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COMMENTARY

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Shared mechanisms in physiological and pathological nucleoplasmic reticulum formation

Marek Mateusz Drozdz and David John Vaux

Sir William Dunn School of Pathology, University of Oxford, Oxford, UK

ABSTRACT
The mammalian nuclear envelope (NE) can develop complex dynamic membrane-bounded invaginations in response to both physiological and pathological stimuli. Since the formation of these nucleoplasmic reticulum (NR) structures can occur during interphase, without mitotic NE breakdown and reassembly, some other mechanism must drive their development. Here we consider models for deformation of the interphase NE, together with the evidence for their potential roles in NR formation.

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Nucleoplasmic reticulum, a widespread organelle

The nuclear envelope (NE) is a unique structure forming a physical barrier between the nucleoplasm and the cytoplasm. It is comprised of 2 phospholipid bilayers, the inner nuclear membrane (INM) and outer nuclear membrane (ONM), with an intervening luminal space between (for a review, see ref. [1]). Underlying the INM is the nuclear lamina, a proteinaceous meshwork of intermediate filament proteins. It is well established that the structure of the nucleus is more complex than just a membrane-bound spheroid containing chromatin, and pierced by nuclear pore complexes (NPC). Nuclei vary in shape not only in different cell types, but also under different pathological and physiological conditions.[2] The NE frequently shows multiple invaginations of the nuclear membrane into the nucleus, forming an often elaborate network of tubules and sheets of INM, and sometimes ONM, continuous with the NE (See Fig. 1). This feature is termed a nucleoplasmic reticulum (NR), so named for its structural resemblance to the endoplasmic reticulum.[3,4] The NR is a widespread feature of many cells and tissues under normal cellular conditions.[5-8] In addition, it is also observed in cells grown in 2D and 3D cultures, including many tumor cell types, for example breast, brain, bladder, kidney, ovary, and prostate.[9] Moreover, NR abundance is altered in various pathologies such as cancer,[10,11] Alzheimer's disease,[12] myotonic dystrophy,[13] Hutchinson-Gilford Progeria Syndrome,[14] and others, suggesting a dysregulation of mechanisms responsible for NR regulation under pathological conditions.

NR structure

NR structures are classified into 2 main classes, type I and type II.[3] Type I invaginations are those where the INM alone invaginates into the nucleoplasm, whereas type II involves invagination of both the inner and outer nuclear membranes, hence type II NR contains a cytoplasmic core. Moreover, in the cytoplasmic core of type II NR microtubules, microfilaments, and mitochondria have all been detected.[15,16] The NR structure can be more complex though, with type I invaginations branching off type II, both as membrane sheets and as tubules. In addition, these complex invaginations may traverse the nucleus, forming cross-nuclear channels.

NR function

Despite the fact that NR is a widely spread organelle, present in multiple cell types, its exact function is still

CONTACT David John Vaux david.vaux@path.ox.ac.uk Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford, OX1 3RE, UK.

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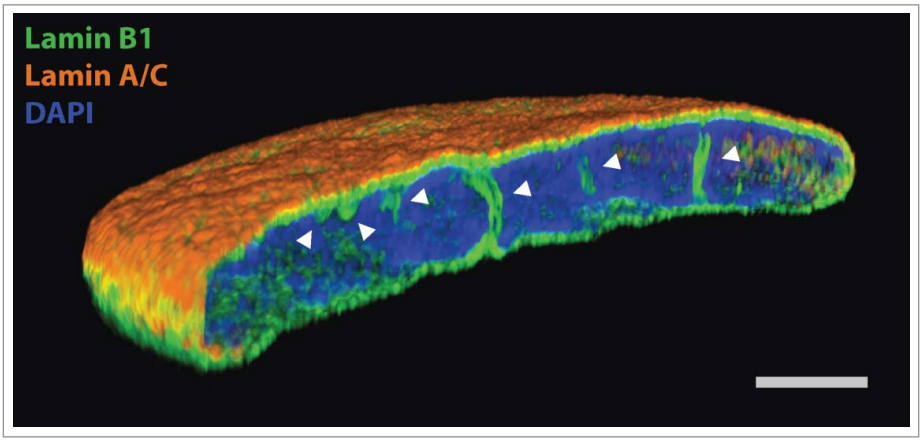

