580a Doxorubicin-Loaded Transferrin-Targeted Polymeric Micelles Rapidly Enter Cancer Cells and Accumulate near the Cell Nucleus

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Polymeric micelles, amphiphilic block copolymers assembled into nanoscopic supramolecular core-shell structures, offer several potential advantages for advanced drug and gene delivery. These include a characteristic size less than 100nm, the capacity to entrap fragile or poorly water-soluble drugs in the hydrophobic core, and the ability to evade removal by the reticulo-endothelial system (RES) due to their small size and hydrophilic shell layer of poly(ethylene glycol). The small size of polymeric micelles may allow for passive targeting to cancer cells due to the leaky vasculature of cancerous tissues relative to normal tissue vessels.

Polymeric micelles traditionally suffer from low drug loading and rapid drug release, hence limiting their application as therapeutic carriers. We synthesized polymeric micelles with high doxorubicin loading, minimal initial burst effect, and prolonged release periods. We further sought to obtain a mechanistic understanding of how these carriers are trafficked in live cells, with the goal of enhancing their transport to the perinuclear region. To this end, multi-color Confocal Particle Tracking (CPT) is used to directly correlate the transport of polymeric micelles with biological location (i.e. intracellular vesicles) in live cells and in real time.

We synthesized 70nm polymeric micelles with a hydrophilic poly(ethylene glycol) shell, which are labeled fluorescently with NeutrAvidin(Rhodamine) and targeted to cells via transferrin ligands. HeLa cells were pre-transfected with genes encoding fluorescent marker proteins for specific organelles: EEA1-GFP for early endosomes (EE) or Niemann Pick C1 (NPC1-GFP) for late endosomes/lysosomes (LE/Lys). This enables live-cell co-localization studies of the polymeric micelles and vesicles within the endo-lysosomal pathway.

Doxorubicin-loaded polymeric micelles with transferrin ligand were found to rapidly enter cells and accumulate in the perinuclear region of HeLa cells after 4 hrs. These carriers were found to have trafficked from EE at this time point (low co-localization with EEA1-GFP) to LE/Lys (~70% co-localization with NPC1-GFP). Doxorubicin delivered by these polymeric micelles displayed significant cytotoxicity against HeLa cells in MTT assays. In comparison, placebo polymeric micelles exhibited negligible cytotoxicity.