Background

Our understanding of the interaction between the host immune system and cancer has evolved rapidly over the previous 10 years due to the clinical success induced by checkpoint inhibition. Previous immunologic work can now be realized in combination strategies. Modified Vaccinia Ankara (MVA) offers significant opportunities due to its natural induction of innate and adaptive immunity, large payload, and excellent safety profile.

Methods

MVA vectors were administered subcutaneously (SC), intravenously (IV) or intramuscularly (IT) into tumor-bearing mice. Cytokine secretion profile in serum was assessed by Luminex analysis. NK and T cell infiltration and activation in various organs and cytolytic activity against target cells were determined by flow cytometry-based assays. PD-1 immune checkpoint blockade (ICB), low dose cyclophosphamide, tumor-targeting rMVA or 15 Gy radiotherapy were administered along with IV MVA.

Results

Recombinant MVA (rMVA) in which tumor antigens and costimulatory molecules are encoded can be customized for maximal effect by route of administration. rMVA administered intravenously (IV) causes superior induction of antigen specific T cells, cytokines and NK cells than previously seen with subcutaneous or intramuscular routes. Encoding CD40L in addition amplifies the effects and efficacy improves in relevant models. This is dependent on T cells and NK cells, indicating a potential solution to one tumor resistance mechanism, MHC loss and/or mutation. Furthermore, the combination of rMVA with tumor targeting antibodies, checkpoint inhibition, radiotherapy or chemotherapy often showed additional synergistic therapeutic effects. Administration of MVA alone intramuscularly (IT) causes innate immune activation through toll like receptors (TLRs) as well as the cGAS / STING pathway. Recombinant antigen encoding rMVA improves systemic and local antigen specific T cell responses. These effects can be bolstered by encoding certain costimulatory molecules.

Conclusions

IV and IT recombinant MVA may offer off the shelf solutions to resolve many of the host tumor immunity interactions that result in lack of efficacy of checkpoint inhibition alone in most patients. Bavarian Nordic plans to initiate clinical trials with existing agents in 2019 applied IV and IT and will create novel constructs to maximize clinical effect, planned to initiate in 2020 and beyond.