Figure 1. Super resolution light microscopy on normal human dermal fibroblasts, labeled with anti-lamin B1 antibody (green), anti-lamin A/C antibody (orange) and DAPI (blue). White arrowheads point to intranuclear NR tubules. Scale bar, 2 μm.

not fully understood. New reports, however, keep emerging, shedding more light on its role. The NR is thought to provide a structural support for the nucleus, as well as to bring functions of the peripheral NE deep into the interior of nucleus and aid in nuclear import-export due to presence of NPC at the invaginations.[17] NR has also been shown to aid in cellular processes such as transcription, DNA repair and lipid metabolism.

Probably the best studied role of the NR is the calcium signaling inside the nucleus. Endoplasmic reticulum, the main reservoir of calcium ions in a cell shares its lumen with the nuclear double membrane, thus it is also continuous with the intervening luminal space of the NR channels. Indeed, it has been shown that calcium can be released from the NE store into the nucleoplasm through channels sensitive to inositol triphosphate (IP3).[18,19] Interestingly, both PIP_2 and phospholipase C (PLC), required for production of IP3, are also present in the nucleus.[20,21] While PLC can associate with the nuclear membrane,[22] the nuclear PIP_2 was suggested to reside within the nuclear membrane forming NR invaginations.[23] Moreover, it has been reported that NR invaginations contain inositol triphosphate receptors (IP3R)[4] as well as ryanodine receptors,[24] which are involved in a selective calcium release into the nucleus, therefore the NR allows for controlled and spatially localized calcium signaling in nuclear functions,[25] including transcription regulation.[26] In addition, it has been proposed that presence of NR allows for not only initiation of localized nuclear calcium signaling, but also for its termination due to presence of IP3-kinase isoform B (IP3KB) at nuclear invaginations[27] which can inactivate IP3[28,29] as well as sarco/endoplasmic reticulum calcium ATPase (SERCA).[30] Moreover, it has been suggested that NR identified in plant cells has a similar role in regulation of nuclear calcium signaling,[31,32] hence implying a conserved role for this structure between the two kingdoms.

It has been widely observed that NR invaginations often associate with nucleoli[5,33,34] and are found in close proximity to fibrillarin-positive regions or point toward UBF-1-positive nucleolar compartments.[35] These are sites of active transcription of ribosomal genes, thus, association of type II NR channels with cytoplasmic core, and pierced by NPC, could suggest a role for the NR in facilitating a nuclear export of rRNA. However, these are microscopy co-localization studies, therefore further experiments are required to determine whether rRNA export truly occurs and dominates such associations. In addition, cells treated with the histone-deacetylase inhibitor trichostatin A show higher abundance of NR,[36] thus it may further support the hypothesis that NR helps with increased gene expression and RNA export in general. Moreover, NR channels have been observed to closely associate with repressive complexes such as BMI1-positive Polycomb group proteins (PcG) - related bodies and heterochromatin marker HP1β,[35] which could further facilitate NR involvement in chromatin organization and transcription regulation. Indeed, soluble intra-nuclear lamin A/C was shown to interplay and regulate PcG-mediated transcriptional repression,[37,38] thus lamin A/C underlying NR channels could offer additional anchor points of PcG

compartmentalization. It may seem contradictory that NR channels associate with repressive PcG complexes, and yet become more abundant upon chromatin relaxation induced by a histone-deacetylase inhibitor.[36] Association with the NE, however, has also been shown to promote both chromatin activation and silencing, depending on context and interactors,[39-41] thus NR as an intranuclear extension of nuclear envelope may exhibit similar properties. Legartova and colleagues also observed a tight association of NR tubules with γH2AX-positive DNA lesions, induced by γ-radiation, and with 53BP1, a regulator of cellular response to DNA damage,[42] implying a role for a dynamic NR in DNA damage repair.[35]

