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Enhancing Cancer Immunotherapy: A Novel Approach through the Integration of Oncolytic Virotherapy with CAR-T and NK Cell Therapies

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Abstract. A two-pronged approach to fighting cancer, oncolytic virotherapy (OV) combines direct tumor cytotoxicity with potentiation of anti-tumor immunity. Combining OVs and cell therapies, such as CAR-T and NK cells, has been proposed as an enhanced therapeutic approach. Additionally, it has been demonstrated that adding oncolytic virotherapy to combination medicines increases their therapeutic potential. This article explains the mechanisms underlying oncolytic viruses, the beneficial interactions between them and immune cell therapies, as well as the drawbacks and difficulties of this strategy. We highlight the novel approach of combining CAR T/NK cell treatments and oncolytic virotherapy, highlighting current developments and speculating on the future trajectories of this frontier in cancer immunotherapy.

Keywords: oncolytic virotherapy; CAR-T cell therapy; NK cell therapy; tumor microenvironment; immunotherapeutic effects; combination therapies.

1. Introduction

The innovative realm of oncolytic viruses (OVs) has birthed transformative implications for cancer treatment [1]. Characterized by their unique capability to selectively target and destroy tumor cells, OVs have evolved as powerful allies in the fight against malignancies [2]. Their modus operandi not only relies on direct oncolysis but also capitalizes on the subsequent unleashing of tumor-associated antigens, which in turn galvanizes the immune system against tumor residues. The tumor microenvironment (TME) plays a pivotal role, often creating barriers to treatment. Yet, OVs exhibit the potential to remodel this environment [3], making it more conducive to anti-tumor responses.

In parallel, the field of cellular immunotherapy, marked by the rise of Chimeric Antigen Receptor T-cell (CAR-T) and Natural Killer (NK) cell therapies, has ushered in an era of precision medicine targeting malignancies. The premise of amalgamating these two potent therapeutic modalities - OVs and immune cell therapies - presents a tantalizing avenue to potentially enhance anti-cancer effects. This review delves deep into the synergy of combining oncolytic virotherapy with CAR T/NK cell therapies. As we traverse through the mechanistic intricacies of OVs, we cast light on their promise and pitfalls, and elucidate how their combination with cell therapies could shape the future contours of cancer immunotherapy.

2. Revolutionizing Oncology: The Emergence of CAR-T and CAR-NK Cell Therapies

2.1. The revolutionary strategy in cancer therapeutics

Harnessing the immune system's robust and precise arsenal has been a revolutionary strategy in cancer therapeutics. The Chimeric Antigen Receptor T cells (CAR-T) and the Chimeric Antigen Receptor Natural Killer cells (CAR-NK) are at the core of this paradigm change. The patient's own T cells that have been genetically altered to express a synthetic receptor that targets tumor-specific antigens give rise to CAR-T cells.

Prominent among these antigens is CD19, a protein universally expressed on the surface of B cells. Once these modified T cells encounter their target antigen, they become activated [4], leading to the

destruction of the cancerous cell. This strategy, however, has faced challenges [5]. The robust response can sometimes be too aggressive, leading to a cytokine release syndrome (CRS). This syndrome is a consequence of the excessive activation of the immune response, releasing a cascade of inflammatory cytokines. Though daunting, CRS can be managed using corticosteroids, potent anti-inflammatory agents that dampen the exaggerated immune response. An unintended consequence of targeting CD19 is B-cell aplasia, a condition where normal B cells are also eliminated, given that they express the same target antigen. This can lead to immunodeficiencies, given the pivotal role B cells play in immunity. Yet, there is an emerging consensus that administering fewer CAR-T cells could both achieve therapeutic outcomes and reduce adverse effects.

Prominent companies have pioneered the commercial aspects of CAR-T therapy. Novartis with its product, Kymriah, and Gilead's Yescarta have set the pace [6]. Justifying the significant costs, they argue that the potential curative impact, coupled with the bespoke nature of the therapy — tailored to each individual — warrants the pricing. To ensure safety, some CAR-T constructs incorporate "suicide genes [7]," which when activated, can swiftly eliminate the CAR-T cells, offering a mechanism to control or halt therapy if severe adverse reactions ensue.

