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Cover story

Insight into extravasation and internalization of nanoparticles

For the last few decades nanoparticles have been used extensively for targeted drug delivery to tumors, and recently for overcoming the blood–brain barrier. The excitement of the potential of nanoparticles was mainly driven by successes in improved drug delivery in small animal models. Numerous research articles have demonstrated better efficacy of the same drug in nanoparticle formulations as compared with the free drug formulations. Despite the apparent advantages of nanoparticle formulations in small animal experiments, nanoparticle formulations have struggled in improving efficacy or reducing side effects in clinical trials.

The reasons for the difficulty in clinical translation may be manifold. The nanoparticle uptake by the reticuloendothelial system in humans may be very different from that in (often immuno-compromised) small animal models. In addition, drug retention in nanoparticles may be lower in humans as compared in small animals due to huge volume differences. More importantly, tumor physiology, in particular vascular structure, between the xenograft models and spontaneous tumors grown differs greatly. Furthermore, drug distribution in the tumor is not homogeneous, and such high heterogeneity is exacerbated by the use of nanoparticles. The diffusion of nanoparticles beyond the vasculature is severely reduced with increasing particle size, contributing further to the already problematic inhomogeneity of the tumor vasculature. Despite an overall increase in average drug amount delivered to the tumor with the use of nanoparticles, it is clear that a significant portion of the tumor may still have little exposure to the drug.

Better understanding of drug delivery to target tumors requires a more in-depth study of drug and nanoparticle behavior than the results obtained by typical biodistribution methods, which provide only organ-level information. The paper of Rapoport and coworkers in this issue makes good use of intravital microscopy to compare in near real time the extravasation and uptake of polymeric micelles, polymer-stabilized perfluorocarbon nanodroplets, and encapsulated paclitaxel in a tumor xenograft model [1]. It was found that in the normal tissue (thigh muscle), the extravasation of individual copolymer molecules (unimers) occurred extremely fast. The authors hypothesized that for micelles with elastic or soft cores, fast extravasation of unimers into the "sink" offered by normal tissues may be a major mechanism responsible for premature micelle degradation since unimers are expected to be constantly released from micelles in order to maintain unimer/micelle equilibrium in circulation. For nanodroplets, extravasation was much faster in the tumor than in the normal tissue, which is a basis of tumor targeting. However, for both micelles and nanodroplets, the extravasation was non-uniform: small capillaries appeared to be leakier than larger and better organized blood vessels. This caused an inhomogeneous drug distribution in the tumor.

The study by the Rapoport group suggests that extravasation and diffusion rates need to be balanced by cellular uptake and subsequent drug release. This is a process that can only be observed by the microscopic visualization system in a living system, although some of the pertinent parameters can be obtained from suitable in vitro studies. The study by the Martel team in this issue also utilized a microscopic imaging system to gain insights into the effect of hyperthermia on nanoparticle permeation through the blood–brain barrier [2]. An analysis of nanoparticle uptake and drug delivery on the microscopic level in small animal studies is essential to understanding and predicting therapeutic effects. Ultimately, however, it is the clinical studies that can confirm the efficacy and safety of nanoparticle formulations. Considering the fact that the results in small animal models have not been able to predict the nanoparticle efficacy in clinical studies, conducting pilot human study, as done by the Mitragotri group in this issue [3], may be necessary for certain nanoparticle formulations. For obvious reasons, however, clinical studies for testing various formulations under development are not practical. Thus, finding other experimental methods producing data relevant to clinical applications are urgently needed.

References

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