TIMING AND SEQUENCING OF AR-SPECIFIC VACCINATION COMBINED WITH ANDROGEN DEPRIVATION THERAPY AFFECT ANTI-TUMOR RESPONSES IN MURINE PROSTATE CANCER MODELS

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Background Androgen deprivation therapy (ADT) is the cornerstone treatment for recurrent and metastatic prostate cancer. ADT has several immunomodulatory effects including T cell infiltration into the prostate and enhancing antigen processing and/or presentation. Previous studies have demonstrated that immunizing tumor-bearing mice with a DNA vaccine encoding the androgen receptor significantly slowed tumor growth and prolonged survival. Furthermore, combining ADT with vaccination further augmented the anti-tumor response compared to AR-targeted vaccination alone, and this was greatest if DNA vaccination was given prior to ADT. We observed a transient increase in T cell infiltration post ADT and a significant accumulation of MDSCs in the tumor microenvironment. In this study, we characterized CD8+ T cells for antigen specificity following vaccination and determined if depletion of MDSCs could increase anti-tumor efficacy.

Methods 6-week-old male FVB mice were implanted subcutaneously with Myc-CaP tumor cells. DNA vaccination consisted of the pTVG4 vector alone (control) or the DNA vector encoding the AR ligand binding domain (pTVG-AR) started either one day after tumor implantation, or one day following ADT. The sequence of administration was evaluated for effect on tumor growth, and groups of mice were euthanized at different time points to characterize the tumor-infiltrating immune populations by flow cytometry. Further, CD8+ T cells were isolated from tumors and tested for AR specificity by IFNγ ELISPOT using an AR-specific dominant FVB epitope, AR-25. In a similar study, tumor-bearing mice were treated with control or clodronate liposomes twice a week post ADT and infiltrating immune populations were characterized.

Results Vaccination prior to ADT rather than after ADT significantly improved anti-tumor responses and flow cytometry analysis of tumor immune infiltrates revealed a higher infiltration of CD4+ and CD8+ T cells in this group. Infiltrating CD8+ T cells were found to be AR-specific by IFNγ ELISPOT. Depletion of these cells resulted in significantly worse survival. MDSCs were significantly increased in tumors following ADT in all combination groups and depletion of these cells using clodronate liposomes resulted in improved anti-tumor response and overall survival.

Conclusions Vaccination prior to ADT rather than after ADT significantly improved anti-tumor responses and this affected the infiltrating immune populations. Depletion of MDSCs using clodronate liposomes significantly improved anti-tumor responses and increased infiltration of CD4+ and CD8+ T cells into prostate tumors. Since ADT causes accumulation of MDSCs within the tumors, current studies are investigating the intermittent use of ADT as an alternative to continuous treatment when combined with anti-tumor vaccination.

REFERENCES


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