Blueprints for the construction of nuclear pores deciphered

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In a recent study, a team of researchers led by Alwin Köhler at the Max F. Perutz Laboratories (MFPL) belonging to the University of Vienna and the Medical University of Vienna offer new insights into how nuclear pores are constructed in the nuclear envelope. Nuclear pores regulate the exchange of macromolecules between the interior of the nucleus, where genetic information is stored, and the cytoplasm, where these blueprints are used to produce many different cellular building blocks. More than a million macromolecules are transported through the 3,000 – 4,000 nuclear pores in a human nucleus every minute. This exchange is a vital function and transport errors are associated with

cancer, ageing and autoimmune diseases. The results of this study have now appeared in the renowned technical journal *Developmental Cell*.

Cells are the basic building blocks of all life forms. Some living organisms consist of only one cell, whilst a human is made up of more than 100 billion different cells. The shape and function of the cells differ according to the type of organism, as do the cells of different types of tissue within the same organism. However, an essential distinction can be made between living organisms without a nucleus, prokaryotes, and those with a nucleus, eukaryotes. All higher life forms such as humans and animals are eukaryotes. Their cells are characterized by an organelle, which envelops and protects their genetic material: the nucleus.

The nucleus is surrounded by a double membrane, which delimits it from the rest of the cell. In the same way as a mediaeval city, it is surrounded by two walls. Just as the inhabitants need to be able to transport goods and food in and out of their city, a controlled interchange of molecules between the nucleus and the cell interior is vital for cells. The gates in the city wall are the nuclear pores. These enormous protein complexes form a highly selective channel, which penetrates through the entire nuclear membrane, broadening out in the nuclear interior to form a structure similar to a basketball basket, the technical term for which is actually a "nuclear basket".

One of the focuses of the research being conducted by ERC and START prize-winner Alwin Köhler and his team at the Max F. Perutz Laboratories of the Medical University of Vienna and the University of Vienna is to gain a better understanding of the structure and function of this "nuclear basket".

"Up until now it has been assumed that the basket serves primarily as a docking station for the transported goods (Note: e.g. ribonucleic acids). However, when we over-expressed basket proteins, that is to say allowed

the cell to produce far too much, we saw dramatic changes in the nuclear structure: the nuclear membrane was massively deformed compared with its normal spherical shape," explains Alwin Köhler. These observations gave the researchers the idea of investigating whether the "basket proteins" also have the ability to directly bind and model nuclear membranes.

In order for a new nuclear pore to be formed in the double membrane surrounding the nucleus, a modification first has to be made at this site and a "hole" created in the membrane. For this to happen, the two membranes have to come towards each other, bow out and finally fuse. PhD student Noémi Mészáros explains: "It's as if you were trying to push part of the outer city wall in a bit and part of the inner wall out a bit, in order to create an opening for a new gate." The joint lead author of the study, Jakub Cibulka, adds: "Our experiments showed that basket proteins can even deform membranes in a test tube. Furthermore, we were able to show that nuclear membranes become unstable without basket proteins and the nuclei are extremely deformed." These findings confirm the researchers' hypothesis that basket proteins are more than merely docking stations for transported goods. They actively assist in converting the nuclear membrane for construction of a nuclear pore.

These new findings not only provide researchers with a better understanding of the extremely complex molecular gate but also, in the longer-term, help with research into the role of the nuclear pores in cancer and ageing processes. Alwin Köhler's team is now working to gain a more detailed understanding of the principle of nuclear membrane (re)construction, for which this study has provided a foundation. "Once again this project has reminded us that biology is always full of surprises. Basic research is not always predictable, but it provides important insights for medicine. It is highly probable that deformation of the nucleus changes its overall function and disrupts medically relevant functions," says Alwin Köhler.

More information: "Nuclear pore basket proteins are tethered to the nuclear envelope and can regulate membrane curvature." *Developmental Cell*, May 2015. DOI: dx.doi.org/10.1016/j.devcel.2015.02.017

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