On the other flank of this therapeutic revolution are the CAR-NK cells. Natural Killer (NK) cells, traditionally touted as sentinels of the innate immune system, are recognized for their ability to identify and destroy aberrant cells without prior sensitization. They balance their activity through a dynamic interplay of activating and inhibitory receptors. Among the activating receptors are the Natural Cytotoxicity Receptors (NCRs), namely NKp30, NKp44, and NKp46, and NKG2D, which recognize stress-induced ligands or tumor-associated antigens. Inhibitory receptors, on the other hand, like the killer cell immunoglobulin-like receptors (KIRs) and the CD94/NKG2A receptor, recognize MHC class I molecules, ensuring that healthy cells remain untouched. These receptors guide NK cells as they unleash their cytotoxic prowess, releasing granules packed with molecules like perforin and granzymes. Moreover, the ability of NK cells to recognize antibodies bound to target cells through their CD16 (FcγRIII) receptor allows them to mediate antibody-dependent cellular cytotoxicity (ADCC).

2.2. Innate and adaptive immunity

However, as research delves deeper into the biology of NK cells, the once-clear boundary between innate and adaptive immunity blurs. Recent studies reveal memory-like properties in NK cells, especially after specific viral challenges such as with cytomegalovirus (CMV) [8]. This redefined understanding emphasizes their potential not just as passive guards but also as dynamic responders with a memory of past encounters.

Exploiting these properties, scientists now engineer CAR-NK cells that target tumor-specific antigens with impressive efficacy. Novel strategies, such as the dual-targeting CARs, are addressing tumor heterogeneity. Some engineered CAR-NK cells are designed to produce specific cytokines like IL-12 or IL-15, amplifying their cytotoxic potential, especially in the hostile tumor environment. Others are geared to navigate the dense extracellular matrices of solid tumors, and some armored against the tumor's immunosuppressive tactics by silencing or blocking inhibitory receptors like PD-1.

Given their lineage, NK cells predominantly function in blood, evolved to scout and eliminate cellular anomalies in circulation, making them especially potent against circulating tumor cells. But there's more to their story. Beyond the bloodstream, tissue-resident NK cells inhabit various organs and exhibit functional attributes distinct from their circulating counterparts. Yet, as with CAR-T cells, patient safety remains paramount. Hence, even CAR-NK constructs often come equipped with suicide genes, providing an "off-switch" to ensure patient safety. Together, the emergent CAR-T and CAR-NK therapies represent not just an evolution but a paradigm shift in oncology — the promise of turning the immune system into a precise, adaptive, and enduring ally against cancer.

3. Oncolytic Virus-Mediated Immunotherapy

Viruses naturally possess tropism levels governed by cell species, tissue origin, and histologic lineage, with entry necessitating target cell surface receptors. For instance, the CD155 receptor, often overexpressed in cancer cells, facilitates entry for poliovirus. Such specific receptors determine the permissiveness of a cell to viral infections, impacting both innate and adaptive immunity. Cancer cells, due to their de-differentiation and metabolic reprogramming, often lose species and tissue-type barriers that restrict OV infection. OVs wield their therapeutic might through several mechanisms: direct tumor cell lysis, vascular disruption, the expression of therapeutic transgenes, and the amplification of antitumor immunity. The significance of each mechanism can differ based on the OV variant and the targeted cancer type [9]. However, augmenting antitumor immunity is consistently pivotal for therapy success. This immune boost arises from initial T cell cross-priming, propelled by the tumor immunogenic cell death (ICD) upon OV infection and subsequent presentation of released antigens to dendritic cells. These cells then facilitate antigen presentation to T cells in tumor-associated lymph nodes or tertiary lymphoid structures.

The OVs also activate both innate and adaptive immunity, introducing pathogen-associated molecular pattern molecules (PAMPs) that stimulate innate cells and enhance ICD, which subsequently releases both damage-associated molecular pattern molecules (DAMPs) and PAMPs, stimulating dendritic cells. These complex interactions have led researchers to view OVs as potential therapeutic cancer vaccines. With the capability to transform immune-sparse tumors into immune-rich zones [10], OVs present a promising combination with therapeutics requiring a pre-existing immune-rich environment. For instance, combining OVs with immune checkpoint inhibitors has demonstrated synergistic effects in numerous models [11]. Two such OV examples that gained regulatory approval are Oncorine (H101) for nasopharyngeal carcinoma treatment in China and T-VEC for advanced melanoma in the US. The primary challenge noted in clinical trials is the tumor microenvironment's immunosuppressive nature, especially in advanced-stage patients. The focus is now on integrating potent OVs with other anti-cancer strategies to negate tumor-associated immune suppression while promoting therapeutic inflammatory responses.

4. Synergistic Assault: Merging CAR-T/CAR-NK Therapies with Oncolytic Virotherapy in Cancer Treatment

The frontiers of cancer therapeutics are continually expanding with the integration of chimeric antigen receptor (CAR) modified T-cells, CAR-modified natural killer (NK) cells, and oncolytic virotherapy, offering a two-pronged assault against malignancies. The amalgamation of these modalities is reshaping therapeutic paradigms, providing sophisticated strategies against the ever-evolving tumor landscape.

