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Smac Mimetics and Oncolytic Viruses Work together to Drive Anticancer T-cell Responses *via* Complementary Pathways

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Editorial

To directly kill cancer cells, second mitochondrial activator of caspase (Smac)-mimetic drugs and oncolytic viruses were produced. Smac-mimetic chemical and oncolytic virus therapy, on the other hand, modify host immune responses in ways that we thought would complement one another in enhancing anticancer T-cell immunity. We show that Smac-mimetic drug and oncolytic virus therapy work together to drive CD8+ T-cell responses against malignancies via separate mechanisms. LCL161 administration of smac-mimetic compounds reinvigorates fatigued CD8+ T lymphocytes within immunosuppressed malignancies by targeting tumor-associated macrophages for M1-like polarisation. Oncolytic viral treatment with Vesicular Stomatitis Virus (VSVM51) enhances CD8+ T-cell recruitment and activation within tumor-draining lymph nodes. LCL161 and VSVM51 treatment, when combined, results in CD8+ T-cell-mediated tumour suppression in multiple aggressive mice cancer models. Both smac-mimetic compounds and oncolytic viral therapeutics are in clinical trials, and their combination therapy is a promising way to enhancing anticancer T-cell immunity.

Therapies that target a patient's adaptive immune system have been validated for cancer treatment, representing one of the most significant developments in clinical oncology in decades. While monotherapies are highly effective in a limited number of patients, rationally developed combination treatments have demonstrated activity in a greater proportion of clinical trial participants. These promising findings give compelling evidence for treating cancer with a combination of treatments that induce antitumor T-cell activity in diverse but complementary ways. Recently, it was shown that smac-mimetic compounds (SMCs) and Oncolytic Viruses (OVs) work together to promote tumour regression in mouse models of cancer. SMCs are a class of small compounds that are meant to block the Inhibitor of Apoptosis (IAP) proteins and make cancer cells more susceptible to death caused by inflammatory cytokines like Tumour Necrosis Factor alpha (TNF). OVs are a class of naturally occurring and manmade viruses that have been designed to preferentially infect and kill tumours based on genetic abnormalities found in cancer cells.

Cell culture studies revealed that the anticancer synergy between SMC and OV therapy is caused by apoptosis in SMC-treated cancer cells, which is driven by TNF released during OV infection. Both SMC and OV treatments, on the other hand, are potent immunostimulants. This motivated us to look into whether their combined treatment could work in vivo by boosting anticancer immunity. We show that SMC and OV treatments work together to treat immunogenic malignancies by inducing anticancer T-cell responses via complementary mechanisms. SMC therapy indirectly rejuvenates fatigued CD8+ T cells by targeting Tumor-associated Macrophages (TAM) for M1-like polarisation in animal models, whereas OV therapy enhances CD8+ T-cell recruitment and serves as a non-specific immune system adjuvant. Surprisingly, we discovered that TNF-mediated cancer cell death via its canonical receptor TNFR1 is not essential for in vivo anticancer immunity and treatment response. Finally, immune checkpoint inhibition (ICB) employing PD-1 antibodies improves SMC/OV therapy, with triple SMC/OV/ICB therapy resulting to long-term tumour remission in almost 90% of tumor-bearing mice.

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