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How does "Open Sesame" Function for Viruses?

Max Planck scientists have found the optimal size with which viruses and nano-particles are able to enter cells

The nanoscale size of many viruses may have evolved to minimize their time to enter cells via a process called receptor mediated endocytosis, according to new research conducted by scientists from the Max Planck Institute for Metals Research and Brown University. While it has been previously assumed that the endocytosis of viruses is associated with the formation of clathrin coats at the cell membrane, recent experiments have shown that influenza viruses can enter cells even if the formation of clathrin coats are inhibited. The Max Planck and Brown researchers developed a mathematical model of a cell membrane with diffusive mobile receptors wrapping around a ligand coated cylindrical or spherical particle. The model predicted an optimal particle size for the smallest wrapping time and provided an explanation of how particles in the size range of tens to hundreds of nanometers can enter or exit cells even in the absence of clathrin or caveolin coats. (Gao et al., PNAS, 22 June 2005.)

Many viruses and bioparticles enter animal cells via receptor mediated endocytosis which is one of the most important vesicular traffic mechanisms in cellular transport. Viruses come in thousands of different shapes and sizes; most of them having a characteristic size in the range of tens to hundreds of nanometers. The life cycle of a virus follows a sequential route through various compartments of the host as illustrated in Fig. 1 (a-d). In receptor mediated endocytosis, viruses or particles enter and leave animal cells via the binding interaction between ligand molecules on the viral capid (such as hemagglutinin in the case of influenza viruses) and their receptor molecules on the cell membrane, which causes the membrane to wrap around the viral particle. Some enveloped viruses are transported in the intracellular compartments via similar wrapping processes shown in Fig. 1 (e-i).

The endocytic pathway is also of interest to understanding mechanisms by which nanomaterials might enter into human or animal cells, a significant issue for the development of gene and drug delivery tools as well as for assessing the potential hazard of nanotechnology on ecology and human health. Experimental studies on targeted drug delivery into cells have identified particle size as an important factor in cellular uptake of nanomaterials. It has been shown that particles with radii smaller than 50 nm exhibit significantly greater uptake compared to particles larger than 50 nm and that there is an optimal size around 25 nm. Other studies have shown that carbon nanotubes can enter animal cells without apparent toxicity.

