

CHAPTER 2

Integral Proteins of the Nuclear Pore Membrane

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The nuclear envelope contains three distinct membrane domains. The outer nuclear membrane faces the cytoplasm and is continuous with the rough endoplasmic reticulum (ER). Like the rough ER, the nuclear outer membrane is covered with ribosomes engaged in translating secreted and integral membrane proteins. The inner nuclear membrane faces the nucleoplasm, has its own unique protein composition and interacts with the fibrous meshwork of the nuclear lamina (reviewed in ref. 6). The inner and outer nuclear membranes fuse to form the third membrane domain, termed the pore membrane domain. Nuclear pore complexes (NPCs) are anchored at the pore membrane domain and mediate both passive diffusion and active nucleocytoplasmic transport. Active transport requires signals on the imported or exported macromolecules, termed nuclear localization signals (NLS) and nuclear export signals (NES), respectively. Transport is mediated by soluble NLS and NES receptors (termed importins/exportins/karyopherins/transportins), whose direction of movement is determined by Ran, a small GTP-binding protein (reviewed in refs. 22, 48 and 50). NPC structure includes soluble proteins, termed nucleoporins (nups) and integral membrane proteins, termed POMs. The NPC is anchored to the pore membrane by binding to POMs.³⁷ POMs are also proposed to have roles in nuclear pore assembly, nucleocytoplasmic transport and NPC organization (see below).

The protein composition of the yeast NPC has been determined.³⁸ Yeast NPCs consist of multiple copies of at least thirty distinct proteins, with a total estimated mass of 50 MDa. The size and complexity of the NPC appears to have increased during evolution. For example, the vertebrate NPC has an estimated maximum mass of 120 MDa, with an estimated forty different proteins;³⁵ (reviewed in ref. 48). Many vertebrate nucleoporins have orthologs or functional homologs in yeast and plants. Overall, NPCs are significantly conserved in both structure and protein composition between yeast and humans. One possible exception to this trend are the POMs, which have no obvious similarity between yeast and vertebrates.

Yeast POMs

Five integral membrane proteins have been localized to the pore membrane domain in the yeast *Saccharomyces cerevisiae* (reviewed in ref. 7). These five POMs are named Snl1,²⁹ Pom152,⁵⁵ Ndc1,⁵ Pom34³⁸ and Brr6.¹¹ Yeast POMs are discussed below.

SNL1 was identified in a genetic screen for high copy suppressors of the lethal phenotype caused by over-expression of the carboxy-terminal 200 residues of Nup116 (*NUP116-C*), in the *nup116* null background. Loss of *NUP116* function causes the nuclear membranes to

herniate and cover the NPCs. Over-expression of *SNL1* also suppresses the temperature-sensitive phenotypes of mutations in two other genes:²⁹ *gle2*, which is essential for NPC assembly,³⁶ and *nic96*, which is involved in the transport of polyadenylated RNA and possibly in protein transport.²¹ Cells that lack *SNL1* expression are viable, and so are double-null mutants for *snl1* plus a second POM named *pom152*. Lack of synthetic lethality between *SNL1* and *POM152* suggests a possible functional redundancy with other, possibly unidentified, POMs.²⁹

A fraction of Snl1 is localized to the ER,²⁹ which suggests that Snl1 might shuttle between the pore membrane domain and ER. It would be interesting to compare the diffusional mobility of Snl1 at the NPC versus the ER, to determine if Snl1 proteins in the ER are actively exchanging with pore-localized Snl1.

Pom152 was identified as a glycoprotein with N-linked high mannose oligosaccharide modifications,⁵⁵ which localized to NPCs.⁵⁵ Pom152 is an integral membrane protein that spans the pore membrane once, using only one of its two predicted transmembrane domains. Its short amino tail (175 residues) faces the NPC, and its long carboxy-tail (1141 residues) is localized in the lumen space between the inner and outer nuclear membranes.⁴⁶ *S. cerevisiae* strains that lack the *POM152* gene are viable. However, mutations in *pom152* are lethal in combination with mutations in other genes, including *NUP188* and *NUP170*,¹ which are both involved in establishing the functional diameter of the NPC.³⁹ It is not clear why mutations in *POM152* are 'synthetically lethal' in combination with mutations in *NUP188* or *NUP170*, but these findings suggest that Pom152 might also be involved in determining the diameter of the pore or NPC. Over-expression of Pom152 reduces the growth rate of cells, for reasons not yet understood.⁵⁵

When *POM152* is ectopically expressed in mammalian cells, it is correctly localized to the pore membrane domain.⁵⁵ This result indicates a functional conservation of the pore membrane domain between yeast and mammals. Though there is very little homology between the yeast *POM152* and the vertebrate *GP210* (see below), several characteristics are shared between these pore membrane proteins. Notably, both proteins have a predicted hydrophobic region that is not embedded in the membrane. It would be interesting to test whether *GP210* can functionally complement *pom152* mutations.

