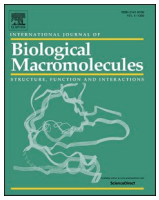
International Journal of Biological Macromolecules 313 (2025) 144104

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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



Review

Dynamic structure and function of nuclear pore protein complex: Potential roles of lipid and lamins regulated nuclear membrane curvature

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ARTICLE INFO

Keywords:
Nuclear pore complex (NPC)
Nuclear membrane curvature (NMC)
Transport function
Lipid
Lamin

ABSTRACT

The nuclear pore complex (NPC), a massive and highly sophisticated protein assembly, forms a channel embedded in the nuclear envelope (NE) of eukaryotic cells. As a critical gateway, NPC mediates the bidirectional transport of macromolecules between the cytoplasm and the nucleus. Here, we overview the structure and transport function of this protein complex, and highlight the selective barrier model of NPC transport functional modules. Nuclear membrane curvature (NMC) is a critical parameter for quantifying nuclear deformation. We discuss the mechanism by which NMC regulates dynamic NPC structure, function and distribution. Furthermore we highlight the role of two key factors, i.e. lipid composition and lamins distribution, in NMC and NPC dynamics while elucidating their regulatory mechanisms. The investigations on the dynamic structure and function of NPC modulated by NMC provide a new avenue for understanding the role of NPC in different pathological conditions. This knowledge could contribute to the development of novel therapeutic strategies.

1. Introduction

The nuclear pore complex (NPC), as one of the largest protein assemblies in eukaryotic cells, serves as the sole channel embedded in the double-layered nuclear membranes. It selectively facilitates the transport of macromolecules between the nucleus and the cytoplasm [1]. Recent development of techniques such as super-resolution microscopy and cryogenic electron microscopy (cryo-EM) has enabled the detailed visualization of NPC architecture at molecular-scale and atomic-resolution. Researches reveal that there are approximately 30 kinds of nucleoporins (Nups) that assemble the ~1000-protein complex [2]. Increasing evidences recognized that NPC is not merely a regulator of nucleocytoplasmic transport. Various Nups interact with key components within the nucleus, including chromatin and nuclear matrix. These interactions are crucial in regulating chromatin spatial organization, DNA repair, etc. [3,4]. The close interaction between NPCs and the lamina network, located beneath the inner nuclear membrane contributes to sensing mechanical stimuli and regulating cell functions [3,5].

Emerging studies have suggested that alterations in the geometrical, biochemical, and mechanical properties of the nuclear membrane significantly affect the architecture and function of NPCs [6,7]. Notably, researchers have discovered that the structure, function and distribution of NPC strongly correlates with the nuclear membrane curvature (NMC), which is an effective parameter in quantifying the degree of irregular nuclear membrane patterns [8]. For example, NPCs are stretched at larger curvature, leading to increased nuclear localization of transcription factors represented by Yes-associated protein (YAP) [9–12]. Additionally, inhomogeneous distribution of NPCs has been found at nuclear blebs and nuclear invaginations, which are characterized by higher NMC [8].

This review aims to pursues four key objectives: (1) systematically summarize existing FG-Nups models and evaluate their capacity to explain NPC transport function, especially under conformational changes; (2) discuss how NMC modulates the dynamic structure, function, and distribution of NPC; (3) highlight the roles of lipids and lamins in these processes while elucidating their regulatory mechanisms; and (4) propose that future NPC models should integrate additional factors, including NMC, lipid composition, and osmotic pressure, to improve their explanatory power and accuracy. This integrated approach aims to advance the understanding of NPC dynamics and establish foundations

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https://doi.org/10.1016/j.ijbiomac.2025.144104
Received 16 December 2024; Received in revised form 5 May 2025; Accepted 8 May 2025
Available online 9 May 2025

for future research in this field.

2. Basic structure and transport function of NPCs

NPC, a giant protein assembly, plays a key role in facilitating nucleocytoplasmic transport and gene regulation [1]. The structure of NPC is highly conserved among eukaryotic cells which has been analyzed for several decades [1]. The development of cryo-EM allowed detailed and artifact-free analysis of NPCs embedded in physiological buffer [13].

2.1. Nuclear pore structure module

NPC is composed of the multicopy of ~30 kinds of Nups forming ~1000 protein-complex. Although the exact constituent and number varies from species to species [1], the structural scaffold is considered highly conserved. From the cytoplasm to the nucleoplasm, current view identifies five major NPC structure modules: cytoplasmic filaments (CF), membrane ring (MR) connected to a pair of coaxial symmetric inner rings (IR) and outer rings (OR), as well as nuclear baskets (NB) [14,15] (Fig. 1).

For more details on the structure of NPCs, we recommend several recent comprehensive review by Kim, Seung Joong et al [14], Zhu et al [16], and Akey et al. [17].

2.2. Transport function of NPC

The main function of NPC is to facilitate the selective nucleocytoplasmic transport of various macromolecules across the nuclear envelope (NE) and can actively mediate up to 1000 translocations per second per complex [18]. The transport from nucleus to cytoplasm mainly includes mRNA and ribosomal proteins, while the transport from cytoplasm to nucleus mainly includes proteins (such as DNA polymerases and lamins), carbohydrates, signaling molecules (such as transcription factors), and lipids [19].

As a critical gateway, NPC facilitates the bidirectional transport through two main categories: passive diffusion and active transport. Small molecules with a molecular weight <40 kDa always diffuse freely through the NPCs, while macromolecules such as proteins and RNA require specific mechanisms to traverse the selective barrier of NPCs [17]. The selective barrier is primarily mediated by highly flexible, dynamically fluctuating FG-Nups [20] (rich in Phe-Gly repeats) in the central channel and the Y-complex (Nup107/160 subcomplex) in the outer ring [19].

FG-Nups are characterized by extensive intrinsically disordered regions (IDRs) containing multiple Phe-Gly (FG) repeats. In vertebrates, FG-Nups mainly include Nup54, Nup58, Nup62, Nup98, Nup42, Nup214, Nup50, Nup88, Nup153, and TPR. These Nups establish selective barriers through cohesive and non-cohesive interactions that permit the transport of cargos with macromolecule exceeding the size threshold [21].

The Y-complex consists of Elys, Nup133, Nup96, Sec13, Nup107, Nup85, Seh1, Nup160, Nup37, and Nup43 [21]. The conformation of the Y complex is highly flexible. This flexibility arises from the modular organization of multiple Nups combined with each other through short linear motifs to maintain structural plasticity. The flexibility of the Y complex enables the dynamic conformational changes to facilitate the passage of large cargos through the central transport channel [13].

In addition to the selective barrier established by FG-Nups and Y complex, the active passage of macromolecules is also precisely regulated by the concentration difference of RAN-GTP and transport factors, particularly Karyopherin-β (Kap) [22,23]. For protein-import, Kap binds to the leucine-rich nuclear localization signal (NLS) on the protein to form a transport complex that transiently disrupts the selective barrier and then enters the central pore [19]. Subsequently, the import complex binds to Nup153, progressively weakening the hydrophobic interactions

