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For more than a decade, extensive research has been focused on tumor-targeted drug delivery using nanoparticles. The number of research articles on nanoparticle-based targeted delivery has been increasing steadily over time. In this issue, seven out of 14 of the articles deal with targeted drug delivery to tumors. They describe new approaches showing improvements in efficacy in decreasing tumor size in small animal models. The amount of drug accumulated at the tumor is increased by using non-invasive methods such as heat activation [1], focused ultrasound [2], optical modulation [3], and tumor priming [4], or by using new micelles [5], aptide–drug conjugates [6] and peptide ligand–conjugated liposomes [7].

In this issue, the work by Professor Katherine Ferrara and her colleagues presents an important result that enhances our understanding on targeted drug delivery [7]. Liposomes conjugated with a low concentration of a peptide with affinity for neuropilin-1 were effectively internalized in tumor cells bearing the receptor in vitro and were long circulating in vivo. The paper explores the changes in the receptor density and liposome accumulation over a 4-week course of treatment. Using ultrasound molecular imaging, the authors demonstrated that the vascular density of neuropilin-1 decreased over time for treatment with either the targeted or non-targeted particles containing doxorubicin. The quantitative information on the expression of the target receptor is invaluable in understanding the efficacy of the nanoparticle formulations. This change in receptor density has a far greater effect on the accumulation of the targeted particle: after 4 weeks of treatment, the accumulation of the targeted particle was significantly reduced compared with the non-targeted particles. Still, the targeted and non-targeted particles similarly limit tumor growth to a small fraction of that observed for the saline control. The important observation, however, is that the treatment with targeted liposomes resulted in far lower toxicity than an equivalent regimen of non-targeted nanoparticles. The use of the aptide–docetaxel conjugates also showed a reduction in toxicity [6].

Most of the studies on targeted systems in small animal models have focused on the increase in drug delivery to the target, but none has yet been successfully translated into clinical application. The experimental conditions that work well in small animal models cannot be easily reproduced in humans [8]. Furthermore, a perspective article on complex adaptive therapeutic strategies for cancer treatment describes why it is difficult to treat tumors, and argues that simply delivering more drug to the target site may not be sufficient [8,9]. It appears that a major benefit of nanoparticle formulations may lie in reducing the toxicity of the drug. After all, Doxil® (PEGylated liposome formulation delivering doxorubicin) has been used clinically for its reduced cardiotoxicity, not for its increased efficacy [10]. Since reduced side-effects are a result of altered biodistribution of the drug, the future studies may need to examine the changes in biodistribution over time. As clearly shown by the Ferrara team, the expression of the target receptor changes over time [7]. Thus, the concept of targeting tumor cells based on overexpression of a target receptor is naïve when applied in the absence of information on the receptor density on the target cells. The information presented in this issue collectively indicates that the future studies on targeted drug delivery may require time-dependent biodistribution of a drug, expression of the target receptor, and accumulation of the free drug at the target site.

References


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