Molecular Therapy
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Commentary

Harnessing the power of viroimmunotherapy to overcome challenges in cancer therapy

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Oncolytic viruses are novel anticancer agents that have been increasingly employed as key components of therapeutic regimens. Recently, the field of viroimmunotherapy has developed at a breathtaking rate as investigators can now better understand and modulate aspects of the immune system to optimize cancer treatment strategies.

One of the strengths of virus-based therapeutics is their ability to encode therapeutic and/or imaging transgenes to facilitate multimodal approaches to cancer treatment, which ultimately enhance the anticancer potential of the virus. Importantly, different transgenes can target various molecular pathways, thereby allowing for a more comprehensive attack on the heterogeneous population of cancer cells to overcome tumor resistance mechanisms.

In this work, Hong et al. use a previously described vaccinia virus platform[1] and have developed a novel viral vector (known as KLS-3020) that expresses three genes: (1) hyaluronidase PH-20, (2) the cytokine interleukin 12 (IL-12), and (3) an extracellular domain of programmed cell death 1 fused to the Fc domain of immunoglobulin G (sPD-1-Fc).[2]

The authors have specifically selected each transgene to overcome key obstacles to the success of an oncolytic virus. It is no secret that a fibrotic tumor stroma can make it more challenging for the virus to spread within a given tumor.[3] Hyaluronidase is an enzyme that facilitates the degradation of hyaluronic acid, which is known to make up a large portion of the tumor extracellular matrix. Consequently, the authors demonstrated that the virus encoding for PH-20 resulted in increased intratumoral virus spread when compared to control vectors lacking hyaluronidase enzymatic activity. Additionally, IL-12 is a proinflammatory cytokine with a multitude of downstream immunologic effects, but widespread clinical adoption and utility were limited by severe systemic toxicities.[4] In this manuscript, the authors explored local, intratumoral delivery of IL-12 via a vaccinia vector and demonstrated increased T cell activation and differentiation to the T_h1 phenotype within the local tumor microenvironment. Furthermore, a limitation to successful immune checkpoint inhibition therapy is a "cold" tumor microenvironment, which is known for having low levels of immune cell infiltration. Programmed cell death ligand 1 (PD-L1) is a transmembrane glycoprotein that is expressed on the surface of select immune cells but is importantly located on the surface of many cancerous cells. When bound to PD-1, it promotes a tumorigenic environment by virtue of a decrease in T cell activation and proliferation.[5] Here, the authors use an extracellular domain of PD1 fused to the Fc domain of immunoglobulin G to target PD-L1 as the third transgene within the viral construct. The data presented in the manuscript demonstrated a significant increase in T effector cells in both murine models.

In the early years of the development of the field of oncolytic virotherapy, there was concern that antiviral immunity and stimulation of the immune system would limit the efficacy of oncolytic vectors. In today's research landscape, our perspective on the immune system has radically shifted, as now we are exploiting the immune response to viral infection to improve our cancer treatment strategies. In addition, the rationale of combining therapeutic approaches with complementary mechanisms, including those stimulating the immune response against cancer cells, has gained widespread acceptance across different malignancies resulting in enhanced treatment efficacy and the ability to overcome drug resistance.[6]

As the field of viroimmunotherapy continues to develop, other important factors must be explored to move the field forward. One area of interest lies in predicting the response to virotherapy treatment and how we can identify patients who will benefit most from such strategies. Additionally, it will be key to consider the way in which we integrate viruses into other therapies, such as surgical resection, radiotherapy, chemotherapy, immune checkpoint inhibitors, and CAR-T cell therapy. Factors such as the route of viral delivery (intravenous versus intratumoral), as well as the timing and sequence of combination strategies, must also be considered in creating personalized cancer treatment plans for each patient.

In conclusion, the development of a vaccinia virus engineered with a three-pronged approach represents a promising advancement in oncolytic virotherapy. This approach addresses not only key challenges in cancer therapy but also opens new strategies of combining three transgenes to develop a new, more robust vaccinia virus. Notably, this strategy can also be applied to other virus-based oncolytics. The preliminary data presented in the manuscript certainly support further exploration, paving the way for clinical trials that could significantly enhance the efficacy of virotherapy.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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