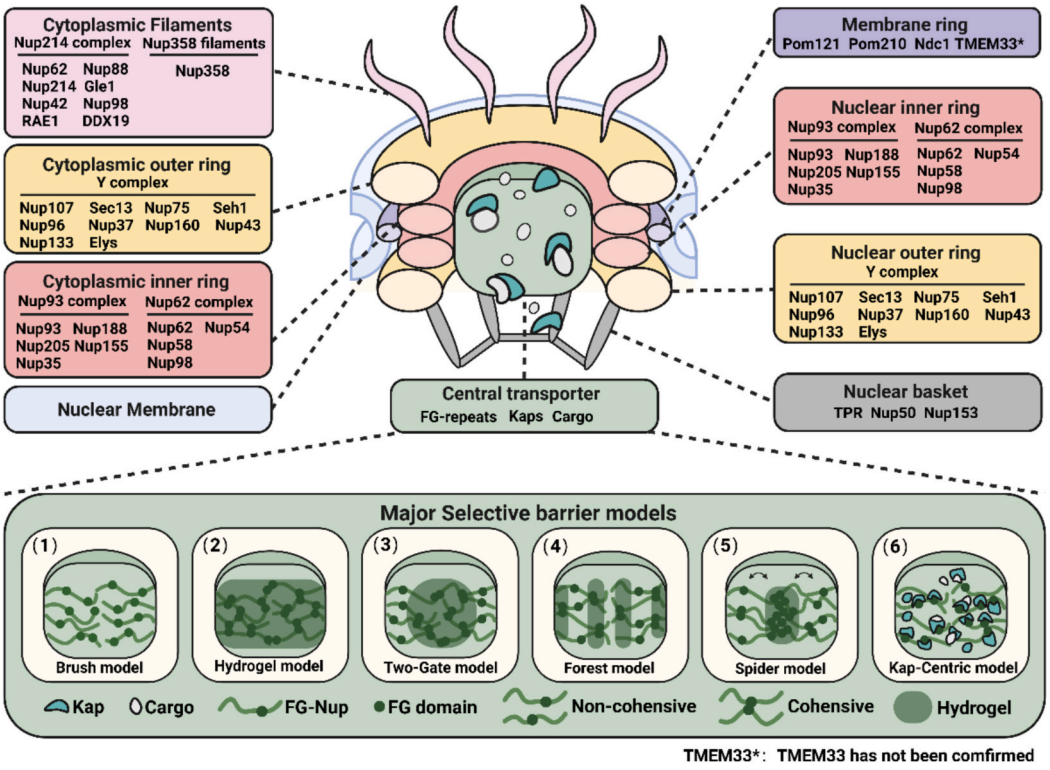

Fig. 1. The structure and function module of NPC. Structure architecture of NPC comprises five major structure modules: cytoplasmic filaments, membrane ring, two inner rings, two outer rings, as well as nuclear baskets. Six main models have been proposed to explain the selective barrier mechanism: (1) the Brush model, (2) the Hydrogel model, (3) the Two-Gate model, (4) the Forest model, (5) the Spider model, and (6) the Kap-Centric model.

Table 1
Several classical FG-Nups models and their theoretical basis, perspectives, transport mechanism and limitations.

Model	Theoretical basis	Perspectives	Transport mechanism	Limitations
Selective Phase model	The earliest assumption was based on verification of hydrophobic forces within the NPC in vivo [33], and then it was subsequently refined by analysis of liquid-liquid phase separation and cohension of FG-Nups in vitro [28,33].	FG-Nups form a dense hydrogel which the strong and saturated FG–FG association [18].	The mesh size of the hydrogel allows small molecules to diffuse freely through the FG mesh, while large cargo requires the formation of a KAP-cargo complex and relies on the interaction of Kap-FG to melt the hydrogel [18,51].	The high concentration of NTRs accumulation in NPC and the periphery preference of Kap-Cargo complex could not be explained [51]
Virtual Gating model	Based on entropy analysis of FG-Nups and nuclear transport process [34].	The barrier consists of a highly dynamic, non-cohesive polymer brush of FG-Nups with weak FG–FG associations [34].	Small molecules can pass freely through the brush. Kap-cargo complexes obtain enthalpy from hydrophobic Kap–FG associations to compensate the entropic penalty of FG-Nups [34].	It is difficult to explain the barrier breakdown caused by replacing cohesive FG-Nup98 with non-cohesive FG-Nup98 [28].
Two-Gate model	Based on Selective phase model, Virtual gating model, more accurate FG-Nup cohesion analysis in vitro [35], and single-molecule fluorescence (SMF) observation of peripheral translocation of Kaps [3] in vivo.	The cohesive hydrogel-like FG-Nups anchor at the NPC center, operate as a size-selective meshwork of filaments [35] (selective phase). The non-cohesive brush-like FG-Nups anchor at the NPC periphery act as repulsive bristles [35] (virtual gate).	The center gate is used for passive transport of small molecules, and the periphery gate is used for transport of Kap-cargo complex [35].	The model does not contain high concentrations of Kaps in NPCs [35].
Forest model	Based on Virtual gating model and superposition of single FG-Nup MD [36,42], which is consistent with the "central plug" observed in electron microscopy (EM) [14] and SMF observation of peripheral translocation of Kaps [3].	FG-Nups are classified into short 'shrubs' and tall 'trees' based on their relative location of their regions with high cohesion [36], which forms an alternating arrangement of cohesive and non-cohesive regions [18,37,41]. The concept of two nuclear transport zones is proposed [41].	Only non-cohesive regions can be used for nuclear transport [37]. Non-cohesive region is divided into central traffic zone (zone 1) and periphery annular traffic zone (zone 2) [37]. Both zone 1 and zone2 permit the diffusion of small molecular. Kaps carrying large cargoes tend to pass through Zone 1, while Kaps carrying empty or small cargoes tend to pass through Zone 2. While some Kaps carrying large cargo may be prepared to enter zone1 by combining with zone2 [37].	This model does not explain the presence of many NTR binding sites in highly cohesive FG-Nup, nor does it accept the successful construction of selective barriers with cohesive FG-Nup in vitro. Moreover, a simple single FG-Nup superposition cannot accurately explain their structural arrangement [41].
Theory with Pairing model (MTP)	Based on the whole NPC coarse-grained (CG) heteropolymer simulations [36,41]	MTP model considers the hydrophobic pairing between FG motifs and the cohesiveness of certain spacers, and depicts the mosaic distributions of the three major FG motifs (FG, GLFG and FxFG motifs) [41]. The MTP model also reveals that the whole picture of the FG-Nups is more than the sum of individual FG-Nups [38,41].	The MTP model considers the rapid and selective transport of NPC is regulated by the combined effect of entropic, electrostatic and FG steering [38].	The use of simplified coarse-grained (CG) heteropolymer simulations reduces the ultrastructure and chemical details of the NPC. In addition, Kaps are not included in the simulation [41].
Spider model	Based on the dynamic capture of NPC in vivo, using high-speed atomic force microscopy (HS-AFM) [29,32]	Nuclear transport factors act as "spidermen", and the cobwebs are mainly composed of FG-Nups [29]. FG-Nup wriggles and twists in the interaction and forms reversible "transient mesh"-knots -central plug phenotypes through phase separation [29,32].	The rapid and selective transport of NPC occurs by repelling inert material (>5 nm) or melts through the cobweb with Ran GTP gradient [29].	The current HS-AFM technology can only achieve slow motion state and cannot accurately capture the ultrafast transport of NPC [29,32].
Reduction in Dimension model	Based on virtual gating model, optical single transporter recording, and constructing nanopores with an NPC-like transport selectivity in vitro [28].	Reduction in dimension considers that when transport complexes are larger than the channel radius, parallel permeation is impossible, and single-file diffusion becomes effective [28].	The Kaps collapse the three-dimensional (3D) network of FG-Nups into a two-dimensional (2D) coat and realize the transport [41].	Cannot explain the high concentration of NTR within the NPC but the NPC barrier is always present [28].
Kap Centric model	Based on Virtual gating model, Reduction in dimension model, and multivalent binding kinetic analysis of Kap and FG-Nups in vitro [40].	Kap centric model points out that the FG-Nups are insufficient for NPC barrier and transport function, the NTRs also constitute the NPC [18]. The barrier, transport, and cargo release functions establish a continuum under a mechanism of Kap-centric control [18,40].	The Kap-centric model considers that the promiscuous binding of Kapβ1 influence nuclear transport, which explains the transport variance between the central and periphery of FG-Nups [18,40].	It contradicts that FG-Nups can perform selective barrier function even in the complete absence of Kap [28].

between FG repeats, and then enters the nucleus [24]. Similarly, during nucleus exporting, the export complex primarily binds to Nup214. Additional Nups, including Nup42, Nup50, Nup62, Nup98, Gle1 and TPR also contribute to the transporter recruitment and complex stabilization throughout the transport process [21].

Intriguingly, recent research has revealed a novel osmotic pressure-mediated transport manner within NPCs [25], describing a direct correlation between increased NPC diameter and enhanced transport

capacity. Mechanical forces exerted on the NE have been shown to increase NPC diameter, thereby reducing the mechanical restriction primarily caused by FG-Nups and facilitating the transport of mechanosensitive cargo [9,26,27]. Utilizing the Hagen-Poiseuille model and the porous flow model, Patrick et al. have quantitatively described the osmotic imbalance-driven fluid flow across an individual NPC in *D. discoideum*. NPC diameter dilates by approximately 14 % under hypoosmotic condition (hypo-OS) compared to hyperosmotic condition (hyper-OS). In accordance with this structural change, the fluid flow across the NPC central channel under hypo-OS is approximately three-fold greater than that under the hyper-OS [25].

The transport mechanisms, particularly the specific organization and interaction dynamics of FG-Nups that constitute the selective barrier, remain under debate. Several theoretical models have been proposed to explain these complex processes.

