STRUCTURAL BIOLOGY

Locking down the core of the pore

A highly stable heterotrimeric protein complex lines the central channel of the nuclear pore

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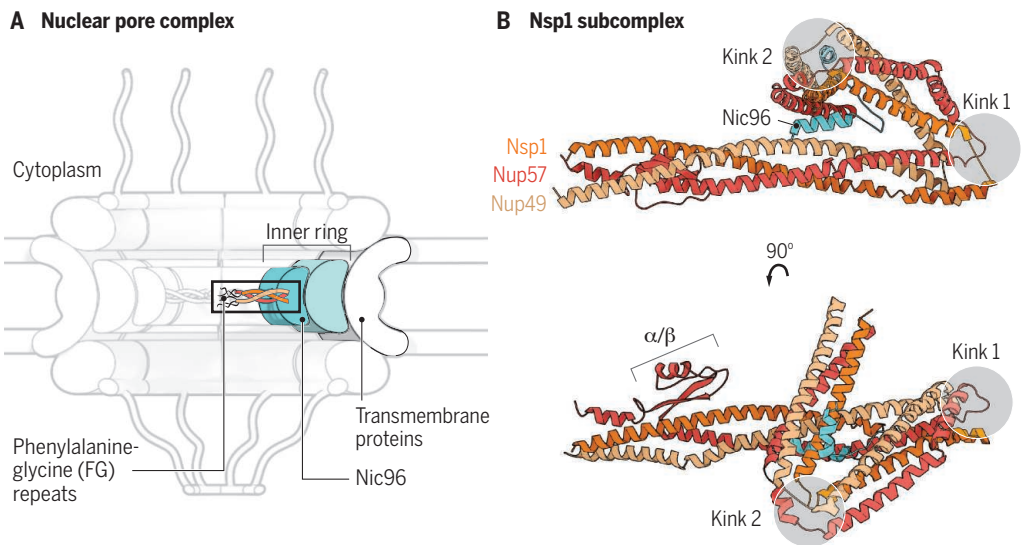
Nuclear pore complexes (NPCs), first observed by electron microscopy 65 years ago, mediate selective transport of macromolecules between the nucleus and cytoplasm of eukaryotic cells. Although the exact size and protein composition of NPCs can vary between species, these massive and complex machines are highly conserved in their overall organization, which consists of multiple copies of ~30 nuclear pore proteins, or nucleoporins (Nups), in a symmetrical eightfold radial arrangement. Deciphering the structure of this immense complex has required ongoing multifaceted approaches (*1*). On page 106 and 56 in this issue, Chug *et al.* (*2*) and Stuwe *et al.* (*3*), respectively, have employed parallel approaches in very distant species and arrived at remarkably similar and informative structures of an essential subcomplex of the NPC.

The mechanism by which nuclear transport receptors (NTRs) selectively carry cargo through the NPC has been much debated. Models are focused on the phenylalanine-glycine (FG) repeat domains found in a subset of Nups and, in particular, how the FG domains of the central channel are anchored within the NPC core (see the figure). Discrimination between models has been complicated by the surprising lack of a definitive picture of the Nup62/Nsp1 (*4*) subcomplex found in the central channel of the NPC. Nup62/Nsp1 and its subcomplex partners Nup58/Nup49 and Nup54/Nup57 were among the first Nups identified more than 20 years ago and are crucial for nuclear import (*5, 6*). Nonetheless, even the stoichiometry of this subcomplex has been controversial (*7*), and a structure encompassing the full ordered domains of all members has proven elusive.

Chug *et al.* tackled the metazoan NPC by reconstituting proteins from the frog *Xenopus laevis*, whereas Stuwe *et al.* capitalized on a thermophilic fungus (*Chaetomium thermophilum*) pioneered for improved protein stability and crystallization (*8*). Both studies began with proteins lacking the FG domains and then trimmed additional residues, testing many versions to obtain the largest fragments that assembled a single homogeneous complex. Structures were stabilized by inclusion of single-chain antibodies. Chug *et al.* show that an antibody that recognizes only the assembled complex could isolate the endogenous Nup62 subcomplex from *Xenopus* egg extract, confirming the physiological relevance of these structures.

Both structures reveal a 1:1:1 heterotrimeric parallel coiled coil. There are multiple contacts between the three intertwined chains, and the interactions extend further throughout the domain than previously appreciated. Toward the carboxyl termini, all three chains bend back sharply, producing a kink that is stabilized by interactions between the post-kink coil and the main coiled domain. A second kink in all three chains leads to the third coil segment, solved in the fungal structure, which binds to the adapter Nup, Nic96. The Nic96 helix lies in close proximity to all three coiled segments, increasing overall stability through contacts to each domain. This configuration is consistent with the finding of both studies that all members of the Nup62/Nsp1 subcomplex are required for Nup93/Nic96 binding. An unexpected feature is a distinct α/β domain in Nup54/Nup57. A role for this module remains to be determined, as potential interaction partners are as yet unknown.

