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Oncolytic Viral Nanoparticles: A Combination Of Targeted And Immunotherapeutic Approach For Cancer Treatment: A Review

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Abstract

Human health and survival have always been seriously threatened by cancer. Although surgery, radiation therapy, and chemotherapy could improve the survival rate of cancer patients, most patients with chronic cancer have a poor survival rate or cannot afford the high cost of treatment. The development of oncolytic viruses provides us with a new technique for treating or even curing malignant cancers. Oncolytic viruses (OVs) have gained interest as a potential approach in cancer therapy because of their potential to selectively infect and destroy tumor cells, without affecting healthy cells . They also work against cancer by releasing immunostimulatory chemicals from dead cancer cells. Oncolytic virotherapy, like other anticancer therapies, has various limitations, including viral transport to the target, tumor mass penetration, and antiviral immune responses. Nanoparticles (NPs) have gained a lot of interest in clinical studies because of their distinctive appearance characteristics. However they have encountered challenges due to the inefficiency of drug delivery to the tissue of interest and their dispersion in bloodstream. In this scenario, various chemical alterations can be employed to the nanoparticle surfaces to boost their efficacy in drug delivery. To improve the functioning of these two therapeutic methods, the sophisticated technique of OVs encapsulated with nanoparticles can be employed, which has shown significant therapeutic outcomes in the treatment of various malignancies. This review focuses on the clinical advancements of oncolytic viruses and nanoparticles in cancer therapy and their combinational effects on tumor cells. This review also provides insight into the future prospects by assessing both the advantages and disadvantages of nano-based oncolytic virotherapy.

Keywords: Cancer, Oncolytic viruses, Virotherapy, Nanoparticles, Drug delivery.

INTRODUCTION

Cancer is one of the most significant health problems in the world. Cancer incidence is expected to rise by 2025, with more than 20 million new cancer cases each year, based on worldwide demographic trends (Ajam-Hosseini et al., 2023; Zugazagoitia et al., 2016). Malignant tumors are becoming one of the top causes of mortality worldwide. Although there are currently numerous therapies available, including surgical therapy, radiotherapy, chemotherapy, and the most recent immunotherapy, they have certain limits. Surgical therapy is mostly used for people with the early stages cancer, but the considerable side effects of radiotherapy and chemotherapy make them difficult for patients to tolerate (Cao et al., 2020). Furthermore, conventional immunotherapy has various limitations, for example, the overall success rate of patients undergoing immunotherapy is roughly 10 to 30%, therefore enhancing immunotherapeutic functioning is necessary (Ajam-Hosseini et al., 2023; Iwai et al., 2017).

In general, existing cancer therapy procedures are essentially inadequate, and new treatment approaches with accurate tumor targeting, potent tumor-killing characteristics, and minimal harmful side effects must be presented (Cao et al., 2020). As a result, the researchers focused on gene and viral therapies to treat oncotherapy (Ajam-Hosseini et al., 2023). The very first gene therapy was conducted in 1990 (Misra, 2013), paving the way for a new therapeutic approach, and other gene therapy products were granted approval after much work. It should be mentioned that cancer is now the most prevalent condition treated with gene therapy, accounting for more than 60% of clinical studies (Ajam-Hosseini et al., 2023). Viruses seem to be causing 20% of all malignancies in humans. The Epstein-Barr virus, hepatitis B and hepatitis C, are the causes of Burkitt's lymphoma, liver cancer and Kaposi's sarcoma, respectively (Iwai et al., 2017). Duran I Reynals had already accepted viruses for the treatment of diseases in addition to their involvement in tumor formation (Alemany, 2013). (Alemany, 2013) Gradually, the anticancer properties of viruses were recognized in the late nineteenth century. Dr. George Duck identified the first recorded link between a natural viral infection and a possible anticancer impact in 1904. According to this research, following a natural influenza virus infection, a lady with leukemia reported a decrease in leukocyte counts (Arabi et al., 2022)