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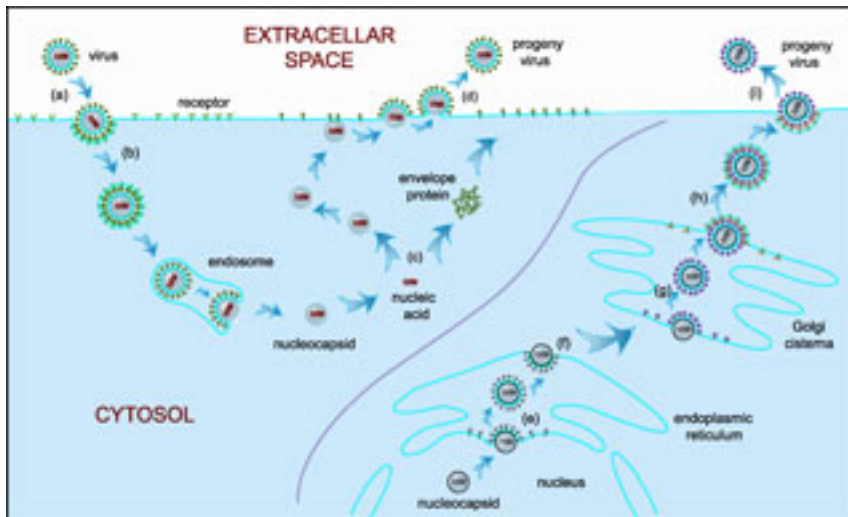
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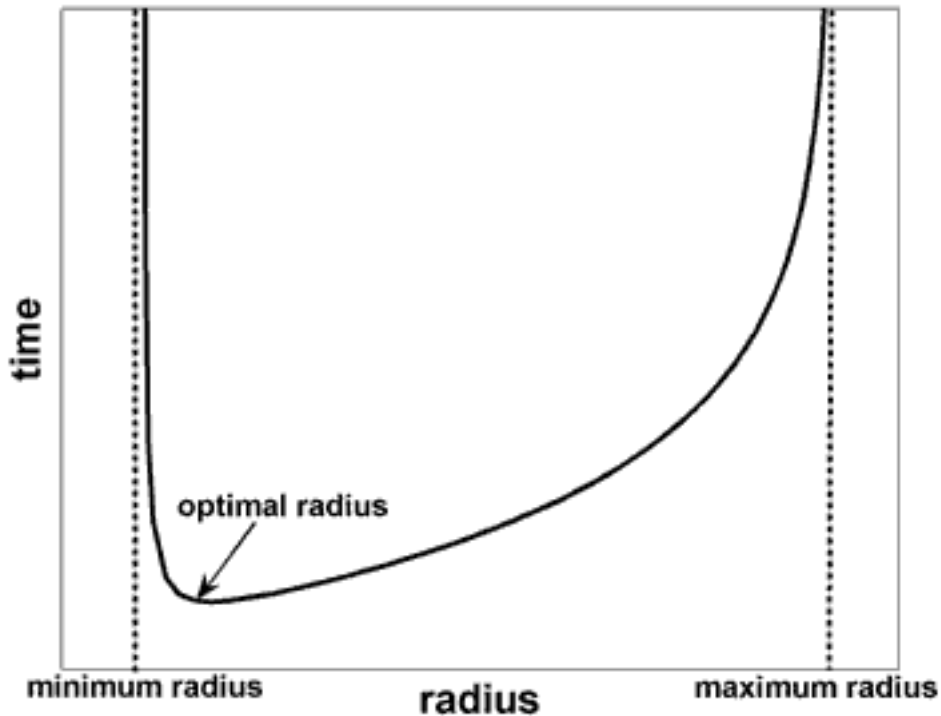
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- 1** *The life cycle of an animal virus. (a) Adsorption or docking with receptor proteins on the host membrane; (b) entry into the host cytoplasm; (c) biosynthesis of viral components; (d) budding from the host cell. (e-i) Some viruses (such as herpes virus) also follow membrane trafficking pathways within the host cell. (e) Budding through the inner nuclear membrane; (f) fuse with the outer nuclear membrane (endoplasmic reticulum); (g) budding into the Golgi apparatus; (h) budding out again on the other side. (i) fuse with the cell membrane. (Schematic figure adapted from Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J. D. (1994) *Molecular Biology of the Cell* (Garland, New York).)*

Image: Max Planck Society

It has been generally assumed that the endocytosis of viruses is associated with the formation of a clathrin coat at the inner membrane leaflet. However, it has been recently shown that influenza viruses can enter cells even if the formation of clathrin coats is inhibited. Scientists from the Max Planck Institute for Metals Research (H. Gao, W. Shi) and Brown University (L. B. Freund) developed a mathematic model to understand clathrin-free receptor mediated endocytosis by adopting a mathematical framework that had previously been used to study curved cell membranes spreading on flat substrates. The researchers considered cylindrical or spherical particles coated with fixed ligand wrapped around by a cell membrane containing compatible diffusive mobile receptors without clathrin coats. According to their model, the particle size can significantly affect the endocytotic time, with a typical behavior shown in Fig. 2. The results showed that particles in the size between a minimum and a maximum particle radius can enter or exit cells via wrapping even in the absence of clathrin coats. There exists an optimal particle size for the smallest wrapping time. The theoretical model predicts an optimal radius around 27~30 nm for spherical particles.



Prediction of the endocytosis time as a function of the particle radius (units not shown here for simplicity). The model predicts an optimal radius for the smallest wrapping time, as well as a minimum and a maximum particle radii for receptor mediated endocytosis.

Image: Max Planck Institute for Metals Research

Original work:

H. Gao, W. Shi and L. B. Freund

Mechanics of receptor mediated endocytosis

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