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Minireview

What can *Caenorhabditis elegans* tell us about the nuclear envelope?

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Abstract The nuclear envelope (NE) of the eukaryotic cell provides an essential barrier that separates the nuclear compartment from the cytoplasm. In addition, the NE is involved in essential functions such as nuclear stability, regulation of gene expression, centrosome separation and nuclear migration and positioning. In metazoa the NE breaks down and re-assembles around the segregated chromatids during each cell division. In this review we discuss the molecular constituents of the *Caenorhabditis elegans* NE and describe their role in post-mitotic NE re-formation, as well as the usefulness of *C. elegans* as an in vivo system for analyzing NE dynamics.

Keywords: Nuclear envelope; Nuclear pore complex; Chromatin; Nuclear lamina; Mitosis

1. Introduction

The interphase nuclear envelope (NE) is composed of a structurally and functionally distinct pair of membranes, the outer (ONM) and the inner nuclear membrane (INM), which are joined at the nuclear pore complexes (NPCs). The lumen between these two membranes is called the periplasmic (or perinuclear) space (PS). The lumenal domains of integral ONM and INM proteins may interact in this space. The ONM is continuous with the endoplasmic reticulum (ER), to which it is functionally related. The INM harbors a unique set of membrane proteins, many of which interact with the chromatin and/or with the intermediate filaments of the nuclear lamina. This entire protein interaction network provides stability to the NE. In metazoan organisms this seemingly stable interphase structure is dynamically rearranged during cell division. During prophase the NE breaks down (NEBD) allowing the spindle microtubules to reach, anchor and segregate the sister chromatids. During late anaphase and early telophase the NE reforms on the surface of the segregated chromatids. The molecular mechanisms involved in NE formation are incompletely understood. Most current knowledge has come from various cell-free experimental systems, such as the *Xenopus leavis* egg extract system. However, it is also essential to better understand how NE formation occurs in living organisms.

Caenorhabditis elegans is a powerful metazoan experimental system to study NE formation because these nematodes can easily be manipulated with well-established genetic approaches, double-stranded RNA-mediated interference (RNAi) and transformation with different fluorescently-labeled transgenes. The efficacy of RNAi in *C. elegans* means that whole genome screens can be readily performed even if screening is done via light microscopy. Thus, whole chromosome and whole genome screens have been performed screening for defects in zygotic nuclear assembly [1]. The major disadvantage of *C. elegans* is that it is impossible to obtain cell-cycle stage specific embryonic extracts and thus many biochemical assays cannot be performed.

2. The early *C. elegans* embryo as a model system

The self-fertile *C. elegans* hermaphrodite has two symmetric U-shaped gonads that produce both sperms and oocytes. At the distal end of each gonad germ cells divide mitotically and, as they move towards the proximal end of the gonad they enter meiosis and develop into oocytes. The most proximal oocyte then enters the spermatheca where it is fertilized. The meiotic divisions are completed after transfer into the uterus. After the second meiotic division the female and male pronuclei are formed and closed NEs are assembled. The female pronucleus migrates towards the male pronucleus at the posterior pole of the zygote where they meet, attach and migrate into the center of the embryo. Here they go through the first zygotic division. This produces a larger anterior AB and a smaller posterior P1 cell (Fig. 2). In general, the development of *C. elegans* embryos follows a deterministic pattern, making it a very suitable model system to follow mitotic events such as NE formation. We have analyzed NE formation in young embryos from the pronuclear stage until the four-cell stage, when the nuclei are still relatively large and can easily be monitored by transmission and fluorescence confocal time lapse microscopy.

3. Protein composition of the *C. elegans* NE

The nuclear lamina functions as a nucleoskeleton that attaches to the NPCs, the INM and chromatin and thus provides stability and shape to the NE during interphase. The lamina also regulates gene expression in a way that is mechanistically

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Abbreviations: NE, nuclear envelope; INM, inner nuclear membrane; ONM, outer nuclear membrane; PS, perinuclear space; NPC, nuclear pore complex; NEBD, nuclear envelope breakdown; ER, endoplasmic reticulum

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not understood [2]. The major components of animal nuclear lamina networks are lamins, type-V intermediate-filament proteins, which can be classified as A- and B-types on the basis of their biochemical properties [2]. Only B-type lamins are essential and are constitutively expressed in all metazoan cells. In the *C. elegans* genome there is a single lamin gene of the B type. Lamin proteins are composed of a short N-terminal head domain, a long central α-helical domain, able to form a segmented double-stranded coiled-coil, and a C-terminal Ig domain globular tail. B-type lamins are post-translationally modified for anchoring to membranes. Assembly and stable association of lamin filaments with the INM during interphase also requires interactions with proteins embedded in the INM. In mammalian cells, 78 putative integral NE proteins have been identified by proteomics [2,3]. The *C. elegans* NE contains fewer identified integral NE proteins.

One of the most abundant groups of lamin-binding proteins shares a conserved ~40 residue long N-terminal nucleoplasmic LEM (*l*amina-associated polypeptide2-*e*merin-*M*AN1) domain [4]. In *C. elegans* three LEM domain-containing proteins have been identified, LEM-2, LEM-3 and emerin [5] (Fig. 1). While emerin and LEM-2 contain one or two transmembrane domains, respectively, LEM-3 does not have any. Additionally, LEM-2 contains a conserved C-terminal MSC (MAN1-Src1p) domain, but it is different from vertebrate MAN1 proteins since it lacks a C-terminal RNA recognition motif. In contrast, vertebrates contain a much larger number of INM and peripheral lamin-binding proteins [2,3].

