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FLASH radiation reprograms lipid metabolism and macrophage immunity and sensitizes medulloblastoma to CAR-T cell therapy

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Abstract

FLASH radiotherapy holds promise for treating solid tumors given the potential lower toxicity in normal tissues but its therapeutic effects on tumor immunity remain largely unknown. Using a genetically engineered mouse model of medulloblastoma, we show that FLASH radiation stimulates proinflammatory polarization in tumor macrophages. Single-cell transcriptome analysis shows that FLASH proton beam radiation skews macrophages toward proinflammatory phenotypes and increases T cell infiltration. Furthermore, FLASH radiation reduces peroxisome proliferator-activated receptor-γ (PPARγ) and arginase 1 expression and inhibits immunosuppressive macrophage polarization under stimulus-inducible conditions. Mechanistically, FLASH radiation abrogates lipid oxidase expression and oxidized low-density lipid generation to reduce PPARγ activity, while standard radiation induces reactive oxygen species-dependent PPARγ activation in macrophages. Notably, FLASH radiotherapy improves infiltration and activation of chimeric antigen receptor (CAR) T cells and sensitizes medulloblastoma to GD2 CAR-T cell therapy. Thus, FLASH radiotherapy reprograms macrophage lipid metabolism to reverse tumor immunosuppression. Combination FLASH-CAR radioimmunotherapy may offer exciting opportunities for solid tumor treatment.