystrophy-causing lamin A mutations remodels local and global chromatin architecture** Nolwenn Briand, Norway		12:15 - 12:30
Cardiolaminopathies: **Haploinsufficiency and dominant negative effects of mutant lamin A/C both contribute to the increased severity of L-CMD compared with EDMD** Anne Bertrand, France		12:30 - 12:45
Conclusions		12:45 - 13:00
LUNCH		13:00 - 14:30

END OF ENL MEETING

Inositol Phosphates functions in regulation of gene transcription

Pavel Hozák

Dept. of Biology of the Cell Nucleus & Microscopy Centre, Institute of Molecular Genetics CAS, Prague, Czech Republic

Even though the majority of knowledge about phospholipids comes from their cytoplasmic functions, in the last decade, it has been shown that nuclear phospholipids and their building blocks, inositol phosphates, have many important roles in the cell nucleus. I will focus on less known functions of nuclear phospholipids in connection with the epigenome and transcription regulation as they appear from our recent research.
We showed that PIP2 directly interacts with histone lysine demethylase PHF8 and represses demethylation of H3K9me2 through this interaction. We identified the C-terminal K/R-rich motif as PIP2-binding site within PHF8, and addressed the function of this PIP2-PHF8 complex. The results identify the function of nuclear PIP2 in the fine-tuning of rDNA transcription.
We also described a novel type of nuclear structure - nuclear lipid islets (NLIs). They are of 40-100 nm with a lipidic interior, and phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P2] molecules comprise a significant part of their surface. Most of NLIs have RNA at the periphery. Consistent with that, RNA is required for their integrity. The NLI periphery is associated with Pol II transcription machinery, including the largest Pol II subunit, transcription factors and NM1 (also known as NMI). The PtdIns(4,5)P2-NM1 interaction is important for Pol II transcription, since NM1 knockdown reduces the Pol II transcription level, and the overexpression of wild-type NM1 [but not NM1 mutated in the PtdIns(4,5)P2-binding site] rescues the transcription. Importantly, Pol II transcription is dependent on NLI integrity, because an enzymatic reduction of the PtdIns(4,5)P2 level results in a decrease of the Pol II transcription level. Furthermore, about half of nascent transcripts localise to NLIs, and transcriptionally active transgene loci preferentially colocalise with NLIs. We hypothesize that NLIs serve as a structural platform that facilitates the formation of Pol II transcription factories, thus participating in the formation of nuclear architecture competent for transcription.
This demonstrates the importance of nuclear phospholipids in the regulation of cellular processes, and should encourage further research of nuclear phospholipids and inositol phosphates.

This work was supported by the Grant Agency of the Czech Republic (Grant nos. 15-08738S; 16-03346S and 17-09103S); by the Czech Academy of Sciences (Grant no. JSPS-18-18) and the Institutional Research Concept of the Institute of Molecular Genetics (Grant no. RVO: 68378050). The Microscopy Centre was supported by the MEYS CR (LM2015062 Czech-BioImaging, and by the European Regional Development Fund-Project “Modernization and support of research activities of the national infrastructure for biological and medical imaging Czech-BioImaging” (no. CZ.02.1.01/0.0/0.0/16_013/0001775).

Endothelial progerin expression causes cardiovascular pathology through a paracrine profibrotic signaling

Selma Osmanagic-Myers[1], Maria Eriksson[2], Roland Foisner[1]

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Hutchinson-Gilford progeria syndrome (HGPS) is a premature aging disorder characterized by accelerated cardiovascular disease with extensive fibrosis and loss of vascular smooth muscle cells leading to atherosclerosis and heart failure. Genetically, HGPS is caused by a mutation in *LMNA* leading to the expression of a truncated prelamin A (progerin) in the nucleus. Cardiovascular disease is also found during normal aging, where it is usually linked to impaired function of the vascular endothelium, but the contribution of the endothelium to the cardiovascular pathology in HGPS was unclear. To address this clinically highly relevant open question, we generated an endothelium-specific HGPS mouse model with selective progerin expression in endothelial tissue. These transgenic mice developed interstitial myocardial- and perivascular fibrosis and left ventricular hypertrophy associated with diastolic dysfunction and premature death, phenocopying the pro-fibrotic cardiovascular pathology in HGPS. The endothelium-specific mice, however, did not show pathologies in the vascular smooth muscle cell layer of the vessel, indicating that vascular smooth muscle cell loss in patients is caused by vascular smooth muscle cell intrinsic defects upon progerin expression.
Our lab aims at elucidating the endothelium-mediated molecular disease mechanisms leading to cardiovascular pathologies in HGPS patients in order to allow development of novel more effective therapeutic strategies. We find that progerin-expressing endothelial cells show impaired shear stress response due to deregulation of mechanoresponsive components at the nuclear envelope leading to the impairment of the mechanoresponsive myocardin-related transcription factor-A (MRTF-A) pathway. Gene expression profiling revealed that mechanoresponse-defective progerin-expressing endothelial cells initiated a p53-linked senescence pathway associated with a profibrotic and proinflammatory senescence-associated secretory phenotype (SASP). In line with this finding, we find profibrotic effects of progerin-expressing endothelial cells on healthy fibroblasts in co-culture models, indicating active endothelium-mediated SASP signaling involving various proteins and presumably microRNAs (miRs).
Overall our data provide evidence that progerin-induced SASP signaling of endothelial cells contributes to cardiovascular fibrosis and heart impairment, major hallmarks of HGPS pathology. In addition our studies set the ground for the development of new therapeutic drugs targeting SASP signaling, particularly miR-neutralizing oligonucleotides.

