PEG Improves Intracellular Transport of Drug/gene Carriers as Revealed by Real-Time Particle Tracking

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Surface-modification of drug/gene delivery vehicles with polyethylene glycol (PEG), or PEGylation, may prevent unwanted binding of particles to biological obstacles to drug/gene delivery. Specifically, PEGylation of particles may improve their cytoplasmic transport (once the particles have escaped endosomal vesicles) by minimizing attractive forces to cytoskeletal elements, such as actin filaments or microtubules. To quantitatively study the effects of PEGylating drug/gene carriers, multiple particle tracking (MPT) was used to compare the real time transport of nanoparticles, with or without PEG, in live cells.

Diamine PEG (3400 MW) was attached to 100 nm carboxylated polystyrene particles (PS) using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDAC) chemistry. PS particles, either PEGylated or unmodified, were microinjected directly into the cytoplasm of live HeLa cells. The intracellular transport of particles were quantified with real-time live-cell MPT in conjunction with epifluorescence microscopy. Briefly, 20 s movies of particle transport within HeLa cells were analyzed with Metamorph™ software (Universal Imaging) to give 2-dimensional positional data, from which their mean-squared displacements (MSD) were calculated. $MSD = 4D_{eff}\tau$, where D_{eff} is the effective diffusivity of each individual particle and τ is time scale.

The diffusion of both PEGylated and unPEGylated nanoparticles was restricted in the cell cytoplasm, with their ensemble-averaged D_{eff} decreasing with τ (a characteristic of anomalous sub-diffusion). PEGylated particles displayed diffusivities statistically greater than unmodified particles at a time scale of 1 s ($p<0.01$ as determined by Kruskal-Wallis test). At the longer time scale of 10 s, however, the difference in transport rates was no longer statistically significant ($p>0.05$). PEGylated particles exhibited a wider distribution of MSD values than unmodified particles, indicating PEGylation increases the heterogeneity in intracellular particle transport. This can be due to heterogeneity in the PEGylation reaction, resulting in a population of particles displaying heterogeneous surface properties.

Our results show PEGylation of nanoparticles improves their cytoplasmic transport rates (outside of endosomal vesicles), possibly by reducing non-specific adhesion to cytoskeletal elements. This further adds to the list of key advantages of attaching PEG to drug/gene delivery vectors. Studies are currently underway to determine if PEG will improve the cytoplasmic transport of all drug delivery nanoparticles.