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Cover story

A two-step external activation for targeted intracellular delivery

Ultrasound allows non-invasive deposition of thermal and mechanical energy deep inside the human body. Since ultrasound can be concentrated within a region of about 1 mm in diameter, focused ultrasound (FUS) opens a path towards new therapeutic strategies with improved spatial precision, reliability, and reduced associated trauma. Magnetic resonance imaging (MRI) has been used to define the target region as well as to provide temperature mapping, and thus it can guide the FUS energy delivery. The technique, referred to as MR-FUS or MR-HIFU (High Intensity Focused Ultrasound), is currently applied clinically for the ablation of uterine fibromas, for palliative pain relief in bone metastases, and in research towards tumor ablation.

In this issue, Anna Yudina and colleagues [1] present a dual ultrasound approach combining the local release of drugs from temperature-sensitive nanocarriers with a sonoporation step using microbubbles (clinically approved ultrasound contrast agent). A model drug used in the study is TO-PRO-3, a chromophore that does not cross the cellular membrane. It displays a significant increase in fluorescence upon binding to nucleic acids, thus serving as a 'sensor' for cellular internalization and providing a simple fluorescence read-out. This preclinical study was built on their previous report on the two-step approach in cell culture [2].

Ultrasound-mediated permeabilization in the presence of microbubbles followed by temperature-controlled release was applied to tumor bearing mice with *i.v.* injection of temperature-sensitive liposomes containing the model drug. The efficacy of this approach was evaluated by in vivo fluorescence imaging followed by histological analysis. A 2.4-fold increase of fluorescence signal was observed and intracellular delivery of TO-PRO-3 was confirmed by a characteristic nuclear staining. These results demonstrate the feasibility of this new drug delivery system to tumors comprising of local cell permeabilization by US followed by in situ release of the payload from thermosensitive liposomes.

This method is a promising approach with possible applications for the local and controlled intracellular delivery of molecules with otherwise limited bioavailability. It, however, requires further studies and considerations before translation into clinical applications. First, the short blood circulation time of microbubbles and the size of microbubbles do not allow effective extravasation into tumor tissues while cell-bubble contact seems to play a major role in US-mediated delivery. Thus, the sonoporation effects may be limited to the cells in immediate proximity of the vasculature. Second, an optimal timing of each of the two steps is an important aspect to consider as well. In their previous work, the authors applied a temperature mediated release step first, followed by a pressure mediated sonoporation step. However, under in vivo conditions the concentration of available free drug can rapidly decrease due to adsorption to other compounds present (e.g., albumin) or wash-out from the blood and interstitial space. Therefore, the order of the two steps was inversed in the current study taking advantage of the effective duration of the effects of the sonoporation step. Variations of the dual ultrasound protocol are possible and may take into consideration the enhancement of extravasation by heating and/or ultrasound. Third, the increase in fluorescence intensity, indicating cellular uptake, is still only 2-fold. This is the level of increase that is routinely observed by other nanocarriers. The two step approach based on thermosensitivity and sonoporation, however, may be useful in reducing the toxicity of many drugs. While the advances in the area of targeted drug delivery have been slow, many small advances accumulated over time will collectively lead to a big advance that we are looking for. We simply have to understand the difficulty involved in targeted drug delivery.

References

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