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The Role of Newcastle Disease Virus in Cancer Therapy: A Systematic Review

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ABSTRACT

Recently, immunotherapy has become a hopeful option for cancer therapy. Taking advantage of pathogens is a well-established method of cancer immunotherapy. It has been shown that the Newcastle disease virus (NDV), an avian virus with oncolytic properties, can be used to treat cancer. This study was designed to offer a comprehensive overview of the role of NDV in cancer treatment, focusing on its attributes, mechanisms of action, preclinical and clinical trials, and future perspectives. A systematic literature review was performed to gather relevant information about NDV in cancer therapy. The inclusion criteria of this study included studies conducted *in vitro* and *in vivo* as well as clinical trials to investigate the anti-cancer effects and mechanisms behind the action of NDV. A total of 34 out of 176 academic articles, preclinical studies, clinical trials, and review articles were analyzed to collect key findings.-In addition to replicating selectively through invading cancerous cells, NDV has been shown to induce apoptosis in *in vivo* studies. There is evidence that it can induce apoptosis, induce oncolysis, and modulate immune function in preclinical research. Studies have demonstrated that combining this therapy with chemotherapy, immunotherapies, and targeted therapies provides encouraging results regarding effectiveness and safety in animal models. As a result of NDV's ability to induce immunogenic cell death, the immune system is activated when it reacts to cancer cells. In addition, NDV infection promotes the recruitment and activation of immune cells, especially cytotoxic T cells, by releasing cytokines and chemokines. This dual mechanism triggers anti-cancer immune responses. An interesting new approach to cancer treatment is based on the selective replication of NDV, which can induce immunogenic cell death in tumor tissues and interfere with oncogenic signaling pathways. Research in preclinical models has yielded valuable information, as well as evidence of the effectiveness and safety of clinical trials. A synergistic effect has been demonstrated when chemotherapy, immunotherapies, and targeted therapies are used in conjunction.

Keywords: Cancer, Immune responses, Newcastle disease, Targeted therapy

INTRODUCTION

To treat cancer effectively, there is a constant demand for innovative and reliable treatment methods worldwide (Cheng et al., 2021; Asouli et al., 2023; Sadr et al., 2023a). A variety of cancer treatments, such as chemotherapy, surgery, and radiotherapy, have made substantial progress in recent years (Butler et al., 2021; Debela et al., 2021; Wang et al., 2021; Sadr et al., 2023b). The problem is that common treatments such as chemotherapy, surgery, and radiotherapy possess toxicities, resistance capabilities, and impermeability in the presence of cancer cells (Zhao et al., 2023). Therefore, it is imperative to develop novel approaches for detecting tumor cells and killing them with minimal damage to healthy tissues (Hajjafari et al., 2022; Saeed et al., 2022; Sadr et al., 2023c). A new field of investigation is the study of oncolytic virotherapy, in which viruses are used as cancer-fighting agents (Zheng et al., 2019; Nakao et al., 2020; Cheng et al., 2022). A virus is considered oncolytic if it is engineered or naturally

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occurs with the ability to selectively infect and destruct neoplastic cells, thereby regressing tumors (Lin et al., 2023). It is the inherent mechanisms of viruses that permit them to replicate in cancer cells selectively and lead to the death of the tumor cells without affecting healthy cells, providing a promising approach (Kooti et al., 2021; Ghasemi Darestani et al., 2023).

Known as a member of the Paramyxoviridae family, the Newcastle disease virus (NDV) has recently been considered an option for cancer therapy (Zamarin and Palese, 2012; Cheng et al., 2016). Various bird species are affected by NDV, leading to mild to severe symptoms of respiratory infections and neurological disorders. The NDV, however, can kill a wide range of human neoplastic cells, such as hematological malignancies and solid tumors (Russell, 2002; Cuadrado-Castano et al., 2015).

The NDV's distinctive features make it a suitable choice for oncolytic virotherapy (Garmaroudi et al., 2022). Within tumor cells, NDV replicates preferentially due to modifications of the signaling pathways within the cells and weakened antiviral defenses (Shao et al., 2019; Palanivelu et al., 2023). Furthermore, NDV can trigger immunogenic cell death, thereby increasing the efficacy of NDV by enhancing the immune system's ability to fight cancer (Buijs et al., 2015; Koks et al., 2015). NDV has received considerable attention due to these properties in terms of its efficacy as a cancer treatment approach (Apostolidis et al., 2007; Song et al., 2019).