Another cellular process in which NR has been implicated is lipid metabolism. Recently, it was shown that type I NR closely associates with lipid droplets and their number correlates with the amount of type I NR in a promyelocytic leukemia nuclear body-dependent manner.[43] Nuclear lipid droplets appear to incorporate newly synthesized lipid esters and stain positively for diacylglycerol O-acyltransferase 2 (DGAT2) and CTP:phosphocholine cytidylyltransferase α (CCTα), the key enzymes in triglyceride and phosphatidylcholine synthesis, respectively.[44,45] Interestingly, NR formation can not only be induced by CCTα,[46] but also depends on this enzyme.[17] Moreover, CCTα upon activation translocates to the NE and the NR, thus, bearing in mind a wide spectrum of functions performed by CCTα in lipid metabolism[45] and its close links with NR, it could suggest additional roles for NR in lipid signaling.

NR formation

NR tubules can be a result of post-mitotic reassembly of the nucleus, when the fusion of recruited NE sheets is imperfect and some get trapped within the nucleus.[47] However, a number of reports showed clearly that new NR channels can form in a cell-cycle-independent manner in post-mitotic primary cells,[48] in cycle-arrested cells,[5,17] and during interphase in free-cycling cells,[17] thus suggesting the existence of a controlling mechanism for NR formation in an interphase nucleus.

Nuclear architecture is complex and various physical forces affect the organization and shape of the NE, both from within the nucleus and/or from the cytoplasm.[49-54] Proliferation of highly curved NR channels is an energy demanding process, because pure lipid bilayers, a major component of NE, remain flat unless energy is provided to stimulate them to curve.[55] The energy that aids in curvature introduction to the cellular membranes could be sourced from either modification of lipid composition or bilayer asymmetry, or from membrane-associated proteins (for a review, see ref. [56]). Protein mechanisms vary and can rely purely on the shape of transmembrane proteins, further enhanced by partitioning or crowding effects of the protein insertion, or on docking of hydrophobic protein domains in the membrane. Oligomerization of protein monomers and formation of protein coats can greatly enhance and stabilize membrane curvature (for a review, see ref. [57]).

This diversity of regulated membrane curvature inducing processes leads to a range of possible mechanisms that could cause the drastic alterations to the properties of the NE and drive NR formation (See Fig. 2). Although relying on different principles, these models are not mutually exclusive.

Pulling in

Nuclear architecture may be defined by interactions between chromatin and the NE, as a substantial literature on chromatin-lamina and chromatin-INM protein interactions attests (for reviews, see refs. [58-60]). It is well established that chromatin organization is not random and higher order chromosomal territories exist (for reviews, see refs. [61,62]), although their organization seem to be cell-type specific. Distribution of chromosomes can be dictated either by their size[63] or gene density.[64] In addition, in an interphase nucleus, dynamic chromatin movements occur as a result of chromosome condensation.[65,66] Thus, NR invaginations could be driven by rearrangements of chromatin tethered to the NE and pulling in the nuclear membrane (Fig. 2). This observation was made for NR formation in polytene nuclei from *Drosophila melanogaster* salivary glands.[67] Conversely, however, a link between NR and chromatin decondensation could be implied by the observation that mouse embryonic fibroblasts treated with histone-deacetylase inhibitor show an increased abundance of type II NR.[36]

Pushing in

Alternatively, the pressure on the NE that curves the membrane and induces NR formation may come

