State of the Field: Focused Ultrasound Immunomodulation

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High-intensity focused ultrasound (HIFU) has emerged as a viable alternative to surgical resection of solid tumors. “The main advantage of HIFU is that it is less invasive than a surgical procedure, resulting in an associated reduction in mortality, morbidity, hospital stay, cost, and improved quality of life for cancer patients” (Wu, 2013). However, focused ultrasound has also been shown to potentially boost the body’s immune response, which can help combat metastases as well as local recurrence of the targeted tumor.

In an experiment with mice given an H22 hepatocellular carcinoma, those that were treated with HIFU therapy had an 88% survival rate after 60 days as compared to 36% and 16% for the sham-HIFU and control groups, respectively (Zhang et al., 2010). Other mouse models have shown a significant decrease in the growth rate of tumors during a second challenge (Yang et al., 1992). Focused ultrasound treatment also enhances the ability of dendritic cells to infiltrate tumors (Hu et al., 2007). Clinical trials have revealed numerous beneficial side effects of HIFU such as increasing the CD4+/CD8+ ratio (Rosberger et al., 1994) and increasing CD3+, CD4+, and CD8+ lymphocytes in the tumor (Lu et al., 2009) as well as CD4+ lymphocytes in the circulation (Wu et al., 2004). Most of the data looks promising, however, some of the studies have shown no statistical difference in long-term survival rates between control groups and HIFU treated groups (Deng et al., 2010; Zhang et al., 2010).

There are three proposed methods by which this immunotherapeutic response occurs. First, thermal ablation causes tumor cells to up-regulate danger signals such as heat shock proteins (HSP60 and 70) and ATP, which can act as tumor vaccines and increase the immunogenicity of the tumor (Hu et al., 2005; Hundt et al., 2007). Second, focused ultrasound mitigates tumor-induced immunosuppression. This is supported by Zhou et al. (2008) who recorded a significant decrease in the serum levels of VEGF, TGF-ß1, and TGF-ß2 - all immunosuppressive cytokines - after HIFU treatment. Third, mechanical cavitation creates tumor debris that act as antigens for antigen presenting cells, enhancing the immune response. Deng et al. (2010) determined that dendritic cells can be activated by such tumor debris.

A couple of studies have shown that tweaking the parameters of the focused ultrasound treatment can enhance the immune response. The potency of dendritic cell infiltration and activation was improved when sparse-scan mode was used compared to dense-scan mode (Liu et al., 2010). Lui et al. (2012) also demonstrated that using low-pressure, pulse-mode focused ultrasound in the presence of microbubbles can elicit an anticancer immune response. Another study found that HIFU combined with low-dose external beam radiotherapy to treat prostate cancer showed good efficacy and a comparable disease-specific survival to conventional-dose external beam radiotherapy while significantly decreasing radiation-related toxicity (Wu et al., 2011). Future research still needs to be done to optimize the HIFU treatment method, find other combinational therapies, and to further investigate the cause and extent of the antitumor response.

Relevant Publications:

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