NDC1 was originally discovered as an essential gene, which is required at a late stage of spindle pole body (microtubule organizing center) duplication.⁵³ Yeast spindle pole bodies are embedded in the nuclear envelope, like NPCs, and Ndc1 localizes at both types of structure. This may indicate a functional or assembly-related link between these two nuclear membrane-embedded organelles.⁵ In *ndc1*-null cells, the spindle pole body fails to be inserted into the nuclear envelope, but NPCs are positioned and function normally. The lack of a nuclear transport phenotype in cells with mutations in *pom152*, *ndc1* or both, suggests functional redundancy between these POMs and other nucleoporins. Interestingly, in *pom152*-null cells with defective Ndc1 protein, the spindle pole bodies are again inserted into the nuclear envelope, suggesting that *pom152* mutations suppress *ndc1* mutations. Though it is not known if Ndc1 and Pom152 interact directly, it was proposed that the lack of Pom152 releases 'defective' Ndc1 molecules from the NPC, allowing them to function (weakly, but in higher numbers) at spindle pole bodies.⁵

Pom34 was recently identified by mass spectrometry as a component of biochemically-purified yeast NPCs, and localized to the pore membrane domain.³⁸ Biochemical extraction also revealed that *POM34* encodes an integral membrane protein. Pom34 has a predicted leucine zipper motif and two putative transmembrane domains.³⁸ Neither the topology of Pom34 in the pore membrane domain, nor its requirement for cell growth or viability, have been determined.

BRR6 was identified by complementation of the *brr6* cold sensitive nuclear transport mutant.¹¹ *BRR6* encodes a 22.8 kDa integral membrane protein located at the nuclear rim in a

punctate pattern characteristic of NPC proteins. Genetic analysis revealed that Brr6 interacts with several soluble nucleoporins including Nup1, Nic96 and Nup188. Depletion of Brr6 from cells causes all NPCs to aggregate in one region, suggesting that Brr6 is required for the normal distribution of NPCs. *BRR6* is also required for normal morphology of the nuclear envelope, since its depletion causes nuclear envelope herniations. Both phenotypes resemble those produced by *gle2* and *nup116* mutations,^{36,51} indicating that these proteins may function in the same genetic pathway. Brr6 spans the nuclear envelope once, through a transmembrane domain located at its C-terminus, and its longer N-terminal domain faces the NPC. Brr6 may also be involved in nuclear transport, since mRNA molecules and NLS/NES-GFP fusion proteins all accumulate at the nuclear periphery in *brr6-1* mutants.

Vertebrate POMs

Only two genes encoding integral proteins of the pore membrane have been identified so far in vertebrates, named *POM121* and *GP210*.

POM121 encodes a wheat germ agglutinin (WGA) binding protein in mammals, and is localized at the pore membrane domain.²⁵ Pom121 contains six XFXFG repeats characteristic of certain nucleoporins that are posttranslationally modified by O-linked GlcNAc. Pom121 is an integral membrane protein that spans the pore membrane once, with its short N-terminal head domain in the lumen. The large C-terminal domain faces the NPC, and is localized to the central spoke ring of the NPC.⁴³ When this large exposed region of Pom121 was over-expressed in green monkey COS cells, it accumulated in cylindrical intranuclear bodies, most of which localized near the inner nuclear membrane.⁴⁵ The first 128 amino acids of POM121, which are not predicted to contain a signal peptide, target the protein to ER membranes, but targeting of Pom121 to the NPC requires the region between residues 129 and 618.⁴⁴ Pom121 is a highly stable and immobile component of the NPC during interphase;⁸ and is therefore likely to anchor NPCs at the pore membrane in vertebrates.