The main objective of the current review is to summarize the clinical and preclinical research designed to assess the therapeutic potential of NDV in various cancer types. Through a thorough review of the existing data, the review looks at the oncolytic characteristics of NDV, underlying mechanisms, safety risks, and efficiency. Clinical and preclinical studies are both involved. Additionally, this study aimed to investigate the molecular processes behind NDV's anti-cancer activities, such as its interaction with neoplastic cells and the microenvironment surrounding tumors.

METHODOLOGY AND SEARCH STRATEGY

A contemporary perspective has been included in the review by taking into account studies that were published from 2000 to 2023. An extensive search strategy was employed across multiple databases, including Scopus, Embase, PubMed, and Web of Science, in order to initiate the review process. Several search terms were used, including "Newcastle Disease Virus," "NDV," "cancer therapy," "oncolytic virotherapy," and "oncolytic viruses." Boolean operators (AND, OR) were used with appropriate truncations to assure coverage of all relevant terms (Karimi et al., 2010).

Several inclusion criteria were established in order to include *in vitro* and *in vivo* studies along with a clinical trial, and this is aimed at assessing NDV's anti-cancer properties and unraveling its mechanisms of action. The current study was applied to the selection of studies specifically focusing on the therapeutic effects of NDV in cancer treatment. It is intended to limit the publication of *in vitro* and animal models, as well as clinical trials, to publications in English. Focusing on recent developments, a detailed description of study characteristics such as the authors, study year, study design, cancer type, NDV strains employed, participant populations, methodologies, major findings, and the outcome of cancer therapy were extracted. This systematic approach allows for the extraction of consistent data from multiple studies. The exclusion criteria for the study included any viruses other than NDV, and these viruses were specifically excluded from the analysis.

OVERVIEW OF NEWCASTLE DISEASE VIRUS

Characteristics of Newcastle disease virus

As one of the members of the Paramyxoviridae family, NDV belongs to the Avulavirus genus (Suarez et al., 2020). NDV is a single-stranded RNA virus, which is highly contagious among avian species (Getabalew et al., 2019; Behboudi and Hamidi Sofiani, 2021). Various hosts have been identified for NDV infection, including poultry, wild birds, and rarely mammals, like humans (Ashraf and Shah, 2014; Ul-Rahman et al., 2022). Electron microscopy indicates that the virus displays a pleomorphic morphology with filamentous or spherical particles (Rush et al., 2020). Oncolytic virotherapy presents a potential application of NDV because of its special capabilities, such as directly killing tumor cells and stopping angiogenesis (Bello et al., 2020). Mononegavirales viruses are non-segmented and have an envelope (Samal, 2021). NVD contains a negative-sense RNA genome encoding six main structural proteins, including matrix proteins (Ms), phosphoproteins (Ps), hemagglutinin-neuraminidase proteins (HNs), nucleoproteins (NPs), fusion proteins (Fs), and large polymerase proteins (Chen et al., 2015). Viruses and their hosts' replication, assembly, and interaction depend on these proteins.

Newcastle disease virus strains and oncolytic properties

Based on their virulence in poultry, several strains of NDV are categorized into distinct pathotypes (Choi et al.,

2013; Fentie et al., 2014; Dimitrov et al., 2016). The most common strain types are velogenic (highly virulent), mesogenic (moderately virulent), and lentogenic (avirulent) (Liu et al., 2007a). Several strains of NDV have demonstrated oncolytic properties, namely the ability to target and destroy cancerous cells (Davis and Fang, 2005; Everts and van der Poel, 2005). It has been extensively studied that a number of NDV strains exhibit the ability to treat cancer partly by selectively replicating only in tumor cells without causing harm to the normal cells (Howells et al., 2017). By exploiting the tumor microenvironment, NDV takes advantage of the unique properties of tumor cells to multiply and cause cell death, namely dysfunctional signaling pathways of interferons, impaired antiviral defenses, and altered surface proteins (Zhao et al., 2012).

