Checkpoint Blockade Therapy

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RECOMBINANT MYXOMA VIRUS MC509-N1 DEMONSTRATES ANTITUMOR EFFICACY AS MONOTHERAPY AND IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

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Background There are several obstacles to effective cancer immunotherapy including the heterogenic immune profile and the state of the tumor microenvironment. Oncolytic virotherapy provides an opportunity to overcome some of these limitations through high viral replication and the expression of therapeutic transgenes (TGs) within the tumor tissue. Myxoma virus (MYXV) belongs to the family of Poxviridae and represents a potent oncolytic virus and a safe platform as this virus is non-pathogenic in any hosts apart from lagomorphs. Importantly, MYXV has a high capacity of encoding for multiple TG payloads. Here we engineered MC509-N1, a novel double-encoding transgenes (TG1 and TG2) oncolytic MYXV designed for intravenous (IV) injection. The therapeutic TG1 acts to modify and remodel the immune state of the tumor microenvironment, and TG2 allows for prolonged self-evasion from the host immune defense.

Methods Transgenes expression upon infection was detected by ELISA and by flow cytometry. To determine anticancer efficacy, syngeneic B16F10 melanoma or MC38 colorectal cancer-bearing C57BL/6 mice were injected with MC509-N1 intratumorally or IV with or without immune checkpoint inhibitor (ICI). Tumor growth and survival was monitored after treatment and the immune profile within the tumor microenvironment was analyzed by flow cytometry. Mice cured of their tumors from the original treatment were rechallenged with primary tumor cells to examine anticancer immunity.

Results Cells upon infection with MC509-N1 were found to express both transgenes at high levels and stimulate downstream mechanisms. Importantly, the engineering of both transgenes did not affect MC509-N1 infectivity and productivity as compared to wild-type MYXV. Intratumoral injections of MC509-N1 effectively suppressed tumor growth and improved overall survival of both syngeneic cancer models. Furthermore, MC509-N1 therapy effectively modulated the immune profile within the tumor microenvironment, especially the ratio between tumor infiltrated CD8+ cytotoxic T cells and CD4+FoxP3+ T regulatory cells. In addition, IV injections of MC509-N1 showed improved inhibition of tumor growth compared to wild type MYXV. The combination therapy of MC509-N1 with the ICI anti-PD-L1 further promoted inhibition of tumor growth as demonstrated by higher rate of complete regression and improved survival rate. Furthermore, rechallenge experiments revealed that this combination regimen established specific anticancer immune memory and protected from cancer recurrence.

Conclusions Our results demonstrate that the novel engineered MC509-N1 exhibits potent anticancer efficacy, adequately modulates the immune state of the tumor microenvironment, and acts synergistically to eliminate cancer in combination with ICI.

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