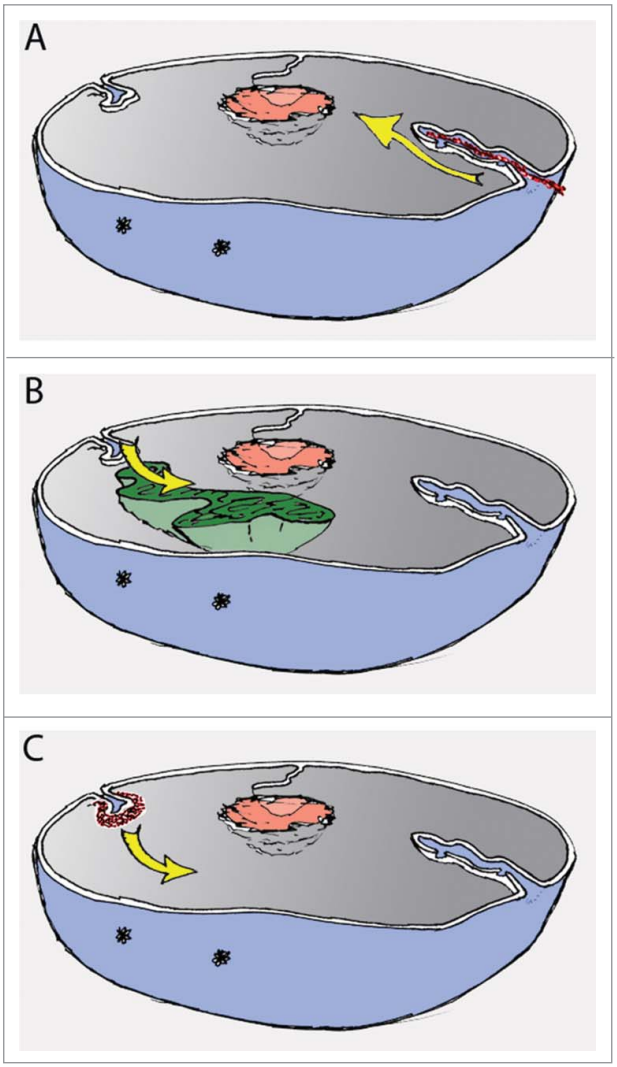

Figure 2. Schematic representation of nucleus with possible mechanisms driving NR formation. (A) Pushing the NE by cytoskeleton (red) as visualised by yellow arrow; (B) Pulling the NE by chromatin movement (green), movement indicated by yellow arrow; (C) Focal and *de novo* assembly and growth (yellow arrow) of NR invaginations (red) by dedicated machinery.

from outside of the nucleus (Fig. 2). It is well established that the cytoskeleton can counterbalance internal forces of chromatin and the nuclear lamina, thus playing a pivotal role in stabilization of nuclear architecture.[50,51,68] It is possible then that the cytoskeleton exerts a force on the NE and pushes it in, driving invagination. In fact, it has been shown that type II NR invaginations contain microtubules and microfilaments in their cytoplasmic core.[3,5,69,70] In addition, a close proximity of centrioles to major nuclear invaginations of granulocytic cells was shown, with the suggestion that centrosomes exhibit the tensor force curving the NE through cytoskeletal proteins.[71] Although likely to be relevant under some conditions, a putative cytoskeleton-driven formation of NR cannot explain proliferation of type I NR, consisting of the INM only.

Selective recruitment

The final scenario suggests the existence of dedicated machinery that assembles the NR structure *de novo*, rather than through rearrangement of pre-existing NE (Fig. 2). In fact many cellular machineries exist dedicated specifically to induction of lipid bilayer curvature and cellular membrane invaginations.[56]

One of the best studied is clathrin-mediated endocytosis, which is initiated by focal assembly of a clathrin lattice at a flat membrane area, a process orchestrated by adapter proteins in conjunction with actin polymerisation.[72-74] Several other clathrin-independent mechanisms of plasma membrane invagination have been characterized as well. They also require specific interactions of mediator proteins and can lead to varying membrane morphologies such as tubular or vesicular structures. Clathrin-independent carriers/glycosylphosphatidylinositol-enriched early endosomal compartment pathway,[75] endophilin-mediated endocytosis[76] or caveolae formation.[77,78] are just a few of them.

Phospholipid bilayer deformation is not limited to the plasma membrane. Many intracellular structures exist as membrane-bound organelles compartmentalising the cell interior and rely on membrane curvature in order to perform their functions, such as the endoplasmic reticulum. Reticulons and DP1/YOP1 (defective in polyposis/yeast ortholog) proteins are regulators of membrane curvature, involved in the formation of tubular ER in animals, fungi, and plants.[79-81] Moreover, reticulons can generate arc-shaped scaffolds by an oligomerization process further contributing not only to induction, but also to the maintenance of high membrane curvature.[82] Therefore, reticulons can influence the balance between the ER sheet and ER tubule proliferation, favoring conversion of sheets into tubules. Interestingly, some reticulons have been suggested to be involved in NPC insertion at the NE.[83] Moreover, reticulon 4a was found in junctions between ER and the edges of growing NE in both *Xenopus* oocytes and in *in vitro* nuclei assembly system,[84]

thus, this protein appears be involved in facilitating NE growth by stabilizing high curvature where new membrane is added to the re-forming nuclei. Therefore, it is tempting to speculate that reticulons might also aid in NR development through positive curvature generation in the nuclear membrane.

