Perspective

Biology

Oncolytic Virus
A Promising Immunotherapy to Treat Tumors

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Oncolytic viruses are a type of virus that infects and kills tumor cells more than other cells. They act as "immune modification platforms" that express immune checkpoint inhibitors, tumor antigens, cytokines, and T cell engagers. They can be engineered or tested to selectively multiply and kill cancer cells. Targeting strategies include deleting the gene for the virulence factor and using abnormal signaling pathways in cancer cells to stop them from multiplying and becoming lethal.

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ONCOLYTIC viruses (OVs) are types of viruses that infect and kill tumor cells preferentially (1). At an early stage, OVs preferentially infect and destroy some tumor cells through replicating and multiplying within tumor cells, generating new infectious virus particles to infect and destroy other tumor cells (2). OVs exert their oncolytic effects either by directly lysing tumor cells or by inducing the host to create anti-tumor immune cells (3). OVs function as "immune modification platforms" that enable the virus to express immune checkpoint inhibitors, tumor antigens, cytokines, and T cell engagers; and bypass the barrier of T cell immunity to tumor cells as a novel anticancer process mechanism (4).

OVs can be created or screened to amplify and kill cancer cells selectively (5). OVs are capable of infecting and metastasizing inside the human system or allowing them to function at both in situ and metastatic tumor sites (6). Several OVs targeting methodologies have been widely studied, and a general design approach is to eliminate the virulence factor gene of the virus by employing the aberrant signaling pathway in cancer cells, so that it cannot reproduce in normal cells but persists in cancer cells (7).

Currently, the Wnt signaling pathway genes, such as RAS, TP53, RB1, PTEN, etc., are well-established; they are also associated with other tumor-related genes and signaling pathways, including the primary viral defense in mammalian cells (8). Interferons and cytokines are mediated, but cancer cells inhibit this pathway, allowing the virus to replicate and proliferate freely in cancer cells (9).

Vesicular stomatitis virus (VSV) and Maraba virus, which are modified rhabdoviruses, are typical representations of this type of route (10, 11). Talimogene laherparepvec (T-VEC; Imlygic™), the first oncolytic virus therapy approved by the FDA, is produced from an HSV-1 virus engineered to remove two genes, ICP34.5 and ICP47 (12). The former will hinder cellular protein synthesis, whereas the latter will inhibit antigen presentation. Pexa-Vec deletes the thymolybdate kinase gene such that it can only replicate in liver cancer cells with strong kinase activity (13).

Oncolytic Viruses and Immunotherapy

OVs may be administered as a single agent or in conjunction with other immunotherapies such that the body's immunity is skewed toward anti-tumor rather than anti-virus. Because major histocompatibility complex (MHC) has a higher affinity for viral antigens than tumor antigens, in OVs treatment protocols, rhabdovirus-induced immunity is more likely to immunize viruses than cancer cells (14). However, studies have shown that using the expression of tumor antigen-associated antigens (TAAs) can effectively solve this issue and make the immune system more anti-tumor (15).

Step 1: T-cell Priming

Any T cell response must first transmit tumor-specific antigens to T cells with homologous TCRs, a procedure that involves APCs (antigen-presenting cells). APC function is frequently impaired at cancer locations, preventing the presentation of TAAs. The tumor-intrinsic-catenin oncogenic signaling pathway, for instance, will block the recruitment of APCs at the tumor site (16).

OVs can kill tumor cells and release intracellular TAAs, PAMPs, and DAMPs when used as in situ vaccines (17). In addition, OV is capable of infecting APCs, promoting their functional maturation, and inducing a type 1 interferon response (18). These antigenic and inflammatory stimuli induce tumor-specific immune responses.

Step 2: T Cell Trafficking and Infiltration

Once recruited, T cells must travel to the tumor location and enter it. CXCL9, CXCL10, and CXCL11 are the chemokines linked to T cell infiltration in human malignancies (19).

There is a strong correlation between the expression levels of these variables and the number of intratumoral T cells and patient survival (20). OVs can stimulate T cell infiltration in tumors in a variety of ways when used to promote intratumoral infiltration (21).

First, it can induce a type 1 interferon response, which stimulates the synthesis of chemokines that recruit T cells. Russell et al. identified a "window of opportunity" for the delivery of oncolytic viruses to brain tumors, which involves breaching the blood-brain barrier, elevating immune cell chemokines, and increasing T cell infiltration in brain tumors (22).

Second, oncolytic viruses can induce inflammatory stimulators such as TNF, IL-1, etc., which upregulate the expression of selectin in endothelial cells and increase T cell infiltration (23).

Third, OVs can be designed to proliferate in tumor cells with immunosuppressive signaling pathways, inverting the signaling pathways into pro-inflammatory mediators. For instance, the tumor-intrinsic Wnt-catenin signaling pathway has an immunosuppressive effect, and numerous OVs have been created to block the Wnt-catenin signaling pathway and control transcription (24). This pathway does not trigger antiviral immunity.