Oncolytic Viruses

Oncolytic viruses (OVs) are an emerging category of cancer therapeutic agents that have attracted the interest of researchers in recent years due to their unique features (Cao et al., 2020). OVs are viruses that specifically target and destroy cancerous cells while ignoring healthy ones (Rahman & McFadden, 2021). OVs can elicit an anticancer response following two different mechanisms: 1. preferential tumor cell replication , resulting in immediate lysis, and 2. development of integrated immunity to tumors (Kaufman et al., 2015). Infection caused by OVs, together with cancer cell death, stimulates the cell-mediated antitumor immune response, altering the tumor micro-environment (TME) (Matos et al., 2020). The virus begins replication and makes viral proteins after infection. Following that, it stimulates signaling pathways involved in autophagy processes by reducing cellular function and increasing oxidative stress (Ji et al., 2022). As they depend on the human immune system's innate capacity to destroy cancer cells, it is essential for OVs to achieve a balance between anti-tumor and antiviral immunity to function effectively in oncotherapy (Gruijl et al., 2015). OVs are classified into two categories based on their development: natural viruses (that is, the wild-type and native type) and genetically engineered viral types. A few of them (notably the reovirus) have an inherent capacity to grow in cancer cells, while others have showed promising results when genetically modified. With the use of genetic engineering, tumor targeting ability, oncolytic activity, or creating robust antitumor immune responses of OVs can be enhanced (Bai et al., 2019; Mondal et al., 2020). Owing to the complexity and heterogeneity of cancer tissues, as well as the probability of tumor cell metastasis, virus selection and administration mechanism are considered tough concerns in the field of OV therapy (Ajam-Hosseini et al., 2023; Mondal et al., 2020).

Oncolytic virotherapy is a type of cancer therapy in which a virus, capable of replicating itself, is used to kill cancer cells. There are many different types of viral species, but not all of them can be modified to be oncolytic viruses (OVs) (Russell et al., 2012). These OVs must be non-pathogenic, capable of targeting and destroying cancer cells, and capable of being genetically modified to create tumor-killing proteins (Ajam-Hosseini et al., 2023; Maroun et al., 2017). Tumor selection is often concerned with the quantity of receptor-mediated cell entry, intracellular antiviral responses, or restriction factors affecting the sensitivity of an infected cell towards expression and replication of viral gene (Cao et al., 2020; Kaufman et al., 2015; Seymour & Fisher, 2016).

The History and Evolution of Oncolytic Virotherapy

The idea of employing viruses to cure cancers has been around for over a century. As early as 1904, it was first reported that the tumor of a 42-year-old leukemia patient had decreased as a result of influenza (Cao et al.,

2020). Then, in 1912, Italian doctors found that a rabies vaccine injection may stimulate the regression of cervical cancer, giving rise to the novel idea of OV therapy and a series of related studies (PELNER et al., 1958). Although various clinical investigations using wild-type viruses to treat tumors were conducted throughout the 1950s and 1970s, the OV eventually fell to second place in cancer therapy because the virus was unable to effectively regulate its pathogenicity. Genetically modified attenuated and highly selective viruses were first introduced in the 1980s, when genetic engineering technology made it possible to alter the viral genome. A genetically modified human herpes simplex virus I (HSV-1) lacking thymidine kinase (TK), was shown to have outstanding safety, increased lifespan, and the ability to inhibit the development of glioma in mice, in preclinical animal studies in 1991 (Cao et al., 2020). Phase I clinical studies for the genetically modified adenovirus, Onyx 015, began in 1996 (Heise et al., 1997; Xia et al., 2004). The first OV to be licensed by regulatory authorities for the treatment of cancer was RIGVIR, a non-pathogenic enteric, cytopathic human orphan virus, which was used to treat melanoma in Latvia in 2004 (Cao et al., 2020). Although the modified adenovirus H101 (Oncorine, recombinant human adenovirus five injection, ankeri) was authorized in China in 2005, its therapeutic efficacy has not been acknowledged globally (Cao et al., 2020; Garber, 2006). In October 2015, the Food and Drug Administration (FDA) approved the commercialization of T-VEC (talimogene laherparepvec, Imlygic). In 2016, T-VEC received approval for commercialization in Europe and Canada, demonstrating the maturity of OV technology for cancer therapy. Three OV medications are now on the market, with six additional OV drugs in phase III clinical trials (Coffin, 2016).

