Disrupting the blood–brain barrier with focused ultrasound: Perspectives on inflammation and regeneration

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Transcranial focused ultrasound (FUS) is promising for the treatment of neurological disorders, and the brain's response to FUS requires full consideration for a safe translation to the clinic. The study by Kovacs et al. (1) provides insights into FUS-induced inflammatory changes that could be associated on the one hand with brain insult and on the other hand with regenerative processes.

Kovacs et al. (1) confirm that FUS triggers transient astrocytic and microglial activation (2). FUS-induced glial activation and inflammation can be caused by mechanical effects of the sonications and their interactions with microbubbles, as well as by factors entering the brain following permeabilization of the blood–brain barrier (BBB), such as albumin (3). Depending on the type and severity of brain injury, activated astrocytes and microglia, as well as infiltrating macrophages, can exacerbate pathology or promote regeneration through secreting growth factors (4, 5). Previous time-course analysis post-FUS demonstrated that both microglia and astrocyte activation resolved by 15 d after FUS, with no progression to a glial scar (2) and no astrocytic proliferation (6), suggesting that FUS treatment does not cause lesion-like gliosis (4).

Additional FUS effects reported by Kovacs et al. (1) include the induction of pro- and antiinflammatory cytokines, as well as the endothelial intercellular adhesion molecule 1 (ICAM1). A recent analysis of the vasculature transcriptome post-FUS supports limited inflammation, which is resolved by 24 h (7). In contrast to Kovacs et al. (1), endothelial ICAM1 activation was not observed (7). This difference could be due to the relatively high concentration (~5- to 10-fold the recommended dose) of microbubbles used by Kovacs et al. (1), which can lead to greater endothelial disruption.

Consistent with other studies, in Kovacs et al. (1) FUS did not induce cell death. FUS treatment did, however, up-regulate erythropoietin (Epo), suggestive of ischemic mechanisms. However, hypoxia-inducible factor 1-α, an upstream transcriptional activator of Epo expression and sensor of ischemia, was not up-regulated. Epo could alternatively be up-regulated in response to hyperoxia (8), which can increase reactive oxygen species and DNA breaks, a phenotype reported in the Kovacs et al. (1) study.

Kovacs et al. (1) also demonstrate that FUS up-regulates proregenerative growth factors. In support of a permissive environment, FUS-induced BBB disruption can promote neurogenesis (6, 9) and increase dendritic branching and complexity (9). In mouse models of Alzheimer's disease, FUS-activated microglia and astrocytes contained greater levels of amyloid, potentially contributing to its clearance (2, 3). Finally, repeated FUS-treatments had positive impact on cognition in mice (3, 9), were safe in non-human primates (10), and are currently in clinical trials for Alzheimer's disease (https://clinicaltrials.gov/ct2/show/NCT02986932?term=focused+ultrasound+alzheimer&rank=1 and https://clinicaltrials.gov/ct2/show/NCT03119961?term=focused+ultrasound+alzheimer&rank=2).

To conclude, the work by Kovacs et al. (1) supports existing data that FUS does not lead to overt brain damage, and brings new insights to acute post-FUS effects. Aside from the impact of FUS itself on the brain, FUS allows for intravenous therapeutics to enter the brain in areas of interest, enhancing the potential of treating neurodegenerative disorders. With advances in FUS technology, including the feedback controller (6, 7, 9), FUS procedures are improving in safety, flexibility, reproducibility, and efficacy. A thorough understanding of FUS-effects on brain and behavior, along with continuous optimization of FUS treatments, are required for a successful translation to the clinic.

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