Single cell discrimination of immunotherapy-induced changes in the prostate tumor microenvironment

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Background: Although immunotherapy prolongs survival in metastatic castrate-resistant prostate cancer, the benefit of agents such as sipuleucel-T is modest, and checkpoint inhibitors benefit <10% of patients. That checkpoint inhibitor-responsive patients often have durable responses, however, raises the question of whether specific known or novel T cell populations are mechanistically linked to these deep responses. We hypothesize that immunotherapy combining checkpoint inhibition with immunostimulatory prostate cancer therapies such as radiation and hormonal therapy induces novel populations of effector T cells whose function and antigenic specificity are enriched in prostate tumors and are not present before therapy.

Methods: We will test this hypothesis using an unbiased high-resolution approach. Single-cell analysis combining whole-transcriptome RNA sequencing coupled to paired T cell receptor (TCR) analysis will characterize known or unanticipated T cell populations that are generated by combination immunotherapy in an ongoing phase II trial testing novel combinations of immunotherapy (anti-PD-1 immunotherapy +/- the Toll-like receptor 9 agonist SD-101) with radiation and androgen deprivation therapy for newly diagnosed oligometastatic hormone-sensitive prostate cancer. This work will interrogate serial prostate biopsies and blood to determine which functional T cell populations and antigenic specificities are enriched in the tumor over blood, and which are pre-existing versus newly induced by immunotherapy.

Results: The first patients have been treated as part of the safety lead-in for this clinical protocol (anti-PD-1 immunotherapy without SD-101), and paired prostate biopsies have been obtained from patients before and after initiation of anti-PD-1 and radiotherapy for single cell sequencing. Ongoing progress in analyzing single-cell RNA sequencing and paired TCR data from these prostate biopsies will be presented.

Conclusions: Single-cell transcriptome and TCR analysis in conjunction with a combined modality trial involving established and novel immunotherapies with radiotherapy and hormonal therapy will reveal novel T cell populations and antigenic specificities that can serve not only as biomarkers of response, but also experimental handles for prospective isolation/enhancement of novel T cell populations as well as novel prostate tumor antigens.

Conflict of interest: None

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