Table 1 : The characteristics of a few selected oncolytic viruses

Viruses	Characteristics	Advantages	Disadvantages	References
Adenovirus (Ad)	**Genome (Size):** dsDNA (~35 kb) **Replication Site:** Nucleus **Vertebrate Host:** Human, Animals	-High lytic activity - -Genetic modification is easily accessible - Ability to infect a wide range of cells (dividing as well as non-dividing) -Improved tumor specificity -The physical and chemical stability of particles - High titre (1010 pfu/ml) - Possessing a broad tissue tropism - Increasing the anticancer effect by combining immunomodulatory agents	-Limited tumor infection -Limited efficacy owing to antiviral immunity -Attenuated viral spread -Replication is difficult to turn off.	(Ajam-Hosseini et al., 2023; J. H. Kim et al., 2006; Niemann & Kühnel, 2017)
Herpes simplex virus (HSV)	**Genome (Size):** dsDNA (~154 kb) **Replication Site:** Nucleus **Vertebrate Host:** Human	- Genetic modification is easily accessible - Drugs exist to turn off undesirable viral replication - Only replicates in cells lacking an anti-apoptotic factor (E1B-19 K) - Inhibition of host antiviral immunity through virus co-treatment with cyclophosphamide	- Possibility of latent native viral infection - Potential inhibition of OV-mediated antitumor immunity - Adverse consequences	(Ajam-Hosseini et al., 2023; Goldufsky et al., 2013; Kaufman et al., 2015)

Poxvirus: vaccinia virus (VACV)	**Genome (Size):** dsDNA (160–190 kb) **Replication Site:** Nucleus **Vertebrate Host:** Human	- Large genome available for genetic manipulation - High insertion capacity - Associated with relatively minor health conditions - Prevents the immune system from recognizing and clearing the virus in circulatory system - Does not have a cognate receptor and can infect any cell type - No host genome integration - Has an innate preference towards tumors - High titre (up to 1010 pfu/ml) - Viral-mediated immunogenic cytotoxicity - Clinical trial experience	- Possible fatal or serious side effects - Difficulty preventing undesired viral replication - Potential cytopathic consequences - Limited intrinsic tumor selection - Limited intrinsic tumor selection - Mild viral infection - Unknown function of several genes - Viral protein-induced immune response	(Ajam-Hosseini et al., 2023; Z. S. Guo & Bartlett, 2004; Haddad, 2017; Thorne, 2011)
Poliovirus (PV)	**Genome (Size):** SS (+) RNA (7.5 kb) **Replication Site:** Cytoplasm **Vertebrate Host:** Human	- Thorough understanding of viral gene function - Oncogenes are not encoded. Inability to integrate into the host chromosome - Penetration of the blood-brain barrier due to the capsid's small size	- Cannot be readily modified genetically - Undesirable viral replication cannot be easily stopped	(Ajam-Hosseini et al., 2023; McCarthy et al., 2019)
Newcastle disease virus (NDV)	**Genome (Size):** SS(−) RNA (15 kb) **Replication Site:** Nucleus **Vertebrate Host:** Birds	- Inherently tumor-selective strain - Naturally occurring immunostimulatory virus - Less immunogenic in humans (avian virus) - Ability to propagate in tumor tissues via multicyclic replication	- Possibility of antiviral immunity - Possibility of systemic toxicity	(Ajam-Hosseini et al., 2023; Burman et al., 2020; Elankumaran et al., 2006)
Reovirus (RV)	**Genome (Size):** dsRNA (23 kb) **Replication Site:** Birds **Vertebrate Host:** Human	- Inherently tumor-selective species - Only replicates in cells with an active Ras-pathway and an impaired PKR - Antigenicity can elicit an immune response - Chemotherapy can boost antitumor response - Associated with relatively minor health conditions - Thorough understanding of viral gene function	-Problems with genetic alteration -Potential for antiviral immunity -Potential for moderate toxicity -No clinical trial experience	(Ajam-Hosseini et al., 2023; Connolly et al., 2000; Errington et al., 2008)

