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The nuclear envelope: emerging roles in development and disease

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Abstract. The chromosomes of eukaryotic cells are separated from the cytoplasm by the nuclear envelope. The nuclear envelope includes two riveted membranes, plus embedded pore complexes that mediate nuclear import and export. In this sense, the nuclear envelope is truly a border zone. However, the envelope also links directly to chromosomes, and anchors two major infrastructures – the nuclear lamina and Tpr filaments – to the nuclear perimeter. Proteins of the nuclear envelope mediate a variety of fundamental activities, including DNA replication, gene expression and silencing, chromatin organization, cell division, apoptosis, sperm nuclear remodeling, the behavior of pronuclei, cell fate determination, nuclear migration and cell polarity. Furthermore, mutations in nuclear lamins and lamin-binding proteins cause tissue-specific inherited diseases. This special issue of *Cell and Molecular Life Sciences* is devoted to recent major advances in the characterization of nuclear envelope proteins and their roles. We offer here an overview of the topics covered in this issue of *CMLS*, and also discuss the emerging recognition that the nuclear envelope is an organelle critical for a wide range of genetic and developmental activity in multicellular organisms.

Key words. Cell cycle; fertilization; development; Emery-Dreifuss muscular dystrophy; germ cells; apoptosis; nuclear migration; nuclear lamins; nuclear membranes; nuclear pore complexes; nucleocytoplasmic transport; plant nuclear envelope; Ran.

Introduction

The nucleus is a beautiful example of the interplay between structure and function in biology. The nuclear envelope includes two joined but spatially distinct (inner and outer) membranes. The outer membrane is continuous with the endoplasmic reticulum. In contrast, the inner membrane contains specialized integral and peripheral membrane proteins whose functions are specific to the nucleus. Holmer and Worman [1, this issue] review the localization mechanisms and functions of these specialized inner nuclear membrane proteins, which include the lamin B receptor (LBR), lamina-associated-polypeptide 1 (LAP1), the LEM-domain family (LAP2, emerin, MAN1, Lem-3) and nurim. Most of these proteins interact directly with two structures: chromatin and the nuclear lamina, which is a meshwork of intermediate filament proteins named lamins. In addition to concentrating near the inner membrane, lamins also ramify throughout the nucleus, potentially in close association with chromatin. The structure and functions of lamins, including nuclear organization and DNA replication, are discussed by Moir and Spann [2, this issue]. Nuclear pore complexes anchor a second system of filaments that extend into the nucleus and are thought to function in nuclear export; Vlcek, Dechat and Foisner [3, this issue] review these filaments, which include the Tpr protein. Vlcek et al. [3] also discuss the structural links between lamins and nuclear pore complexes, and the dynamics of lamin-binding proteins in the nuclear interior. The structure of nuclear pore complexes has been reviewed recently [4, 5]. In this issue, Quimby and Corbett [6] review new findings on the regulation of nucleocytoplasmic transport by Ran, which is a key element of nuclear envelope function. During interphase, cells rely on the stability of the nuclear envelope. However, the opposite is true during mi-

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tosis, when the nuclear envelope and its attached infrastructures must disassemble wholely or in part. The dynamic behavior of the nuclear envelope is critical for multicellular eukaryotes to progress through the cell cycle. Buendia, Courvalin and Collas [7, this issue] discuss the interplay between nuclear envelope proteins and chromatin during nuclear assembly, and at different stages of the cell cycle. Lamins are also critical for the regulated destruction of the nucleus during apoptosis, which is also reviewed by Buendia et al. [7, this issue].

The functions of specific cell types are highly sensitive to the perfect functioning of the nuclear envelope. The most dramatic example is the discovery that mutations in A-type lamins or in emerin (a lamin-binding nuclear membrane protein) cause multiple diseases [8, 9]. The first identified nuclear 'laminopathy' was Emery-Dreifuss muscular dystrophy, which is caused by the loss of emerin [10] or by autosomal dominant mutations in *LMNA* [8], the gene encoding A-type lamins [11]. These discoveries were soon followed by the recognition that three other syndromes, Dunnigan-type familial partial lipodystrophy (loss and redistribution of white fat), limb-girdle muscular dystrophy, and a form of dilated cardiomyopathy with conduction system disease also mapped to *LMNA* (see [8]). The mechanisms by which emerin deficiency and lamin A mutations cause disease are not understood. This question is stimulating a renaissance of theories, models and experimentation centered around the functions of nuclear lamins and lamin-binding proteins (e.g., [12–14]). Given that A-type lamins appeared late in evolution, and are only expressed in flies and vertebrates but not in worms [15], it seems likely that A-type lamins perform highly specialized functions. A variety of perspectives on nuclear lamin-based diseases are provided in this issue by Holmer and Worman [1], Vlcek et al., [3] and Moir and Spann [2]; in particular, Moir and Spann analyze potential molecular mechanisms of laminopathies, compared with diseases caused by mutations in cytoplasmic intermediate filament proteins.