2.3. The selective barrier model

As previously described, FG-Nups contain IDRs with multiple Phe-Gly (FG) repeats [21]. However, there are scientific debates about the interaction mechanisms and distribution patterns of these IDRs. In vitro and in vivo studies have demonstrated that FG-Nups can form biomolecular condensates through liquid-liquid phase separation (LLPS) [2,28]. The IDRs of FG-Nups drive condensate formation, which minimize the solvent accessibility of hydrophobic residues [28]. However, the structural complexity of these condensates poses the challenges for studying FG-Nups behavior in vivo. To address the complex FG-Nups dynamics and their roles in selective nucleocytoplasmic transport, several mechanistic models have been proposed (Table 1). High-speed atomic force microscopy (HS-AFM) observations have demonstrated that the central channel of NPC exhibits a moist cobweb-like architecture [29]. Furthermore, imaging data has provided compelling evidences that FG-Nups exist in an LLPS state within NPC, reflecting their dynamic and fluid-like properties in regulating nucleocytoplasmic transport [30,31].

Initially, Selective Phase model [33] and Virtual Gating model [34] focus on the cohesive properties of FG-Nups (Table 1, Fig. 1). Subsequently, Two-Gate model [35] integrates these two models and provide the enhanced insights into the distinction between passive diffusion and KAP-mediated transport (Table 1, Fig. 1). More recently, Forest model [36,37] (Table 1, Fig. 1) and Molecular Theory with Pairing (MTP) model [38] (Table 1) are developed through molecular dynamics simulation. Spider model is proposed based on HS-AFM [29,32]. While Reduction in Dimension model [36] (Table 1) and the Kap-Centric model [18,39] (Table 1, Fig. 1) emphasize on the role of Kap in FG-Nup organization and function. Collectively, these models provide explanation, at least partial, for the interactions between FG-Nups, and suggest the mechanisms of nuclear transport.

However, the structural and functional dynamics of NPCs under physiological conditions are considerably more complex. NPC architecture exhibits pronounced conformational flexibility, with the central channel diameter dynamically adjusting in response to different signals [7]. Studies have identified two distinct NPC states: a constricted form and a dilated form [7]. These structural states directly regulate nucleocytoplasmic transport kinetics of NPC [7], which will be discussed in detail in Section 3.4.

As summarized in Table1, current FG-Nup models possess inherent strengths and limitations in explaining the dynamic conformation and function of NPC. For example, although Two-Gate model, Forest model and MTP model provide explanations for the transport acceleration of material including YAP through the expansion of the central channel network, they fall short in addressing the influence of Kap on the structure and function of NPC [41]. The Spider model provides a particularly valuable framework by characterizing FG-Nups as a structurally dynamic yet interconnected meshwork that resembles a cobweb-like architecture, whose thickness variations directly correlate with NPC transitions between contracted and dilated states. However, the precise mechanisms by which this network architecture modulates nuclear transport efficiency, and how Kaps induce structural remodeling of the FG-Nup web, remain critical questions requiring further investigation [29,32]. Kap-Centric Model advances our understanding by emphasizing Kaps' dual roles in facilitating diffusion through promiscuous binding while maintaining transport selectivity for Kap-cargo complexes. However, the mechanism of selective barrier formation and the change of Kaps under NPC stretching and contraction conditions remain unclear [40]. These limitations nevertheless highlight critical directions for developing more comprehensive NPC models in the future.

In recent years, the application of HS-AFM has made it possible to resolve the dynamic motion of individual intrinsically disordered protein molecules [20,42]. More revolutionary technological development will promote the full disclosure of NPC material transport mechanism.

Beyond the well-characterized function in nucleocytoplasmic transport, NPCs also interact with chromatin and participate in gene regulation [43,44]. These functions can be categorized into the following functional modules: (1) gene expression regulation module, (2) chromosome organization module, (3) DNA repair module. The distinct functional modules represent active areas of research where significant consensus has yet to be established. For a comprehensive discussion of these chromatin-related NPC functions, we recommend referring to the recent review by Capelson et al. [43].

3. Nucleocytoplasmic transport function and nuclear membrane curvature (NMC)

Recent studies have demonstrated that the nucleus is a dynamical organelle. It is a paramount element in mechanotransduction and exhibits intrinsic mechanical properties characterized by viscosity and elasticity [5,8]. By response to both internal and external mechanical influences, such as the extracellular stress transmitted through the cytoskeleton or the stress from the chromatin cohesion, the nucleus can translate the mechanical stimuli into biochemical signals and regulate cell functions [45,46]. Growing evidences indicate that the nucleus plays a vital role in how cells perceive mechanical stimuli and respond accordingly by dynamically altering its structure and morphology [45,46]. It has been demonstrated that nuclear deformation occurs in various processes, including cardiac and skeletal muscle contraction [47,48], and cellular adhesion to flat and rigid substrates [45,49]. Many diseases are characterized by the irregular morphology of nucleus, especially many cancer types and progeria syndrome [8]. However, the mechanism by which the nucleus converts mechanical stimuli into biochemical signals remains unclear. In recent years, the concept of NMC has emerged as a novel avenue for investigating this issue. Several nuclear deformations, including nuclear invagination and micronuclei, are typified by an increase in the absolute value of NMC. Concurrently, researches have demonstrated that NMC is a reliable indicator of nuclear membrane stress [50], nuclear membrane lipid composition [51,52], and the lamina network beneath nuclear membrane [53]. It is notable that the structure of NPC is closely related to all these factors above. Furthermore, the inhomogeneous distribution of NPCs along the nuclear membrane with elevated NMC has also been observed [52]. The NMC-related regulatory mechanism of NPC is unclear, uncovering the regulatory mechanism may provide new ideas for understanding the role of nuclear deformation in converting mechanical stimuli into biochemical signals.

3.1. Nuclear deformation and nuclear membrane curvature

Depending on the degree of deformation, nuclear deformation can be classified into global shape changes and local abnormalities in nuclear membrane shape. Global nuclear shape changes typically occur in the context of dramatic changes in internal and external mechanical environment, including processes such as cell migration, cell adhering and

cell differentiation [5]. Furthermore, when cells are spread on a flat and rigid substrate, the compressive force exerted by actin fibers on the nucleus can flatten the nucleus [45,54,55]. These all lead to a significant deformation of the nuclei. In addition to the aforementioned overall shape changes, nuclear deformation also manifests as local nuclear membrane abnormalities including nuclear blebs, nuclear membrane invaginations, and micronuclei [8]. It is noteworthy that nuclear membrane abnormalities occur infrequently in normal cells, they are frequently observed in abnormal cells in diseases states, especially in laminopathy [56–58]. Many types of cancer were also characterized by nuclear deformation, and morphometric analysis of the nuclear shape in cancer biopsies is widely used to assess both cancer stage and prognosis [8,50,59].

In recent years, researchers have adopted a variety of parameters and metrics to quantitatively characterize nuclear deformation and NE abnormalities. NE shape factors include nuclear volume, nuclear roundness, and eccentricity are commonly used [8]. However, these parameters are more suitable for characterizing abnormalities in the overall nuclear shape. They lack the precision required to describe and differentiate focal NE morphological abnormalities, such as nuclear blebs and nuclear invaginations. A typical example is that nuclear structures with disparate shapes may exhibit a similar degree of roundness [8]. Emerging studies have employed curvature to accurately and quantitatively describe NE deformation [60,61].

The curvature of a circle is inversely proportional to its radius, hence the curvature is measured in meters^{-1}. In geometry, curvature can be defined as the degree by which a curve deviates from a straight line, or the amount by which a surface deviates from a plane [62] (Fig. 2). Importantly, the concept of curvature is applicable to three-dimensional shapes. The two principal curvatures, denoted by the symbol κ, define the curvature of a surface. If the maximum and minimum radii of a shape are projected onto a plane, the principal curvature is the reciprocal of the radius of the resulting circle [61]. Two prevalent quantifications facilitate the visualization of membrane curvature: Gaussian curvature (K), defined as the product of the two principal curvatures, and mean curvature (H), which represents their average. Gaussian curvature elucidates the extent to which a surface approximates a sphere (positive values) or a saddle shape (negative values) [50,62] (Fig. 2).

The concept of curvature has also been introduced into biomembrane. Membrane curvature refers to the bending or deformation of the lipid bilayer, resulting in a curved shape [63,64]. The membrane curvature arises through multiple interdependent mechanisms, including: (1) intrinsic properties of lipids, such as those with conical shapes (e.g., phosphatidylethanolamine), promote curvature due to their molecular geometry [6]; (2) curvature-inducing protein interactions, such as membrane-associated proteins containing BAR, induce or stabilize curvature by binding to and deforming the membrane [65]; (3) asymmetric transbilayer lipid distribution [6]; and (4) active cellular processes including endocytosis and organelle morphogenesis [63,64]. The curvature variations are observed ubiquitously within the cell and across various scales, in structures such as endosomes (positive curvature) and the cytokinetic furrow (negative curvature) [50]. Due to its accuracy and applicability to both two-dimensional and three-dimensional, curvature is an effective parameter to quantify the degree of membrane deformation especially irregular nuclear membrane patterns including micronuclei, invaginations and blebs.

