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Mechanobiology of the Nuclear Pore Complex Machinery

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The nuclear pore complex (NPC) is a vital nanomachinery that resides in the nuclear envelope (Fig. 1) and functions as the primary gateway for nucleocytoplasmic transport in eukaryotic cells [1]. As the largest macromolecular complex in the cell, the NPC is responsible for shuttling vital cargos such as various proteins and different types of RNAs across the nuclear envelope. By controlling the import of genetic materials and transcription factors and export of mRNAs across the nuclear boarder, NPCs are believed to regulate gene expression processes and may therefore play a foundational role in cellular mechanotransduction, as was originally proposed over a decade ago [2]. The building blocks of the NPC are a family of proteins called nucleoporins (nups). Nearly one-third of nups contain the hydrophobic, natively unfolded phenylalanine-glycine (FG)-repeat motifs, which are believed to play the key role in the transport of cargos through the NPC. Despite the high throughput of ~1000 translocations per NPC per second, the NPC strictly controls and regulates the bi-directional passage of individual cargos. While cargos smaller than ~5–9 nm can passively diffuse through the NPC, larger cargos up to ~39–40 nm actively transport through the pore, which only occurs if they are bound to a nuclear transport receptor (NTR). Inert cargos that are not small enough to passively diffuse, and lack NTRs to actively transport, are prohibited by the NPC from crossing the nuclear envelope. Despite the vital importance of the NPC and nucleocytoplasmic transport in cell biology, little is known about the mechanics and dynamics of the NPC and nucleocytoplasmic transport. The mechanism of nucleocytoplasmic transport is an active topic of debate and has led to the suggestion of several hypotheses to explain the rapid, yet selective, nature of the transport processes. The complex, yet delicate, geometry of the NPC and the fine spatiotemporal resolution at which the nucleocytoplasmic transport takes place have so far hindered the direct, experimental investigation of this exquisite nanopore. Computational models offer a strong platform for capturing the nanosecond-scale interactions between cargo and FG-repeats in a nanometer spatial resolution to shed light on the details of transport phenomena through the nuclear pore.

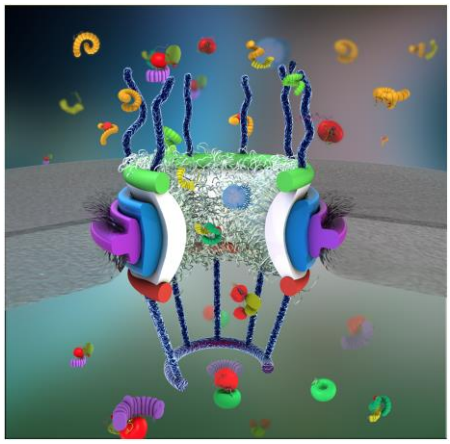

Figure 1: A schematic representation of the NPC structure with the cargo-complex indicated as an NTR-bound blue sphere inside the central channel. For more descriptive figures of the NPC along with different biochemical agents see [1].

Using a hybrid of computational modeling approaches, ranging from finite element [3] to coarse-grained Brownian dynamics [4] to molecular dynamics techniques [5] to new agent-based modeling methods [6-8], we study the structure and function of the nuclear pore complex and the dynamics of nucleocytoplasmic traffic.

Understanding the mechanobiology of the nuclear pore complex and nucleocytoplasmic transport will broadly

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impact our understanding of viral diseases and may revolutionize therapeutic approaches (e.g. gene therapy) and open the door to many industrial applications of biomimetic artificial nanopores.

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