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Targeting HIF-1α to Stimulate Immunity after SBRT

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Abstract
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Abstract

Objective: The intratumor environment is intrinsically hypoxic and it becomes further hypoxic when tumors are irradiated with high-dose irradiation such as stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) due to radiation-induced vascular damage. Despite the well-known role of hypoxia in resistance to various treatments, invasion and metastasis, relatively little is known about the potential contribution of hypoxia to cancer immune escape. A hypoxic environment upregulates hypoxia inducible factor alpha (HIF-1α), the "master" transcription factor for oxygen homeostasis. HIF-1α-driven transcription protects tumor cells by increasing antioxidant pools, confers radioresistance to tumor cells by shifting metabolic cascades, and promotes angiogenesis via upregulating vascular endothelial growth factor (VEGF). In addition, HIF-1α has been increasingly implicated in the suppression of antitumor immunity by directly increasing expression of immunosuppressive programmed death-ligand 1 (PD-L1) on tumor and immune cells such as MDSCs and expression of programmed death-1 (PD-1) and cytotoxic lymphocyte antigen 4 (CTLA-4) on CD8+ T-cells. In this regard, PD-L1 and HIF-1a expression have already been observed to be overexpressed in many aggressive human cancers. SBRT treatments deliver 15-50 Gy to extracranial tumors in 1-5 fractions and SRS delivers 15-30 Gy to cranial lesions in only 1-2 fractions. These hypo-fractionated radiotherapy regimens have been shown to be highly effective in at least temporarily controlling various types of solid tumors. Our major focus is to identify the potential of blocking the HIF-1α stress/metabolic pathway to boost anti-tumor immunity in tumors after SBRT/SRS. We are studying the use of existing inhibitors of HIF1 and also designing a miRNA therapeutic to block HIF1 driven pathways after SBRT.

Methods: We have generated gene-edited HIF-1α knockout or wildtype cells to identify the predominant HIF1α-driven pathways after high dose radiation exposures in aerobic or hypoxic Lewis lung carcinoma (LLC) and endothelial cells using RNA sequencing to identify genes involved as well as candidate microRNAs that could be targeted. Induction of HIF-1α in tumor, endothelial or immune cells correlates with immunosuppressive protein expression and we performed tumor cell clonogenic studies to assess the radiation sensitivity of the cells in aerobic or hypoxic (0.5% Oxygen) conditions. We studied the combined effects of HIF-1α inhibitors and single dose radiation on tumor growth delay of FSaII fibrosarcoma and LLC tumors grown in immunocompetent mice.

Results: We have recently observed that inhibition of HIF-1α upregulation with small molecule drugs can markedly prohibit the radiation-induced upregulation of HIF1α, thereby downregulating the expression of immunosuppressive PD-L1. LLC cells that do not have HIF1 have significantly less resistance to radiation under hypoxia. In vivo, FSAII tumor growth is delayed when known inhibitors of HIF1 and given before radiation (Metformin or PX478). Lastly, HIF1 knockout LLC cells grow more slowly than wildtype cells in vivo.

Conclusion: Unfortunately, in many patients the vascular damage and hypoxia caused by SBRT/SRS increases HIF-1α expression which drives the deleterious pathways described above leading to continued tumor progression as either recurrence, metastasis or both. We expect that preventing expression of immunosuppression by inhibiting HIF-1α combined with currently used immunotherapy using antibodies against the PD-1/CTLA-4/PD-L1 axis to specifically and maximally boost anti-tumor immunity in the tumors treated with SBRT/SRS will increase tumor control, while avoiding increasing off target immune reactions. Our results are a step forward in knowledge for generating tumor-specific immune activity in combination with radiotherapy by exploiting the HIF-1α driven pathways in the stress-response after SBRT/SRS and will likely lead to expanded studies and translation in due time.