The ability to create OVs to generate T-cell chemokines provides a direct answer to the genetic and epigenetic abnormalities of related genes in tumor cells. Once immune cells reach the tumor microenvironment (TME), they must traverse a network of body cells and the extracellular matrix (ECM). Via inflammatory factors and host kinases, OVs can induce alterations in the tumor microenvironment by attracting neutrophils (25).

OVs can be constructed to convey ECM editors in order to increase this effect. Everts et al. demonstrated that tumor antiviral gene expression is inhibited by cancer-driven TGF-β and that VSV can selectively replicate and kill cancer-associated fibroblasts (CAFs) (26). Considering that CAFs are tumor connective tissue, a stromal component of tumor immunosuppression, this suggests that OVs can enhance T cell infiltration.

Step 3: Avoid Immunosuppression

T cells that enter tumors must still combat immunosuppressive cells and other suppressors present in the TME. Both tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) can release potent immunosuppressive factors such as IL-10, TGF-β, IDO, and arginase (27, 28). These substances block the majority of essential immunological functions, including dendritic cell maturation, antigen presentation, the manufacture of inflammatory cytokines, and the activity of cytolytic factors.

By eliciting a robust pro-inflammatory T helper 1 (TH1) cell-polarized immunological response, OVs can neutralize the immunosuppressive impact and drastically modify the TME (29). This TME reset caused by an OV infection is accompanied by the activation of many pro-inflammatory factors. And according to prior findings, OV can proliferate and kill immunosuppressive cells, but VSV destroys CAF (30). Furthermore, OVs can convert immunosuppressive cells into pro-inflammatory cells (e.g., using polio viruses to infect macrophages) (31).

Make Indolent Tumors Sensitive to Immune Checkpoints Again

Immune checkpoint networks have evolved in humans to reduce immune-induced pathological reactions, possibly especially against viral infections (32). As a result, immune checkpoint inhibitors are targeted by interferon products and attract T cells during OV-mediated oncolysis, therefore reducing the inflammatory response. Consequently, adding immune checkpoint inhibitors (ICIs) such as PD1 and CTLA4 while using OVs can greatly enhance the effect and lengthen patient survival (33).

Recent study suggested that OV treatment renders immune-inert cells immune to checkpoints since even individuals with low levels of immune cell infiltration and negative IFN signaling before treatment can respond well to OVs paired with ICI treatment (34). The toxicity of the combination therapy was also equivalent to that of the single-agent regimen, but it was lower.

Using OVs to Deliver Immune Checkpoint Inhibitors

Combining PD1 and CTLA4 boosted efficacy but also doubled toxicity in advanced melanoma (35). Encoding ICIs in OVs is one option for addressing this issue, as it reduces the requirement for combination therapy. Utilizing the vaccinia virus backbone, infected tumor cells and other components of the microenvironment could proliferate and create viruses modified to express PD1, which were more effective than either treatment alone (36). The current difficulty is discovering how the OV can

reach each anatomical region and exercise function.

Step 4: Engaging Tumor Cells

The recognition, engagement, and lysing of tumor cells by T cells is the last requirement for immunotherapy to be effective. Tumor cells downregulate some elements, including antigen production and presentation pathways like TAP1, LMP2, LMP7, and TAP-associated proteins, in order to escape identification (37, 38). Through the loss of 2-tubulin or particular MHC alleles, tumor cells can also downregulate MHC type 1, and OV can undo these results (39). Reovirus, for instance, can boost the production of type 1 and type 2 MHC in tumor cells and APCs by activating type 1 interleukin (40). OVs can promote the invasion of NK cells and neutrophils, which can kill tumor cells through antigen and MHC pathways, respectively, even in cells lacking the antigen-presenting gene (41).

Conclusion

There are numerous adoptive immunological T cell treatment options available right now. T cells from the patient's body are removed for treatment, transformed, and expanded, and then reinfused into the patient's body. The best option is for cells with little differentiation; however, in vitro expansion frequently causes T cells to terminally differentiate. Finding strategies to get beyond the different obstacles T cells face when they function, however, should be a more practical answer.

In order for T cells receiving ACT therapy to multiply more effectively, continue to move, and perform physiological functions, OVs can regulate the immune system and the tumor microenvironment. In several preclinical and clinical investigations, OVs in combination with ACT treatment performed more efficiently with fewer T cells. In addition to acting as adjuvants, OVs can also trigger the release of TAAs, which results in a more thorough T cell response.

To better fulfill the aforementioned possible OV methods, the systemic delivery capability of the current OVs must be improved, as well as their dissemination and durability in the TME. On the other hand, a deeper comprehension of how the immune system reacts to tumors and viral diseases can help create a wider range of anti-tumor OV vectors.

Besides, in order to obtain various immunotherapeutic effects, we must assess the best OV platform. For instance, in the oncolytic virus vaccine strategy, a virus with a simple genome and a pro-inflammatory response that can spread quickly and function in the TME and secondary lymphoid tissues is preferable. However, if OV is used as a carrier to deliver immune molecules to the TME, a more complex and lower replication virus is preferable. OVs must be created to control the spatiotemporal expression of transcribed genes to fully achieve their potential roles. For instance, immature immune responses can be prevented by expressing ICIs, BiTEs, and MiTes after several OV infection and transmission stages.■

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