(Source: Adapted and modified from (Ajam-Hosseini et al., 2023)

Anticancer Mechanism of Oncolytic Viruses (OVs)

The unique ability of OVs to selectively grow in cancer cells, resulting in inflammation and even cell death, as well as inducing host immune responses as a result of exposure to cancer-associated antigens, makes them potential cancer gene therapy agents (Lichty et al., 2014). The direct oncolysis or cytotoxicity of the OV against cancer cells, as well as indirect generation of bystander effects (such as tumor blood vessel damage)

and immunotherapy against tumors, together make up its anticancer mechanism (Russell et al., 2012; Russell & Peng, 2007). After infection, viruses can take control of the protein factory of tumor cells, preventing it from producing enough protein for growth requirements, compromising the physiological processes that are normally carried out by tumor cells. Furthermore, by eliciting an immune reaction, tumor cells can be destroyed. Infected tumor cells have the ability to produce cytokines or chemokines, release tumor-derived antigens following apoptosis, and then draw in a variety of immune cells, including cytotoxic T lymphocytes, natural killer cells, dendritic cells, and phagocytic cells, leading to a tumor-specific immune response and possibly eradicating uninfected cancer cells (Chen et al., 2012; Prestwich et al., 2009). Eventually, the immune response is coupled with a "immune-associated" bystander effect, wherein the production of local cytokine may cause immunological responses in nearby tumor cells even in the absence of antigen expression (Schietinger et al., 2010). Apart from the ones stated above, OVs can also kill tumor blood vessels, decreasing or even preventing tumor blood flow, causing oxygen and nutritional deficiency in tumor cells (Breitbach et al., 2007, 2013). OV-induced necrosis can also result in the production of damage-associated molecular patterns (DAMPs), which excite dendritic cells and acquired immunological responses (Jiang & Fueyo, 2014). Despite the fact that oncolytic virotherapy can kill cancer cells directly and activate the immune system, the tumor may prevent the anticancer immune response by interfering with nearly every stage of immune activation thereby creating an immune-suppressive tumor microenvironment (Puré & Lo, 2016; Rabinovich et al., 2007). Especially, in immunologically "cold" tumors, the OV can enhance overall immune responses by arming itself with immune-modulating genes, such as those encoding immune checkpoint inhibitors, tumor antigens, and targets for chimeric antigen receptor T cells (Achard et al., 2018). Solid tumors, on the other hand, are complex, heterogeneous formations that impair the oncolytic action of OVs. OVs can be modified to increase their oncolytic capacity by expressing modulatory compounds that target the composition of the tumor microenvironment to kill tumor cells and prevent tumor growth Additionally, it has been found that OVs combined with immunostimulatory molecules enhances the development of anticancer immune responses (Cao et al., 2020). T-VEC was only recently granted approval by the US FDA for the treatment of melanoma by expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) (Dolgin, 2015). In contrast to systemic GM-CSF injection, T-VEC therapy for metastatic melanoma was risk-free and produced an overall response rate of 10.8% (Andtbacka et al., 2015). Oncolytic virotherapy, therefore, represents a new age of promising opportunities for cancer virotherapy (Cao et al., 2020).

Anticancer Mechanism of Nanoparticles (NPs)

The transport of therapeutic chemicals to the site of action is a significant concern in the treatment of various illnesses (Wilczewska et al., 2012). To avoid adverse reactions on the surrounding organs , it is critical to direct the medicine to the desired location, where the predicted therapeutic action is desired to take place (Doroudian et al., 2023). As a result, employing a controlled system of delivering drugs is a primary technique for increasing therapeutic molecule safety and efficacy, and it has the ability to overcome these constraints (Farjadian et al., 2022). The drug treatment impact has been significantly increased by inventing and building intelligent nanoplatforms for drug targeting and regulated drug release, which has the potential to fundamentally transform the way autoimmune inflammatory illnesses are treated (Ajam-Hosseini et al., 2023; Zhu et al., 2022).