Coatomer protein complex I and II (COPI and COPII) have well defined roles in vesicle budding from the Golgi and ER.[85,86] It is a process requiring membrane deformation in which COPI and COPII are orchestrated by small GTPases Arf1 and Sar1, respectively, and stabilize curvature.[87,88] Interestingly, it was shown that COPI may be involved in NE mitotic breakdown in *Xenopus* by formation of vesicles and tubular structures with the ER.[89] Components of COPI are recruited by nucleoporins and are critical for disassembly of the NE.[90,91] Of note, it was proposed that nucleoporins share a common ancestor with COPI, COPII and clathrin/adaptin complexes and diverged during the evolution of internal membrane systems that ultimately led to the acquisition of the nucleus.[92,93] Moreover, depletion of Rab5, a GTPase with a well established role in endocytosis,[94,95] was also shown to impair mitotic NE breakdown and membrane remodelling.[96] Post-mitotic NE reassembly is a process requiring a massive rearrangement of membrane as well. Recently, it was reported that the endosomal sorting complex required for transport (ESCRT)-III proteins, classically involved in membrane fission during formation of multivesicular endosomes, enveloped virus budding and cytokinetic abscission,[97] are also responsible for annular fusion in the reassembling NE.[98,99] These observations indicate a wider role of membrane bending and modifying proteins at the NE, potentially also involved in the NR regulation.

Cells have developed a multitude of membrane deformation mechanisms. They appear to be tightly regulated and multistage, with an array of molecular sensors of curvature and machineries allowing for controlled proliferation of membrane tubules and vesicle formation. Thus, it is very likely that selective mechanisms also exist in the process of NR induction and stabilization of intranuclear channels.

Role of proteins and lipids in NR development

Over-expression of some NE proteins has been reported to increase NR abundance. Most notably, overexpression of lamins harbouring C-terminal CaaX motif was a strong inducer of NR proliferation.[100] In agreement, progerin, a lamin A mutant expressed in Hutchinson-Gilford Progeria Syndrome which exhibits farnesylation of the cysteine in a retained CaaX motif, causes NR proliferation.[101] Inhibition of the lamin A maturation process which leads to build up of precursor prelamin A, retaining farnesylation at the cysteine, was also shown to induce NR proliferation.[17,102] The presence of the isoprenylated cysteine at the protein C-terminus most likely increases its affinity for the INM and may affect membrane curvature by exhibiting additional physical strain on the nuclear membrane.[103] Blocking lamin A farnesylation, by using farnesyl transferase inhibitors, improves the dysmorphic nuclear shape by displacing prelamin A to the nuclear interior; processing of the protein to its mature form still fails, but the product is not held at the NE by a persistent hydrophobic interaction.[103,104] Similar observations were made for progerin.[105] It is also possible that retention of farnesylation at the C-terminus of lamin A impacts its interaction with the lamin B network, which normally remains permanently farnesylated and forms a closely associated, but separate fiber meshwork.[106] Thus mixing of the 2 and potential perturbation of their normal assembly could also prove relevant in regard to formation of nuclear membrane invaginations. Interestingly, other lamin A mutants associated with Emery–Dreifuss muscular dystrophy or Dunnigan-type familial partial lipodystrophy have also been shown to increase NR prevalence.[107]

Other inducers of NR proliferation such as overexpression of INM protein LAP2β[108] or nucleolar shuttling protein NOPP140[109] have also been reported. It should be noted, however, that overexpression of any nuclear membrane protein will perturb the nuclear envelope by changing protein overload and access for interactions, which may result in a distorted nuclear rim, but not necessarily in the NR structures as defined earlier. Interestingly though, in certain cell types knock-down of SUN proteins, components of the linker of nucleoskeleton and cytoskeleton (LINC) complex,[110] can also increase abundance of type I NR,[43] presumably by decoupling the INM and ONM, permitting a morphogenic process to operate on either membrane alone.

