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Moderate enhancement in tissue permeability by preclinical focused ultrasound

Increasing a local drug concentration in the tumor microenvironment is expected to improve the therapeutic efficacy by enhancing the drug exposure at the target site. Targeting agents that interact with tumors or tumor-associated endothelium have a better chance to stay in the tumor microenvironment and interacting with the tumor cells. The therapeutic efficacy can be increased more by cumulating more drug remotely and noninvasively using techniques, such as high intensity focused ultrasound (HIFU). HIFU can alter the local tumor environment using sound waves and increase tumor drug exposure [1–3]. To date, most HIFU in clinics use very high energy levels to essentially ablate the targeted tissue or tumor. Alternative non-ablative HIFU techniques are emerging to alleviate this problem while increasing tumor drug concentration. For example, a number of groups have shown a possibility that HIFU in conjunction with microbubble injections improves drug permeation through the blood-brain barrier (BBB). HIFU was also used to gently heat engineered stem cells to secrete cytokines to open the BBB (4). Both of these applications use significantly less energy than in ablative HIFU procedures, enabling large areas to be treated with less harm. For peripheral tumors, HIFU can be used to gently heat tissue to release the drug from temperature sensitive liposomes or increase the leakiness of the local tumor vasculature [4].

Dr. King Li and his colleagues in the article in this issue examined the dose and timing effects of pulsed HIFU (pHIFU) in a normal rabbit and VX2 tumor for the purpose of defining parameters of pHIFU for future translation [5]. After pHIFU exposure, both normal and tumor-bearing rabbits were treated with radiolabeled integrin antagonist (IA) that targets the $\alpha v \beta 3$ tumor/tumor vasculature biomarker found in various different tumors [6]. The Li team first optimized the pHIFU parameters in normal tissue and found a temperature of 46 °C to be the threshold of effect based on MRI parameters of edema. They subsequently tested the permeability of VX2 tumors with the optimized parameters and found a significant (~35%) increase in tumor concentration of radiolabeled IA on SPECT/CT imaging. While other previous studies using nanoparticle contrast demonstrated a higher increase in small animal tumor models, VX2 tumors are known to contain highly permeable vasculature without intervention, likely blunting the increased effect compared to other models. In addition, the targeted delivery of IA to the angiogenic endothelium also created a background that would blunt the increase in accumulation after HIFU treatment. Furthermore, the focus of this work is to study the non-destructive effects of HIFU, which explains why the window for increased vasculature is likely not sustained. It is noted that disrupting the vasculature permanently with higher energy may increase risk of adverse effects and theoretically risk giving tumor cells access to the systemic circulation. Given the non-destructive nature of this technique, however,

one can conceivably repeat the procedure multiple times if enough time elapses between treatments, possibly increasing the translational application of HIFU.

The study by the Li team is important in many aspects. In particular, the study focused on systematic study on the mechanistic understanding of the pHIFU process as a synergistic engineering approach with traditional chemotherapies. Through careful optimization studies, they found an optimum treatment temperature of 46 °C that maximizes the efficacy without serious damage to the tissue. Such an understanding allows repeated treatments for better efficacy, and this type of treatment can be easily translated to the clinic. As new HIFU equipment enters routine clinical use, innovative approaches like the one described by the Li group will have increasing translational relevance and more widespread use.

References

- [1] B.E. O'Neill, H. Vo, M. Angstadt, K.P. Li, T. Quinn, V. Frenkel, Pulsed high intensity focused ultrasound mediated nanoparticle delivery: mechanisms and efficacy in murine muscle, *Ultrasound Med. Biol.* 35 (2009) 416–424.
- [2] A. Khaibullina, B.S. Jang, H. Sun, N. Le, S. Yu, V. Frenkel, J.A. Carrasquillo, I. Pastan, K.C. Li, C.H. Paik, Pulsed high-intensity focused ultrasound enhances uptake of radiolabeled monoclonal antibody to human epidermoid tumor in nude mice, *J. Nucl. Med.* 49 (2008) 295–302.
- [3] S. Dromi, V. Frenkel, A. Luk, B. Traugher, M. Angstadt, M. Bur, J. Poff, J. Xie, S.K. Libutti, K.C. Li, B.J. Wood, Pulsed-high intensity focused ultrasound and low temperature-sensitive liposomes for enhanced targeted drug delivery and antitumor effect, *Clin. Cancer Res.* 13 (2007) 2722–2727.
- [4] X. Xiong, Y. Sun, A. Sattiraju, Y. Jung, A. Mintz, S. Hayasaka, K.C. Li, Remote spatiotemporally controlled and biologically selective permeabilization of blood-brain barrier, *J. Control. Release* 217 (2015) 113–120.
- [5] Y. Sun, X. Xiong, D. Pandya, Y. Jung, A. Mintz, S. Hayasaka, T.J. Wadas, K.C.P. Li, Enhancing tissue permeability with MRI guided preclinical focused ultrasound system in rabbit muscle: From normal tissue to VX2 tumor, *J. Control. Release* 256 (2017) 1–8.
- [6] B.-S. Jang, E. Lim, S.H. Park, I.S. Shin, S.N. Danthi, I.S. Hwang, N. Le, S. Yu, J. Xie, K.C. Li, Radiolabeled high affinity peptidomimetic antagonist selectively targets $\alpha v \beta 3$ receptor-positive tumor in mice, *Nucl. Med. Biol.* 34 (2007) 363–370.

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