Mertk is a therapeutic target in combination with radiation to promote adaptive immune tumor responses

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Abstract

Background: Mertk is a member of the Tyro3-Axl-Mertk (TAM) family of receptors and regulates phagocytosis of dying cells by macrophages. Cancer cells killed by radiation therapy direct reorganization of macrophages into immune suppressive phenotypes. Mertk-/- mice grafted with immunogenic tumors have enhanced tumor control following ionizing radiation compared to wild type mice. Gata3 is the endogenous ligand for Mertk and its ability to signal through Mertk requires a post-translational vitamin K-dependent modification that is inhibited by warfarin.

Methods: Mertk-/- and WT mice were injected subcutaneously with 5x10^4 CT26 cells (BALB/c) or 5x10^4 Panc02-SIY cells (C3BL/Bl) and allowed to grow to 5 mm before treatment with 250 µg anti-CD45 antibodies, warfarin (1.25 mg/L drinking water) and subjected to a single dose of ionizing radiation (12.5 Gy) followed by 250 µg of anti-OX40 or PBS I.P. 1-day post-RT. Peripheral blood was collected 6 days after RT and evaluated by Flow Cytometry for SIY+CD8+ T-cells in CD8+ T-cells.

Results: Mertk-/- mice have increased survival following RT in CT26 tumor models. CT26 tumor cure in Mertk-/- BALB/c mice was abrogated by depletion of CD8 T-cells indicating that ligation of Mertk in tumor macrophages suppresses endogenous anti-tumor immunity following radiation therapy. Similarly, warfarin-treated mice had higher rates of tumor cure following radiation that was also abrogated by CD8 depletion. In C3Bl/Bl mice, Mertk-/- alone does not affect responses to radiation therapy in the Panc02-SIY tumor model, but the combination of radiation therapy with anti-OX40 co-stimulation of T cell responses resulted in an increase in peripheral blood SIY+ CD8+ T cells 5 days after treatment, and significantly improved survival compared to radiation alone.

Improved survival in Mertk-/- mice treated with RT

Tumor cures after RT in Mertk-/- mice are CD8-dependent

Warfarin enhances RT control in a CD8-dependent manner

Conclusions

• Mertk-/- mice show increased responsiveness to RT in immunogenic CT26 tumors
• Mertk-/- mice experience CT26 tumor cure after RT in a CD8-dependent manner
• Poorly immunogenic pancreatic tumors do not have increased responses to RT in Mertk-/- mice
• In poorly immunogenic pancreatic tumors, the combination of RT and anti-OX40 significantly increased overall survival compared to RT alone, and resulted in increased numbers of long-term cures in Mertk-/- mice
• Warfarin alone at 1.25 mg/L in drinking water did not affect growth of CT26 tumor grafts, but enhanced RT control of tumor growth in a CD8-dependent manner similar to Mertk-/- mice
• Mertk expression in tumor macrophages prevents tumor cure by tumor antigen-specific T cells following radiation therapy. In poorly immunogenic tumors, combining RT with additional immune therapy is needed to increase T cell responses, but tumor cure is still limited by expression of Mertk.

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