This study is supported by grants from the Austrian Science Fund (FWF) and Progeria Research Foundation (PRF).

Lipodystrophy-causing lamin A mutations remodels local and global chromatin architecture

Nolwenn Briand

University of Oslo, Faculty of Medicine, Department of Molecular Medicine, Oslo, Norway.

At the nuclear periphery, the genome is anchored to A- and B-type nuclear lamins in the form of large heterochromatic lamina-associated domains (LADs). A-type lamins also associate with discrete chromatin regions in the nuclear interior, and this nucleoplasmic lamin A environment tends to be euchromatic, suggesting distinct roles of lamin A in the regulation of gene expression in peripheral and more central regions of the nucleus. The hot-spot lamin A R482W mutation causing familial partial lipodystrophy of Dunnigan-type (FPLD2) affects lamin A association with chromatin both at the nuclear periphery and in the nuclear interior. 3-dimensional (3D) genome models of patients' cells show a repositioning of LADs toward the nuclear interior, which may reflect a redistribution of heterochromatin domains toward the peri-nucleolar region. At the gene scale, defective binding of the mutated lamin A at promoters and enhancers elicits changes in the 3D conformation and in epigenetic patterns of developmental genes thereby deregulating gene expression. This collectively argues towards a remodelling of large-scale and local spatial genome organization by lipodystrophy-causing lamin A mutations.

Haploinsufficiency and dominant negative effects of mutant lamin A/C both contribute to the increased severity of L-CMD compared with EDMD

Anne T. Bertrand[1], Astrid Brull, Feriel Azibani, Monika Zwerger, Colin Stewart, Ohad Medalia, Gisèle Bonne[1]

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A-type lamins (mainly lamins A and C) are encoded by LMNA. Together with B-type lamins, they form the nuclear lamina, a protein meshwork that underlies the inner nuclear envelope (NE). A minor proportion of A-type lamins is also found in the nucleoplasm. Functions of A-type lamins include roles in nuclear resistance to mechanical stress and in regulating gene expression through interaction with chromatin, nuclear histones and transcription factors.
Mutations in LMNA are responsible for a wide variety of pathologies, including Emery-Dreifuss muscular dystrophy (EDMD) and LMNA-related congenital muscular dystrophy (L-CMD). Both pathologies presented with 1) muscular contractures, 2) muscle weakness and wasting and 3) dilated cardiomyopathy with conduction defects, although L-CMD symptoms appear much earlier and are more pronounced. To date, no real genotype-phenotype correlation exists.
Our analysis of human primary fibroblasts from healthy controls, EDMD (LMNA p.R453W and p.H222P) and L-CMD (LMNA p.K32del and p.R249W) patients revealed an increased in nucleoplasmic lamin A/C in L-CMD fibroblasts. Similar results were obtained from mouse primary myoblasts derived from LmnaH222P and LmnaK32del homozygous KI-mice where lamin A/C is exclusively found in the nucleoplasm of LmnaK32del myoblasts, with overall reduced lamin A/C expression level. Upon myoblast differentiation, LmnaK32del myotubes are unable to upregulate expression of a subset of muscle specific genes with major roles in myogenesis. All NE proteins analyzed are mislocalized, leading to extremely deformed myonuclei that seemed to have undergone nuclear fusion. Using mouse primary myoblasts from Lmna-KO mice or stably expressing DARPin molecules that lead to the displacement of lamin A/C from the NE to the nucleoplasm, we determined that the gene regulation defect was linked to the decrease lamin A/C expression while the NE protein mislocalization and nuclear fusion were related to accumulation of nucleoplasmic lamin A/C. None of these defects were observed in LmnaH222P myoblasts or myotubes. In conclusion, combination of haploinsufficiency and dominant negative effects contributes to the variability of the cellular laminopathic phenotype.

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