ZERNIKE INSTITUTE COLLOQUIUM

Thursday, November 6th, 2014

16:00h, Lecture Hall: 5111.0080 **Coffee and cakes from 15:30h**

Nanobiophysics and the nuclear pore complex

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The manner by which specific macromolecules are sorted and transported in the complex environment of living cells is unprecedented. In particular, we are enthralled with the manner by which proteins selectively accumulate against concentration gradients in cell nuclei. This defines the driving impetus in our lab to resolve the modus operandi of the nuclear pore complex (NPC), which regulates macromolecular traffic between the nucleus and the cytoplasm.

As a ~ 50 nm-diameter physical pore, the biological marvel of the NPC lies in its ability to restrict or promote cargo translocation via biochemical selectivity and not size exclusion per se. The NPC machinery comprises of several intrinsically disordered proteins that are rich in phenylalanine-glycine (FG)-repeat motifs (i.e., FG Nups). Prevailing mechanistic views reason that the barrier-like FG Nups reject non-binding proteins whilst providing exclusive access to cargo-carrying transport receptors (karyopherins or Kaps) that exert multivalent binding interactions with the FG Nups.

Closer inspection, however, reveals a contradiction because strong binding (i) tends to slow transport down rather than to speed it up, and (ii) is inconsistent with the rapid Kap transport speeds achieved in vivo.

Here, we apply nanoscience approaches and biophysical thinking to resolve the fundamental underpinnings that underlie the NPC transport process. These range from (i) correlating in situ mechanistic with equilibrium affinity and kinetic aspects of Kap-FG Nup binding using surface plasmon resonance; (ii) assessing the diffusive properties of Kap-cargo complexes by optical trapping; and (iii) testing for authentic transport functionality using biomimetic nanopores.

In my talk, I will describe how these efforts provide new insight into the underlying principles governing molecular mechanics, selectivity and transport in the NPC with potential ramifications with respect to selective transport control in artificial environments.

References

1. Lim et al, Nanomechanical basis of selective gating by the nuclear pore complex, *Science* 318 340 (2007)
2. Kowalczyk et al, Single-molecule transport across an individual biomimetic nuclear pore complex. *Nature Nanotechnology* 6 433 (2011)
3. Schoch et al, Nuclear transport receptor binding avidity triggers a self-healing collapse transition in FG-nucleoporin molecular brushes. *PNAS* 109 16911 (2012)
4. Kapinos et al, Karyopherin-centric control of nuclear pores based on molecular occupancy and kinetic analysis of multivalent binding with FG-Nucleoporins. *Biophys. J.* 106 1751 (2014)
5. Schleicher et al, Selective transport control on molecular velcro made from intrinsically disordered proteins. *Nature Nanotechnology* 9 525 (2014)

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