3.2. *Curvature is an important biochemical signal*

Membrane curvature, particularly plasma membrane curvature, is no longer viewed merely as a geometric feature. Emerging evidences recognize membrane curvature as biophysical regulator that orchestrates diverse cellular processes [63,64]. Of note, an array of proteins, particularly those with a BAR domain, has been observed to induce, sense, or maintain the specific curvature of the membrane [65,66]. Recent studies have shown that membranes with specific curvatures can promote the recruitment of specific proteins in vivo [67] and in vitro [68]. For example, localization of MreB polymers, actin-like proteins in bacteria, is enriched near zero Gaussian curvature [67]. Jensen et al. found that membrane with high curvature facilitate the enrichment of some autophagy-related proteins [68]. These potential mechanisms illustrate the crucial role of membrane curvature in regulating the structure and oligomerization of proteins [63,64]. Through these underlying mechanisms, membrane curvature may able to influence numerous cellular processes such as cell migration [69], and cell junction formation [70].

Many subcellular compartments also have the membrane curvature features. Nuclear membrane dysmorphology, notably characterized by

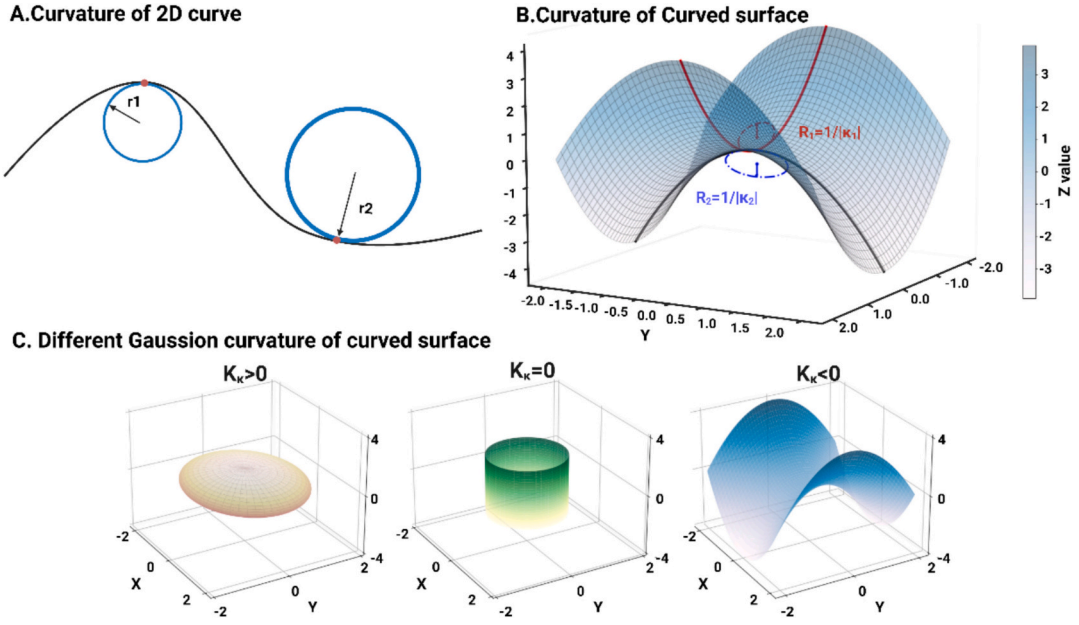

Fig. 2. Geometric representation of curvature principle. (A) 2D curve curvature analysis. (B) 3D surface curvature analysis, where κ_1 and κ_2 represent the maximum and minimum curvatures, respectively, at the saddle point of the surface. (C) Visualization of surfaces with distinct Gaussian curvatures values: positive (left), zero (middle), and negative (right).

curvature abnormalities, have emerged as a significant cellular feature in a range of diseases, including cancer [46,59]. Nevertheless, the mechanisms of how NMC alters downstream signaling pathways remain to be elucidated. The field of curvature-related nuclear mechano-transduction is still in its infancy and is characterized by a lack of consensus on several fundamental issues. For example, whether proteins, such as NPC, linker of nucleoskeleton and cytoskeleton LINC) complex, and Lamins, distributed on and near the nuclear membrane are capable of sensing and responding to changes in NMC and whether membrane curvature-dependent signaling pathways are ubiquitous across the entire bio-membrane system. Further research is needed to address these questions.

3.3. Curvature is an important biomechanical parameter

Membrane curvature also provides insight into the underlying functions of membrane stress and membrane tension [71–73].

1. Membrane stress, defined as the force per unit area within the membrane, comprises two components: (1) In-Plane Stresses are defined as the distribution of forces within the plane of the membrane, incorporating both normal (tensile/compressive) and shear components. For example, shear stresses are defined as forces that are perpendicular to the direction of the membrane's deformation [74]. These forces are exerted on the membrane when cells are subjected to shear forces. (2) Bending Stresses arises from curvature-induced membrane deformation and is quantitatively characterized by the bending modulus, which resists such deformations [74].
2. Membrane tension represents a special case of stress. In circumstances where the stress within the membrane surface is isotropic and devoid of shear components, the stress tensor reduces to membrane tension. In the absence of external forces, the spontaneous curvature of the membrane determines the membrane tension, which in turn determines the shape of the membrane [50].

The composition and distribution of membrane lipids dictates their mechanical properties, including the bending modulus κ_{bend}. Compositionally distinct lipid bilayers achieve different energy-minimized configurations through their bending elasticity properties. Scientists describe this characteristic using a physical quantity called intrinsic spontaneous curvature (m), which determines how curved the membrane will become when it reaches its lowest energy state. And the spontaneous tension is equal to $2\kappa_{bend}m^2$, which represents the basic tension scale of curvature elasticity [72]. The bending stress is closely related to the curvature, which can be calculated using Helfrich model, also called a spontaneous curvature model.

$$E_{be} = \int dA 2\kappa_{bend}(M-m)^2$$

The A represents the surface area of a specific membrane and the M refers to the mean curvature [75].

Membrane curvature and stress exhibit significant coupling. High curvature region (e.g. membrane protrusions or tubular structures) corresponds to significant bending stresses. Whereas, anisotropic in-plane stresses, especially shear stresses, drive non-uniform membrane bending resulting in complex curvature distributions, such as the spiral deformation of membranes [74]. Recent studies reveal that local membrane stress can be regulated by multiple processes including protein binding, which triggers downstream processes in various ways. For example, during endocytosis, Clathrin/BAR proteins binding to the membrane surface produces localized bending moments, creating high curvature and elevated in-plane stress [76,77], thereby driving membrane deformation and vesicle formation. Notably, the fundamental mechanisms underlying the coupling between membrane curvature and stress still need further investigation. Understanding the interplay and the molecular mechanism are crucial for analyzing membrane mechanics in NPC dynamics.

Of note, a paucity of studies examines the mechanical effects of curvature at the cellular level. It has been established that nuclear components play a pivotal role in mechano-transduction within the cell. A multitude of nuclear components contribute to mechano-transmission, with the majority of these distributed on or near the nuclear membrane. These components include NPCs, LINC, Lamins and the perinuclear cell skeletons [9,78]. The mechanical forces that affect the nucleus are primarily transmitted to and redistributed by the NE and nuclear lamina beneath the envelope, thereby altering the nuclear membrane stress and curvature [71]. Recently, several studies have revealed that NPCs and lamins can respond to curvature changes caused by external forces [3,53]. However, the mechanobiological mechanism remains to be elucidated.

3.4. NMC affects the structure and function of individual NPC

NPCs are the sole channels anchored across the nuclear membrane that regulate the translocation of biomolecules between nucleoplasm and cytoplasm. Many transcription factors, including NF-κB and STAT, depend on nuclear import via NPCs for their functions. Researches have demonstrated that NPC transport activity significantly influences the nuclear translocation of these transcription factors, thereby altering cellular functions [79–82]. A large number of studies have shown that the number of NPCs is closely related to nucleocytoplasmic transport capacity, and the variations of NPC abundance can significantly impact signaling pathways associated with nuclear entry of transcription factors [79,83,84]. For example, during the development of mouse cardiomyocytes, a reduction in NPC number leads to a significant decrease in nuclear translocation of NF-κB and ERK. This decline in NPC abundance also alleviates adverse myocardial remodeling by downregulating the related pathways. In addition to NPC quantity, structure changes of NPCs, especially in their diameter, have also shown to markedly affect nuclear transport function.

