

Solvay Colloquium



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Decoding Molecular Plasticity in the Dark Proteome

The mechanisms by which intrinsically disordered proteins (IDPs) engage in rapid and highly selective binding is a subject of considerable interest and represents a central paradigm to nuclear pore complex (NPC) function, where nuclear transport receptors (NTRs) move through the NPC by binding disordered phenylalanine-glycine-rich nucleoporins (FG-Nups). In the first part of my talk, I will present a combined single molecule, ensemble spectroscopy, solvation approach that paired with atomic simulations revealed that a rapidly fluctuating FG-Nup populates an ensemble of conformations that are prone to bind NTRs with diffusion-limited on-rates. This is achieved using multiple, minimalistic, low affinity binding motifs that are in rapid exchange when engaging with the NTR, allowing the FG-Nup to maintain an unexpectedly high plasticity in its bound state. Since site-specific labeling of proteins with small but highly photostable fluorescent dyes inside cells remains the major bottleneck for directly performing such high resolution studies in the interior of the cell, I will demonstrate an approach on how to overcome this limitation in the second part of my talk. We have now developed a semi-synthetic strategy based on novel artificial amino acids that are easily and site-specifically introduced into any protein by the natural machinery of the living cell. Expressed proteins only differ from their natural counterparts by very few atoms, constituting a ring-strained cyclooctyne or cyclooctene functional group. This allowed rapid, specific "click" labeling and even multi-color studies of living cells and subsequent super resolution microscopy.

References

Nikic I, Estrada Girona G, Kang JH, Paci G, Mikhaleva, Koehler C, Shymanska NC, Ventura Santos C, Spitz D, Lemke EA*. Debugging Eukaryotic Genetic Code Expansion for Site-Specific Click-PAINT Super-Resolution Microscopy. *Angew Chem Int Ed Engl*, Dec 23;55(52):16172-16176 (2016)

Milles S, Mercadante D, Aramburu IV, Jensen MR, Banterle B, Koehler C, Tyagi S, Clarke J, Shammas S, Blackledge M, Gräter F, Lemke EA. Plasticity of an ultrafast interaction between nucleoporin and transport receptors. *Cell*. 2015 Oct 22;163(3):734-45. doi: 10.1016/j.cell.2015.09.047. Epub 2015 Oct 8.

Nikic I, Plass T, Schraadt O, Szymanski J, Briggs JA, Schultz C, Lemke EA*. Dual-color super-resolution microscopy via genetic code expansion technology and tune click reactions. *Angew Chem Int Ed Engl*, 2014, Feb, 53(8), 2245-2249 (2014)

Tuesday 27 March 2018 at 4.00 P.M.

COFFEE AND TEA WILL BE SERVED AT 3.45 P.M. IN FRONT OF THE SOLVAY ROOM

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