GP210 is the only evolutionarily conserved pore membrane gene among multicellular organisms, including *Arabidopsis*, *C. elegans*, *Drosophila* and humans (see ref. 7 and Fig. 1), indicating that it has fundamental roles in NPC formation or function, or both. Rat Gp210 was originally identified as an integral glycoprotein of the NPC.¹⁹ Gp210 spans the pore membrane only once, through a hydrophobic region positioned close to its carboxy terminus. Only a small region of gp210 (its short carboxy-tail) faces the NPC, whereas 95% of its mass is positioned in the perinuclear space.²⁴ Rat Gp210 has two predicted transmembrane domains, but only one actually spans the membrane. It was hypothesized that the second hydrophobic domain plays a role in membrane fusion during pore formation (see below). The luminal domain of Gp210 is glycosylated by N-linked high mannose oligosaccharides, and it therefore binds the lectin concanavalin A.⁵⁴ Gp210 is organized mostly as dimers, plus higher order multimers.¹⁴ In contrast to Pom121, which is quite stable at the NPC, Gp210 is mobile; at any given time about 20% of all Gp210 molecules are dissociated from NPCs and can diffuse freely throughout the nuclear/ER membrane network (Brian Burke, unpublished observations). During mitosis, Gp210 is phosphorylated on Ser¹⁸⁸⁰ by cyclin B-p34^{cdc2} or a related kinase.¹⁵

Gp210 appears to have a major role in NPC structure, since the luminal expression of antibodies against the luminal domain of Gp210, in mammalian cells, inhibited both active transport and passive diffusion through the NPC.²³

Cell Cycle Dynamics of the NPC

The closed mitosis in yeast does not allow mitotic breakdown and reassembly of the NPCs. Thus in yeast, there are no cell cycle 'dynamics' of nuclear pores. In contrast, higher eukaryotes undergo an open mitosis, in which the nuclear envelope and NPCs disassemble, and nuclear

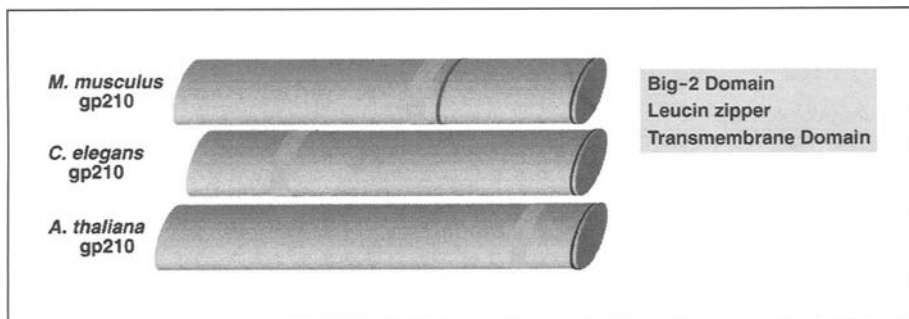


Figure 1. Schematic diagram of the conserved protein domains in Gp210, between vertebrates (*M. musculus*), invertebrates (*C. elegans*) and plants (*A. thaliana*). Big-2 domain is a bacterial Ig like domain found in many bacterial and phage surface proteins (reviewed in ref. 7)

membranes merge into the ER.¹³ The timing of NPC disassembly varies among different metazoans. In *C. elegans*, disassembly of the NPCs begins after prometaphase,³¹ whereas in *Drosophila* and vertebrates NPC disassembly begins as early as prophase.^{18,27} Disassembly of the NPCs is proposed to be a key triggering event for nuclear envelope disassembly.⁴⁷ Nuclear envelope reassembly begins at the same time, during late anaphase/early telophase, in all metazoans analyzed. The assembly of NPCs does not require de novo protein synthesis, suggesting that NPC components are both stable and recycled.³⁴ NPC breakdown and assembly are regulated by cell-cycle dependent phosphorylation of several nucleoporins, including Nup358, CAN/Nup214, Nup153 and Gp210.^{15,33}

NPC assembly is being studied in cell-free extracts of *Xenopus* eggs. Assembly initiates in patches of flattened nuclear membranes, which are usually attached to chromatin but do not need to be attached to chromatin. NPC formation begins before the chromatin is fully enclosed by membranes, and proceeds in an asynchronous and rapid manner.^{32,33,52} A pathway for NPC assembly has been proposed based on the discovery of structures termed dimples, holes and star-rings, in nuclei assembled in vitro in *Xenopus* cell-free extracts.²⁰