NPs are particles with a dimension of below 100 nm and specific properties not commonly seen in bulk specimens of the same substance (Farjadian et al., 2022). The desirable optical, chemical, and physical characteristics of nanoparticles make them suitable for use in biomedical applications such tissue engineering, chemical sensing, drug administration, cellular imaging, diagnostics and therapies (Mejía-Méndez et al., 2022).Because of their significant and distinctive features, such as their significantly higher surface-to-mass ratio than other particles, their quantum properties, and their ability to adsorb as well as transport other compounds, these nanoparticles are appealing for clinical applications (Jong & Borm, 2008). Over the last few decades, drug delivery techniques using NPs have advanced significantly in the treatment of a variety of solid tumors (Pierce et al., 2021). Banham et al. proposed for the first time in 1965 that NPs, as an efficient delivery method, could transport diverse substances through biological membranes (Ajam-Hosseini et al., 2023; Doroudian, Azhdari, et al., 2021).

Initial cell attachment is determined by the physical and chemical surface characteristics of NPs, and this affects further processes of cell development, proliferation, differentiation, and migration (Staehlke et al., 2019). One of the most commonly used polymer ligands for shielding nanoparticle surfaces is polyethylene glycol (PEG), due to it's excellent hydrophilicity, biocompatibility, and durability in high salt concentrations and pH extremes (Guerrini et al., 2018). Polyethyleneimine (PEI) is another polymer that is available as both a branched or linear

structure. Branching PEI, which has a molecular weight of 25 kDa, is considered as the gold standard for gene transport due to its extremely high cationic charge, creates stronger and more compact DNA complexes than linear PEI (Patnaik & Gupta, 2013). Another ligand is arginyl-glycyl-aspartic acid (RGD), which is the most common peptide motif in the extracellular matrix and is in charge of regulating cell adhesion to integrin. Because integrins are overexpressed in many cancer cells, it is assumed that RGD-coated NP penetrates the cell readily via integrin-mediated endocytosis (Ajam-Hosseini et al., 2023; Hajipour et al., 2019).

Table 2 : The properties and therapeutic applications of a few selected nanoparticles

Nanoparticles	Characteristics	Advantages	Disadvantages	Tumors targeted	References
Liposome	Drugs that are lipophilic or water-soluble can be loaded into liposomes, which are closed vesicular nanocarriers with lipid bilayers and an internal aqueous cavity.	Anti-drug degradation protection It is less cytotoxic. Amphiphilic and self-assembly properties A large payload Extended time of activity Drugs that are both hydrophilic and lipophilic can be loaded. Non-immunogenic, biocompatible, and biodegradable	High manufacturing costs Condensed drug molecule fusion in vivo Inadequate regulation of drug release rate Inability to overcome biological barriers Adequate drug loading without the use of pH or ionic gradients Phospholipids are oxidizable and hydrolyzable.	Breast, Colon, Lungs, Ovarian cancer Kaposi's sarcoma	(Adepu & Ramakrishna, 2021; Ajam-Hosseini et al., 2023; Deng et al., 2019; Lee, 2020; Milewska et al., 2021; Souri et al., 2022; Zheng et al., 2022)
Polymeric nanoparticles	Polymeric nanoparticles are colloidal nanocarriers that are solid, sphere-shaped, and have particle sizes less than 1000 nm which are used to dissolve and disseminate therapeutic substances in polymer matrix.	Effect of enhanced permeability and retention (EPR) Model of Controlled Drug Release Enhanced storage stability as a result of chemical and physical protection Targeted drug delivery to cells and tissues, with minimal systemic absorption. Natural polymer nanoparticle biodegradability Possibility of low toxicity Biocompatibility	Natural polymers' batch-to-batch heterogeneity in nanoparticle manufacturing Natural polymer purification challenges Problems with retaining active compounds' biological activity through the formation of polymeric nanoparticles	Liver and renal cancer Ovarian cancer Advanced solid tumors	(Ahmed et al., 2022; Ajam-Hosseini et al., 2023; Deng et al., 2019; Ghasemiyeh et al., 2022; Rao & Geckeler, 2011; Souri et al., 2022; Zheng et al., 2022)
Polymeric micelles	Block copolymers self-assemble to produce polymeric micelles, which have a hydrophobic polymer core and a hydrophilic shell.	Nano-sized Reduce pharmacological adverse effects by reducing dosage frequency. Increases cell internalization	Non-specific targeting Unregulated drug release	Breast, Skin, Lungs Head an d neck cancer	(Ajam-Hosseini et al., 2023; Chaudhuri et al., 2022; Deng et al., 2019; Hsu et al., 2021; Pham et al., 2021; Souri et al., 2022)
Dendrimers	Due to their multiple peripheral functional groups, dendrimers, which are short, compact molecules with an average size of less than 12 nm, have a high drug loading capacity and	Molecular weight, size, shape, and branch length uniformity A high degree of branching produces a large surface area. The availability of polyvalent interior cavities	Synthesis process is complicated. Possible terminal group incomplete reactions Production of high generation dendrimers is hindered by steric hindrance of the core	Breast, Skin, Lungs	(Adepu & Ramakrishna, 2021; Ajam-Hosseini et al., 2023; Hsu et al., 2021)

