Molecular signatures of combination immunotherapy of prostate cancer using a Listeria-based PSA vaccine and radiation

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Abstract

Background- Radiotherapy (RT) has the potential to amplify immune responses triggered by tumor vectors, including ADXS-PSA, a live attenuated Listeria monocytogenes (Lm) based vector expressing human PSA. Earlier observations suggest that the two treatment modalities cooperatively induce regression of syngeneic mouse prostate cancer cells expressing human PSA (TPSA23), though immune correlates of efficacy and tumor recurrence are poorly understood.

Methods- We compared efficacy of different sequencing regimens of combination RT/vaccine treatments on TPSA23 tumor growth in syngeneic mice. Using the best sequencing protocol, tumors were collected post implantation to assess immune infiltrate and function during initial tumor regression (day 20) and upon resumption of tumor growth (day 38). Correlates of treatment efficacy were determined by transcriptome analysis, phenotypic analyses of immune infiltrates and T1D sequencing.

Results- We confirmed that combination RT/ADXS-PSA is superior to single modality treatments. Concurrent administration of RT/ADXS-PSA was the most effective treatment schedule and was associated with enhanced T cell activation and robust IFNγ signatures in the tumor microenvironment. This was reflected in increased intratumoral CD8+ and CD4+ T cell infiltration in mice receiving RT/ADXS-PSA. Time-course sequencing revealed elevated and sustained T cell diversity in tumor tissues of RT/ADXS-PSA treated mice, when compared with mice receiving single modality treatments. In these residual tumors resident and/or memory T cell phenotypic markers were increased. Transcriptome analyses of recurring tumors further revealed induction of PD-L1 as a function of treatment. Targeting of the PD1/PD-L1 axis via a PD1 blocking antibody administered in addition to RT/ADXS-PSA triple combination further amplified tumor growth inhibition in mice receiving dual RT/vaccine Therapy.

Conclusions- Combining RT with the ADXS-PSA vaccine leads to effective tumor growth inhibition and induces robust, persistent antitumor immunity within the tumor environment. Transcriptome analysis during treatment revealed increased PD1 expression as a potential resistance mechanism and a PD1 blocking antibody provided further therapeutic benefits. These results support the rationale for combining cancer-based vaccines with radiation in the clinic.

Background

ADXS-PSA is an attenuated Listeria monocytogenes (Lm) vector genetically engineered to secrete a fusion protein composed of tumor antigen PSA and a truncated neurotoxic listeriolysin O (LLO-Lm) (Advaxis). LLO is taken up by antigen-presenting cells (APCs) and secretes LLO to escape the phagolysosome and enter the cytosol.

The LLO-PSA fusion protein is processed into peptides, which are subsequently presented to T Cells via HLA molecules.

Immuno-radiotherapy utilizes radiation, a common cancer therapeutic modality, to induce immunogenic cell death.

Methods and Results

Combining subtherapeutic doses of RT and ADXS-PSA vaccine inhibits TPSA23 tumors more effectively than individual modalities.

Combination RT and PSA vaccination induces a distinct and sustained TCR repertoire shift.

Expression of resident/tumor cell markers and immune checkpoints in recurring tumors.

Conclusions

- Combination therapy with subtherapeutic doses of RT and PSA vaccine cooperatively reduces tumor burden compared to single modality treatments, confirming prior observations.
- Concurrent RT + PSA vaccination is more efficacious than either pre- or post-RT vaccination schedules.
- Dual RT + PSA vaccine promotes enhanced iIFNγ signaling in the tumor microenvironment.
- Increased levels of genes associated with T cell activation and signaling in dual-treated animals are accompanied by higher frequencies of CD8 and CD20 cells in the tumors.
- Intratumoral T cell diversity is increased and maintained in dual-treated mice.
- Combination therapy induces intratumoral abundance of transcripts associated with testable checkpoints potentially relevant to resistance development.
- Targeting PD-L1, which is upregulated in recurring tumors further increases efficacy of dual therapy.

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