Poxvirus-Based Active Immunotherapy with PD-1 and LAG-3 Dual Immune Checkpoint Inhibition Overcomes Compensatory Immune Regulation, Yielding Complete Tumor Regression in Mice.

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Public Summary: Poxvirus-based active immunotherapies mediate anti-tumor efficacy by triggering broad and durable Th1 dominated T cell responses against the tumor. While monotherapy significantly delays tumor growth, it often does not lead to complete tumor regression. It was hypothesized that the induced robust infiltration of IFN-γ-producing T cells into the tumor could provoke an adaptive immune evasive response by the tumor through the upregulation of PD-L1 expression. In therapeutic CT26-HER-2 tumor models, MVA-BN-HER2 poxvirus immunotherapy resulted in significant tumor growth delay accompanied by a robust, tumor-infiltrating T cell response that was characterized by low to mid-levels of PD-1 expression on T cells. As hypothesized, this response was countered by significantly increased PD-L1 expression on the tumor and, unexpectedly, also on infiltrating T cells. Synergistic benefit of anti-tumor therapy was observed when MVA-BN-HER2 immunotherapy was combined with PD-1 immune checkpoint blockade. Interestingly, PD-1 blockade stimulated a second immune checkpoint molecule, LAG-3, to be expressed on T cells. Combining MVA-BN-HER2 immunotherapy with dual PD-1 plus LAG-3 blockade resulted in comprehensive tumor regression in all mice treated with the triple combination therapy. Subsequent rejection of tumors lacking the HER-2 antigen by treatment-responsive mice without further therapy six months after the original challenge demonstrated long lasting memory and suggested that effective T cell immunity to novel, non-targeted tumor antigens (antigen spread) had occurred. These data support the clinical investigation of this triple therapy regimen, especially in cancer patients harboring PD-L1neg/low tumors unlikely to benefit from immune checkpoint blockade alone.

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