Targeting TGF-β in Ovarian Cancer results in Decreased Tumor Burden and Improved T cell Immune Response

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Introduction

• There is a known association between elevated levels of Transforming Growth Factor-β (TGF-β) and progression of various cancers including advanced stage ovarian cancer
• Levels of TGF-β can be correlated with tumor dissemination and worse overall clinical outcomes in ovarian cancer patients
• TGF-β promotes tumor growth through various mechanisms within the tumor microenvironment, including immunosuppression
• TGF-β signaling can be used to give insight to prognosis in ovarian cancer patients and as potential target for potential therapeutic options

Figure 1: TGF-β mechanisms to promote tumor growth

Figure 2: TGF-β effect on various immune cell populations

Results

Figure 3. Establishment of intraperitoneal tumor model using ID8-p53-/- cells occurs within 7 days

(A) Bioluminescent imaging of mice 7 days after tumor cell injection with luciferase tagged ID8-p53-/- cells. (B) Comparison of normal mouse omentum weights to omental weights in the tumor model after 7 days. (C) Significant increase in mean expression for all three TGF-β ligand isoforms and both receptors, with trending increase in TGF-β score demonstrated via nanostring. (** p < 0.01, *** p < 0.001, bars represent SEM)

Figure 4: Treatment with anti-TGF-β monoclonal antibody in the ID8-p53-/- tumor model.

(A) Schema of treatment dosing. (B) Ascites volume is significantly reduced following treatment with anti-TGF-β antibody. (C) Omental weights are similar between treated and untreated mice. (D) Favorable changes in T-cell response – (D) trending increase in proportion of CD8 T cells, (E) decrease in TrgPs and (F) increased in CD69/Treg ratio, occur following treatment (* p < 0.05, *** p < 0.001, ms - non-significant, bars represent SEM; dotted line – mean weight of naïve mouse omentum).

Figure 5: Inhibition prior to tumor cell injection results in reduced tumor burden as well as ascites.

(A) Schema of prophylactic dosing (B) Similar decrease in ascites volume is seen with anti-TGF-β antibody administered prior to tumor challenge compared to treatment over five weeks. (C) Reduction in omental weights with single dose of anti-TGF-β antibody prior to tumor cell injection. (D-F) Again, favorable changes in T-cell response (D) increased proportion of CD8 T cells, (E) decrease in TrgPs and (F) increased in CD69/Treg ratio, occur with this treatment strategy. (* p < 0.05, ** p < 0.01, bars represent SEM; dotted line – mean weight of naïve mouse omentum).

Figure 6: Continuous therapy with anti-TGF-β monoclonal antibody starting prior to tumor cell injection and continuing for 6 weeks.

(A) Maintenance therapy scheme. Decrease in both (B) ascites volume and (C) omental weights. (D-F) Consistent pattern of T-cell profile with treatment including (D) CD8 T cells, (E) TrgPs and (F) CD69/Treg ratio. (G) Overall survival is improved (median survival of 57.5 days vs 70 days) with continuous anti-TGF-β therapy (* p < 0.05, ** p < 0.01, bars represent SEM; dotted line – mean weight of naïve mouse omentum).

Conclusions

• Our preclinical model using ID8-p53 -/- for murine ovarian cancer shows that tumors are established within 7 days of tumor inoculation as indicated by increased omental weights and this correlates with increased expression of TGF-β related proteins.
• The timing of TGF-β inhibition is important in its impact on reducing cancer progression.
• TGF-β inhibition during tumor growth is able to reduce ascites volume; however tumor progression is not decreased. However, inhibition of TGF-β prior to tumor inoculation results in decreased tumor burden as well as ascites volume.
• By treating with anti-TGF-β therapy prior to tumor cell injection and continuing throughout, we see a sustained decrease in tumor growth and ascites volume that results in increased overall survival.
• Our findings suggest that TGF-β inhibition may be useful in reducing tumor burden, in particular, in the maintenance setting to prevent the establishment of tumors and increasing disease free survival.