In recent years, NPCs have been identified as mechanosensitive channels with highly dynamic structures capable of rapid response to changes in the mechanical microenvironment around the cell [3,7,9]. Furthermore, some emerging studies have demonstrated that local curvature abnormalities of nuclear membrane act as key mechanical signals, modulating NPC function and, in turn, altering the gene expression profile of the cell [9,11,60].

NPC architecture is highly dynamic in conformation, and the diameter of NPC changes in response to different signals [7]. It has been reported that NPC exhibits two distinct states: a constricted form and a dilated form [7]. These states are characterized by the different conformation of Nups within the NPC channel, especially two FG-Nups, i.e. Nup54 and Nup58 [7,85]. The binding of a transport factor with FG-repeats exerts an allosteric effect on the conformational state of NPC, thereby converting the constricted form with a diameter of ~20 nm into the dilated form with a diameter of ~40 nm [85]. The diameter of the NPC has a significant impact on the activity of the transport process. Under energy depletion, the reduction of NPC central channel diameter is concomitant with a reduction of both passive diffusion and active nuclear transport and increase in local FG-domain concentration [7]. NPCs are constantly subject to mechanical stress exerted on the nuclear membrane. Due to its dynamic architecture, NPCs possess high mechanical flexibility.

Under osmotic stress condition, the NE and its embedded NPCs undergo pronounced structural remodeling, characterized by the quantifiable alterations in both nuclear membrane stress and NPC lumen diameter. A study in *S. pombe* have revealed the ruffling of NE and the constriction of NPCs under hyper-OS condition [7]. However, the cell wall of *S. pombe* limits observation under hypo-OS. A recent research using *D. discoideum* revealed a consistent result with NE stretching and NPC diameter elevation under hypo-OS condition.

Furthermore, different components of NPCs exhibit different

responses to the stress exerted on the NE in distinct ways. The constriction and dilation of NPCs are predominantly facilitated by the IR spokes and LR, while the CR and NR scaffolds maintain structural stability against stress-induced diameter changes [25]. These studies collectively support a model in which NE stress induced by external forces regulates NPC architecture, leading to reversible NPC constriction and dilation.

As detailed in Section 3.3, membrane curvature serves as an indicator of membrane stress. Generally, higher curvature represents larger membrane tension. This relationship has been verified at the nuclear membrane. Elevated nuclear curvature is frequently caused by nuclear deformation, which induces NPC stretching and the consequent expansion of NPC diameter [45]. Therefore, a consistent relationship emerges between high curvature and increased NPC transport capacity.

A series of studies has indicated that nuclear curvature can alter the profile of gene expression by regulating the nuclear-cytoplasmic transport of transcription factors via NPC [11,12,61,86]. Stretched NPCs with decreased mechanical restriction facilitate the cytoplasm-nuclear transport of multiple transcription factors and improve their cytoplasm-nuclear localization [9,27]. Recently, Andreu et al. established a nuclear transport model regulated by mechanical forces [87]. For cargos with small molecular weight or weak NLS signal, passive diffusion dominates, whereas large cargo or strong NLS signal rely on active transport. Both mechanisms are independent of mechanical forces exerted on the nucleus. However, cargos with intermediate molecular weight and NLS signal exhibits significant mechano-sensitivity in nuclear transport [87]. Notably, several key transcription factors, including YAP, NFκB and Twist, display this mechanical sensitivity [87–89]. Among these transcription factors, YAP had been the most extensively studied regarding its mechano-dependent nuclear import and its relationship with nuclear deformation.

YAP is a transcriptional cofactor that transfers between the cytoplasm and the nucleus by Hippo signaling pathway induced phosphorylation/dephosphorylation [90]. After dephosphorylation, YAP transports to the nucleus and activates TEAD transcription factors, thereby modulating the expression of genes associated with cell differentiation, proliferation and the suppression of apoptosis [91]. In addition to the modulation via Hippo signaling pathway, the cytoplasmic-nuclear transport of YAP is also associated with mechanical signals [11,61,89]. The molecular weight of YAP is 65 KDa, which is close to the transport channel cut-off value of undeformed NPC [9]. Therefore, a minor expansion of the pore may result in a transition of YAP from active to passive transport [10]. This renders the transport of YAP remarkably sensitive to mechanical stress exerted to the nuclear membrane and particularly susceptible to NE deformation. Extensive researches have shown that YAP responds to substrate stiffness and extracellular matrix (ECM) rigidity [11,90]. Intriguingly, recent studies suggest that nuclear curvature may play an essential role in the regulation of YAP through transport via NPC [11,61] (Fig. 3). Ghagre et al. discovered that the fate of YAP-mediated mesenchymal stem cells differentiation has been demonstrated to be primarily determined by nuclear curvature [61]. They identified a correlation between low nuclear curvature and adipocyte differentiation, while high nuclear curvature with increased nuclear localization of YAP was associated with osteocyte differentiation [61]. Dilation of NPCs on the nuclear membrane with increased NMC which facilitate YAP transport may play a crucial role in this process.

YAP also plays a major role in the progression of tumor induced by the tumor mechanical microenvironment [91]. Mechanical signals can be transmitted from the ECM to the cell nucleus through the physical connection among integrin, cytoskeletal elements, LINC and the nuclear lamina [92]. Significant evidences have suggested that changes in stiffness of the substrate induce nuclear deformation, which manifests as the dramatical change of nuclear curvature. Emon et al. investigated the impact of substrate stiffness, perinuclear cell force, and nuclear deformation on the localization of YAP in human colon cancer-associated fibroblasts cultured on two-dimensional (2D), 2.5D, and three-dimensional (3D) substrates [60]. Unexpectedly, their findings revealed that the nuclear translocation of YAP is contingent upon the degree of nuclear deformation, independent of dimensionality, stiffness, and total force. Among the various parameters that describe the degree of deformation, the curvature of the NE is found to correlate most strongly with the translocation of YAP, and significantly affect tumor growth [60].

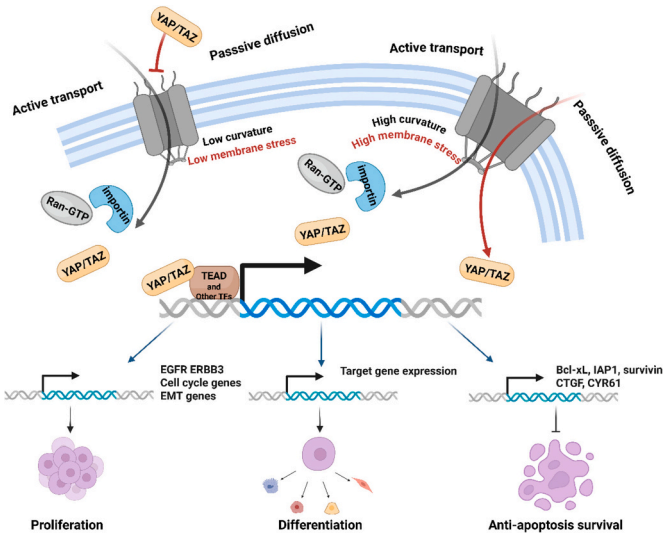

Fig. 3. Correlation between nuclear membrane curvature and YAP transport. Elevated nuclear membrane stress at high curvature facilitates passive transport of YAP into the nucleus, thus promoting cellular proliferation, differentiation, and anti-apoptosis survival.

In addition, the nuclear translocation of many other transcription factors has also been shown to exhibit mechano-sensitivity. Increased matrix stiffness in the tumor microenvironment upregulates TWIST1 nuclear translocation, which directly activates epithelial-mesenchymal transition (EMT) and promotes tumor invasion and metastasis [89]. Jacchetti et al. demonstrated that altering nuclear morphology by culturing mesenchymal stem cells on a microfabricated 3D substrate significantly affect the intranuclear transport of the transcription factor MyoD, which is correlated with the degree of nuclear deformation [93,94]. Furthermore, DN-KASH has been demonstrated to disrupt the LINC complex, thereby preventing mechanical force transmission to the nucleus. Overexpressing DN-KASH in mouse embryonic fibroblasts abolishes the mechano-sensitivity of nuclear translocation for several transcription factors, including SMAD3, Snail and TWIST1 [89].

These studies highlight the pivotal role of nuclear mechano-transduction and deformability in modulating cellular mechano-responsive signaling [11,61]. Notably, a novel role of NPCs in mechano-transduction has generated intense curiosity. Mechano-sensitive molecules such as Lamins, LINC complex, and the nuclear membrane's lipid bilayer, are widely distributed on the nuclear envelope. These components transmit external forces to NPCs, resulting in dynamic structural changes. Currently, the mechanisms underlying mechanical induction of NPC stretch activation and its physiological implications remain poorly understood. Force-induced changes in NMC may represent a key event modulating NPC structure.

