Molecular Therapy
Oncolytics
Commentary

Triple combination therapy for pancreatic cancer remodels stroma and improves survival

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https://doi.org/10.1016/j.omto.2023.03.001

In the current issue of *Molecular Therapy - Oncolytics*, a new study by Yamada and colleagues[1] investigates the effects of combining oncolytic virotherapy with focal adhesion kinase (FAK) inhibition and immune checkpoint blockade in mouse models of pancreatic ductal adenocarcinoma (PDAC). PDAC is a highly lethal and aggressive disease with dismal prognosis. It is characterized by a dense stroma composed of fibroblasts and extracellular matrix (ECM) components, which impair the access of therapeutics into the tumor while stimulating tumor growth, making PDAC notably resistant to therapeutic interventions. This study uses multiple murine models to evaluate the impact of this novel combination therapy to destroy this deadly disease.

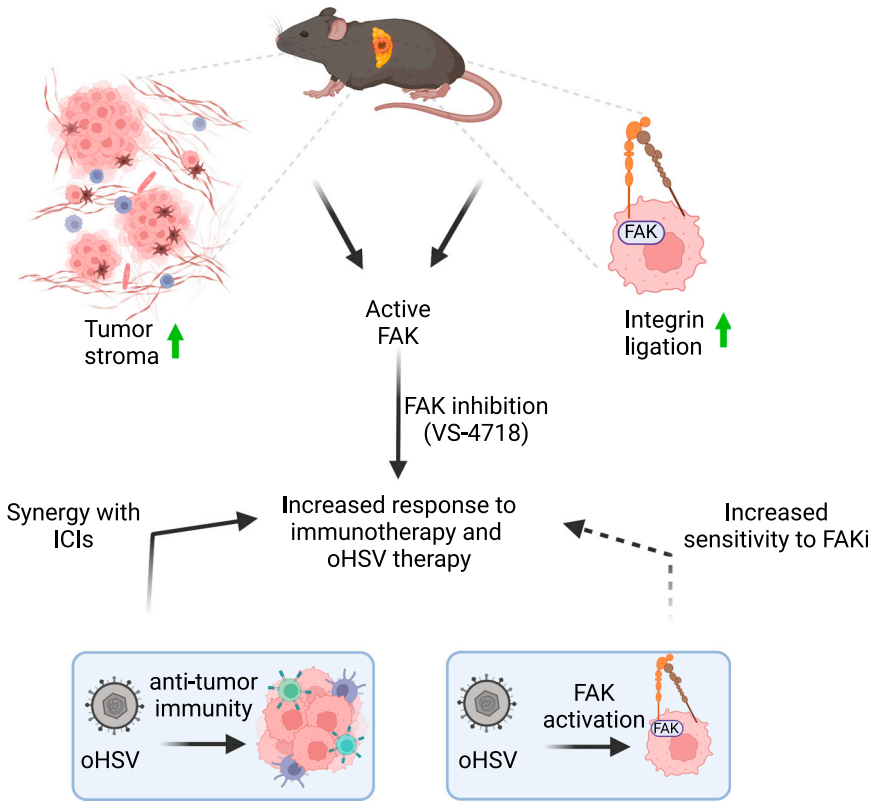

Figure 1. VS-4718-mediated blockade of stroma-induced signaling improves response to immune checkpoint blockade therapy combined with oncolytic viral therapy

The current study suggests a synergistic effect of ICI therapy with anti-tumor immunity induced by oncolytic HSV (oHSV). It is likely that virus-induced integrin activation also contributes to this synergy by sensitizing to FAK inhibition (FAKi; dashed arrow indicates extrapolation from other studies) and further contributes to therapeutic efficacy.

G47Δ, the oncolytic HSV-1-derived virotherapy used in this study, has recently been approved for treatment of patients with recurrent glioblastoma (GBM) in Japan, giving this study high translational importance.[2]

As the name suggests, FAK is a kinase that localizes at cellular sites of adhesion in response to integrin ligation and/or growth factor stimulation. Apart from its well-documented role in cellular growth and motility, FAK also localizes to the nucleus, where it can promote p53 degradation and orchestrate inflammatory gene expression.[3] Drugs that target and block FAK activity are thus an important and active area of investigation. Interestingly, FAK inhibition has been reported to induce anti-tumor immunity in mouse models of PDAC by reducing tumor fibrosis and by inhibition of immunosuppressive cell recruitment.[4] Currently, this approach of combining FAK inhibition with immune checkpoint therapy is being evaluated for patients with PDAC, and preliminary results from this trial look promising.[5] Since oncolytic viral therapy also harnesses anti-tumor immunity to deliver a potent anti-cancer punch, its addition to this combinatorial approach appears logical.

Interestingly, apart from anti-tumor immunity, HSV-1 interactions with integrins have been well documented. Integrins support viral infection wherein cell surface integrins are an essential component of initial virus-cell interactions to initiate entry. Interestingly, while integrins are important for virus entry, their activation can also promote anti-viral signaling in the tumor microenvironment (TME),[6] and their inhibition promotes oncolysis.[7] Blockade of integrin activation with Cilengitide and integrin-blocking antibodies has been reported to improve the outcome of virotherapy in

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preclinical models.[8,9] Here, Yamada et al. analyzed the changes induced in the TME after treatment and identified a shift toward immune stimulation characterized by an increase in both $CD4^+$ and $CD8^+$ T cells and a decrease in the immunosuppressive MDSC population, primarily granulocytic MDSCs. The authors show that a triple combination of VS-4718 (FAKi), G47Δ, and the immune checkpoint inhibitors (ICIs) anti-PD-L1 and anti-CTLA4 has the greatest effect in tumor growth inhibition and mouse survival (Figure 1). The authors postulated that the therapeutic effect of combining FAK blockade with oncolytic HSV therapy is mediated by inhibition of immune suppression by VS-4718 treatment. HSV-1 infection has been previously reported to induce the downstream phosphorylation of FAK,[10] and given the prior reports about integrin blockade and oncolytic HSV therapy, it is probably also likely that apart from FAK-mediated immune activation, oncolytic HSV treatment-induced sensitization to FAK blockade also contributes toward the observed synergy.

In the current study, oncolytic HSV-1 G47Δ alone or in combination with ICIs had no effect in the PKF ($Ptf1a^{cre/+}$;$LSL\text{-}Kras^{G12D/+}$;$Tgfbr2^{fl/fl}$) transgenic mouse model of human PDAC, which develops a dense stroma, highlighting the need to target the TME for efficient delivery of therapeutics into this tumor type. Throughout this study, G47Δ efficacy was seen only in tumors derived from human PDAC cells and not murine. The authors claim that this effect is likely due to the virus being more efficient at killing human PDAC cells compared with their murine counterparts. This underscores the need for better murine models to evaluate biological therapies like oncolytic viruses. Determining ways to modify the oncolytic viral vectors to maintain their replication capability in various tumor microenvironments will be crucial for maximal therapeutic efficacy.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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