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Cover story

Focused ultrasound for targeted nanoparticle delivery to tumors

Targeted drug delivery has been the focus of extensive studies for decades, but it still remains elusive. For successful treatment of cancers, the right amount of a drug needs to be delivered to the target site *in vivo*. While many anticancer agents are shown to be effective in killing tumor cells in cell culture, they are usually unable to reach tumor cells *in vivo* at the concentration high enough to kill the tumor cells. The difficulty of targeted drug delivery *in vivo* is due to resistance of blood flow to tumors caused by abnormalities in both vasculature and extracellular matrix of tumor tissues. Furthermore, high interstitial fluid pressure in tumors reduces fluid transport through the tumor interstitial space [1]. Such barriers lead to poor transvascular and interstitial transport, resulting in low bioavailability and efficacy of chemotherapeutic agents.

Tissue penetration of current nanovehicles is limited to perivascular regions so that viable cells in the core of a solid tumor are not exposed to lethal concentrations of anticancer drug. Thus, the key to successful treatment of solid tumors resides in more effective delivery of anticancer agents in sufficient amounts. The current targeted delivery to the tumor site has been based on the well-known phenomenon of the "enhanced permeation and retention" (EPR) effect of particulate drug delivery vehicles. For increased accumulation of drug delivery nanovehicles at the tumor site beyond the EPR effect, it may be necessary to apply localized external energy, such as magnetic field, ultrasound, or heat. Recently, focused ultrasound (FUS) was employed for overcoming the difficulties posed by vascular barriers and other microenvironment factors to increase vascular permeability and intracellular uptake [2–4]. One effective use of ultrasound is to provide nonlethal temperature elevation to enhance the delivery of therapeutic agents to tumors. Furthermore, ultrasound sonication in the presence of microbubbles (an ultrasound contrast agent) is able to promote the effectiveness of nonthermal delivery [5]. The oscillation and destruction of microbubbles as well as microstreaming and radiation forces are thought to be responsible for the transient rupture of vascular barriers and subsequent increase in the tumor's vascular permeability.

The article in this issue from the groups of Professors Win-Li Lin and Fu-Hsiung Chang at the National Taiwan University examined the effects of FUS on the deposition of nanoparticles in tumors [6]. They used lipid-coated quantum dot (LQD) nanoparticles in combination with optical imaging to detect the nanoparticle deposition in the sonicated tumor tissue under harmonic generation microscopy (HGM). The size of LQD nanoparticles ranged from 30 to 180 nm. HGM was used to obtain microscopic evidence regarding the extravascular deposition of nanoparticles in tumors. Their results show that the FUS-mediated microbubble destruction enhanced LQD nanoparticle delivery into tumor tissues. Atomic absorption spectrometry, photoluminescence spectrometry, and HGM were employed for quantitative and qualitative evaluation of the deposition of different sizes of LQD nanoparticles in the tumor tissues. Immunoblotting analysis was also used to identify the characteristics of the vascular rupture. Their experiments have demonstrated that FUS sonication in the presence of microbubbles enhances delivery of LQD nanoparticles into tumor tissues in a mouse tumor model by a factor of 4.

Even though the tumor microenvironment sets a formidable obstacle for proper delivery of anticancer agents, effective use of FUS sonication was able to overcome the resistance of blood flow to tumors and high interstitial fluid pressure in tumors. Probably the biggest advantage of the FUS sonication is that it may change the tissue microenvironment and facilitate the delivery of LQD nanoparticles to a region farther away from the blood vessels. It is interesting to note that FUS sonication was also shown to promote possibly tumor growth as examined by P-selectin expression. As indicated in the article by Professors Lin and Chang, the effects of ultrasound-mediated microbubble destruction need to be fully understood for more effective use in treating tumors.

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