Background Virus-based vaccines and appropriate costimulation potently enhance antigen-specific T cell immunity against cancer. In the present study, we exploit both innate and adaptive immune responses triggered by a novel recombinant modified vaccinia virus Ankara (rMVA) encoding a Tumor-Associated Antigen (TAA) and the costimulatory CD40L against solid tumors in combination regimes to overcome tumor-induced resistance to immunotherapy.

Material and Methods Subcutaneous murine tumors were induced in C57BL/6 or Balb/c mice using syngeneic tumor cell lines. When tumors were established (60–80 mm³) mice were intravenously injected with rMVA-CD40L. Tumor growth monitoring and immune cell analysis was performed.

Results Therapeutic treatment with rMVA-CD40L resulted in the control of established tumors in several independent tumor models. This antitumor effect was based on the generation of non-exhausted, systemic tumor-specific cytotoxic CD8+ T cells that was essential for therapeutic efficacy. Strikingly, rMVA-CD40L also induced strong NK cell activation and enhanced cytotoxicity. Moreover, the combination of rMVA-CD40L and tumor targeting antibodies resulted in increased therapeutic antitumor efficacy. This therapeutic combination relied on Fcγ receptor-expressing immune cells as well as on NK cells.

Conclusion We describe a novel and translationally relevant therapeutic synergy between viral vaccination and CD40L costimulation. We show strengthened antitumor immune responses when both rMVA-CD40L-induced innate and adaptive immune mechanisms are exploited by combining immunotherapeutic regimes, such as TAA targeting antibodies. This finding could have a direct positive impact in therapeutic regimes where TAA targeting antibodies could be employed.

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