CAR-T cells, bioengineered to express CARs targeting tumor-associated antigens like CD19, have paved the way for unprecedented remission rates in previously untreatable hematological malignancies. These cells recognize their targets, then utilize the signaling domains, typically encompassing regions from CD28, 4-1BB, and CD3ζ, to trigger T-cell proliferation, cytokine secretion, and cytolytic activity against the tumor. The introduction of oncolytic viruses into this equation enhances therapeutic outcomes [12]. Oncolytic viruses inherently prefer tumor cells over normal cells due to tumor-specific altered physiological states, such as their deregulated signaling pathways. The viral replication within the tumor cells causes direct oncolysis, leading to the release of tumor-associated antigens, which, in turn, can serve as targets for CAR-T cells.

Concurrently, CAR-NK cells, traditionally viewed as circulatory components of the innate immune system, are gaining traction in the therapeutic domain. These cells, equipped with receptors such as KIRs and CD94/NKG2A, balance activation and inhibition, while other receptors, including the NCRs and NKG2D, amplify tumor cell recognition. The union of CAR-NK cells with oncolytic viruses offers an intriguing advantage. The viral oncolysis can release a slew of tumor antigens and associated danger signals [13], creating an environment conducive to NK cell activation. Additionally,

certain oncolytic viruses can be engineered to express ligands or cytokines that further activate NK cells or enhance their recruitment to the tumor site.

When CAR-T or CAR-NK therapies are administered in tandem with oncolytic viruses, a multifactorial anti-tumor response ensues. The virus instigates tumoral destruction, modulating the tumor microenvironment [14] and releasing tumor antigens, thus priming the ground for CAR-modified immune cells. This facilitates increased infiltration and activation of these immune cells within the tumor site, thereby enhancing therapeutic efficacy.

Furthermore, the safety protocols embedded within these cells, such as suicide genes in CAR-NK cells, ensure that potential toxicities can be managed. For instance, the therapeutic onslaught might trigger overwhelming inflammatory responses, but with integrated safety switches, adverse reactions can be contained.

In essence, the confluence of CAR-T/CAR-NK cells and oncolytic virotherapy offers a multifaceted, dynamic, and adaptative approach against tumors. By orchestrating direct oncolysis with precise immunological attacks, this combination therapy stands poised to set a new benchmark in cancer therapeutics, harnessing the full might of both the innate and adaptive immune systems in concert with the tumoricidal capabilities of oncolytic viruses.

5. Conclusions and Perspectives

The field of cancer immunotherapy has experienced a sea change from its early days with the advent of interleukin 2 therapies. Recent years, especially post-2010, have witnessed a tremendous leap in our understanding and application of novel strategies. The spotlight has particularly been on genetically modified T and NK cells, specifically CAR T and CAR NK cells, given their ability to effectively target tumor cells. A complementary approach, oncolytic immunotherapy, has also emerged as a powerful tool, with the approval of oncolytic viruses like T-VEC for treating advanced-stage melanoma, signaling the potential of this modality.

In this discourse, we underscored the synergy between CAR T/NK cells and oncolytic virotherapy. By exploiting the innate tumor-targeting capabilities of oncolytic viruses, and their ability to modulate the tumor microenvironment, they can serve as perfect allies to CAR T and CAR NK cells, which are specifically engineered to recognize and eliminate cancer cells. Emphasizing this interplay, the introduction of BiTE- or TriTE-armed oncolytic viruses could address the enduring challenge of resistance in advanced-stage solid tumors [15].

Yet, challenges persist. While the prowess of CAR T therapy is undeniable, with notable FDA-approved agents like Kymriah by Novartis and Yescarta by Gilead, and the innate capabilities of NK cells that bridge innate and adaptive immunity, the resistance of advanced solid tumors remains an obstacle. Addressing this, we explored the potential of combining these therapies with oncolytic viruses, proposing a unified assault on the tumor fortress.

As we peer into the horizon, it's evident that optimizing these combined strategies will be paramount. Incorporating suicide genes into CAR T constructs, understanding and mitigating side effects like cytokine release syndrome (CRS) through corticosteroids [16], and harnessing the unique receptors on NK cells such as KIRs, NCRs, and NKG2D are just a few pivotal considerations [17]. The journey ahead requires a nuanced understanding of the tumor milieu and an integrated approach that could combine three or more therapies targeting essential pathways in the tumor environment. This comprehensive strategy, interlinking CAR T/NK cells, oncolytic viruses, and checkpoint inhibitors, might be the transformative solution that redefines cancer therapeutics.

