The anti-tumor efficacy of TIM-3 blockade in a murine model of sarcoma

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Background

TSR-022 is an anti-TIM-3 antibody that is currently undergoing clinical development in combination with TSR-042, an anti-PD-1 antibody (NCT02817633). TIM-3 is an immune checkpoint receptor that negatively regulates T-cell activity and is implicated in resistance to PD-1 blockade. In addition, TIM-3 is also expressed on myeloid cells and has been shown to regulate dendritic cell activity. We previously reported a case study of a patient with leiomyosarcoma who had a partial response to TSR-022 monotherapy [1]. Here we explore the mechanism of the antitumor effect of TIM-3 blockade in a preclinical mouse model of fibrosarcoma.

Methods

A/Jcr mice were inculcated with murine fibrosarcoma SaL/N cells. Mice were randomized into 4 groups of 8 mice each at tumor volumes of 80-120 mm³ and treated with isotype control, anti-mouse PD-1, anti-mouse TIM-3, or a combination of both. A total of 5 doses were administered in a twice-weekly schedule. Mice with complete tumor regression were re-challenged with SaL/N cells along with a fresh cohort of 5 mice to serve as a control group. The mice were monitored for tumor regrowth until all the mice in the control group were euthanized due to tumor burden. In a follow-up study to understand the mechanism of efficacy, the mice were randomized at tumor volumes of 200-300 mm³, treatment initiated, and tumors collected for immunoprofiling using flow cytometry.

Results

Both anti-PD-1 and anti-TIM-3 treatment resulted in antitumor efficacy with 73% and 53% tumor growth inhibition, respectively, which improved to 98% in the combination group. In addition, 2 mice in the anti-PD-1 group and 6 in the combination group showed complete tumor regression. The mice with complete regression were re-challenged and monitored for tumor growth. The tumors in the control cohort of mice grew normally; however, no tumor growth was observed in the re-challenged mice, consistent with the induction of immune memory. Tumor immune contexture correlated with the anti-tumor efficacy seen.

Figure 3. At baseline, SaL/N tumors are myeloid rich with PD-1 and TIM-3 expressed on tumor infiltrating T cells

• Sal/N tumors have between 30-50% CD45⁺ infiltrate at baseline.
• Approximately 40% of immune infiltrate is comprised of cells of the monocyte/macrophage lineage (CD11b⁺).
• PD-1 and TIM-3 are expressed on tumor infiltrating T cells (TIL) and to a lesser degree on the myeloid infiltrate.

Figure 4. Co-blockade of PD-1 and TIM-3 is more efficacious than either single agent and induces immunological memory

• Doses (10 mg/kg) were administered twice weekly for a total of 5 doses.
• Both PD-1 and TIM-3 blockade result in moderate tumor growth inhibition as monotherapy treatment.
• The combination of anti-PD1 and anti-TIM-3 was more efficacious than either as single agents, resulting in complete responses in 6/8 animals.

Figure 5. Co-blockade of PD-1 and TIM-3 increases intra-tumoral CD8⁺ T cells and decreases M2 macrophages

• TIM-3 is upregulated on intra-tumoral T cells following PD-1 blockade.
• Intra-tumoral CD3⁺ cells increase upon treatment with anti-PD-1 as well as the combination of anti-PD-1 and anti-TIM-3.
• Co-blockade of PD-1 and TIM-3 increases CD8⁺ TIL.
• While there is a trend towards an increase in M1 macrophages, there is a statistically significant reduction in M2 macrophages following combo treatment.

Conclusions

• Sal/N is a myeloid rich murine model of sarcoma with PD-1 and TIM-3 expression on intra-tumoral T cells and a subset of intra-tumoral myeloid cells.
• While single agent PD-1 or TIM-3 blockade results in a modest inhibition of tumor growth, the combination induces complete regression in most animals treated.
• Tumor regressions are associated with immune memory in both PD-1 treated and combination treated animals.
• Pharmacodynamic analysis shows TIM-3 is upregulated on intra-tumoral T cells following PD-1 blockade.
• Intra-tumoral CD3⁺ cells increase upon treatment with anti-PD-1 as well as the combination of anti-PD-1 and anti-TIM-3; however, a significant increase in CD8⁺ TIL is seen in the combination only.
• While there is a trend towards an increase in M1 macrophages following treatment, there is a statistically significant reduction in M2 macrophages following combo treatment.
• In conclusion, the combination of PD-1 and TIM-3 blockade induces tumor regressions in the syngeneic Sal/N model that is associated with an increase in intra-tumoral CD8⁺ T cells and a reduction in M2 macrophages.

References