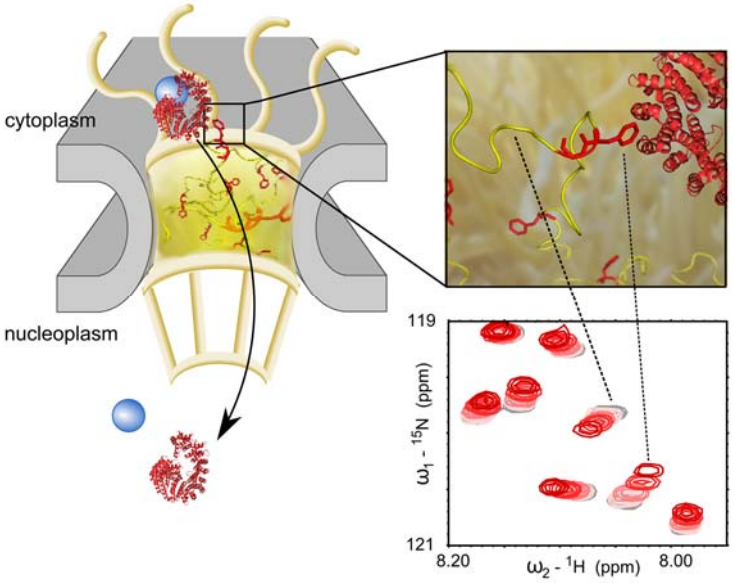
The essential mechanism by which molecules are transported into the nucleus of the cell has been revealed by an international collaboration implicating researchers at the Institut de Biologie Structurale (Grenoble), the EMBL (Heidelberg), the Heidelberg Insitute of Theoretical Studies, and the University of Cambridge. Combining *in vitro* and *in vivo* experimental observations and simulation, the consortium was able to demonstrate how nucleoporins, highly flexible proteins present in the pores of the nuclear envelope, create a selective barrier by exploiting multiple, weak interactions with the transporting proteins, allowing for rapid but selective passage into the nucleus. These results are published in Cell (8 October 2015).

The nucleus is the control centre of the cell, containing the vast majority of the genetic information in the form of DNA, and orchestrating the cellular reactions necessary for biological function. The double membrane surrounding the nucleus also acts as a protection of the vital genetic information. Cellular function however requires the continual exchange of certain proteins and other signalling molecules (cargoes) between the cytoplasm and the interior of the nucleus, an exchange that is selective and mediated by proteins called 'transportins'. The transportin-cargo complexes traverse the only entry points, the nuclear pores, through interaction with the disordered nucleoporins, highly flexible proteins in permanent conformational flux, that fill the central channels of these transport conduits. How the interaction between nucleoporins and transportins can be highly specific and allow rapid molecular transit into and out of the nucleus at the same time has remained elusive until now.

The authors of the study combined different experimental techniques, high field nuclear magnetic resonance (NMR) spectroscopy, fluorescence and molecular simulation, to understand the molecular basis of this transport mechanism. They were able to identify, and monitor, a multitude of weak, yet specific interactions between specific sites on the nucleoporins, and the transportins.



Representation of a nuclear pore and the transport of molecules between the cytoplasm and the nucleus. Transportins are shown in red and the nucleoporins in yellow. The nucleoporins form a molecular filter between the inside and outside of the nucleus. Right: NMR experiments, in combination with fluorescence and molecular simulation identify the interaction sites between transporters and nucleoporins. Top : an illustration of the interaction, bottom : zoom of an NMR spectra showing the interaction of different amino acids with the transporter. © Sigrid Milles / CEA

NMR was used to identify, at atomic resolution, the regions of the disordered nucleoporins implicated in the interaction mechanism and the nature of the interaction.

They found that the interaction is highly localised to short regions concerning one or two amino acids, with the rest of the nucleoporin remaining flexible, even upon interaction. The high specificity is directly linked to the local composition of the amino acid sequence, while the rest of the disordered chain hardly participates in the interaction.

The researchers then investigated the kinetics of the interaction, using a combination of NMR, fluorescence and molecular simulation, showing that not only is each interaction very weak, it is also rapid, with the transporter fleetingly attaching and detaching from different interaction sites on the ensemble of nucleoporin molecules.

Putting all of this information together, they were able to propose a model for the fast passage of the transporter from the cytoplasm to the nucleus. The transporter interacts rapidly and superficially at specific points on the nucleoporins, which allows it to interchange partners as it passes through the pore, thereby remaining specifically attached to the ensemble of nucleoporins, but diffusing from one side of the channel to the other. This physiological efficiency is based on the high plasticity of the intrinsically disordered nucleoporins, and the multiplicity of their interaction sites.

Références : "*Plasticity of an ultrafast interaction between nucleoporins and nuclear transport receptors*", Sigrid Milles *et. al.*, *Cell*, Octobre 2015, http://dx.doi.org/10.1016/j.cell.2015.09.047