Reassembly of NPCs involves the ordered recruitment of NPC components, many of which are sub-complexes of nucleoporins that remain associated during mitosis.¹⁵ However, the order in which different nucleoporins arrive to the site of the NPC is not fully understood, and somewhat controversial. In mammalian cells NPC formation begins during late anaphase, and one of the earliest proteins to accumulate is Nup153,^{3,26} a constituent of the nuclear basket.³⁷ In contrast, in *Xenopus* assembly extracts Nup153 accumulates at NPCs rather late during mitosis, and is reported to bind lamins, which also assemble rather late.⁴² As telophase progresses there is the sequential accumulation of Pom121, p62 (a constituent of the central channel),¹⁰ Can/Nup214,¹⁶ and later Gp210 and Tpr (found at NPC baskets and intranuclear structures).²⁸ However, it is likely that a fraction of Gp210 proteins are present continuously during nuclear envelope formation, even though most gp210 does not accumulate at the nuclear envelope until later in G1.^{3,4}

Membrane Fusion and Nuclear Pore Formation

Electrostatic repulsion between phospholipid headgroups in an aqueous environment prevents spontaneous membrane fusion. To fuse, biological membranes must overcome this repulsion. The stalk formation hypothesis of membrane fusion^{40,41} predicts several fusion intermediates. Fusion begins with the formation of a stalk between facing phospholipid bilayers. This stalk then forms a dimple. Further horizontal pulling of the dimple produces a hemifusion

diaphragm, followed by opening of a fusion pore and its dilation by unknown mechanisms (reviewed by ref. 20).

Membrane fusion plays key roles in many cellular pathways including secretion, synaptic release, endocytosis and ER dynamics, and also in several viral infections.² Fusion is also crucial for nuclear pore formation, which occurs within the nuclear lumen, and may therefore resemble the membrane fusion events that take place during viral infection.

Viral fusion proteins (fusogens) are glycoproteins that span the viral membrane once, and contain a relatively large tail exposed on the viral surface.²⁰ There is very little, if any, sequence similarity between different viral fusogens, yet they all share a key structural feature: a short helical amphiphilic domain with alternating hydrophobic and charged residues. This 'fusion peptide' interacts directly with the target membrane.

Fusion of the influenza virus membrane is triggered by the low pH (pH 5-6) within endosomes, whence the virus fuses to enter the cytoplasm. Low pH induces conformational changes in hemagglutinin (HA), the influenza fusogen, exposing the N-terminal fusion peptide. Once exposed, the fusion peptide inserts into the target membrane,¹² and possibly also into the viral membrane.⁴⁹ This insertion is proposed to produce a stalk structure that connects the viral and target membranes. At this stage, expansion of this structure produces a hemifusion diaphragm between the inner leaflets, where a small fusion pore subsequently opens. Dilation of this small pore completes the fusion event.¹⁷ Fusion mediated by influenza HA is cooperative, involving the aggregation of at least three, and probably four, HA trimers.⁹

The fusion mechanism involved in nuclear pore formation would also require a fusogenic protein to overcome surface charge repulsion between the facing leaflets of the inner and outer nuclear membranes. Gp210 has been proposed as a possible fusogen in vertebrates,⁵⁴ because it has a large domain in the nuclear lumen that includes a possible amphiphilic helix, similar to viral fusogens, and because it forms multimers (see ref. 14). The evolutionary conservation of gp210 is also consistent with such a fundamental function. These data make Gp210 an excellent candidate fusogen for pore formation, but direct studies will be required to test this model.

In structural terms, NPC formation in yeast is even less well characterized than in vertebrates. Yeast POMs have no obvious metazoan orthologs, though the mechanisms of pore membrane fusion are likely to be conserved. The yeast Pom152 protein might be involved in pore membrane fusion events, since Pom152 resembles Gp210 in having a large luminal domain with a possible amphiphilic helix. Assuming that the mechanisms of pore formation are conserved in all eukaryotes, the yeast findings might predict that pore membrane fusion involves more than one kind of protein, since yeast with null mutations in *pom152* are viable. Further study of the null phenotypes for vertebrate gp210 and Pom121, and their comparisons with yeast POMs, should help reveal the mechanisms of pore formation.

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