	can deliver drugs just to tumor cells (Ahmed et al., 2022)	allows for increased loading and targeting. Water solubility is quite high. Biocompatibility and lack of immunogenicity	molecule and dendrons.		
Carbon nanotubes	Carbon nanotubes are hydrophobic, thin needle-like structures whose toxicity in biological fluids is a major limiting issue.	Nanotechnology-based techniques to assisted reproduction Embryogenesis Oncology of the reproductive system	Side effects of oxidative stress on sexual hormones Induction of ovarian tissue alterations	Breast, Skin, Lungs	(Ahmed et al., 2022; Ajam-Hosseini et al., 2023; Sinha & Yeow, 2005; Zare-Zardini et al., 2022)
Gold NPs (AuNPs)	Due to their physicochemical properties, including size, surface plasmon resonance, shape, and surface chemistry, AuNPs, solid colloidal particles with a size range of 1 to 100 nm, are used in biology.	Biocompatible excellent optical properties Modification potential Capable of absorbing near-infrared light Enough for deep tissue imaging	Can lead to oxidative damage It is not biodegradable. Organic polymers must be coated to increase solubility, biostability, and biodegradability.	Various cancer Breast cancer	(Agabeigi et al., 2020; Ajam-Hosseini et al., 2023; Sibuyi et al., 2021; Singh et al., 2018; Younis et al., 2022)
Solid lipid nanoparticles	In general, solid lipids are disseminated in aqueous environments, stabilized by surfactants, and form a non-polar core by substituting liquid lipids with solid lipids at room temperature.	High level of stability Decreased toxicity Drug entrapment protection against sensitive environments Improved bioavailability of bioactive substances that are not readily soluble in water Capability of site-specific targeting with more payload capacity than other carriers Specific targeting Long-term stability Modified drug administration Both hydrophilic and lipophilic drugs can be used. Increase intracellular drug delivery.	Changes in the polymorphism of lipid particles After-storage drug elimination Microbial activity following storage Active targeting can be challenging. Drug loading capacity is limited. Polymorphism, inconvenient physical handling	Breast, Colon, Lungs, Pancreatic	(Ajam-Hosseini et al., 2023; Ghasemiyeh et al., 2022; Khairnar et al., 2022; Milewska et al., 2021)

Source: Adapted and modified from (Ajam-Hosseini et al., 2023)

Combination Therapy of OVs and NPs

As OV therapy advances, the difficulties with OV-mediated treatment becomes more obvious. For instance, OV clearance caused by the host's innate or adaptive immune responses and viral liver tropism, non-targeting of tumor tissue, and passive accumulation result in inadequate virus distribution to tumor cells, disrupting the therapeutic procedure (Goldufsky et al., 2013). With the varying clinical efficacies of OV-mediated oncotherapy, the emphasis has turned toward various therapeutic agent shielding techniques, including nanoparticle carriers (Ajam-Hosseini et al., 2023). In case of the shielding technique, the targeted organ or tissue depends on the active delivery process (Yokoda et al., 2017), and that it is feasible to regulate viral