A key feature of many current models of the transport mechanism is the self-association of hydrophobic FG domains to form a permeability barrier. NTRs traverse this barrier by transiently competing for interaction with the FG repeats (*9, 10*). Recently, an alternate mechanism emerged in which NTR binding to FG domains triggers a dramatic rearrangement (or "ring cycle") of the Nsp62 subcomplex within the NPC central channel to enable passage of NTR-cargo complexes (*11, 12*). The trimeric structure presented by Chug *et al.* and Stuwe *et al.*, however, is highly stable, with multiple interactions between each of the three members in an equimolar ratio. This configuration is seemingly incompatible with the ring-cycle model, which was inferred from smaller fragments of structure that may have been atypical lower-affinity partnerships formed when protein regions interact out of context.



The NPC core. (**A**) Cross-sectional arrangement of the core nucleoporin subcomplexes is shown. For brevity, only *C. thermophilum* nomenclature is shown. Transmembrane proteins, inner ring structures, and the coiled and FG domains of the Nsp1 subcomplex are shown. (**B**) Structure of the *C. thermophilum* Nsp1 subcomplex coiled-coil domain. [Adapted from (*3*)]

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Stuwe *et al.* additionally addressed the interactions that anchor the Nsp1 subcomplex to the inner ring complex of the NPC. Binding of the Nsp1 heterotrimer to Nic96 was essential to target the heterotrimer to the NPC, and disruption of this binding decreased nuclear export and had severe effects on growth in the yeast *Saccharomyces cerevisae*. Interaction between Nic96 and Nup192 of the inner ring complex was also defined and structurally characterized. Unexpectedly, disruption of the binding interface through mutation of either Nup192 or Nic96 did not displace the heterotrimer from the yeast NPC, although it led to severe growth and export phenotypes. These results suggest that additional connections will be identified between Nic96 and other nucleoporins of the inner ring, and, overall, that gaps remain in our knowledge of how these proteins make vital contributions at the NPC core.

The new structural information from Chug *et al.* and Stuwe *et al.* is a launching pad for elucidating many aspects of pore function. In particular, there is now a context for considering posttranslational modifications and processing, which occur under various circumstances ranging from progression of the cell division cycle to viral infection. These structures may also illuminate a familial mutation of Nup62 that is associated with a neurological disorder (*13*). The highly conserved heterotrimeric structure provides a point of reference against which new information can be compared, such as the structural basis for Nup62/Nsp1's participation in a second, independent subcomplex of the NPC (*14, 15*). Overall, structural information for this central subunit of the nuclear pore and new insights into its connections to other pore components represent an important stride forward in deciphering the NPC, both its architecture and its fundamental functions. ■

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CLIMATE CHANGE

The IPCC at a crossroads: Opportunities for reform

Increase focus on policy-relevant research

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The Intergovernmental Panel on Climate Change (IPCC) has proven its value as an institution for large-scale scientific collaboration to synthesize and assess large volumes of climate research for use by policy-makers, as well as for establishing credibility of findings among diverse national governments. But the IPCC has received considerable criticism of both its substance and process. The new IPCC leadership to be elected in October could help guide the IPCC to a clear, shared understanding of future objectives and could shape procedural reforms. We identify key opportunities for reform by addressing two related questions: Is the IPCC doing the right things? Is the IPCC doing things right?

POLICY

DOING THE RIGHT THINGS? To remain policy-relevant, the IPCC needs to shift focus and increasingly address response options to climate change. The information base for making decisions on climate stabilization and related public policies is fragmented. Providing clear and integrated information regarding climate impacts and policy options for mitigation and adaptation at various scales (subnational, national, and international) along alternative climate stabilization pathways—and about their respective costs, benefits, and risks—would better inform decision-makers and societies about consequences associated with alternative policy choices. This does not mean that the IPCC should choose among policy options but rather provide the information to facilitate choices by policy-makers.

A major reason for this fragmentation of key information is that IPCC Assessment Reports (ARs) are organized by Working Groups (WGs) focused on the physical science of climate change (WGI), adaptation and impacts (WGII), and mitigation options (WGIII). A different organization might achieve more integrated analysis of policies. For example, one WG could focus on natural-science aspects of climate change, and a second could provide a more integrated perspective on mitigation, adaptation, and the

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