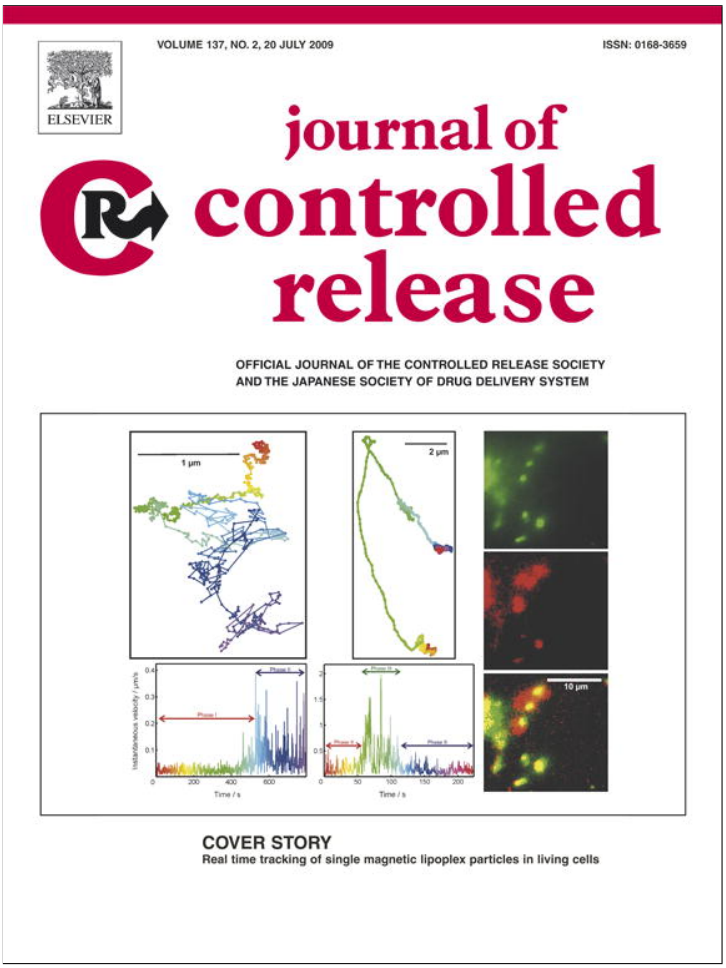

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Cover Story

Real time tracking of single magnetic lipoplex particles in living cells

In delivery of particulate systems into cells most studies are based on ensemble measurements regarding dose–response profiles and kinetics of particle delivery. The study of nonviral gene delivery is not an exception. For a detailed insight into the mechanisms of uptake and transport of gene delivery particles, however, it is important to look behind the averaging effect of ensemble methods and take the view of a single particle tracking method in real time. Highly sensitive fluorescence widefield microscopy can be used to track such a particle and obtain its trajectory in space and time. This reveals the mechanistic details of internalization and transport of a particle within the living cell. Anna Sauer and colleagues from the Bräuchle and Plank groups in Munich, Germany used this method in their article in this issue [1]. They followed the pathway of single magnetic lipoplexes in living cells. Magnetic lipoplexes are nucleic acid vectors associated with magnetic nanoparticles that can be localized on target cells or specific areas in the body by means of a magnetic gradient field. This is called magnetofection. Until now, little is known about the details of cellular uptake and intracellular processing of magnetic complexes used in magnetofection.

The single particle tracking experiments of Sauer et al. with magnetic lipoplexes in living HuH7 cells show three distinct phases of motion. During phase I magnetic lipoplexes are attached to the cell surface and show slow cooperative transport behavior with very small instantaneous velocities. The transport seems to be mediated by transmembrane proteins connected to the underlying actin cytoskeleton. Internalization of the magnetic lipoplexes appeared to be endocytosis-driven by colocalization with a fluid phase marker. Phase II takes place inside the cell and is characterized by anomalous and confined diffusion with higher instantaneous velocities. In this phase the particle filled endosomes feel the obstacles in the crowded cytosol during their movement. Phase III represents fast active transport of the endosomes with motor proteins along microtubules. Velocities as high as 2 μm/s were observed. On later time points endosomes containing magnetic lipoplexes were found to fuse and transiently accumulate in a perinuclear ring. Endosomal release of the magnetic lipoplexes was not observed with this method.

One of the most important findings by Sauer et al. is that the application of a magnetic field in combination with the use of magnetic particles affects only the extracellular phase of lipoplex delivery but does not, for example, induce a direct entry of the lipoplex into the cytoplasm via the plasma membrane. In this sense, magnetofection is not sufficient to avoid or overcome the current cellular barriers for gene transfer. This finding is highly significant, because it has been commonly misunderstood that applying magnetic field would increase transmembrane movement of magnetic particles. The study highlights the importance of combining improved gene delivery strategies with single particle tracking to assess the benefit of existing nonviral vectors in detail on a cellular level. This will undoubtedly lead to a better understanding of existing vectors and further optimization in the design of new vector systems.

Reference

[1] A.M. Sauer, K.G. de Bruin, N. Ruthardt, O. Mykhaylyk, C. Plank, C. Bräuchle, Dynamics of magnetic lipoplexes studied by single particle tracking in living cells, J. Control. Release 137 (2009) 136–145.

Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu.

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