transmission to the target tissue by modifying both the physical and chemical characteristics of nanoparticles, which has shown mixed results (Ajam-Hosseini et al., 2023; Howard & Muthana, 2020).
Because of more effective drug delivery capabilities, increased specificity of drug release, and synergistic benefits, many combined techniques for smart nanodrug delivery have attracted considerable attention (Doroudian, Neill, et al., 2021). AuNP, one of the most often utilized NPs in viral treatment, can be employed to enhance DNA permeation into tumors even when neutralizing antibodies are present (Sendra et al., 2020). Coating Ad vectors with AuNPs having quaternary ammonium groups and an RGD peptide results in a biocompatible compound which is extremely effective at propagating target cells while suppressing internalized trafficking, viral infection, and deciphering (Gonzalez-Pastor et al., 2021). Biodegradable polymers with a PEG linker targeting RGD to deliver oncolytic Ad improve effective transduction and lung carcinoma cell death. It is also more effective at bypassing the host's innate and adaptive immune responses than naked Ad (J. Kim et al., 2014). In vitro and in vivo, oncolytic adenovirus plasmid DNA encapsulated with liposome (rather than Ad alone) inhibited adenovirus-neutralizing antibody production and had powerful anticancer actions on colon cancer cells. The nano-sized liposomes are particularly stable throughout circulation, thus aids in the activity of the complex (Aoyama et al., 2017). Tseng et al. employed recombinant adeno-associated virus serotype 2 coated with iron oxide nanoparticles (approximately 5 nm) to facilitate remote administration under a magnetic gradient to alleviate the constraints of intratumoral injection. They also utilized photodynamic treatment, which resulted in a significant decrease in tumor progression via apoptosis (S.-J. Tseng et al., 2016). The use of a PH-responsive polymeric nanoparticle complex containing 2,3-dimethylmaleic-anhydride-PEG--poly-L-lysine-doxorubicin or lapatinib as a combination therapy is possible. This combination achieved a favourable therapeutic outcome, highlighting the tremendous potential of synergistic therapy in the field of oncology (Z. Guo et al., 2020) . Ligands include antibodies like cetuximab and growth factors like epidermal growth factor receptor (EGFR) (Grapa et al., 2019; S.-H. Tseng et al., 2015). Cetuximab, a monoclonal antibody, has a greater affinity for human EGFR than natural ligands. This ligand has been authorized by the FDA as the first therapy for EGFR-positive metastatic colorectal cancer. It is also used as part of a combination therapy for other malignancies (S.-H. Tseng et al., 2015). EGF coupled nanoparticles have demonstrated promising outcomes in delivering drugs, treatment of EGFR overexpression tumors, and imaging (Grapa et al., 2019). Interestingly, OV and NP published the first clinical study in the field of oncotherapy in 2000, which has had a considerable rising trend till now (Ajam-Hosseini et al., 2023).

