Renal

Radiation induces dynamic changes to the T cell repertoire in renal cell carcinoma patients

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Abstract

Clinical studies combining radiation and immunotherapy have shown promising response rates, strengthening efforts to sensitise tumours to immune-mediated attack. Thus, there is an ongoing surge in trials using preconditioning regimens with immunotherapy. Yet, due to the scarcity of resected tumours treated in situ with radiotherapy, there has been little investigation of radiation's sole contributions to local and systemic antitumour immunity in patients. Without this access, translational studies have been limited to evaluating circulating immune subsets and systemic remodeling of peripheral T cell receptor repertoires. This constraint has left gaps in how radiation impacts intratumoural responses and whether tumour-resident T cell clones are amplified following treatment. Therefore, to interrogate the immune impact of radiation on the tumour microenvironment and test the hypothesis that radiation initiates local and systemic expansion of tumour-resident clones, we analysed renal cell carcinomas from patients treated with stereotactic body radiation therapy. Transcriptomic comparisons were evaluated by bulk RNA sequencing. T cell receptor sequencing monitored repertoires during treatment. Pathway analysis showed radiation-specific enrichment of immune-related processes, and T cell receptor sequencing revealed increased clonality in radiation-treated tumours. The frequency of identified, tumour-enriched clonotypes was tracked across serial blood samples. We observed increased abundance of tumour-enriched clonotypes at two weeks postradiation compared with pretreatment levels; however, this expansion was not sustained, and levels contracted toward baseline by four weeks posttreatment. Taken together, these results indicate robust intratumoural immune remodeling and a window of tumour-resident T cell expansion following radiation that may be leveraged for the rational design of combinatorial strategies.