Seminars in Cell & Developmental Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Nuclear matrix, nuclear envelope and premature aging syndromes in a translational research perspective

Pierre Cau[a,b,c,*], Claire Navarro[a,b,1], Karim Harhouri[a,b,1], Patrice Roll[a,b,c,1,2], Sabine Sigaudy[a,b,d,1,3], Elise Kaspi[a,b,c,1,2], Sophie Perrin[a,b,1], Annachiara De Sandre-Giovannoli[a,b,d,1,3], Nicolas Lévy[a,b,d,**]

[a] Aix-Marseille Université, UMR_S 910, Génétique Médicale et Génomique Fonctionnelle, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France
[b] INSERM, UMR_S 910, Génétique Médicale et Génomique Fonctionnelle, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France
[c] AP-HM, Service de Biologie Cellulaire, Hôpital La Timone, 264 Rue Saint Pierre, 13385 Marseille Cedex 5, France
[d] AP-HM, Département de Génétique Médicale, Hôpital d'enfants Timone, 264 Rue Saint Pierre, 13385 Marseille Cedex 5, France

ARTICLE INFO

Article history:
Available online xxx

This review article is dedicated to the children affected with progeria and progeroid disorders, and in the memory of Ben, Megane, Serena, Sam and Nestor.

Keywords:
Nuclear matrix
Lamins
Aging
Progeria
Aging diseases

ABSTRACT

Lamin A-related progeroid syndromes are genetically determined, extremely rare and severe. In the past ten years, our knowledge and perspectives for these diseases has widely progressed, through the progressive dissection of their pathophysiological mechanisms leading to precocious and accelerated aging, from the genes mutations discovery until therapeutic trials in affected children.

A-type lamins are major actors in several structural and functional activities at the nuclear periphery, as they are major components of the nuclear *lamina*. However, while this is usually poorly considered, they also play a key role within the rest of the nucleoplasm, whose defects are related to cell senescence. Although nuclear shape and nuclear envelope deformities are obvious and visible events, nuclear matrix disorganization and abnormal composition certainly represent the most important causes of cell defects with dramatic pathological consequences. Therefore, lamin-associated diseases should be better referred as laminopathies instead of envelopathies, this later being too restrictive, considering neither the key structural and functional roles of soluble lamins in the entire nucleoplasm, nor the nuclear matrix contribution to the pathophysiology of lamin-associated disorders and in particular in defective lamin A processing-associated aging diseases.

Based on both our understanding of pathophysiological mechanisms and the biological and clinical consequences of progeria and related diseases, therapeutic trials have been conducted in patients and were terminated less than 10 years after the gene discovery, a quite fast issue for a genetic disease. Pharmacological drugs have been repurposed and used to decrease the toxicity of the accumulated, unprocessed and truncated prelaminA in progeria. To date, none of them may be considered as a cure for progeria and these clinical strategies were essentially designed toward reducing a subset of the most dramatic and morbid features associated to progeria. New therapeutic strategies under study, in particular targeting the protein expression pathway at the mRNA level, have shown a remarkable efficacy both *in vitro* in cells and *in vivo* in mice models. Strategies intending to clear the toxic accumulated proteins from the nucleus are also under evaluation. However, although exceedingly rare, improving our knowledge of genetic progeroid syndromes and searching for innovative and efficient therapies in these syndromes is of paramount importance as, even before they can be used to save lives, they may significantly (i) expand the affected childrens' lifespan and preserve their quality of life; (ii) improve our understanding

* Corresponding author at: INSERM, UMR_S 910, Aix Marseille Université, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France. Tel.: +33 0491 32 43 01/0491 38 82 10; fax: +33 0491 79 72 27/0491 38 46 76.
** Corresponding author at: INSERM, UMR_S 910, Aix Marseille Université, Faculté de Médecine, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France. Tel.: +33 0491 32 43 01/0491 38 77 87; fax: +33 0491 79 72 27/0491 38 46 76.
E-mail addresses: pierre.cau@univ-amu.fr (P. Cau), nicolas.levy@univ-amu.fr (N. Lévy).
[1] Tel.: +33 0491 32 43 01; fax: +33 0491 79 72 27.
[2] Tel.: +33 0491 38 82 10; fax: +33 0491 38 46 76.
[3] Tel.: +33 0491 38 77 87; fax: +33 0491 38 46 76.

http://dx.doi.org/10.1016/j.semcdb.2014.03.021
1084-9521/

of aging-related disorders and other more common diseases; and (iii) expand our fundamental knowledge of physiological aging and its links with major physiological processes such as those involved in oncogenesis.

Contents

1. Nuclear envelope, nuclear matrix and lamins

In eukaryotic cells, nuclear genome is packed in the form of the highly organized chromatin within nucleoplasm, delineated by the nuclear envelope (NE). The NE is a specialized cisterna of endoplasmic reticulum (ER), separating nuclear from cytoplasmic compartments and made of two distinct membrane domains only interconnected through nuclear pore complexes (NPC) [1,2]. The outer nuclear membrane (ONM) exhibits several membrane and luminal ER characteristics as well as functions (from ribosome-linked synthesis to post-traductional processing of proteins...). The inner nuclear membrane (INM) harbors an unique set of about 80 transmembrane proteins (NPC proteins being excluded), that are synthetized by and inserted into ER or ONM, and reach INM after crossing NPC [3].

Less than 10 of these INM proteins are well characterized because they are yet known to be involved in human genetic diseases [4]. However the great majority of INM transmembrane proteins, most of them discovered through proteomic studies, remain still uncharacterized, even if they could be good candidates for yet unidentified human diseases [5]. Moreover, the expression of some of these INM proteins is cell- or tissue-specific [6–10]. Therefore, these INM proteins could contribute to the phenotype variability exhibited by patients harboring a mutation in the gene encoding an interactor of these INM proteins.

Besides nuclear genome and all the enzymatic and non-enzymatic machinery required for nuclear genome functions, the nucleoplasm also contains a protein network called nuclear matrix (NM) [11], whose peripheral region, known as nuclear *lamina*, interacts with INM proteins, NPC nucleoplasmic domain and peripheral chromatin [12].

Please cite this article in press as: Cau P, et al. Nuclear matrix, nuclear envelope and premature aging syndromes in a translational research perspective. Semin Cell Dev Biol (2014), http://dx.doi.org/10.1016/j.semcdb.2014.03.021