Synergistic cancer immunotherapy combination of MVA-CD40L with tumor targeting antibodies or checkpoint blockade to achieve strong antitumor immune responses against large, established tumors

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BACKGROUND

- Virus-based vaccines and appropriate costimulation enhance potent antigen-specific T cell immunity against cancer.
- Here we exploit both innate and adaptive immune responses triggered by a novel recombinant modified vaccinia virus Ankara (rMVA) encoding costimulatory CD40L against solid tumors in combination regimes to overcome tumor-induced resistance to immunotherapy.

EXPERIMENTAL LAYOUT

Vectors:

rMVA-OVA/rMVA-OVA-CD40L

rMVA-TAA/rMVA-TAA-CD40L
TAA: string of epitopes→ p15E-AH1_A5-Trp2

rMVA-HER2-CD40L

Readouts:

Tumor follow up

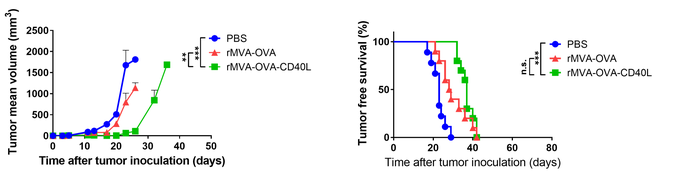
Analysis of immune infiltrates

Combination with checkpoint blockade or tumor-targeting antibodies

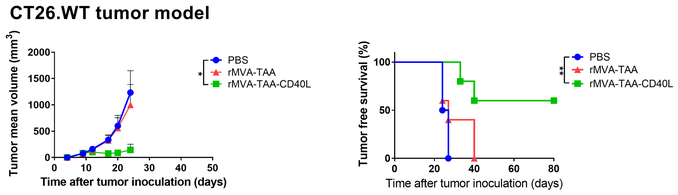
RESULTS

rMVA-CD40L PROMOTES TUMOR GROWTH CONTROL IN UNRELATED TUMOR MODELS

B16.OVA Tumor model

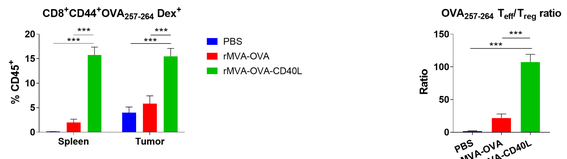


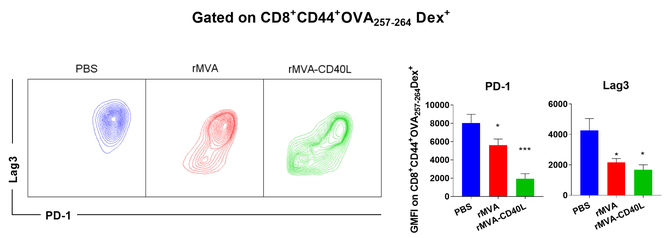
CT26.WT tumor model



rMVA-CD40L INCREASES T CELL INFILTRATION OF NON EXHAUSTED, ANTIGEN-SPECIFIC CD8$^+$ T CELLS IN THE TUMOR MICROENVIRONMENT

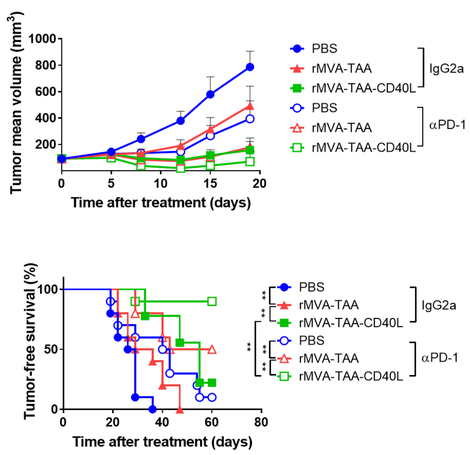
B16.OVA tumor model





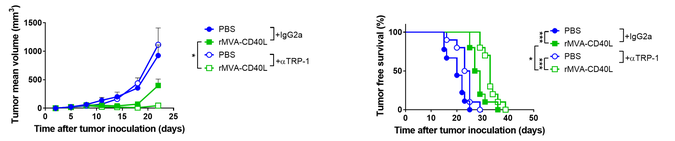
PD-1 IMMUNE CHECKPOINT BLOCKADE SIGNFICANTLY INCREASES rMVA-CD40L ANTITUMOR ACTIVITY

MC38.WT tumor model

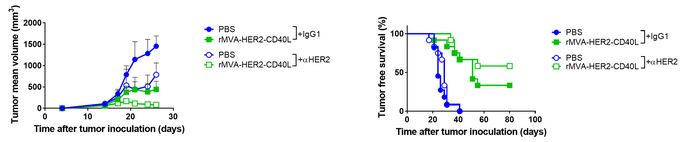


SYNERGISTIC EFFECT OF CD40L ADJUVANTED rMVA WITH ANTI TRP-1 ANTIBODY *IN VIVO* IN THE B16.OVA TUMOR MODEL

B16.OVA tumor model **TAA mAb: αTRP1**



CT26.HER2 tumor model **TAA mAb: αHER2**



CONCLUSIONS

- We describe a novel and translationally relevant therapeutic synergy between viral vaccination and CD40L costimulation.
- IV immunization with rMVA-CD40L leads to Treg reduction in the tumor microenvironment and concomitant expansion of antigen-specific CD8$^+$ T cells with a non-exhausted phenotype, crucial players for rMVA-CD40L tumor growth control.
- We show strengthened antitumor immune responses when both rMVA-CD40L-induced innate and adaptive immune mechanisms are exploited by combining immunotherapeutic regimes, such as checkpoint blockade and TAA targeting antibodies.
- This novel immunotherapeutic approach could translate into clinical cancer therapies where ADCC competent TAA targeting antibodies and PD-1 checkpoint blockade are employed.

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