Development, particularly at early stages, is also sensitive to nuclear envelope function. The high sensitivity of early development is seen at several points, including gamete formation/structure, pronuclear fusion after fertilization, embryonic cleavage divisions and cell fate determination. For example, the structure and composition of the nuclear envelope of sperm differ from that of other cell types [16–18]. The sperm-specific lamin B3 in mouse is thought to determine the unique shape of the sperm nucleus, since nuclei of cultured cells engineered to express lamin B3 acquire sperm nucleus-like shapes [19]. After fertilization, remodeling of the sperm nuclear envelope is essential to convert the condensed sperm nucleus into a functional male pronucleus, as reviewed by Buendia et al. [7, this issue] and Poccia and Collas [20]. Then, the male and female pronuclei migrate towards each other to fuse and combine the parental genomes. Female pronuclear migration has been modeled in vitro using nuclei reconstituted on DNA-coupled magnetic beads [21]. Movement of such 'bead nuclei' along microtubules is dynein dependent and requires that the bead nuclei have intact nuclear envelopes. An attractive model is that a protein complex in the nuclear membrane of the female pronucleus anchors dynein and thereby allows it to 'motor' the female pronucleus along microtubules to the site of pronuclear fusion [21, 22]. After pronuclei associate, they must combine their genomes and initiate the mitotic cleavage divisions. In *Drosophila*, initiation of cleavage by newly formed zygotes requires a maternally provided nuclear lamina protein, named Young Arrest [YA; 23, 24]. In the absence of YA, which normally associates with both the lamina and the chromatin [25, 26], embryos arrest after meiosis because they are unable to enter the first mitotic cell division cycle. *Drosophila* embryos also arrest at approximately this stage if there are defects in importin β, probably because they cannot reassemble a functional nucleus without nucleocytoplasmic transport [28, 29]. Even after mitotic cleavage divisions begin, special functions of the nuclear envelope are required. For example in *Drosophila*, a nearly ubiquitous transcriptional repressor named germ cell-less (GCL) is essential for pole cell determination in the mid-cleavage stages [30, 31]. GCL interacts directly with the DP subunit of the transcriptional activator E2F-DP, and also binds directly to the nuclear membrane protein LAP2β [32]. Furthermore, coexpression of GCL and LAP2 inhibits the expression of a reporter gene as effectively as retinoblastoma protein [32]. This finding suggests that LAP2 (and potentially other LEM-domain nuclear membrane proteins such as emerin) can play direct roles in gene expression, and might therefore regulate tissue-specific gene expression. Later developmental events also clearly depend on a functional nuclear envelope. In *Caenorhabditis elegans*, the nuclear migrations that give rise to embryonic hypodermal tissue require a nuclear membrane protein named UNC-84 [33], which exhibits lamin-dependent localization at the nuclear envelope. In *Drosophila,* cell polarity in tracheal terminal cells and developing oocytes, including asymmetric localization of critical patterning messenger RNAs (mRNAs) in oocytes, is defective in strains carrying mutations in the *Drosophila* B-type lamin (lamin Dm_0) [35]. Although it is not yet clear how lamin defects in the nucleus can disrupt the localization of mRNAs in the cytoplasm, this finding adds to growing evidence that lamins can influence specific cell functions in subtle ways. Understanding lamins and lamin-associated proteins will be central to a full understanding of fertilization and early development, as well as some later developmental events.

Until now, cell biologists studying the nuclear envelope have focussed almost entirely on animals and unicellu-

lar eukaryotes. Although plants are also multicellular eukaryotes, and also have differentiated cells and tissues, progress towards understanding the plant nuclear envelope has been rather neglected in the 'animal cell' literature. Despite having conserved nuclear pore complex proteins, plant nuclei lack lamins and lamin-binding proteins [15], and may represent a distinct solution to the problem of organizing large genomes during evolution. We think the contrasts between plant and animal nuclei are both interesting and instructive. We therefore include a review by Meier [36, this issue] that details the many differences, and a few potentially significant similarities, between the nuclear envelopes of plants and animals.

Conclusions

The study of nuclear envelope functions is providing remarkable new insight into fundamental aspects of nuclear structure and dynamics. The nuclear envelope and nuclear infrastructure play critical but incompletely understood roles in gametogenesis, fertilization, early development, the transition between meiosis and mitosis, cell fate determination, cell polarity, nuclear migration and several serious diseases. We believe that this issue of *Cell and Molecular Life Sciences* will be helpful and timely for understanding the structure of the nuclear 'organelle' and its roles in mitosis, gene expression and communication with the cytoplasm. This understanding will provide the basis from which to understand its roles in development and disease.

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