Analysis of NPC diameter changes under physiological conditions remains a technically challenging endeavor. For the analysis of NPC structure, the utilization of cryo-EM is commonly employed. This requires the isolation of the nucleus and can only examine the conformational changes of a single NPC [7,85]. This approach restricts the investigation of conformational changes in NPCs under physiological conditions in response to mechanical stimuli, such as nuclear membrane stress under high curvature. In recent years, several successful attempts have been made in a variety of studies through the combination of super-

resolution microscopy imaging and mathematics modeling. Super-resolution fluorescence microscopy, such as Structured Illumination Microscopy (SIM), Stochastic Optical Reconstruction Microscopy (STORM) and Single Molecule Localization Super-Resolution Microscopy (SMLM) have a resolution of 100 nm to 10 nm. Such super-resolution microscopy makes it ideal for observing NPCs with a diameter of approximately 130 nm in living cells [95]. Based on super-resolution microscopy imaging, emerging studies have described the changes in morphology and mechanical properties of various parts of the NE with a combination of mechanical and numerical modeling [9]. Moreover, the development of appropriate models for quantifying nuclear deformation is also essential for a comprehensive analysis of the mechanical signal transduction associated with nuclear deformation. Continuous innovation in research methods and techniques are required to further understanding the morphology-function of NPC.

4. Curvature preference of the nuclear membrane for NPC dynamic distribution

As described above, the curvature of the NE can affect the structure and function of a single NPC. Recent studies have paid attentions to the relationship between the curvature of nuclear membrane and the overall distribution pattern of NPCs. Studies have shown that when cells are stimulated by external stimuli, the nuclear membrane will appear obvious morphological abnormalities, characterized by changes in curvature [8]. For example, increasing nuclear membrane stiffness reduces local curvature [10], while mechanical interventions such as microcolumns and micropipette suction induce local hypercurvature [64]. It was previously assumed that the distribution of NPCs on the NE is random [96], while the distribution of NPCs has been proved to change dynamically after exposed to external or internal stimuli by recently researches, and the curvature is a key modulator [52,97]. However, the relationship between NPC distribution and NMC is complex and the underlying mechanism is still unclear. Here, we introduce the relationship between NMC and NPC distribution from two key factors that change NMC, i.e. lipid composition and lamin distribution, and propose our hypothesis.

4.1. Lipids participate in the curvature preference of NPC distribution

The important structure of the cellular biomembrane is a variety of lipid molecules, including (glycerol) phospholipids, sphingolipids, and sterols [6]. The morphology and fluidity of the biomembrane are mainly determined by two features of lipid: lipid geometry especially the relative cross-sectional area of the hydrophilic head group, and lipid composition including the degree of unsaturation in the hydrophobic fatty acyl chain [6]. For instance, cylindrical lipids (e.g., phosphatidylinositol and lysophosphatidylcholine), inverted cone lipids (phosphatidylethanolamine, diglycerides) spontaneously form single-molecule membranes with negative, zero, and positive curvatures. Additionally, double bonds in lipid acyl chains cause unsaturated lipids to occupy more space, thus changing membrane curvature [6]. Therefore, the lipid composition and saturation of biomembrane play critical roles in its morphology.

The nuclear membrane consists of two concentric lipid bilayers, i.e. the inner and outer nuclear membrane, which are structurally connected with the endoplasmic reticulum (ER). The mammalian nuclear membranes exhibit distinct lipid composition compared to the plasma membrane, characterized by higher levels of phosphatidylcholine but lower levels of lysophosphatidyl-choline, sphingomyelin, and cholesterol [98]. Of note, phosphatidylcholines in both animal and yeast species typically possess unsaturated fatty acid side chains, while sphingomyelin and lysophosphatidyl-choline commonly contain saturated fatty acid chains [98]. This distinct difference enhances the flexibility of the nuclear membrane. The curvature of the nuclear membrane is also regulated by the asymmetric distribution of lipids. The asymmetric distribution of lipids between bilayers results in distinct lipid composition in the bilayer, which changes the curvature of the nuclear membrane. These factors complicate the influence of lipid composition on the process of NPC formation more complicated [6]. The dynamics of the lipid composition of the nuclear membranes is also regulated by lipid metabolism. For example, the inner nuclear membrane itself has lipid metabolic activity and produce diacylglycerol which is prone to form curved membrane and produces lipid droplets (LDs) in the nucleus [75]. A variety of lipid metabolism enzymes (such as phospholipase C, Sphingomyelinases, etc.) are also involved in regulating the lipid composition of the nuclear membrane [6,46].

In addition to the three transmembrane Nups (GP210, POM121, and NDC1) that insert directly into the lipid bilayer, many Nups including Nup133, Nup120, Nup153, Nup59, Nup60, and Nup160, have amphipathic lipid packing sensor (ALPS) motif capable of binding to one leaflet of the lipid bilayer [98]. Therefore, lipids are crucial for the stability of NPCs, but the curvature-regulating role of lipids in NPC formation and distribution is often overlooked.

4.1.1. Nups bind to lipids to recognize and stabilize high curvature

The assembly of NPC occurs through two distinct pathways that are tightly coordinated with the cell cycle. During mitosis, the NE is broken down, and new NPCs are assembled on the reformed nuclear membrane - a process termed postmitotic assembly [99]. In contrast, during interphase, the nucleus grows and expands, and new NPCs are assembled by de novo formation - a process termed interphase NPC assembly [99].

During interphase assembly, the nascent NPC inserts into the cavity formed by the fusion of the inner and outer nuclear membranes, which require a locally reshaped of inner nuclear membranes into a highly curved structure outwards the outer nuclear membranes. This requires a negative curvature at most positions in the membrane, while an extremely positive curvature strain needs to be imposed at the neck region [100]. Interactions between Nups and lipids through ALPS motif are thought to contribute to the formation of positive curvature in the neck region [6] (Fig. 4A–D).

Nups with ALPS motif can recognize the high-curvature portion at nuclear membranes. In vitro experiments by Doucet et al. demonstrated that Nup133 containing multiple histidine tags exhibit specific binding to liposomes with a radius of 30 nm, while showing no binding affinity toward 400 nm liposomes, suggesting a preferential association of Nup133 with high-curvature biomembrane region [101]. The fusion of ALPS motif with the EGFP induces localization of fusion protein to the high curvature region of the lipid bilayer. In yeast, podocytes, embryonic stem cells, the ALPS motif mediates the proper localization of Nup107, which are critical for interphase NPC assembly [102–104].

In addition to recognition, Nups with ALPS motif also induce high curvature. For example, Nup60 (in yeast) can be inserted into one leaflet of the lipid bilayer via ALPS to form a high curvature at a specific location, setting a stage for the subsequent fusion of the inner and outer nuclear membranes and the identification and localization of other Nups [105]. Therefore, Nups with ALPS can recognize and induce high curvature, playing a significant role in the fusion of the inner and outer membrane.

4.1.2. Lipid saturation affects NPC localization and distribution

As mentioned above, the membrane remodeling process in NPC formation is crucial to the correct assembly of the NPC. Nups can change the morphology of the membrane, but the deformability of the lipid layer is not the same under different saturation, which also implies the role of lipid saturation in the assembly and localization preference of NPC.

Since the nuclear membrane is a complex bilayer structure, it is challenging to detect the saturation degree of the nuclear membrane lipid at the living cell level. Romanauska team has developed a lipid saturation (LipSat) sensor, which makes it possible to quantify the

