Predictive models of nanoparticle transport in solid tumors

For more than a decade the drug delivery field has been obsessed with nanotechnology-based drug delivery systems which have been manifested into various forms of nanoparticles (NPs). Despite many important diseases to treat, nanoparticle formulations have been mainly used for delivering drugs to target tumors. NP systems may be used to deliver diverse cargo ranging from small molecules to genes. Potential target sites in cancer are tumor interstitium (e.g., diagnostics or therapeutics), cell membrane (e.g., antibodies), or intracellular compartments (e.g., RNAi). It has been assumed that the properties of NPs can be tailored for specific intended functions through judicious selection of material, controlling the NP size and surface charge, and modification of surface properties. In the absence of any guiding principles, however, development of nanoparticle formulations has been largely based on a trial-and-error approach.

Engineering NP properties has been often accompanied by unexpected and opposite effects on their in vivo distribution and processing. For example, conjugation with targeting ligands to enhance selectivity also retards NP transport due to ligand binding to cells. Pegylation increases NP circulation times, but it also decreases NP endocytosis. Another complication in using NPs is the well-recognized tumor heterogeneity in size, vascularization, growth rate, capillary permeability, extracellular proteins, and tumor cell density. Many of these properties are dependent on the host (e.g., larger tumors in humans than in mice), and can change with time (e.g., growth) or with treatments (e.g., apoptosis and increased porosity due to chemotherapy). Changes in one property can affect other properties. For example, increase in tumor size may retard vascularization and NP delivery, while treatment-induced changes in vasculature and vessel pore size may favor extravasation of larger NPs. In view of these multiple and intertwining dynamic processes, NP design needs to be optimized through better understanding on the NP transport to the intended target sites through quantitative analysis.

In this issue, Professor Au and her team evaluated the applications and limitations of the predictive models for cationic NP, using eight cationic liposomes comprising pegylated lipids, neutral lipids, cationic DOTAP (1,2-dioleoyl-3-trimethylammonium propane) and fusogenic DOPE (1,2-dioleoyl-sn-glycero-3-phospho-ethanolamine) [1]. They made a few important findings. In monolayer cultures, increasing the DOTAP content did not affect the size whereas increasing the DOPE content led to a several fold increase, and increasing DOTAP led to greater cell binding whereas increasing DOPE led to greater internalization in cells. In spheroids, liposomes show slow and time-dependent diffusion with penetration limited to the first few cell layers, with greater uptake for liposomes with higher surface charge (due to DOTAP content) and deeper penetration for liposomes with high DOPE content (20 mol%). Furthermore, in spheroids, only the diffusion of low-DOPE liposomes (≤10 mol%) agreed with the model predictions. The inferior model performance for the high-DOPE liposomes was not due to liposome aggregation or depletion. These findings indicate the presence of >10 mol% DOPE in cationic liposomes altered the liposome interaction with cells or cellular components, resulting in changes in liposome structure and diffusion. In silico results obtained with the predictive models provided quantitative measures of the effects of surface charge on the localization of cationic liposomes in three spheroid subcompartments (interstitial space, cell-bound, and intracellular). For liposomes comprising 10-30 mol% DOTAP (plus 1 mol% DOPE), their delivery and residence in spheroids, as reflected by the amount-spheroid depth profiles, were primarily determined by their cell binding at early times (e.g., first 6 hours) and by their internalization at later times.

The studies by Professor Au and her group show the successful application of computational models that use NP-cell biointerface parameters obtained from monolayer cultures to predict the diffusive transport of NPs with different sizes (20–135 nm) and surface charges (−49 to +44 mV) in 3D systems. Multiscale models that integrate these diffusive models with models of other transport mechanisms (e.g., interstitial transport via fluid flow, diffusive and convective transvascular transport), NP interaction with other tumor components (e.g., vessel wall, stromal tissues), and NP disposition on the systemic level (e.g., distribution to other organs, elimination), such as the one developed by this team for the in vivo tumor spatiokinetics of intraperitoneal paclitaxel therapy [2], may accelerate the development of NP diagnostics and therapeutics. The real benefit of NP formulations can be found only when they improve the safety and efficacy of various anticancer drugs in clinical applications. The significance of the Au team’s work is that it shows that the development of clinically useful NP formulations can be achieved through rational NP design, a sign of real progress in the nanotechnology field.

References


Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu