Background Oncolytic viruses are becoming an integral part of immunological approaches to cancer treatment. Induction of inflammatory responses can vary drastically between virus families. Understanding the mechanisms of ligand induced immunogenic cell death (ICD) and stimulation of myeloid cells in the immunosuppressive tumor immune microenvironment (TIME) unique to the utilized virus will enable development of specific strategies to optimize different viral prototypes. We therefore sought to characterize involvement of ligands of the tumor necrosis factor (TNF) receptor superfamily (TNFRSF) in influenza A virus induced oncolysis and tumor associated macrophage (TAM) repolarization.

Materials and Methods WM793b melanoma or HT-29 colorectal cancer cell lines were infected with an H5N1 oncolytic virus prototype expressing a truncated NS1 gene, 116 amino acids in length. TNFRSF ligands were inhibited using biotherapeutic molecules. Cell death was assessed by flow cytometry. M2-like macrophages were obtained by ex vivo polarization from healthy volunteers, stimulated with supernatants of infected co-cultures of cancer cell lines and primary cancer associated fibroblasts and phenotypic features determined via flow cytometry. Subcutaneous syngeneic CT26 tumors were treated with intratumoral virus injections and intraperitoneal TNF-R2-Fc, and tumors assessed for growth and macrophage immune infiltrate.

Results 24 hours after viral infection, the majority of cell death was due to a bystander effect. This bystander cell death was cooperatively induced by FasL and TNF signals upon oncolytic influenza A virus infection in vitro, while TRAIL did not appear necessary. Cell death appeared to be mostly apoptotic in nature. Surprisingly, re-polarization of TAM depended on TNF signaling ex vivo and was independent of caspase or RIPK3 based cell death. Treatment response of CT26 tumors to oncolytic influenza virus injections was completely inhibited by TNF-R2-Fc co-treatment. Similarly, TAM extracted from the murine tumors showed a downregulation of inhibitory phenotypic markers CD163 and CD206, the latter being rescued by TNF-R2-Fc co-treatment.

Conclusions Whereas the oncolytic influenza A virus induced bystander effect was dependent on FasL and TNF, TNF alone was essential for repolarization of TAMs and therapeutic efficiency in a murine animal model.

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P09.18 TNF INDUCTION IN ESSENTIAL FOR ONCOLYTIC INFLUENZA A VIRUS INDUCED CANCER REGRESSION AND TUMOR ASSOCIATED MACROPHAGE REPOLARIZATION


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