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Enhancing Cancer Treatment Efficacy with Intravenously Delivered Oncolytic *Vaccinia virus* by Targeting the PI3K Delta Pathway in Immune Cells

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Abstract

Cancer immunotherapy has seen significant advancements with the use of Oncolytic Viruses (OVs), particularly the *Vaccinia virus*, delivered intravenously. These viruses selectively infect and lyse tumor cells while also stimulating systemic anti-tumor immune responses. However, intravenous delivery of *Vaccinia virus* is often hampered by immune cells, especially neutrophils and macrophage cells. One promising strategy to overcome these challenges is targeting the Phosphoinositide 3-Kinase (PI3K) delta pathway in these cells. The PI3K delta pathway plays a major role in the regulation of immune cell functions, including cell activation, differentiation and migration, as well as in the maintenance of immune tolerance. Inhibiting this pathway can enhance anti-tumor immunity by modulating the activity of various immune cell subsets in blood and within the tumor.

Keywords: Cancer immunotherapy; Oncolytic viruses; Macrophage cells; PI3K

Introduction

This review explores the potential of combining PI3K delta inhibitors with intravenously delivered oncolytic *Vaccinia virus* to enhance the therapeutic efficacy against cancer. We discuss the mechanisms by which the PI3K delta pathway influences immune cell behavior and the subsequent impact on oncolytic virotherapy. Furthermore, we examine preclinical studies that highlight the synergistic effects of this combination therapy. By understanding the interplay between PI3K delta signaling and oncolytic *Vaccinia virus*, we aim to provide insights into optimizing cancer treatment regimens and improving patient outcomes. This review emphasize the need for further research to fully elucidate the therapeutic potential and pave the way for novel combination strategies in cancer immunotherapy.

Literature Review

Oncolytic Viruses (OVs)

Oncolytic Viruses (OVs) can replicate and lyse tumor cells by exploiting aberrations in signaling pathways and the compromised virus defense system in tumor cells, often due to defects in tumor interferon responses. This process not only destroys tumor cells but also activates the Tumor Immune Microenvironment (TME), without affecting healthy cells, showcasing strong potential for cancer treatment. So far, four oncolytic viruses have been approved for clinical use globally, with many more currently in clinical trials. Clinically trialed OVs include Adenovirus (AdV), Vesicular Stomatitis Virus (VSV), Measles Virus (MV), Reovirus (RV), Newcastle Disease Virus (NDV), Herpes Simplex Virus (HSV) and *Vaccinia virus* (VACV) [1-9].

A key consideration in the development of Oncolytic Viruses (OVs) is the delivery method. While initial research focused on direct Intratumoral (IT) injection, this approach has therapeutic limitations and is challenging for treating deep-seated or metastatic tumors. Intravenous (IV) injection is considered a viable alternative as it can target multiple metastatic lesions and deep-seated tumors. However, obstacles in circulation, such as immune cells in peripheral blood, can affect the biological distribution and therapeutic efficacy of OVs.

PI3Ks

Phosphoinositide 3-Kinases (PI3Ks) are a family of intracellular signal transducer enzymes that play a pivotal role in various cellular processes, including growth, proliferation, differentiation, motility and survival [9]. These lipid kinases are divided into three classes based on their structure and substrate specificity: Class I, Class II and Class III. Among these, Class I PI3Ks are the most extensively studied due to their significant roles in oncogenic signaling and immune regulation.

Class I PI3Ks are further subdivided into Class IA and Class IB. Class IA PI3Ks consist of a catalytic subunit (p110α, p110β or p110δ) and a regulatory subunit (p85α, p85β or p55γ) [10]. Phosphoinositide 3-Kinase Delta (PI3Kδ), encoded by the *PIK3CD* gene, is predominantly expressed in leukocytes and is particularly critical in the immune system. This isoform is involved in signaling pathways downstream of various receptors, including antigen receptors on B cells and T cells, cytokine receptors and chemokine receptors [11]. Although single-species ionizing radiation is a just one component of space radiation, there are rare occasions when humans are exposed to whole-body ionizing radiation (e.g., a nuclear event) [8].

PI3Kδ is a critical enzyme predominantly expressed in leukocytes, where it plays a pivotal role in regulating various immune cell functions. Its involvement in signaling pathways downstream of antigen receptors, cytokine receptors and chemokine receptors highlights its

significance in immune responses. Here, we briefly summarize the specific roles of PI3Kδ in different subsets of immune cells [12-14].

- PI3Kδ plays a vital role in T cells for activation and proliferation through TCR signaling, differentiation into effector subsets, and maintaining survival and homeostasis by promoting anti-apoptotic pathways.
- PI3Kδ is essential in B cells for BCR signaling that drives development and activation, supports class-switch recombination and high-affinity antibody production and mediates survival signals to prevent apoptosis.
- PI3Kδ is important for the functions of myeloid cells. PI3Kδ is critical for the maturation and function of dendritic cells, regulating antigen processing and presentation, migration to lymphoid tissues and T cell priming, thereby enhancing adaptive immune responses. PI3Kδ in neutrophils regulates chemotaxis, degranulation and Reactive Oxygen Species (ROS) generation, essential for innate immune responses to infections and initial tumor defense. PI3Kδ influences macrophage polarization and function by regulating cytokine production, phagocytosis and the inflammatory response, thereby affecting immune responses and tumor progression [12].

