Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Cell Biology

The nuclear pore complex core scaffold and permeability barrier: variations of a common theme

Ryo Hayama, Michael P Rout and Javier Fernandez-Martinez

The study of the nuclear pore complex (NPC) is a fascinating endeavor, as it not only implies uncovering the 'engineering marvel' of its architecture and function, but also provides a key window into a significant evolutionary event: the origin of the eukaryotic cell. The combined efforts of many groups in the field, with the help of novel methodologies and new model organisms, are facilitating a much deeper understanding of this complex assembly. Here we cover recent advances on the characterization of the structure of the NPC scaffold and of the biophysical mechanisms that define the permeability barrier. We identify common architectural and functional principles between those two NPC compartments, expanding the previous protocoatomer hypothesis to suggest possible evolutionary origins for the FG nucleoporins and the NPC permeability barrier.

Address
Laboratory of Cellular and Structural Biology, The Rockefeller University, New York, NY 10065, USA

Corresponding author: Fernandez-Martinez, Javier (jfernandez@rockefeller.edu)

Current Opinion in Cell Biology 2017, **46**:110–118

This review comes from a themed issue on **Cell nucleus**

Edited by **Aaron F. Straight** and **Roland Foisner**

For a complete overview see the Issue and the Editorial

Available online 15th June 2017

http://dx.doi.org/10.1016/j.ceb.2017.05.003

Introduction: the nuclear pore complex and nuclear transport

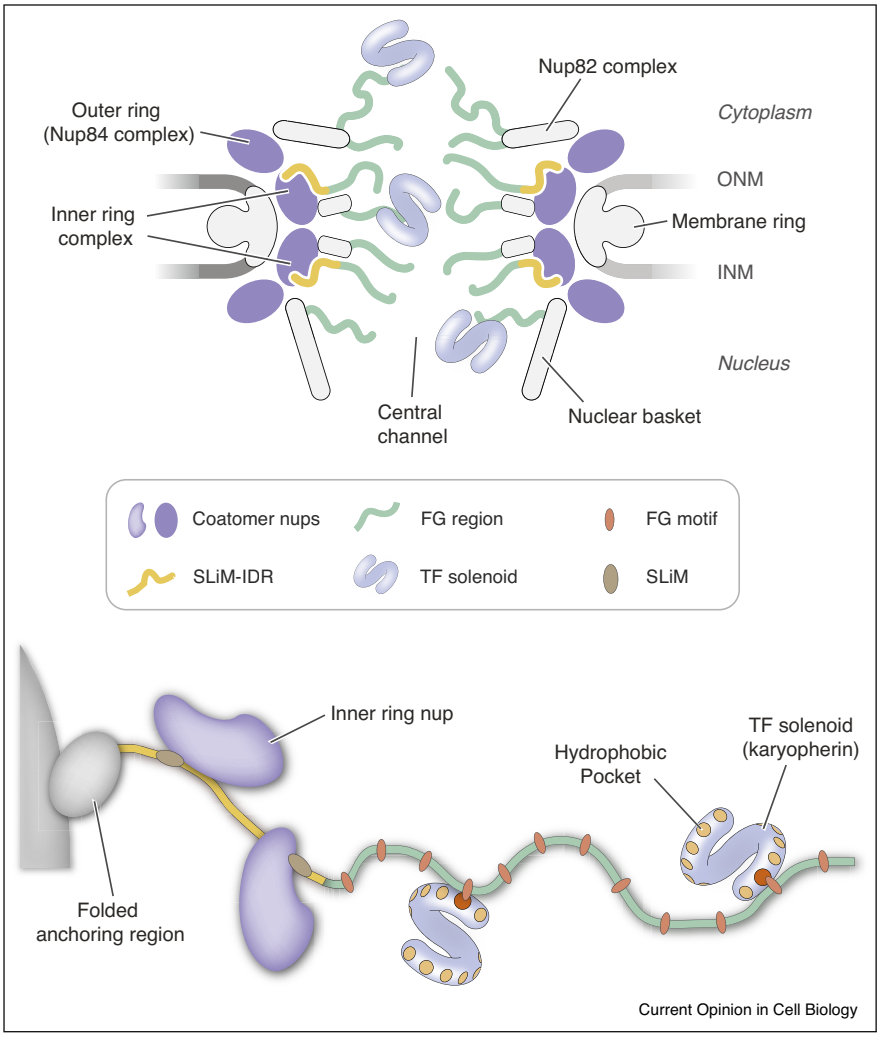
The hallmark organelle of the eukaryotic cell is the nucleus, a compartment delimited by a double membrane termed the nuclear envelope (NE). The nucleus confers the primary compartmentalization within the eukaryotic cell, segregating the DNA, and associated processes in the nucleoplasm, from the cytoplasm; however, compartmentalization comes with a cost, as it requires systems that ensure proper communication and exchange of macromolecules between different cellular compartments. In the case of the nucleus, the nuclear pore complex (NPC) ensures efficient trafficking between nucleus and cytoplasm. The NPC is a massive protein assembly, of 50–100 MDa depending on the organism, that fenestrates the NE and forms a channel of approximately 40 nm wide; it is an eightfold symmetrical assembly, formed by more than 500 copies of 30 different proteins called nucleoporins (nups) [1] that have been shown to be arranged in conserved, biochemically stable subcomplexes acting as the NPC's building blocks [2–4]. These building blocks coat the NE membrane with a highly modular symmetrical scaffold, formed by eight protomers called spokes, connecting radially to form several concentric rings [2,3]: the outer ring—formed by a head-to-tail arrangement of a Y-shaped complex [5–7]; the inner ring; and the membrane ring. Attached to these rings are two asymmetrically localized modules, the cytoplasmic Nup82 complex and the nuclear basket. From the scaffold, a special type of nups, called FG nups for their high content in phenylalanine–glycine repeats, project their intrinsically disordered FG repeat containing domains into the central channel [3] (Figure 1). An estimated ~6 MDa worth of FG disordered domains fill the NPC central channel to form the permeability barrier that confers selectivity and specificity to the NPC. Such a 'cloud' of FG domains prevents passive diffusion of most macromolecules through the NPC, while at the same time provides docking sites for specific transport factors (TFs), mainly belonging to the karyopherin family of TFs [8]; after binding to their cargo, TFs transiently interact with the FG regions and rapidly transit through the central channel in a matter of milliseconds [9].