NR development seems to depend on the enzyme choline-phosphate cytidylyltransferase α (CCTα).[46] It

is the rate limiting enzyme in phosphatidylcholine synthesis, and is crucial for membrane biosynthesis.[45] CCTα is also believed to introduce positive membrane curvature by its insertion into the INM.[111] This causes infolding of the INM, and may further support tubulation of the NR. Interestingly, some interplay between nuclear lamina and CCTα appears to occur in the process of NR formation; knocking-down of either lamin A/C or B1 expression significantly reduced NR development, even after CCTα stimulation.[112]

Despite a clear requirement for new membrane synthesis in order to form NR, as shown by experiments investigating CCTα role, our knowledge of how phospholipids are added to an expanding NE and NR is rather limited. It would be of particular interest to determine whether NR expansion is a result of the free flow of lipids between peripheral endoplasmic reticulum and NE, resulting in rearrangement of pre-existing membranes, or a focal assembly process more akin to coated pit formation exists.

Physiological regulation

The NR appears in many cell types with multiple pathways contributing to its formation. It also occurs as a physiological cellular response to external stimuli. It has long been recognized that a structurally advanced NR, referred to as the nucleolar channel system (NCS) is a hallmark of the endometrium following ovulation.[113,114] Its transient presence manifests in human endometrial cells during a 3 to 4 day period during the midluteal, receptive phase of the menstrual cycle.[115] The NCS structure forms multilamellar and tubular membrane cisternae within the nucleus that are derived from the INM.[109,114] These cisternae exhibit the presence of NPC proteins and a subset of NE-specific components.[115] The proposed significance of the NCS is that it is formed in preparation for blastocyst attachment and implantation to the endometrium. This hypothesis is supported by several reports demonstrating the absence or delayed development of NCS in cases of unexplained primary infertility.[116,117] It is further supported by observations that oral contraceptives interfere with NCS formation.[118,119] It has been demonstrated that the formation of NCS can be elicited by the action of estrogen and progesterone at the time of ovulation.[120,121] While NCS represents a unique tubular structure, its development from the INM suggests that it may originate as an NR invagination which, in response to hormones, gains further complexity, possibly representing an advanced and differentiated form of NR. Of note, human leukemic cell line HL-60, after *in vitro* induced differentiation into granulocytic form, develops highly structured and unique NE invaginations named nuclear envelope-limited chromatin sheets (ELCS).[122] ELCS, predominantly observed in haematological malignancies, is also proposed to originate as an INM invagination,[123] thus may share with NR similar mechanisms for membrane curving, at least at the initial formation stage.

Recently, is has been demonstrated that rabbit preimplantation development is accompanied by changes in NR abundance.[124] Type II NR, although bountiful in rabbit embryos in general, was consistently present at the highest number at the 4-cell stage, after which the number of NR invaginations declined. Interestingly, it correlates with a significant nuclear volume decline that begins at the 8-cell stage. Moreover, these type II NR channels stained positively for NPC and were in close contact with nucleolar precursor bodies, thus suggesting a transient role for the NR in a high protein import demand of nucleolar precursor bodies during that precise developmental stage. Cell differentiation state has also been shown to affect the abundance of NR.[70] Johnson and colleagues not only observed transient NR channels in the nuclei of embryonic cells, but also noted that differentiated cells had significantly fewer nuclear invaginations, than highly de-differentiated or cancerous cells. These observations lend some support to the idea that dynamic NR changes might play a role in the regulation of gene expression programmes.

Concluding remarks

In conclusion, the NR forms a distinct and widespread feature in nuclear organization, therefore gaining further understanding of its form and function is an important aspect of the cell biology of the nucleus. Regulation of the NR is a dynamic process and a number of cellular pathways involved in its regulation have already been identified. However, many questions still remain unanswered. It would be of particular interest to see if dedicated membrane bending machineries are also involved in NR induction/stabilization. The origin of components, such as phospholipid bilayer or nuclear lamina which are the building blocks for the

NR is also not well defined, and would certainly repay further research.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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