Mechanisms of Newcastle disease virus-induced oncolysis

The entry of virus, reproduction, transmission, and triggering death of cancer cells are all steps in the oncolytic process of NDV. The following are some processes that contribute to oncolysis induced by NDV. As soon as NDV reaches the surface of the cancer cells, it binds to specific receptors on the cell surface (Meng et al., 2021). NDV uses sialic acid as its main receptor, which is commonly present in most cancer cells (Matveeva et al., 2015). NDV multiplies itself by injecting genomic RNA into the cytoplasm of its host (Fournier and Schirrmacher, 2013). When viral RNA is translated and replicated, it produces viral proteins and virus particles, which are the byproducts of viral RNA transcription and replication (Randall and Goodbourn, 2008). Via fusion between infected and non-infected cells, an NDV infection forms multinucleated giant cells known as syncytial cells (Krabbe and Altomonte, 2018; Dittmar et al., 2021). Apart from facilitating the virus' spread through tumors, syncytia also enhances the virus' oncolytic activity (Sasso et al., 2020).

The NDV infection stimulates a wide range of innate immune responses, including the release of cytokines and type I interferons (IFNs) (Fournier et al., 2012). These responses have a positive outcome, which is a greater immune reaction towards neoplastic cells since immune cells become activated and recruited. One of the most prominent mechanisms involved in NDV-induced oncolysis is apoptosis, which leads to cell membrane shrinkage, cellular DNA fragmentation, and cell membrane blebbing (Ali et al., 2011; Schirrmacher, 2022a). Tumor cells undergo apoptosis when NDV triggers cell death pathways. Moreover, NDV infection can also lead to necrotic cell death in some cases (Mohammed et al., 2019) (Figure 1).

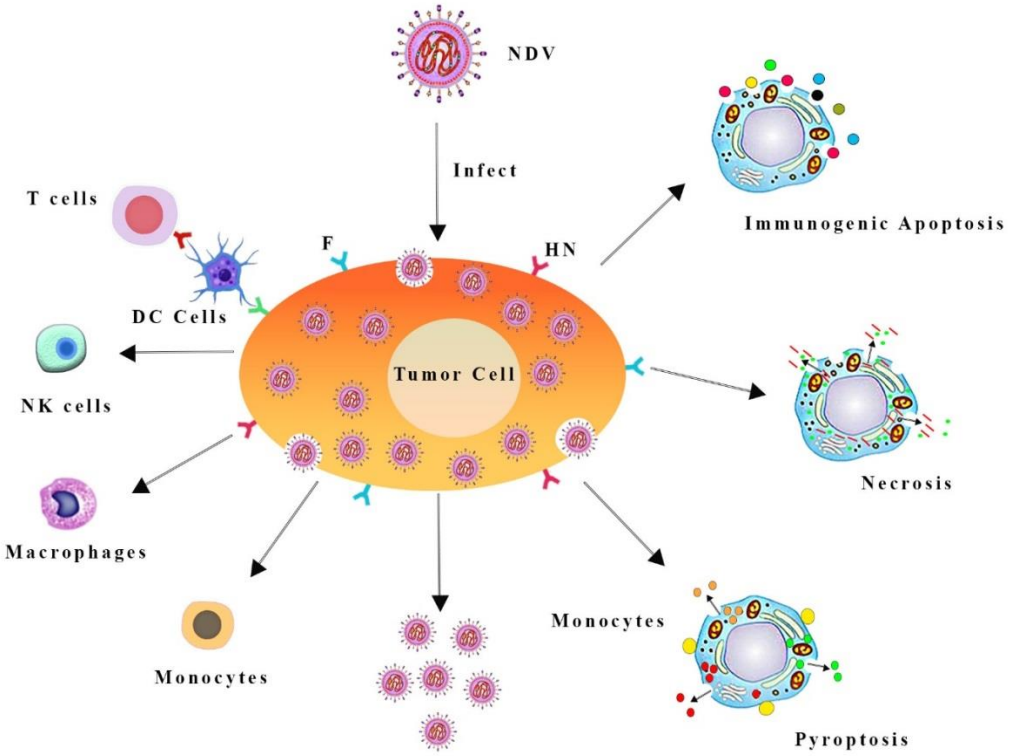

Figure 1. The various mechanisms by which the Newcastle Disease Virus (NDV) induces cell death in cancer cells upon binding to cancer cell receptors. It involves the activation of T cells, Natural Killer (NK) cells, and macrophages, as well as the initiation of apoptosis, necrosis, and pyroptosis pathways (Dendritic cells [DC] play crucial roles in this process).

PRECLINICAL STUDIES

In vitro studies evaluating Newcastle disease virus's anti-cancer effects

To better understand NDV mechanisms and their potential anti-cancer effects, *in vitro* experiments have been undertaken utilizing various cancer cell lines. In these investigations, various techniques are frequently employed to determine whether NDV is cytotoxic, if it replicates within cells, and how it influences cellular interaction (Sánchez et al., 2015; Yurchenko et al., 2018).

