Histotripsy Mediated Immune Responses

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Motivation

There has been evidence showing that focused ultrasound can induce immune responses and enhance immunotherapy. Histotripsy uses focused, microsecond length, high pressure, ultrasound pulses to induce cavitation and subsequently mechanically fractionate tissue. In this study we demonstrate that 1) the addition of histotripsy increases the efficacy of immunotherapy and 2) histotripsy alone induces a potent abscopal effect.

Methods

In the first experiment, C57BL/6 mice received bilateral subcutaneous melanoma inoculations and were treated with either subtotal unilateral histotripsy, checkpoint inhibition (CI, 200 μg anti-CTLA-4 mAb intraperitoneal injections), a combination of both, or no therapy. Histotripsy was administered using 1 cycle pulses from a 1 MHz focused transducer at 100 PRF with an estimated p- of 30 MPa. The immune response in the treated and contralateral tumors was quantified via flow cytometric analysis on day 21. In the second experiment C57BL/6 mice received unilateral subcutaneous melanoma inoculations as well as pulmonary metastases induced via tail vein injection. Half of these mice received unilateral histotripsy while the others received no treatment. Lungs were harvested on day 20 to examine metastases.

Results/Discussion

In the first experiment, histotripsy alone resulted in greater tumor suppression than untreated control and the combination of histotripsy and CI resulted in greater tumor suppression than either checkpoint inhibition or histotripsy alone (Fig 1A). In addition, histotripsy initiates a significant increase in intratumoral $CD8^+$ T-cells in both the treated tumor and the untreated contralateral tumor (Fig 1B). In the second experiment, histotripsy treatment of the subcutaneous tumor dramatically reduced the number of developing lung metastases (Fig 1C). These results demonstrate the immunostimulatory effect of histotripsy and the potential of histotripsy to enhance immunotherapy.

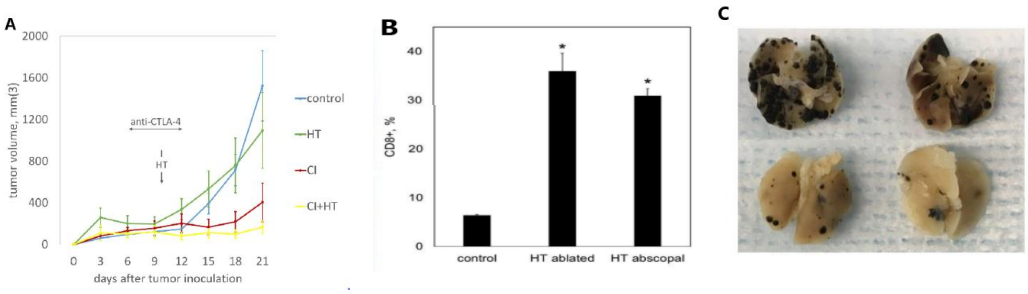

Figure: A) Serial tumor measurements following no treatment (control), histotripsy (HT), checkpoint inhibition (CI) or both (CI + HT). B) Histotripsy induced intratumoral $CD8^+$ T-cell infiltration within treated and untreated contralateral tumors. C) Pulmonary metastases following no treatment (top row) and ablation of subcutaneous flank tumor (bottom row).