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Cover story

Microbubble ultrasound-guided targeted delivery to tumors

Cancer gene therapy remains a promising approach to treating a variety of malignancies by inducing tumor cells to generate gene products that kill cancer cells without hurting healthy tissue. However, cancer gene therapy, as well as gene therapy for other diseases, has been restricted by the difficulty of safe and effective delivery of DNA into the cytoplasm of tumor cells. There are basically two main barriers to overcome. The first is the lack of effective means of systemic targeting, i.e., targeted delivery of the injected DNA to the tumor and homogeneous accumulation throughout the tumor tissue. The second is the poor control of intracellular targeting, i.e., transport of DNA to the nucleus, where it can be transcribed. In this issue, two new important developments to overcome these barriers using ultrasound-guided targeting with microbubbles are described to facilitate cancer gene therapy [1,2].

Ultrasound is used in clinical practice to image and ablate tissue, and efforts are underway to develop ultrasound for noninvasive gene delivery [3,4]. These efforts are often enabled by the use of microbubbles, which serve as ultrasound contrast agents for intravascular imaging. Furthermore, the use of microbubbles with high-intensity ultrasound has been shown to increase extravascular delivery to tissue [5-7]. These attributes provide the potential for microbubble image-guided targeted delivery to tumors; however, intracellular delivery to cancer cells beyond the endothelium remains a significant challenge. The articles by Sirsi and colleagues at the University of Colorado and Columbia University [1] and Bazan-Peregrino and coworkers at Oxford University [2] report on the use of microbubbles for systemic delivery with ultrasound guidance, in which engineered particles are delivered that subsequently provide enhanced intracellular delivery of the DNA cargo.

The paper by Bazan-Peregrino et al. [2] describes a detailed *in vitro* study of microbubble-assisted delivery of viral particles to breast cancer cells embedded in a novel flow phantom. Use of the phantom allowed the authors to illustrate the effects of ultrasound intensity and a co-injection of commercial microbubbles on virus particle delivery to cells in the hydrogel matrix far from the vessel walls. The use of stable cavitation increased the viral infection rate by a factor of 10, while inertial cavitation increased infection by a factor of 60. In a clever control experiment using cells absent the virus receptor, the Oxford team showed that infection was caused by action of the virus rather than sonoporation of the cellular plasma membrane.

The article by Sirsi et al. [1] reports on an *in vivo* study of novel polyplex-microbubble hybrids for ultrasound-guided plasmid DNA delivery to solid tumors in the mouse kidney. The microbubble surface architecture was engineered with a cationic transfection polymer to facilitate DNA loading and protection during intravascular transport. The engineered microbubbles also facilitated intracellular uptake and endosomal escape subsequent to ultrasound-mediated release. Importantly, the Colorado/Columbia team has shown that the polyplex-microbubbles persist in circulation and provide ultrasound-guided tumor transfection of a luciferase reporter gene.

The relevant theme of these scientific articles is the demonstration of a two-step strategy to transfect tumor tissue, in which microbubbles and ultrasound provide systemic delivery to the tumor tissue, allowing the released particles to do their job and transfect the adjacent cancer cells. This two-tier strategy is a promising approach for targeted delivery of genes to cancer. Obviously, the practicality of this approach is not limited only to cancer gene therapy, and is easily extended to systemic targeting of various drugs. The cumulating evidence shows that the grafting of the so-called "targeting moiety," such as antibody or ligand, onto the surface of delivery vehicles or to the drug itself does not really lead to effective systemic targeting. The two-tier strategy described in this issue will provide a valuable alternative and/or supplementary approach for overcoming the shortcomings of the current targeted drug delivery.

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