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (MTT) estimates the functions of mitochondria, whereas the trypan blue exclusion assay determines the integrity of the cell membrane (Ghorbankhani et al., 2023). MTT is commonly used for the assessment of cytotoxicity and viability of cells. These tests allow the quantification of NDV and its efficiency of viral replication via multiple cell lines to determine how it affects tumor cell viability (Jagtap et al., 2017).

Moreover, researchers have attempted to identify how NDV induces oncolysis. Changes in cell morphology and DNA fragmentation initiate apoptotic pathways (Elankumaran et al., 2006). A variety of methods are used to detect apoptosis markers, including Bcl-2 proteins, caspases, and DNA damage markers, utilizing different techniques, such as immunoblotting, flow cytometry, and immunofluorescence (Nirmala and Lopus, 2020; Kari et al., 2022).

Additionally, researchers have studied NDV's immunomodulatory abilities *in vitro* alongside its oncolytic properties (Yang et al., 2021; Hu et al., 2022). Cytokines and chemokines released during infection with NDV have been shown to induce immune cells' recruitment and activation when co-culturing with cancer cells (Tang et al., 2022). In many studies, it has been noted that NDV induces the expression of Major Histocompatibility Complex (MHC) molecules in addition to co-stimulatory molecules, which are involved in presenting antigens and activating immune cells (Burman et al., 2020; Schirrmacher et al., 2022b).

Animal models and their relevance to human cancers

A key part of evaluating NDV in cancer therapy is testing its performance and safety in animal models (bin Umair et al., 2022). Consequently, the oncolytic effects of the virus, its capability of inhibiting tumor growth and metastasis, as well as its tendency to interact with the immune system can be investigated by researchers (Li et al., 2022). Animal models need to be selected considering the purpose of the research, the type of cancer, and the available options (e.g., transgenic or xenograft models). Various animal models have been utilized to examine the effects of implanting human cancer cells into mice with immune deficiencies (Fang et al., 2023).

In addition to evaluating NDV's oncolytic effects *in vivo*, it is also possible to assess tumor regression and virus replication at tumor sites, along with effects on normal tissues (Rius-Rocabert et al., 2020; Kalafati et al., 2023; Sadri et al., 2023). Monitoring tumor growth involves calipers or non-invasive imaging methods like positron emission tomography (PET) or bioluminescence (O'farrell et al., 2013).

It is also possible to explore the therapeutic potential of NDV using genetically modified mice (GEMMs) with spontaneous tumor development (Chen et al., 2022; Tornesello et al., 2022). Several characteristics of these models are similar to those of human cancer, including tumor heterogeneity, stromal interactions, and immune responses. GEMMs offer a more physiologically appropriate way of investigating NDV's effects on cancer growth, metastasis, and immune reactions (Zeng et al., 2021).

Additionally, animal models have been employed to visualize tumor attributes and track treatment efficacy, and NDV biodistribution was assessed by Magnetic Resonance Imaging (MRI) and Positron Emission Tomography-Computed Tomography (PET-CT) (Pierce et al., 2021; Siafaka and Gündoğdu, 2023).

Although animal models cannot completely mimic the complexities of cancers in humans, adequately designed and carefully conducted studies can provide valuable preclinical information for advancements in NDV therapy and the development of clinical trials in humans (Prestwich et al., 2008; Wollmann et al., 2012).

Safety and toxicity profiles

It is paramount to assess the safety and toxicity profiles of NDV in preclinical studies before clinical trials to ensure patient safety. Several studies are being carried out on NDV in order to identify potential side effects, measure its maximum tolerated dose (MTD), and develop safety protocols for human application (Lorence et al., 2007; Koppers-Lalic and Hoeben, 2011; Abdullahi et al., 2018). The animals are closely monitored for signs of distress, behavioral changes, weight fluctuations, and any changes in vital signs. Hematological and

histopathological analyses and blood chemistry tests are carried out to assess NDV's toxicity (Kadhim et al., 2022).

