PERSPECTIVE

Active Intracellular Transport of Nanoparticles: Opportunity or Threat?

Henry Hess[†,*] and Yiider Tseng[‡,*]

[†]Department of Materials Science and Engineering and [‡]Department of Chemical Engineering, University of Florida, Gainesville, Florida 32611

ABSTRACT Active transport mechanisms, relying on motor proteins or polymerization of cytoskeletal filaments, play a central role in the uptake of nanoparticles by cells. While active transport can enhance the effectiveness of nanoparticle therapeutics, it also contributes to the toxicity of nanoparticles released to the environment. In work published in an article in this issue, Galya Orr and colleagues investigated the role of active transport in the interaction of different types of silica particles with alveolar epithelial cells, which are found on the inner surface of the lung.

See the accompanying Article by Orr *et al.* on p 463.

*Address correspondence to hhess@mse.ufl.edu, ytseng@che.ufl.edu.

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Rudolf Diesel may have coughed a few times in 1892 when his newly invented engine spewed out soot, but he had little reason to anticipate that "diesel exhaust particles" would become a source of respiratory health problems.[1] Nanoscientists cannot claim innocence more than 100 years later when creating new nanoparticles, and quite a few nanoentrepreneurs may have nightmares that feature asbestos and tobacco. Without a doubt, nanotoxicology has to mature as a scientific discipline to enable the widespread application of nanoparticles.[2–4]

While nanotoxicology studies focused initially on the poster twins of nanotechnology, fullerenes and carbon nanotubes,[5] many other nanomaterials are now being assessed from several different perspectives. For example, a global view of the toxicity of a nanoparticle may be obtained from an assessment of the oxidative stress response of cultured cells,[6] and the initial steps in the sequence of events leading to a cellular response are often related to the interactions of nanoparticles with proteins.

Two recent studies published in *Nano Letters* and *ACS Nano* further investigate the chain of events connecting the initial contact between a cell and a nanoparticle with an abnormal cellular response. Nabiev *et al.* showed that small quantum dots can penetrate into the nucleus and target histones, chromosome-binding proteins.[7] Orr *et al.* investigated the uptake of silica nanoparticles by alveolar cells, which are found on the surface of the lung.[8] Both studies concluded that the active transport machinery of the cell plays a key role in accelerating particle capture by the cell and particle delivery to the nucleus (Figure 1).

The term "active transport machinery" describes a number of nanoscale systems operating within eukaryotic cells that consume energy by hydrolyzing ATP or GTP and move proteins, RNA, vesicles, and organelles in response to internal programs or external stimuli. For example, a microtubule, a type of cytoskeletal filament polymerized from tubulin proteins, can attach one end to a chromosome and exert forces by reversibly growing or shrinking—steering chromosomes into the appropriate daughter cells during cell division.[9] Similarly, the polymerization of actin filaments exerts forces that propel bacteria and drive cellular movement.[10] Polymerization-dependent transport by cytoskeletal filaments is supplemented by transport using motor proteins. The myosin, kinesin, and dynein families of motor proteins move cargo along cytoskeletal filaments at speeds on the order of micrometers per second, 100-fold faster than filament polymerization velocities.[11]

The purpose of the active transport machinery has been subverted before, when viruses developed the ability to "hijack" dynein motor proteins to accelerate the delivery of their genetic material from the infection site to the nucleus.[12]

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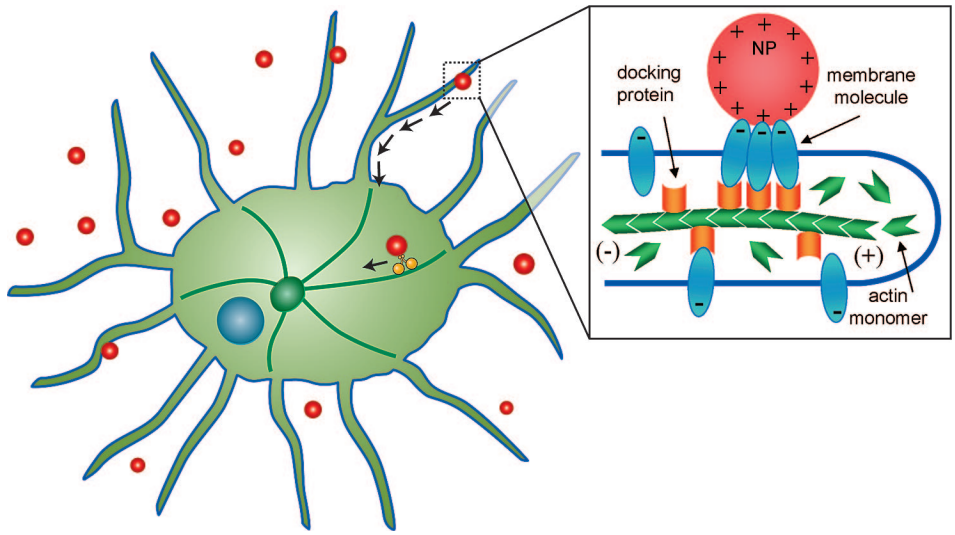

Figure 1. Active transport plays an important role in the uptake of particles into cells. For example, dynein motors can move nanoparticles along microtubules toward the nucleus. In addition, the dynamics of the actin cytoskeleton leads to the transport and internalization of silica particles along the microvilli of alveolar epithelial cells (inset).

Herpes simplex virus I infects neurons and binds to dynein motors moving toward the nucleus, covering distances of up to several feet as a dynein's cargo.[13]

Similar concepts have been developed to exploit active transport for therapeutic purposes. In particular, the efficiency of gene therapy employing synthetic delivery vehicles[14] instead of viral delivery could be improved if dynein motors could be targeted by the delivery vehicle and induced to transport it to the nucleus.[15,16]

Unfortunately, the promise of harnessing active transport for the delivery of therapeutic nanoparticles is complemented by the need to understand the influence of active transport on particle−cell interactions, which potentially increase toxicity to the tissue.[17] Orr *et al.* demonstrated that particle uptake is enhanced for cells whose filopodial morphology increases their surface (and therefore their nanoparticle collection area) because active transport mechanisms can concentrate the nanoparticles.

Orr *et al.* also showed that only positively charged particles are transported along the microvilli, and they proposed a mechanism of actin-dependent trafficking in alveolar cells, analogous to the transport of cationic microspheres along neuronal growth cones.[18] This illustrates that—just like the internalization of viruses and drug delivery vehicles, which follow specific pathways—different types of nanoparticles can exploit different mechanisms to gain entry into the cell. A detailed, mechanistic understanding of particle uptake is thus desirable from the perspective of several fields in biomedical research, including virology, pharmacology, and nanotoxicology.

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