By targeting PI3Kδ, it is possible to modulate the immune landscape in a way that favour anti-tumor responses, providing a rationale for combining PI3Kδ inhibitors with other therapeutic modalities, such as oncolytic viruses, to enhance cancer treatment efficacy.

Combining PI3Kδ inhibition with intravenously delivered oncolytic *Vaccinia virus* in cancer therapy

Oncolytic virotherapy represents a promising approach in cancer treatment, leveraging genetically engineered viruses to selectively infect and lyse tumor cells while stimulating anti-tumor immune responses [15-20]. Among the various oncolytic viruses, the *Vaccinia virus* stands out due to its unique properties and potential for Intravenous (IV) delivery [16,17].

The advantages of intravenous delivery include:

Systemic distribution: IV delivery allows the oncolytic *Vaccinia virus* to reach metastatic sites and disseminated tumor cells throughout the body, which is particularly important for treating advanced-stage cancers with widespread metastases.

Overcoming physical barriers: Intratumoral injection of oncolytic viruses is often limited to accessible tumors. IV delivery bypasses this limitation, potentially improving the reach and efficacy of the treatment.

However, intravenous delivery faces many challenges. Pre-existing immunity to *Vaccinia virus*, due to vaccination or previous exposure, can neutralize the virus before it reaches the tumor. Strategies to overcome this include using immunosuppressive agents, repeated dosing, or engineering the virus to evade neutralizing antibodies. Additionally, immune cells in the blood and tumor microenvironment can hinder the efficacy of oncolytic virotherapy. Combining oncolytic *Vaccinia virus* with agents that modulate immune cells, such as PI3Kδ inhibitors, can enhance viral entry into tumor cells and improve its efficacy.

Neutrophils are the most abundant white blood cells in human peripheral blood, accounting for 50%-70% of peripheral blood leukocytes. Recent research aimed at identifying which type of cells in the blood hinder the intravenous delivery of oncolytic *Vaccinia virus* to tumors revealed that neutrophils are primarily responsible for engulfing and degrading the majority of these viruses in the bloodstream [18]. Depleting neutrophils using the anti-LY6G antibody (1-A8) resulted in an increased accumulation of circulating oncolytic *Vaccinia virus* in the peripheral blood and enhanced deposition at the tumor site, thereby amplifying the antitumor effect. Neutrophils heavily rely on PI3K signaling to sustain their phagocytic process. Additionally, the study found that inhibiting the PI3K delta isoform with idelalisib (CAL-101) suppressed the uptake of oncolytic *Vaccinia virus* by neutrophils. This inhibition led to a greater presence of oncolytic *Vaccinia virus* in both the peripheral blood and at the tumor site, resulting in improved efficacy against the tumor. Given the importance of neutrophils in fighting infections, the transient inhibition of their functions to enhance the efficacy of oncolytic *Vaccinia virus* in tumor treatment remains an attractive strategy. Another study reported that inhibiting the PI3K delta isoform with idelalisib (CAL-101) suppressed the uptake of oncolytic *Vaccinia virus* by macrophages, improving its efficacy in tumor therapy through a mechanism similar to that observed in neutrophils [19].

Discussion

Macrophages are present in large numbers within tumors, and there are also significant numbers of neutrophils in some tumors. Therefore, the inhibition of the PI3K delta isoform in macrophages and neutrophils with idelalisib (CAL-101) enhances the delivery of oncolytic *Vaccinia virus* to tumor cells in two ways. First, by inhibiting the functions of abundant neutrophils in the blood, leading to higher levels of oncolytic *Vaccinia virus* in the bloodstream and increased viral entry into the tumor. Second, by inhibiting the functions of neutrophils and macrophages within the tumor, allowing more viruses to survive uptake by these cells and subsequently infect more tumor cells, thereby enhancing the efficacy of intravenously delivered oncolytic *Vaccinia virus*.

Moreover, inhibiting the PI3K delta isoform with idelalisib (CAL-101) also affected the uptake of oncolytic *Vaccinia virus* by monocytes in the blood [18]. Although monocytes are not present in large numbers in the blood, this inhibition allowed more oncolytic *Vaccinia virus* to survive, contributing to the improved efficacy of intravenously delivered oncolytic *Vaccinia virus*. This comprehensive inhibition strategy not only increases the virus's persistence in the bloodstream but also maximizes its accumulation and therapeutic impact at the tumor site. Thus, targeting the PI3K delta isoform presents a multi-faceted approach to enhancing oncolytic virotherapy, potentially leading to more effective and widespread clinical applications.

Conclusion

Intravenously delivered oncolytic *Vaccinia virus* represents a versatile and powerful tool in the arsenal of cancer immunotherapy. By leveraging its unique properties and addressing delivery challenges, this approach has the potential to significantly improve the treatment of advanced and metastatic cancers. Combining oncolytic *Vaccinia virus* with immune-modulating agents, such as PI3Kδ inhibitors, offers a promising strategy to enhance its efficacy and overcome the barriers posed by neutrophils and monocytes in blood and by neutrophils and macrophages within the tumor microenvironment.

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