838 ONCOLYTIC VIRUS INDUCED TUMOUR-INFILTRATING LYMPHOCYTES (TILS) FOR THE TREATMENT OF COLORECTAL CANCER

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Background Colorectal cancer is the third most common and second deadliest cancer globally, and with the incidence projected to increase, there is a need for new combination therapies. The heterogenous and poorly immunogenic tumor microenvironment of colorectal cancer poses unique challenges for individual immunotherapies. The combination of two immunotherapies, tumor-infiltrating lymphocytes (TILs) and oncolytic viruses, shows promise in overcoming these challenges and improving patient outcomes. While showing promise select solid cancers, TIL therapy has been limited due to the scarcity of lymphocytes within the tumor, especially those that are tumor specific. However, preliminary studies have shown that pre-administration of an oncolytic virus increases lymphocyte infiltration into the tumor, as well as the number of antitumor lymphocytes, that can be harvested for adoptive cell therapy.

Methods We have established a pipeline for harvesting, isolating, culturing, the characterization, and adoptive cell transfer of murine TILs. Using an MC38 colorectal tumor model in C57BL/6 mice, we determined the impact of oncolytic viruses on TILs that can be harvested for adoptive cell therapy. The number of TILs isolated per gram of tumors in combination with IHC were used to assess the impact of individual oncolytic viruses on TIL recruitment to the tumor. The relationship between oncolytic virus pre-administration and TIL composition was characterized using flow cytometry and immune assays. We evaluated the efficacy of the oncolytic virus-induced TILs compared to conventional TILs when adoptively transferred in a lung metastasis model *in vivo*.

Results Pre-administration of an oncolytic virus induces changes in the TIL population that can be harvested for adoptive cell therapy. Oncolytic virus pre-administration increases the frequency of CD8+ T cells in oncolytic virus-enriched TIL population compared to conventional TILs. The oncolytic virus-induced TILs showed greater specificity tumor-specificity compared to conventional TILs and was maintained during expansion. Oncolytic virus-induced TILs were able to impair tumor progression more than conventional TILs when adoptively transferred to a MC38 lung metastasis model, demonstrating *in vivo* efficacy.

Conclusions Oncolytic viruses can be used to overcome some of the challenges that limit the use of TIL therapy for patients with solid cancers. Oncolytic virus-induced TIL therapy fits well within the current treatment landscape and has great potential for improving outcomes for those with colorectal cancer, making it ideal for integration into patient care. Our approach would facilitate the use of highly polyclonal TILs as a viable immunotherapy that currently cannot be used for majority of solid tumors.

Ethics Approval Study obtained ethics approval from the Animal Care Committee at the University of Ottawa.

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