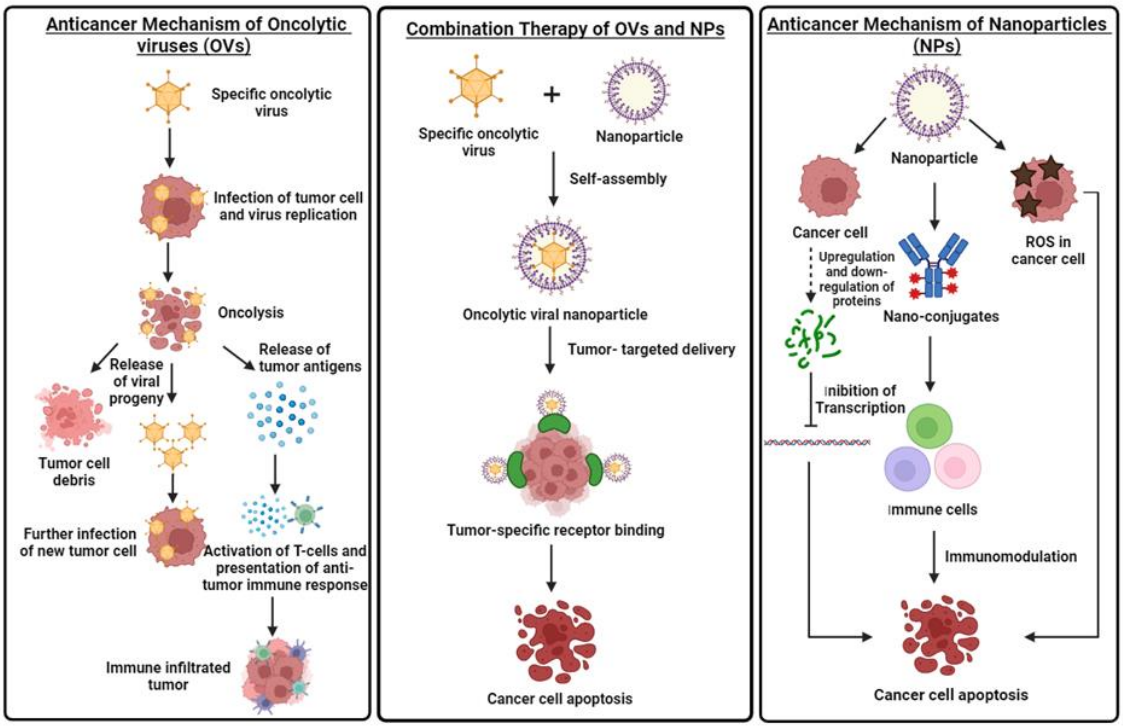

Figure 1: Anticancer mechanisms of oncolytic viruses, nanoparticles and their combination therapy.

CONCLUSION

In oncotherapy, successful approach of drug delivering techniques minimize adverse effects on the normal cells that surround the tumor tissue. However, the oncolytic virus approach faces challenges due to diverse antiviral responses in preclinical animal models. Careful animal studies are necessary to balance between the immunological antiviral and antitumor responses. Advances in cancer treatment through nano-encapsulated oncolytic viruses have reduced restrictions and controlled adverse effects, offering potential for combined cancer therapy. Emerging technologies for nano-based oncolytic viruses also hold great promise for cancer treatment. Plant viruses and bacteriophages are recognized nanotechnologies that have developed to transport and deliver cargo, making them ideal drug delivery experts. VLPs are biocompatible and biodegradable, allowing for vascular transit, cellular absorption and interactions. They are easily designed to produce novel structures that interact with biological systems in predictable ways. In addition to carrying therapeutics or dyes to certain cells and tissues, VLPs can exhibit functional groups that target ligands, imaging dyes, epitopes. Since its introduction, the field of VLPs for drug delivery applications has grown significantly, with the number of virus-based therapies in clinical trials expected to continue growing and eventually lead to advanced therapeutics in the clinic in the near future.

FUTURE PERSPECTIVE

Advances in oncolytic virotherapy (OVs) for cancer treatment have made significant progress, with enhanced tumor cell targeting and strategies for improving immune response. Pre-clinical studies on dosing strategy and delivery routes are crucial for optimum therapeutic efficacy. In order to avoid latent infections, viral shedding, and transmissions, further investigation is needed to examine the efficacy of OVs and find ways to minimize unfavorable outcomes through genetic alterations. Identifying how OVs and the host immune system interact dynamically in the tumor's microenvironment and enhancing those interactions should be the main objective of oncolytic virotherapy in the future. Having a better understanding of the relationships among patient's immunological state, malignancy, tumor mutation profiles, employed oncolytic vectors, and their responses to virotherapy can help in the development of more dependable, personalized treatments. With more notable outcomes anticipated in the future, combining OVs with cancer immunotherapy has become an appealing option. As the therapeutic result depends on a dynamic balance between antiviral and antitumor immune responses, the duration of OV administration should also be taken into account. Viral nanoparticles (VNPs), derived from mammalian viruses, bacteriophages, and plant viruses, as well as their genome-free counterparts, virus-like particles (VLPs), are increasingly being used in nanomedicine. The use of VLPs as drug delivery agents is advancing, and significant research must be conducted on a regular basis in order to deliver these therapies to the clinic.

Conflict of Interest

Authors do not have any competing interest.

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