Large molecules need more help to travel through a nuclear pore into the cell nucleus

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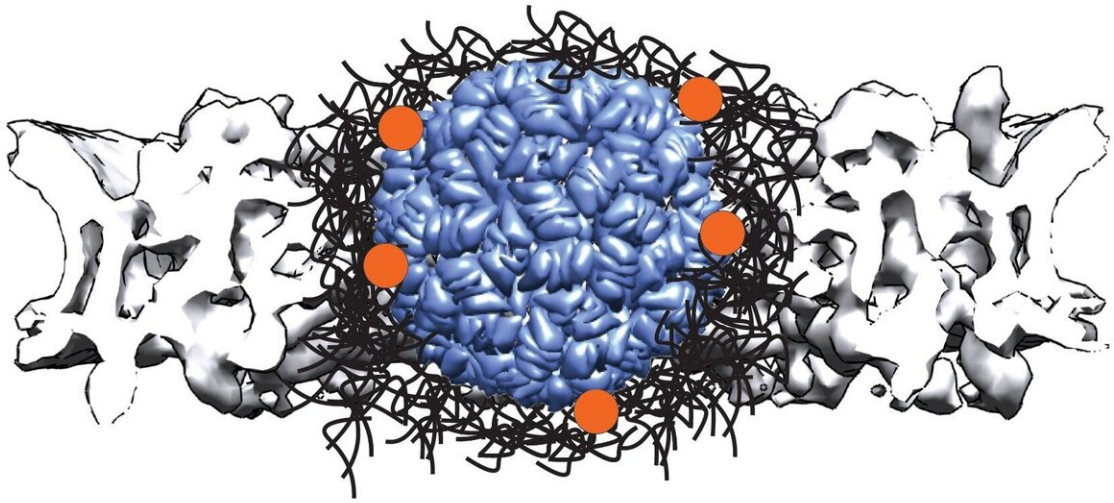

Model of a large molecule (blue, PDB ID:2MS2), bound to multiple transporter proteins (orange dots) that interact with the nuclear pore complex barrier (gray, EMD-8087), a process essential for import into the cell nucleus. Credit: Giulia Paci (CC BY 4.0)

A new study in the field of biophysics has revealed how large molecules are able to enter the nucleus of a cell. A team led by Professor Edward Lemke of Johannes Gutenberg University Mainz (JGU) has thus provided important insights into how some viruses, for example, can penetrate into the nucleus of a cell, where they can continue to

proliferate and infect others. They have also demonstrated that the efficiency of transport into a cell decreases as the size of the molecules increases and how corresponding signals on the surface can compensate for this. "We have been able to gain new understanding of the transport of large biostructures, which helped us develop a simple model that describes how this works," said Lemke, a specialist in the field of biophysical chemistry. He is Professor of Synthetic Biophysics at JGU and Adjunct Director of the Institute of Molecular Biology (IMB) in Mainz.

A typical mammalian cell has about 2,000 nuclear pores, which act as passageways from the cell cytoplasm into the cell nucleus and vice versa. These pores in the nuclear envelope act as gatekeepers that control access and deny entry to larger molecules of around five nanometers in diameter and greater. Molecules that have certain nuclear localization sequences on their surface can bind to structures within nuclear pores, allowing them to enter into the nucleus rapidly. "Nuclear pores are remarkable in the diversity of cargoes they can transport. They import proteins and viruses into the nucleus and export ribonucleic acids and proteins into the cell cytoplasm," explained Lemke, describing the function of these pores. "Despite the fundamental biological relevance of the process, it has always been an enigma how large cargoes greater than 15 nanometers are efficiently transported, particularly in view of the dimensions and structures of nuclear pores themselves."

With this is mind and as part of their project, the researchers designed a set of large model transport cargoes. These were based on capsids, i.e., protein "shells" in viruses that enclose the viral genome. The cargo models ranging from 17 to 36 nanometers in diameter were then fluorescently labeled, allowing them to be observed on their way through cells. Capsid models without nuclear localization signals on their surface remained in the cell cytoplasm and did not enter the cell nucleus. As the number of nuclear localization signals increased, the accumulation of the

model capsid in the nucleus became more efficient. But even more interestingly, the researchers found that the larger the capsid, the greater was the number of nuclear localization signals needed to enable efficient transport into the nucleus.

The research team looked at a range of capsids of various viruses including the hepatitis B capsid, the largest cargo used in this study. But even increasing the number of nuclear localization signals to 240 did not result in the transport of this capsid into the nucleus. This corresponds with the results of earlier studies of the hepatitis B virus that have indicated that only the mature infectious virus is capable of passage through a nuclear pore into the nucleus.

In cooperation with Professor Anton Zilman of the University of Toronto in Canada, a mathematical model was developed to shed light on the transport mechanism and to establish the main factors determining the efficiency of transport. "Our simple two-parameter biophysical model has recreated the requirements for nuclear transport and revealed key molecular determinants of the transport of large biological cargoes on cells," concluded first author Giulia Paci, who carried out the study as part of her Ph.D. thesis at the European Molecular Biology Laboratory (EMBL) in Heidelberg.

More information: Giulia Paci et al, Molecular determinants of large cargo transport into the nucleus, *eLife* (2020). DOI: 10.7554/eLife.55963

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