Most components of the NPC core scaffold have been shown to be structurally and evolutionarily related to vesicle coating complexes [10–13], which led to the proposal of the protocoatomer hypothesis, that suggests a common evolutionary origin for NPCs and coated vesicles in an early membrane-curving module (the proto-coatomer) [10]. However, tracing the evolutionary origin of other parts of the NPC, including the permeability barrier, have been more challenging than that of the scaffold. Here, we give an overview of the recent advances in our understanding of: (i) the detailed architecture of the NPC scaffold; and (ii) the biophysical characteristics of intrinsically disordered FG domains and their molecular behaviors. Finally, we integrate this new knowledge into a hypothesis for the evolutionary origin of the FG nups/karyopherins and the NPC permeability barrier.

Evolving view of the NPC structure

The structural characterization of the NPC has been an especially challenging endeavor, due to the sheer size of

Figure 1



The nuclear pore complex architecture.
Upper part, schematic illustrating the major features of the NPC organization. Lower part, schematic of linker nucleoporins yNup145N/yNup 100/yNup116/hNup98, showing their interaction with the NPC scaffold through their disordered connectors (based on Ref. [20••]) and interaction with transport factors through their FG repeat regions.

the assembly, its intrinsic flexibility, the dynamic nature of some of its components, and the fact that ~1/3 of its mass is predicted to be disordered. Nevertheless, recent groundbreaking advances in the structural analysis of the NPC are revealing exciting new details about this beautifully complex assembly. One of these breakthroughs came thanks to technical advances in cryo electron microscopy [14], that allowed Martin Beck and colleagues to generate a first 30 Å resolution cryo-electron tomography map of the human NPC [15]. The resolution of this map, and that of further refinements achieving resolutions around the 20 Å mark [16••,17••,18••], along with biochemical reconstitutions [19,20••,21,22••] and cross-linking and mass spectrometry data [15,17••], allowed the fitting of available crystal structures [23•,24,25•,26–31] into new hybrid models covering a substantial portion of the NPC symmetric core [17••,18••,22••]. These analyses showed that the outer rings of the vertebrate NPC are formed by a reticulated arrangement of two concentric rings of 8 Y-complexes (32 copies total). The monomeric complexes run in a head-to-tail fashion and seem to connect both through direct contacts and through bridges formed by other nups, like Nup358 [17••,22••]; in yeast, though, the arrangement is simpler [3]. The Y-complexes contact the NE membrane directly through membrane interacting motifs located in the beta-propeller tips of Nup133 and Nup120–Nup160 [32,33]. Similar membrane binding motifs are used to contact the NE by other nups, like vNup155 [18••], yNup60, yNup1 [34•] and Nup53 [35,36], suggesting the presence of a network of contacts