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Virus, vessel, victory: a novel approach to tumor killing

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Summary

Ovarian cancer is intimately dependent on aberrant tumor vasculature. A unique therapeutic approach combining a systemic oncolytic virus with a novel vascular-normalizing agent in ovarian cancer demonstrates the potential to enhance anti-tumor efficacy through improved delivery of the virus and enhanced infiltration of immune cells into the tumors.

In this issue of CLINICAL CANCER RESEARCH, Matuszewska and colleagues report on a novel therapeutic approach incorporating oncolytic therapy with Newcastle Disease Virus (NDV) and vascular targeting in a preclinical model of ovarian cancer.¹ Despite the development of a number of novel anti-cancer agents over the past 20 years, ovarian cancer remains the most lethal gynecologic malignancy. Due to lack of effective screening methods, the majority of ovarian cancer patients are diagnosed at an advanced stage and only approximately 20% of patients are cured. Vascular-targeting agents, such as bevacizumab, a monoclonal antibody targeting VEGF, have been explored in ovarian cancer alone and in combination with chemotherapy in several disease settings.² In all settings, the use of bevacizumab alone or in combination with chemotherapy led to improved disease control, but unfortunately without significant effect on cure rate or overall survival.² These findings highlight the need for exploration of other novel combination partners for vascular-targeted therapies in ovarian cancer.

In recent years, oncolytic viruses have gained momentum in both preclinical research and clinical trials,³ demonstrating potential for application in ovarian cancer. Viruses are remarkable for their ability to hijack host cell machinery for highly efficient replication. Adapted to varying degrees for infectivity and immune evasion, some viruses have been found to be of use as oncolytic agents due to inherent defects in tumor cells that allow for robust viral replication that is not seen in healthy cells.³ In addition to direct cell killing, oncolytic viruses promote activation of both the innate and adaptive branches of the immune system. Dying cancer cells release viral factors known as pathogen-associated molecular

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Conflicts of interest:

D.Z. is named an inventor on 2 patents concerning the use of Newcastle Disease Virus for cancer therapy.

patterns (PAMPS), as well as damage-associated molecular patterns (DAMPs) that attract and activate antigen-presenting cells such as dendritic cells (DCs).³ Upon activation, the DCs produce cytokines that promote migration of innate lymphoid cells that destroy infected tissue. The activated DCs also prime the adaptive immune response by presenting viral and tumor antigens to CD8+ T cells and CD4+ T cells.³ Finally, some oncolytic viruses can directly infect tumor vasculature, resulting in vascular shutdown⁴.

In the current study, Matuszewska et al probed the effects of oncolytic viruses on tumor neovasculature by studying the interactions of Newcastle Disease Virus (NDV) with the tumor microenvironment in an *in vivo* ID8 model of ovarian cancer (Fig. 1).¹ Administration of NDV as a single agent was effective in reducing tumor growth. However, the virus also resulted in vascular shutdown, exacerbating the hypoxic environment often observed within tumors,¹ similar to the findings observed previously with other oncolytic viruses. These findings present a therapeutic conundrum. Although the disruption of tumor vasculature is commonly seen as one of the mechanisms by which oncolytic viruses destroy tumors,³ vascular shutdown can in fact lead to impaired delivery of oncolytic virus and immune cells to the tumor site.¹

The authors thus proceeded to explore the effect of tumor vasculature normalization on NDV efficacy. As a therapeutic strategy targeting vasculature, they used 3TSR protein, which is a recombinant version of the active domain of thrombospondin-1, a large glycoprotein localized in the extracellular matrix with potent anti-angiogenic activity.⁵ While the sheer size and complexity of thrombospondin-1 makes it impractical for application as a therapeutic agent, 3TSR has been shown to retain anti-angiogenic effects with the ability to normalize vasculature and induce tumor regression in an *in vivo* model of ovarian cancer⁵.

