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Stimulating IFN-β Production in Glioblastoma Through Proton Beam-Induced cGAS–STING Activation: A Monte Carlo Study

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Glioblastoma multiforme (GBM) is one of the most aggressive and treatment-resistant brain tumors, characterized by rapid proliferation, diffuse infiltration, and poor prognosis. Despite current standards of care—surgical resection followed by radiotherapy or chemotherapy. A major obstacle to treatment success is the presence of hypoxic tumor niches that harbor cells with metastatic phenotypes and intrinsic resistance to conventional radiation. These regions are poorly oxygenated, genetically unstable, and less responsive to therapies, highlighting the urgent need for new strategies that overcome radio resistance and engage anti-tumor immunity.
In this project, we investigated proton therapy as a precision modality capable of delivering high linear energy transfer (LET) radiation with minimal damage to surrounding healthy tissue. Unlike conventional X-rays, proton beams deposit most of their energy at the Bragg peak, enabling spatially localized dose delivery. Beyond this physical advantage, we hypothesized that proton therapy could stimulate immune responses through activation of the cGAS–STING pathway, which detects cytosolic double-stranded DNA and initiates the production of interferon-beta (IFNβ), a key cytokine in anti-tumor immunity.
Using dose–response data from the U251 GBM cell line, we incorporated IFN-β dose response into the FLUKA Monte Carlo simulation framework. Simulations showed that a dose of approximately 17 Gy optimized IFN-β induction without triggering TREX1, a DNA exonuclease known to suppress immune signaling at higher doses. The biological dose was modulated to selectively cover a virtual subregion within the GTV, suggesting the potential to stimulate localized immune responses in treatment-resistant tumor microenvironment. These findings support the dual role of proton therapy in delivering precise radiation while also enhancing immunogenicity, offering a promising foundation for future biologically guided radiotherapy strategies in GBM. Further validation through in vitro experiments and integration with immunotherapy could help translate this approach into clinical protocols and expand its relevance beyond GBM to other poorly immunogenic tumors

Technical Track

Nuclear Applications and Radiation Processing

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