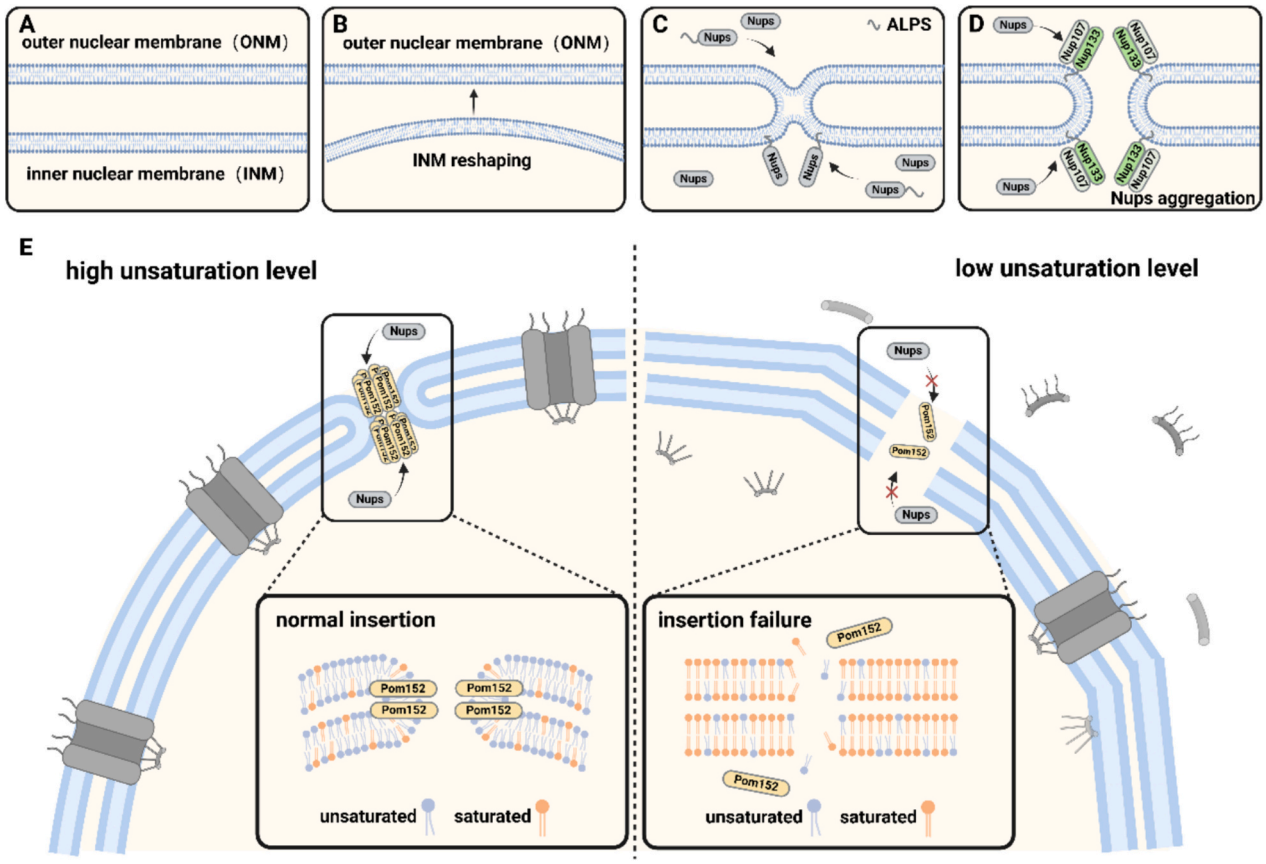

Fig. 4. The role of lipids in dynamic assembly and distribution of NPCs. (A–D) During interphase assembly, Nups with ALPS recognizes and stabilizes high curvature during fusion of inner and outer nuclear membranes. (E) The decrease of lipid unsaturation induces the nuclear membrane rigidification and the curvature attenuation. The reduced elasticity of the nuclear membrane at the polygonal region impairs nuclear membrane bending capacity and Pom152 insertion, which ultimately leads to reduced distribution of NPCs at the polygon.

saturation of nuclear membrane lipids indirectly [51]. Based on this Lipsat sensor, recent studies have shown that changes in lipid saturation significantly affect the morphology and stress of nuclear membranes, as well as the localization and assembly of NPC [51]. In yeast, overexpression of Sct1 (sequesters C16:0-CoA into lipids thereby preventing desaturation by Ole1) reduces the degree of unsaturated lipids in the nuclear membrane, resulting in the ratio of C16:1 acyl chain to C16:0 acyl chain decreased to about a quarter of the control group. That significantly decreases the elasticity of the nuclear membrane and forms a distinct polygon or semicircular structure with the significantly reduced curvature of local nuclear membranes [51,52]. The strongly association between curvature and the degree of saturation of the nuclear membrane suggests that low curvature potentially indicates high saturation, and high curvature indicates low saturation.

Abnormal accumulation of NPC has been observed at the high curvature site, and the number of NPC decreases at the low curvature site. Similarly, using the recombination label conversion technique, the newly assembled NPCs are concentrated in parts with high curvature [51,52]. Although, the universal mechanism underlying this phenomenon has not been uncovered, the interaction of specific Nups with the lipid bilayer which subsequently affect the assembly of NPC may provide an explanation. Studies have shown that increased lipid saturation causes the nuclear membrane to become stiffer and harder to bend, thereby affecting the fusion of the inner and outer nuclear membranes. This further leads to the abnormal insertion of integral protein Pom152 (in yeast) and its ortholog GP210 (in vertebrates) at the fusion of the inner and outer nuclear membranes, thereby affecting the assembly of NPCs [52,106] (Fig. 4E).

4.1.3. NMC and NPC distribution pattern serves as an indicator of composition and saturation of lipid

The local NMC (such as the fusion of the inner and outer nuclear membranes) is affected by the lipid composition and saturation of the nuclear membrane. Conversely, the overall morphology of the nuclear membrane characterized by overall NMC (here refers to the macroscopic nuclear curvature rather than the small abnormal curvature at the fusion of the inner and outer nuclear membranes) can also reflect the lipid composition somewhere in the nuclear membrane. Hence, NMC may serve as a potential indicator for local lipid composition, and becomes a key bridge for lipids to regulate the distribution of NPC.

In summary, the lipid composition and saturation of nuclear membrane play important roles in the assembly and distribution of NPCs by influencing the localization and stability of Nups with ALPS or transmembrane motif. And the overall curvature of the nuclear membrane may be used as a morphological feature of the lipid status of the nuclear membrane and the localization of NPC. Therefore, decoding the relationship between lipid metabolism, curvature regulation, and NPC distribution is of great significance.

4.2. Lamina is involved in the curvature preference in NPC distribution

In addition to the lipids of the nuclear membrane, the nuclear lamina may also be involved in NPC responses to NMC.

The nuclear lamina (mainly consists of Lamin) is an orthogonal fibrous network of nuclear lamina proteins linked to the inner nuclear membrane via lamina protein receptors [3,92]. Lamins are classified as type V intermediate filament, it is composed of two distinct types of proteins, designated as Type A and Type B. Type B fibrous layer proteins

encompass the lamin B1 and lamin B2 proteins, which are encoded by the genes *LMNB1* and *LMNB2*, respectively. In contrast, Type A proteins are encoded by the gene *LMNA*, which undergoes a selective splicing process to yield the lamin A and lamin C proteins [107]. It is noteworthy that these two types of lamins form separate meshwork. The lamin B1 and B2 meshwork is situated in closer proximity to the inner nuclear membrane, while the highest concentration of lamin A/C is found in a position further toward the nucleoplasm [108]. Together, they form an interacting meshwork with a highly branched architecture, which participates in the processes of support, assembly and de-assembly of the nuclear membrane [108,109].

4.2.1. NMC mediates the lamin network

The lamins network is a dynamic structure with high mechanical responsiveness. Lamins play a crucial role in maintaining the mechanical stability of the nucleus by mechano-responses and mechano-transduction [3]. The response of nuclear lamina to forces is also observed in nuclear deformation. The distribution of lamin proteins exhibits anisotropy in response to nuclear deformation. Notably, Srivastava et al. observed that lamin A/C is distributed unevenly across the NE, exhibiting spatial variations parallel to nuclear deformation [109]. Furthermore, recent research has suggested that this anisotropic distribution of lamins may be associated with the alteration of NE curvature induced by external forces. When cultured on the torus structures with different Gaussian curvature (positive, negative and zero), the nuclei deformed, exhibiting parallel morphological alternations depending on the curvature of the substrate. And the intensity of lamin A is significantly enhanced at positive Gaussian curvature, and its spatial distribution presents a Gaussian curvature function [53,109]. Additionally, Nmezi et al. found that different types of lamins react differently to the curvature of NE. Inducing nuclear deformation by micropipette aspiration, the researchers observed a significant reduction in the fluorescence intensity of lamin B1 at the high curvature site, whereas lamin A/C proteins show high levels of expression in both high and low curvature nuclear membrane regions [78]. This indicates that different lamin proteins exhibit distinct response characteristics to NMC.

4.2.2. NPC distribution is regulated in a lamin-dependent manner

Current researches indicate that the lamins and NPCs are interdependent, with changes in one structure leading to changes in the distribution of the other [110]. In wild-type cells, NPCs are uniformly distributed across the NE and housed within the lamina networks [96]. In mouse fibroblasts, the defective expression of lamin A and lamin B1 induces NPC aggregation and asymmetric distribution [111]. Further studies indicate that lamins inhibit the interaction between the kinesin adaptor protein BICD2 and the kinesin on NPCs, thereby maintaining the stability of NPC localization [112]. These researches indicate that the lamina network is a key regulator of NPC distribution.