In *C. elegans*, the nuclear lamina is further required for proper nuclear migration and positioning. This was extensively studied in P-cells, hyp7-precursor cells and the multi-nucleated hypodermal syncytium of *C. elegans* embryos and larvae [6,7]. Briefly, lamin polymers are proposed to bind to the N-termini of UNC-84 and matefin, two putative *C. elegans* INM proteins which contain several transmembrane domains and a C-terminal ~120 residue long *S*ad1p/*UN*C-84 (SUN) domain localized in the PS (Fig. 1). The SUN domain can bind directly or indirectly to the *K*larsicht/*A*NC-1/*S*yne-1 *h*omology (KASH) domains of ONM proteins and thus anchor specific ONM proteins. Specifically, the SUN domain of UNC-84 can bind to the KASH domain of the nematode-specific ONM protein UNC-83, whose cytoplasmic N-terminus is proposed to mediate interactions with microtubules and function in nuclear migration. In a very similar way, UNC-84 interacts with a second KASH domain protein, called ANC-1 (the *C. elegans* nesprin homologue) (Fig. 1). ANC-1 is a ~950 kDa protein which contains two actin-binding calponin-homology domains, that can directly bind to F-actin and anchor the nucleus to the actin cytoskeleton. Similarly, matefin, the other *C. elegans* protein containing the SUN domain, is essential to retain the Hook family member protein ZYG-12 in the ONM. ZYG-12 has three splice isoforms, two of which have a KASH domain

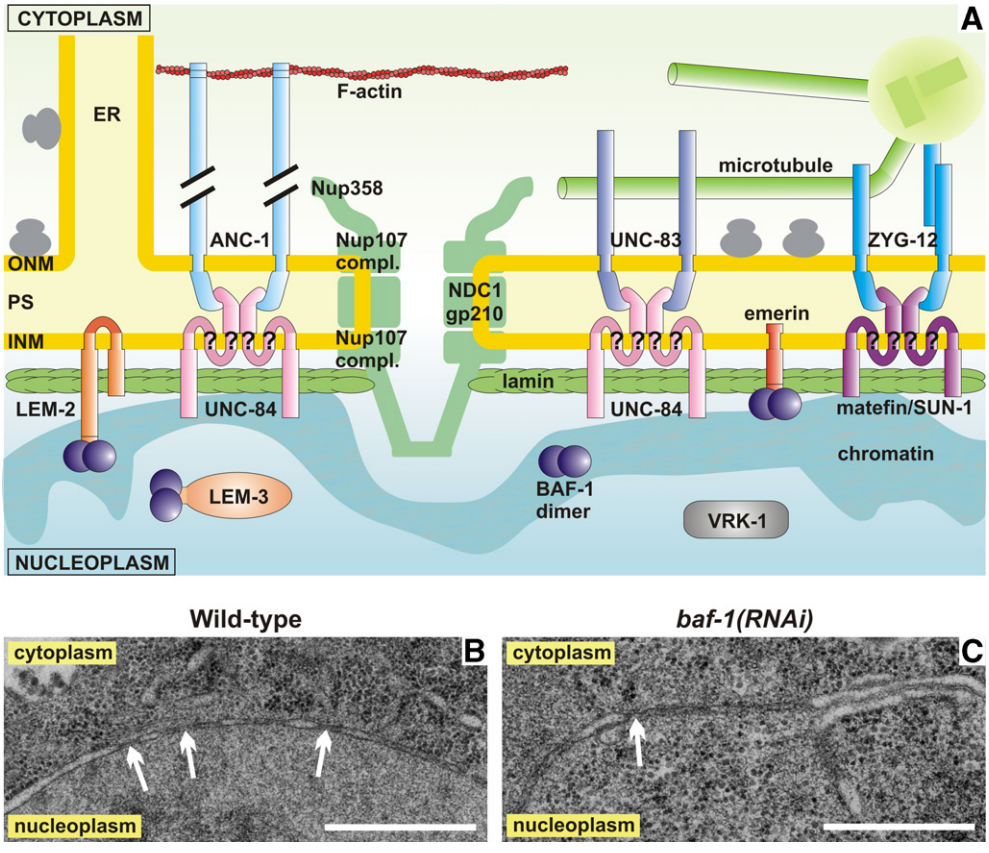

Fig. 1. Schematic and transmission electron microscopic (TEM) illustration of the *C. elegans* NE. (A) Proposed molecular interactions of the integral NE proteins with other integral or peripheral NE proteins, chromatin, the nuclear lamina and cytoskeleton. Note that some of these proteins are not expressed ubiquitously, and thus all these interactions may not exist simultaneously in every cell. (B, C) TEM micrographs of NEs from wild-type and *baf-1*(*RNAi*) young embryos, respectively. While the wild-type NE is continuous and has regularly spaced NPCs (arrows), the shape and the functionality of the NE from *baf-1*(*RNAi*) embryos are dramatically distorted. A closed NE is not formed in *baf-1*(*RNAi*) embryos and the nuclear and cytoplasmic compartments are mixed. This can be seen by the presence of ribosomes inside the nucleus. Bars: 800 nm.