Design principles of binding-induced selective transport through the nuclear pore complex

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A key step in a wide variety of cellular signaling cascades is selective entry into the nucleus. This regulatory step requires the nuclear pore complex (NPC) to act as a selective filter allowing the passage of only a subset of macromolecules. In many biological filters, such as mucus, binding inhibits transport. In contrast, in the NPC binding of specialized proteins called transport factors to disordered proteins called FG Nups specifically enhances their transport. We developed a quantitative theory of the minimal ingredients sufficient for binding-induced selective transport. Our model provides a framework to study how biological filters regulate access to key macromolecules.

Selective filters made of biopolymers are used in living and synthetic systems to control the localization and movement of molecules, nanoparticles, viruses and other organisms [1]. One of these filters, the nuclear pore complex, or NPC, regulates access to cells' genetic material. Controlled passage through the NPC to the nucleus is a key feature of many signaling cascades. For example, transcription factor activation typically includes its nuclear localization. In plants, signaling can also directly affect properties of the nuclear pore, regulating nuclear access for a wide range of pathways [2].

Selective biopolymer filters regulate access to genetic material (the nuclear pore complex, or NPC), cells (the pericellular matrix), tissues (the extracellular matrix), and organs (mucus). How particle binding affects motion and filtering is unclear. Binding of transport factors that bind to proteins in the NPC move rapidly through it. In contrast, binding inhibits the uptake of nanoparticles that bind to airway mucus and many viruses minimize binding interactions [3]. While particle size, charge, and binding interactions are known to affect filtering, the physical principles that underlie mobility and transport in polymeric biomaterials are not fully understood.

Among these filters, the NPC is tuned for selective passage enabled by binding. The NPC selectively filters molecular traffic between the nucleus and cytoplasm of eukaryotic cells, making it important for diverse processes including gene regulation and translation [4]. In particular, it is a key regulatory step in cellular signaling. Post-translational modification or the presence of binding partners can expose a nuclear localization signal (NLS). This marks the protein as a cargo, recognized by a transport factor and so selectively transported.

Transport occurs through the central channel of the NPC, 50 nm in diameter and 100 nm long. The selective barrier filling the central channel is made from disordered proteins, the FG nucleoporins (FG Nups), which contain repeated phenylalanine-glycine (FG) motifs. Transport factors (TFs) that directly bind to the FG repeats can cross the NPC and carry cargo with them. Transport through the NPC is remarkably fast, with pore residence times ~10 ms [5]. Binding between FG Nups and TFs shows diffusion-limited on-rates and transient binding of individual FG repeats to TFs [6,7]. How the FG Nups both block passage (of non-binding molecules) and facilitate passage (of binding molecules) is not fully understood, making the NPC an ideal system to dissect the principles of binding-controlled selective transport.

We address the central contradiction of selective transport through the NPC: how does binding of TFs to FG Nups within the pore increase the flux rather than decreasing it? Using a biophysical model, we demonstrate that TF diffusion and binding are sufficient for selective transport, as long as binding only partially immobilizes TFs. Binding increases the local concentration, and these molecules contribute to the flux if mobile. Thermally-driven diffusion of TFs bound to flexible tethers gives sufficient particle mobility to produce selectivity similar to experimental measurements. Tether flexibility also allows bound TFs to hop between tethers, further enhancing selectivity.

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