

Inactivated vaccinia virus effective against advanced cancers alone or combined with immune checkpoint inhibitors

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Modified vaccinia virus Ankara (MVA), a poxvirus, was found to be safe when administered in an inactivated form in mice, and delivering it into the tumor in addition to systemic delivery of an immune checkpoint inhibitor yielded synergistic antitumor effects in mice with large tumors and those with multiple tumors, according to data presented at the Third CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, held Sept. 6-9.

"Immune checkpoint blockade therapy, such as anti-CTLA-4 and anti-PD1/PD-L1 antibodies, has been approved for the treatment of many advanced or [metastatic cancers](#); however, the response rate to this form of therapy alone is still quite low," said Liang Deng, MD, PhD, dermatologist/investigator and Assistant Member in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York (MSKCC).

One of the reasons for failure to respond or for developing resistance to immune checkpoint inhibitors is that there is paucity of infiltrating [immune cells](#) in these tumors, making them "cold tumors," Deng explained. "Microbial-based cancer immunotherapy has the potential to turn 'cold tumors' to 'hot tumors,'" she added.

Microbes, such as the MVA tested in this study, can be detected by the host immune system as "foreign" and can induce the production of

certain immune substances including interferons (IFN), proinflammatory cytokines and chemokines. "The production of these factors in the tumors by the immune [cells](#) and [tumor](#) cells leads to the activation of immune cells and the generation and recruitment of tumor-specific T cells, which can destroy tumor cells," noted Deng. "Therefore, it is important to develop potent microbial-based agents to 'light the fire' in the tumor microenvironment."

Deng and colleagues found that the combination of intratumoral injection of heat-inactivated MVA (iMVA) and immune checkpoint inhibitors led to efficient eradication of large, established tumors and distant non-injected tumors in mice. They showed that the antitumor activity was possible because iMVA is a potent inducer of type I IFN and proinflammatory immune mediators. Intratumoral injection of iMVA also altered the immunosuppressive tumor microenvironment and generated antitumor CD4+ and CD8+ T cells, which could be amplified by the addition of immune checkpoint blockade. The researchers published these findings in *Science Immunology* in May 2017.

Current oncolytic viruses including talimogene laherparepvec (T-VEC), an engineered herpes simplex virus that has been approved by the U.S. Food and Drug Administration for the treatment of advanced melanoma, are replication competent, said Deng. These infectious agents are generally handled in infection-controlled rooms, and adverse events have been reported in patients when the viruses are administered at high doses or if the patients are immune-compromised. It is not known whether viral replication is necessary for the antitumor effects of the DNA virus when delivered intratumorally. To test this, the researchers compared the antitumor efficacy of live oncolytic vaccinia virus (which can replicate) with its heat-inactivated counterpart (which cannot replicate) in mice. They found that the heat-inactivated oncolytic vaccinia virus induced higher numbers of activated CD4+ and CD8+ T cells than the live virus. This meant that the inactivated form of the virus is both safe and

effective.

"We were pleasantly surprised that inactivated oncolytic vaccinia virus works better than live virus," noted Deng. "These results tell us that in order for viral-based therapy to work, it has to engage the host immune system through induction of innate immunity and activation of tumor antigen-presenting dendritic cells," she added.

"Our results support the intratumoral delivery of inactivated vaccinia [virus](#) as a safe and effective [cancer immunotherapy](#) either alone or in combination with immune checkpoint blockade antibodies," said Deng.

"We anticipate that iMVA could be used in several clinical settings, including patients with metastatic cancers that are resistant to immune checkpoint blockade, or those with metastatic cancers that are initially responsive to immune checkpoint blockade and later develop resistance, or it could be used as a combinatory therapy with immune [checkpoint](#) blockade," she noted. "We plan to bring these viral-based products into clinical trials in the coming years." This work is the result of a collaboration of several investigators at MSKCC, including Deng, Stewart Shuman, MD, PhD, Jedd D. Wolchok, MD, PhD, and Taha Merghoub, PhD.

A limitation of the study is that although heat-inactivated MVA induces IFN and proinflammatory immune mediators in human melanoma cells and [human immune cells](#), the antitumor efficacy data were obtained in murine tumor models, Deng said. "Human clinical trials will be necessary to address whether this approach works in the treatment of human cancers," she added.

More information: Peihong Dai et al. Intratumoral delivery of inactivated modified vaccinia virus Ankara (iMVA) induces systemic antitumor immunity via STING and Batf3-dependent dendritic cells,

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