Moreover, viral shedding and off-target effects are particularly assessed. The researchers may examine how long and how much NDV reproduces in non-tumor tissues if it can infect them (Everts and van der Poel, 2005). This type is evaluated to determine dosage and treatment schedules and identify potential risks associated with systemic administration (Yu et al., 2022). In addition to assessing potential drug interactions, preclinical studies are intended to determine whether NDV interacts with other medications. To enhance cancer treatment's success, chemotherapy, radiotherapy, and immunotherapy are often administered together (Yaghoubi et al., 2019). A comprehensive analysis of the safety and tolerability profiles of NDV-based therapies in preclinical studies allows for the safe translation of NDV-based therapies to the clinic (Al-Shammari et al., 2021; Al-Shammari et al., 2020). As a result, patients can be guided on the best dosing regimens and treatment strategies to suit their needs. This can be a safe and reliable method with minimal side effects (Figure 2).

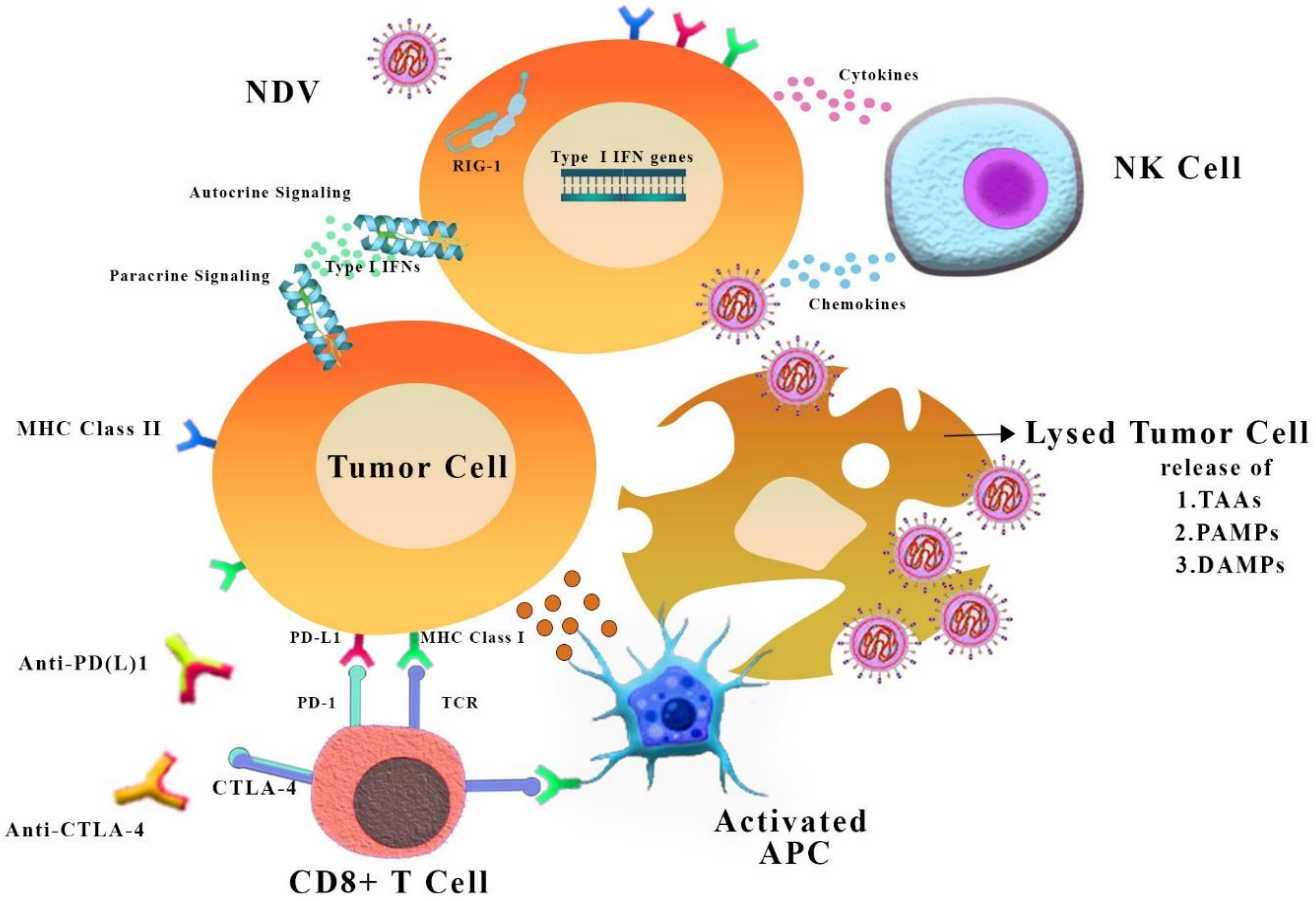

Figure 2. The activation of the immune system by Newcastle virus. The virus enters the cancer cell, triggering the activation of APC cells. Subsequently, CD8+ T cells become activated, and these immune cells lead to the cancer cell's death. APC: Antigen presenting cell, CTLA-4L: Cytotoxic T-lymphocyte associated protein 4, MHC: Major histocompatibility complex, IFN: Interferon, TAAs: Tumor associated antigens, PAMP: Pathogen associated molecular pattern, DAMP: Damage associated molecular pattern, PDL 1: Programmed death ligand-1

