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

**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**

- Implant tumor cells s.c.
- i.v. injection
- l.o. injection
- Vectors: rMVA-CD40L, rMVA-CD40L:CD40L
- PD-1, PD-1R
- Tregs, anti-antigen
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- 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
- PD-1 immune checkpoint blockade significantly increases rMVA-CD40L antitumor activity

**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.