TARGETING ACTIVE MICORGLIA ALLEVIATES DISTAL EDGE OF PROTON RADIATION INDUCED NEURAL DAMAGE

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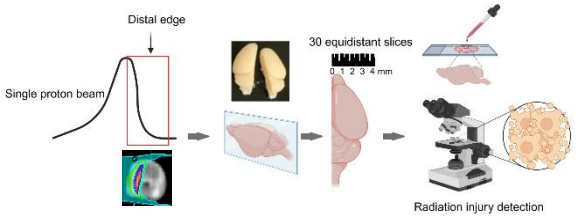
Introduction

Proton therapy (PT) has distinct advantages in its ability to more precisely target tumor while avoiding adjacent normal tissues. However, the distal edge effects of proton radiation on damage of organ at risk have constrains its application. PT induced contrast-enhancing lesions were almost exclusively seen at the distal beam end of the proton beam in patients with brain tumor. Microglia adapts to central nervous system homeostasis imbalance, and their uncontrolled activity can cause persistent and irreversible damage.

This study investigates the brain tissue responses in the distal edge regions of protons as well as comparing the effect with photons.

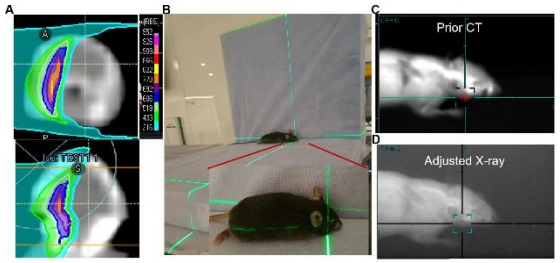
Methods

The damage occurrence of photon and the distal edge of the proton were investigated in a murine model. Bragg peak treatment plans for murine models were optimized. Hematoxylin & Eosin and immunofluorescence staining were carried out along the distal margin. In addition, the approximate distance from the Bragg peak to the neuronal damage sites was calculated. Furthermore, small-molecule inhibitor was investigated to inhibit the activation of microglia.

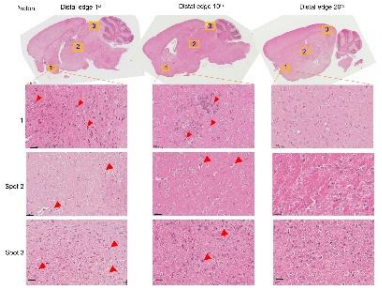


Results

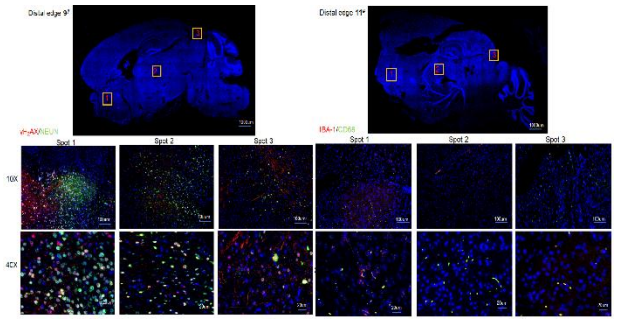
Following clinical protocols, radiation plans were developed and carried out, with routinely optimization following CT scan. A single 10 Gy RBE proton beam was used to target the left hemisphere, such that the Bragg peak was in the left hemisphere but its distal edge, i.e. the low-dose region was in the right hemisphere. Mice were placed in a prone position and given total anesthesia. The X-ray alignment of their jaw was adjusted to meet the irradiation plan.



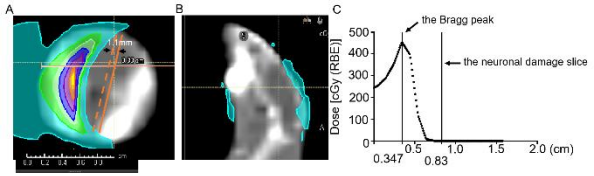
Reactive gliosis and granulovacuolar neuronal degeneration were shown at right hemisphere of proton irradiation group. Neuron injuries were observed at multiple locations (frontal lobe, thalamus and cerebral cortex) ,which is the distal edge of BP or low dose area.



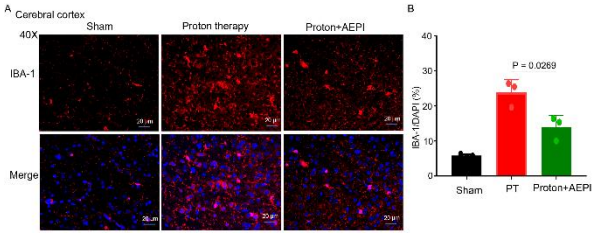
IBA1 and CD68 staining identified activated microglia at the corresponding neuronal damage sites, which mediated irradiation damage.



Meanwhile, the distal edge of Bragg Peak (0.4633 ± 0.01856 cm) gathered abnormal morphology of microglia.



Moreover, asparagine endopeptidase (AEP) inhibitors, which were administrated via intraperitoneal injection, significantly reduced active microglia in cerebral cortex, and relieved brain damage.



Discussion

Multiple spots of damage seen at significant distances from the low-dose zone or end of the range could be related to microglia activation. Also AEP inhibitor was demonstrated to inhibit the activation of microglia to relieve neuron damage in PT. Combined with our results, PT-induced brain damage may be lessened by optimizing irradiation regimens, considering LET, and intervening immune system homeostasis early with brain damage-protective medications.

To summarize, our results showed radiation injuries at the distal margin of the Bragg Peak also occurs in animal models. The injury appears to be influenced by activated microglia and might be prevented efficiently by AEP inhibitors.

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