References

[1] Guo, Zong Sheng, et al. “Bi- and Tri-Specific T Cell Engager-Armed Oncolytic Viruses: Next-Generation Cancer Immunotherapy.” Biomedicines, U.S. National Library of Medicine, 10 July 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7400484/.

[2] Wang, Xianwang, et al. “Oncolytic Virotherapy Evolved into the Fourth Generation as Tumor Immunotherapy - Journal of Translational Medicine.” BioMed Central, BioMed Central, 25 July 2023, translational-medicine.biomedcentral.com/articles/10.1186/s12967 - 023 - 04360 - 8.

[3] Liu, Shiyu, et al. “OX40L-Armed Oncolytic Virus Boosts T-Cell Response and Remodels Tumor Microenvironment for Pancreatic Cancer Treatment.” Theranostics, U.S. National Library of Medicine, 9 July 2023, www.ncbi.nlm.nih.gov/pmc/articles/PMC10405835/.

[4] Chen, Pei-Hsuan, et al. “Activation of Car and Non-CAR T Cells within the Tumor Microenvironment Following Car T Cell Therapy.” JCI Insight, U.S. National Library of Medicine, 18 June 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7406247/.

[5] Sterner, Robert C., and Rosalie M. Sterner. “Car-T Cell Therapy: Current Limitations and Potential Strategies.” Nature News, Nature Publishing Group, 6 Apr. 2021, www.nature.com/articles/s41408-021-00459-.

[6] Albinger, Nawid, et al. “Current Status and Perspective of Car-T and Car-NK Cell Therapy Trials in Germany.” Nature News, Nature Publishing Group, 22 Mar. 2021, www.nature.com/articles/s41434-021-00246-w.

[7] Casucci, Monica, et al. “Extracellular NGFR Spacers Allow Efficient Tracking and Enrichment of Fully Functional Car-T Cells Co-Expressing a Suicide Gene.” Frontiers, Frontiers, 26 Feb. 2018, www.frontiersin.org/articles/10.3389/fimmu.2018.00507/full.

[8] Carmen Campo “Effect of Age and CMV on NK Cell Subpopulations.” Experimental Gerontology, Pergamon, 17 Jan. 2014, www.sciencedirect.com/science/article/abs/pii/S0531556514000114.

[9] Santos Apolonio, Jonathan, et al. “Oncolytic Virus Therapy in Cancer: A Current Review.” World Journal of Virology, U.S. National Library of Medicine, 25 Sept. 2021, www.ncbi.nlm.nih.gov/pmc/articles/PMC8474975/.

[10] Guo, Zong Sheng, et al. “Bi- and Tri-Specific T Cell Engager-Armed Oncolytic Viruses: Next-Generation Cancer Immunotherapy.” Biomedicines, U.S. National Library of Medicine, 10 July 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7400484/.

[11] Rojas, Juan J., et al. “Defining Effective Combinations of Immune Checkpoint Blockade and Oncolytic Virotherapy.” American Association for Cancer Research, American Association for Cancer Research, 14 Dec. 2015, aacrjournals.org/clincancerres/article/21/24/5543/262914/Defining-Effective-Combinations-of-Immune.

[12] Cronin, Michelle, et al. “Bacterial-mediated knockdown of tumor resistance to an oncolytic virus enhances therapy.” Molecular Therapy, vol. 22, no. 6, 2014, pp. 1188 – 1197, https: //doi.org/10.1038/mt.2014. 23.

[13] Gujar, Shashi A., and Patrick W. K. Lee. “Oncolytic Virus-Mediated Reversal of Impaired Tumor Antigen Presentation.” Frontiers, Frontiers, 27 Mar. 2014, www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2014.00077/full.

[14] Jeffrey, Wojton, et al. “Impact of Tumor Microenvironment on Oncolytic Viral Therapy.” Cytokine & Growth Factor Reviews, Pergamon, 17 Apr. 2010, www.sciencedirect.com/science/article/abs/pii/S1359610110000250.

[15] Guo, Zong Sheng, et al. “Bi- and Tri-Specific T Cell Engager-Armed Oncolytic Viruses: Next-Generation Cancer Immunotherapy.” Biomedicines, U.S. National Library of Medicine, 10 July 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7400484/.

[16] Maude, Shannon L, et al. “Managing Cytokine Release Syndrome Associated with Novel T Cell-Engaging Therapies.” Cancer Journal (Sudbury, Mass.), U.S. National Library of Medicine, 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC4119809/.

[17] Maskalenko, Nicholas A., et al. “Harnessing Natural Killer Cells for Cancer Immunotherapy: Dispatching the First Responders.” Nature News, Nature Publishing Group, 21 Mar. 2022, www.nature.com/articles/s41573 - 022 - 00413 - 7.