Entinostat Increases the Frequency of Tumor-Specific Effector T-cells and Their Functionality is Enhanced by Anti-OX40 Leading to Durable anti-Tumor Effects

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Background

The epigenetic deregulation of T-cells and enhanced numbers of immunosuppressive cells in the TME are associated with decreased anti-tumor effects. Hence, targeting the epigenetic modifications using modulators such as histone-deacetylase inhibitors (HDACi) provides the basis for a potential role for these agents in cancer immunotherapy. Entinostat, an HDACi has been shown to reprogram the TME by impacting the numbers of CD8 T-cells and immunosuppressive cells, resulting in enhanced anti-tumor activity when combined with immune-checkpoint blockade [1]. However, the combination effect of Entinostat with anti-OX40 remains poorly explored. Signaling through OX40 is known to enhance the effector functions of CD8 T-cells. In addition, it inhibits production of IL17a cells, which prevent apoptosis of MDSCs. However, as a single agent anti-OX40 has not yet shown promising results in the clinic. Therefore, we hypothesized that the combination of Entinostat with anti-OX40 will enhance the effector-functions of CD8 T-cells while simultaneously reducing the immunosuppressive cells including MDSCs in the TME, leading to improved anti-tumor effects.

Methods

In the TC-1 mouse tumor model, Entinostat (3 mg/kg) in combination with anti-OX40 (1 mg/kg) and tumor-specific vaccine (E7-peptide; 3 doses one-week apart) was given. Tumor growth and mice survival were recorded. Three days after the second immunization, immune-responses were determined in the tumors.

Entinostat synergizes with anti-OX40 leading to complete tumor regression with tumor free survival of mice

Entinostat with anti-OX40 enhances activation of macrophages

**Results**

Entinostat synergizes with anti-OX40 to enhance total and antigen-specific granzyme B+ and IFN-gamma+ CD8+ T-cells in the TME

Entinostat with anti-OX40 reduces the IL17a producing CD4+ and immunosuppressive cells in the TME

Summary and Conclusion

- These results highlight the ability of Entinostat with anti-OX40 in increasing the numbers of effector T-cells in the TME.
- Entinostat with anti-OX40 significantly enhanced the functionality of these tumor-infiltrated effector cells leading to induction of robust and durable anti-tumor responses.
- Importantly, Entinostat with anti-OX40 further decreased the numbers of immunosuppressive populations in the TME.
- In addition, Entinostat with anti-OX40 enhanced the activation of macrophages, which indicates enhanced antigenic presentation in the TME.
- These data highlight that anti-OX40 enhanced the anti-tumor efficacy of Entinostat, which can be a promising strategy for cancer-immunotherapy.

Reference