Lamins also exhibit substantial interactions with the nuclear basket components of NPC, including Nup153 and TPR, which contribute significantly not only to the normal distribution of NPCs but also to the structure of the nuclear lamina network. Nup153 has been demonstrated to interact with both A-type and B-type lamins in vertebrates [113]. Depletion of Nup153 significantly enhances NPC aggregation on the nuclear membrane and reduce the size of the laminated mesh [113]. Co-immunoprecipitation experiments have confirmed that TPR, a key component in the nuclear basket, interact with lamin B1 [83]. Knockdown of TPR leads to lamin B1 network structural defects and uneven distribution of NPC, which can be reversed by the overexpression of lamin B1 [78]. Additionally, ELYS/Mel28, localized at the cytoplasmic ring of the NPC, can bind lamin B receptor (LBR) in a phosphorylation-dependent manner to facilitate NPC assembly [115].

Notably, distinct types of Lamins may exert different effects on the distribution of NPCs. Some studies have discovered the existence of "pore-free islands" in the G1 nuclei of several different cell types in which NPCs are excluded [110]. These pore-free regions are characterized by lamin A/C enrichment and relative paucity of B-type lamin, and overexpression or depletion of lamin A/C indicates a negative effect on the uniform distribution of NPC [116]. Jindřiška et al. also found that abnormal distribution of NPCs can be rescued by overexpression of laminB1 and depletion of lamin A/C [95]. However, whether different types of lamins induce the different distribution of NPCs remains highly controversial. Some studies have suggested that both lamin A/C and lamin B1 are intimately associated with NPCs and they play a redundant role in ensuring homogenous NPC distribution [110]. Furthermore, the different assembly patterns of NPC at different phases of cell cycle may also have a significant impact on the results [110,117,118]. Whether different types of lamins induce different distribution of NPCs remains highly controversial. This issue requires further research to clarify, but it is certain that lamin is closely related to the distribution and localization of NPCs.

4.2.3. NMC serve as an indicator of abnormal distribution of lamin network and NPCs

In view of the above studies, it can be speculated that the altered distribution and composition of lamin under the influence of NMC affect the localization and distribution of NPCs. Current researches on the interaction between lamin and NPC are mainly limited to the expression level of lamins. Its conformation, phosphorylation state, protein composition and distribution pattern will be different under different mechanical stimuli [3]. There is a paucity of studies focused on the relationship between the dynamic variation of lamins and the distribution of NPC.

The study of NMC regulating nuclear lamina distribution could provide new insights into the regulatory mechanism of NPC distribution. NMC changes dynamically during nuclear deformation. Abnormal NMC may be indicative of pathological lamina network and NPC distribution. In nuclear blebs with high curvature, which occur frequently in laminopathies and cancers, researchers observed expanded lamin A/C network and widespread deficiency in both B-Type lamins and NPCs [116]. We speculate that the aberrant distribution of NPCs may represent a pivotal downstream event in the development of externally mediated nuclear deformation. And alterations in the distribution and composition of the lamins network in response to changes in NMC may constitute the primary molecular process mediating this event (Fig. 5). Nevertheless, this hypothesis requires further substantiation through a combination of traditional protein interaction experiments, mechanical loading experiments, and dynamic observation at ultra-high resolution.

5. Conclusions and perspectives

NPC bridges the inner and outer nuclear membranes, serving as a central hub for communication between the nucleus and the cytoplasm. It plays an important role in material transport, gene regulation, chromosome organization, etc. The structure and function of NPCs are highly correlated. Current studies confirm that local NMC can change the architecture of an individual NPC and thus affect its function. However we propose that the overall distribution pattern of NPCs on the nuclear membrane is also of critical important.

However, NPCs are highly complex and dynamic structures. Their function is modulated not only by NMC, but also by various mechanical stimuli, aspects that current computational models (summarized in Table 1) fail to fully capture. To bridge this knowledge gap, future FG-Nups models should adopt a more holistic approach by incorporating: (1) Molecular-scale mechanisms: Elucidate FG-Nups-Kaps interactions by characterizing how cohesive property variations (hydrophobicity, phosphorylation) govern selective transport dynamics; (2) Microenvironmental regulation: Define physiological modulators of NPC function, particularly membrane properties including NMC and lipid composition, as well as biophysical parameters including osmotic pressure.

The overall curvature of the nuclear membrane serves as an indicator to characterize the lipid status of the nuclear membrane and as the result

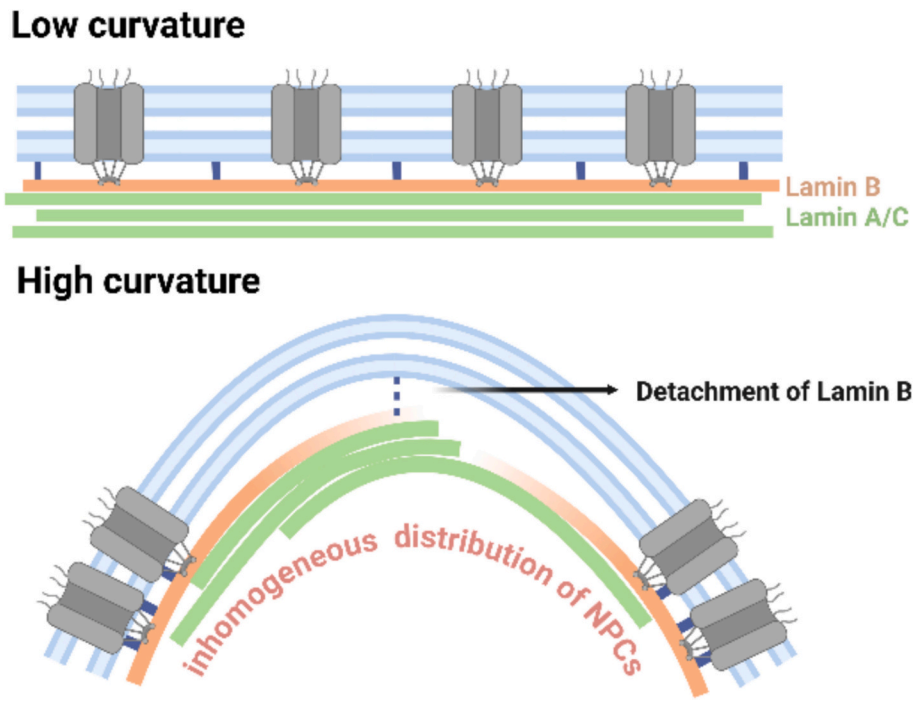

Fig. 5. Schematic representation of NPC inhomogeneous distribution caused by the altered lamin networks at the high curvature site. Detachment of lamin B at high curvature results in the inhomogeneous distribution of NPCs.

of the comprehensive action of various Lamins. Regulation of NMC by lipids and lamin proteins plays a crucial role in modulating the dynamic structure and function of NPCs. This investigation provides a new avenue to understand the involvement of NPCs in various pathological conditions and enables the development of potential clinical treatment strategies. The distribution of NPCs is highly dynamic, and the change of their distribution may reflect the cellular responses to numerous internal and external stimuli. NMC may serve as an important intermediate bridging factor. We hypothesize that when cells are subjected to internal and external mechanical stimulations, the component of lipids in the nuclear membrane and the expressions or modifications of nuclear matrix proteins can respond to the stimulation, changing the NMC and affecting the distribution of NPCs. However, the distribution pattern of NPCs on the nuclear membrane is still inconclusive, and significant research gaps exist in the curvature preference mechanism of NPC assembly. Our unpublished data indicates that the distribution of NPCs in the NE is non random and that the distribution of NPCs in tumor tissues is abnormal. Moreover, NPCs are crucial for material transport, gene expression and the spatial arrangement of chromosomes. Their assembly and architecture are highly modulated by internal and external stimuli. Therefore, the analysis of the spatiotemporal distribution and architecture of NPCs is of great significance for further understanding of the function of NPCs.

Furthermore, the bioprocesses associated with NPCs are highly dynamic, and involve a large number of molecules while current and the available techniques for precise observation of these dynamics in living cells remain limited. Therefore, further breakthroughs in technical, especially high-speed super-resolution living image, mathematical modeling and AI assisted analysis, are of great value for the functional and assembly analysis of NPCs.

CRediT authorship contribution statement

Kun-peng Wu: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Zhi-jie Yan:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Xiao-xi Zhuang:** Methodology, Formal analysis, Data curation, Conceptualization. **Jin-liang Hua:** Visualization, Software, Methodology. **Meng-xiao Li:** Software, Methodology. **Kai Huang:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Ying-xin Qi:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Funding

This research was supported by grants from the National Natural Science Foundation of China (grant numbers 12032003 and 12302409).

Declaration of competing interest

The authors declare that there are no conflicts of interest. All the figures were created by Biorender (https://www.biorender.com/).

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