When 3TSR was co-administered with NDV, the authors observed enhanced tumor perfusion, with normalization of vascular structure and reduction of hypoxia within the tumor. Remarkably, this led to significant improvement of tumor control, evidenced by a reduction in primary tumor growth, ascites and metastases, when compared to either treatment alone. The authors demonstrate that tumors isolated from the animals treated with combination therapy exhibited increased recruitment and activation of T cells, NK cells, and macrophages, and a reduced production of immunosuppressive cytokines such as TGF beta and IL10.¹

Immune cell exclusion is a problem associated with many tumors. Although oncolytic viruses can promote tumor immune infiltration to an extent, there are limitations to this therapy. Multiple aspects of the innate immune system, such as the complement system and sequestration serve to quickly clear the virus from the body upon systemic administration. Neutralization by circulating antibodies and secretion of interferons reduce the ability of viruses to infect new cells. Finally, as shown in this study, vascular shutdown caused by oncolytic viruses can reduce the ability of the virus to penetrate the tumor, and potentially limits T cell entry. Administration of NDV in combination with 3TSR can counteract this effect, allowing for better trafficking of both the oncolytic virus and immune cells to the tumor site.¹

Findings of this study generate a number of questions for further exploration. For example, it may be useful to consider efficacy of anti-angiogenic therapies other than 3TSR in combination with NDV. Anti-VEGF therapy, for instance, can promote vascular normalization through recruitment and activation of vascular progenitors.² Administration of bevacizumab with an oncolytic virus, therefore, may boost delivery of both the virus and immune infiltrate to the tumor. In the current study it also remains unclear whether enhanced therapeutic effect is due to improved delivery of the virus or of the immune cells into the tumor. Interestingly, the antitumor efficacy was observed *in vivo* despite the relatively poor lytic activity of NDV when tested against ID8 cells *in vitro*. This finding suggests that direct lytic activity of the virus likely plays a minor role in anti-tumor effect, further highlighting the likely indispensable role of the immune system.

Furthermore, in addition to targeting endothelial cells, 3TSR may have an additional effect on infiltrating myeloid cells within the tumor microenvironment. Thrombospondin-1 has been previously shown to interact with CD36, which in addition to endothelial cells is expressed by macrophages, and CD47, a macrophage “do not eat me” signal expressed on tumor cells. Interaction of 3TSR with these receptors within the context of NDV therapy may play a significant role in immune-mediated tumor killing, especially considering the increased recruitment of macrophages observed in the tumors treated by 3TSR and 3TSR in combination with NDV.¹ Finally, testing vascular-normalizing therapies with other oncolytic viruses may provide further answers to whether this finding is unique to NDV or can be generalized to this entire class of agents.

Ovarian cancer remains a disease with an unmet need for new therapeutic approaches and combinations. While anti-angiogenic therapies have provided some benefit, the patients invariably develop resistance to these drugs.⁴ Immunotherapeutic approaches such as immune checkpoint blockade, which is active in other disease types, unfortunately demonstrated poor efficacy in ovarian cancer to date, which may be partly driven by immune exclusion in these tumors. A combined approach that emphasizes vascular normalization in conjunction with oncolytic virus administration carries a potential to overcome these problems and may very well be the missing link that could allow for successful immunotherapy in ovarian cancer.

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Figure 1: Vascular normalization potentiates the efficacy of oncolytic immunotherapy.

A) In the untreated tumor, although the vascular bed is quite dense, it is highly disorganized, and often contains immature blood vessels lacking a proper pericyte outer layer. This contributes to hypoxia and immune exclusion within the tumor. B) Administration of 3TSR promotes vascular normalization and reduces hypoxia. Mature blood vessels surrounded by pericytes can be seen. C) Administration of NDV leads to vascular shutdown within the tumor. This limits access of the virus and immune cells to the tumor and promotes hypoxia. D) Administration of 3TSR with NDV results in vascular normalization as well as the recruitment of immune cells including macrophages, NK cells and T cells, leading to improved tumor killing.