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The cytoplasmic escape pathway of polyethylenimine coated nanoparticles is altered by changing the nanoparticle concentration

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Polyethylenimine (PEI) is commonly utilized as a non-viral gene delivery vector because it destabilizes vesicle membranes enabling release of genes to their site of action in the cytoplasm or nucleus. However, the precise mechanism of cytoplasmic release remains unclear. Possibilities include either pore formation or vesicle rupture of either endosomes or lysosomes. Identifying the escape route is critical because lysosomes have digestive enzymes which may impair the gene once inside, and furthermore release of lysosomal contents to the cytoplasm can be detrimental to the cell. To investigate cytoplasmic escape of PEI, we utilized X-ray tomography which can monitor 3D volumes of vitrified cells at 40 nm spatial resolutions without chemical fixation, staining or slicing. With this technique, we find that the mechanism of PEI-nanoparticle (PEI-np) escape to the cytoplasm is concentration dependent. At standard concentrations, PEI-np escapes by rupturing lysosomes. This release mechanism is relatively inefficient with limited nuclear entry of PEI, and with most PEI-np encapsulated within endosomes. Furthermore, we observe morphological signs of apoptosis such as extended mitochondria and chromatin condensation. However, at a ten-fold lower concentration of PEI-np, we detect no ruptured lysosomes and no PEI-np within lysosomes, and importantly we find a higher efficiency of escape to the cytoplasm and nucleus. At these concentrations, we find no mitochondrial elongation and significantly reduced chromatin condensation. In sum, simply by reducing the PEI-np concentration, it appears that PEI-np are directed to a different pathway in which lysosomes are not ruptured, endosomal escape and nuclear entry are more efficient and the adverse effects of PEI-np are reduced. Our results suggest that lower concentrations of PEI-np have multiple benefits for cellular gene delivery.

Biography

Kepsutlu Burcu is a PhD student and has her expertise in "Evaluation of morphological and functional effects of biologically relevant nanoparticles on cells via X-ray tomography". With this technique, she showed that nanoparticles induce a significant remodeling of cellular organelle composition within non-apoptotic cells. She also utilized this relatively beneficial technique to track nanoparticle distribution within individual organelles and define the endocytosis pathway of nanoparticles. She found out that nanoparticles are localized in lipid droplets which may be the reason for nanoparticle localization within liver. She also found out that multivesicular bodies may exist without a limiting membrane. All these findings provide invaluable knowledge in the drug delivery field and can be utilized for investigation of different types of drugs with cells.

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