CLINICAL TRIAL PHASES

The use of the NDV for killing cancer cells has been successfully demonstrated in both *in vitro* and *in vivo* stages. Now, it needs to be investigated in clinical trials, and so far, a few clinical studies have been conducted. Freeman et al. (2006) and Lam et al. (2011) conducted phase I clinical trials as the first step in evaluating NDV for cancer therapy regarding safety, dosage, and effectiveness (Freeman et al., 2006; Lam et al., 2011). A few patients are involved in these studies, which mostly attempt to determine the MTD and identify adverse effects restricting its usage.

A Phase I study administers NDV via various routes, particularly intratumoral injection, intravenous injection, and intranasal injection, to identify its optimal delivery method and safety status (Malogolovkin et al., 2021). A high degree of homogeneity is guaranteed by setting criteria for patients' eligibility based on tumor type, stage of disease, and previous treatment history (Taguchi et al., 2017). Potential adverse events are identified in Phase I trials, the MTD is determined, and the recommended Phase II dose (Laurie et al., 2006). As secondary endpoints, NDV may also be evaluated for its pharmacokinetics and pharmacodynamics (PD), assessed for tumor responses with imaging techniques, and explored for preliminary anti-tumor activity (Liu et al., 2007b). Phase 1 of the study has yielded promising outcomes; however, it is imperative to underscore that these positive results constitute merely a preliminary step in a more extensive and intricate scientific investigation. Subsequent phases, notably Phases 2 and 3, demand rigorous scrutiny and thorough exploration to elucidate further insights, address potential limitations.

COMBINATION STRATEGIES

Combination with chemotherapy agents

Research indicates that NDV, combined with chemotherapy drugs, can enhance cancer treatment outcomes (Jiang et al., 2014). It is based on the potential synergistic effects of both oncolysis induced by NDV and cytotoxicity caused by chemotherapy that justify the use of these medications together (Al-Shammari et al., 2019).

Several mechanisms have been demonstrated in preclinical studies to sensitize cancer cells to chemotherapy by NDV (Zhu et al., 2021; Faranoush et al., 2023). When cancer cells become infected with NDV, they are more susceptible to chemotherapy agents that induce apoptosis, such as caspases, Bax, and Bak (Cuadrado-Castano et al., 2015). Additionally, NDV-induced immunogenic cell death can activate an immune response that enhances chemotherapy effectiveness through tumor-specific antigen release. Furthermore, NDV may be able to overcome chemotherapy resistance. Multiple drug resistance has been associated with its modulation of P-glycoprotein (P-gp) (Garg et al., 2015; Kadhim et al., 2022). The NDV counteracts chemotherapy drug resistance by inhibiting these transporters, which allows drug concentrations to increase inside the cell.

NDV, in conjunction with chemotherapy, appears to have promising results in clinical trials (Cross and Burmester, 2006; Ripp et al., 2022). Many of these trials require determining the most appropriate sequence, dosage, and treatment timing. These combinations improved the progression-free survival rate, overall survival rate, and response rates in several types of cancer, including pancreatic cancer, lung cancer, and ovarian cancer (Turnis et al., 2015).

Combination with immunotherapies

In order to enhance anti-tumor immune responses, NDV can be combined with immunotherapies, such as adoptive cell therapies or immune checkpoint inhibitors (Marchini et al., 2016). NDV is an ideal co-therapeutic agent for cancer standard medications because it induces immunogenic cell death and stimulates tumor antigen release. NDV combined with immune checkpoint inhibitors, such as anti-PD-1 and anti-CTLA-4 antibodies, strengthened the immune reaction against tumors in several preclinical experiments (Zamarin et al., 2014; Hwang et al., 2020). As a result of virus infection, immune checkpoint molecules are expressed more highly within cancer cells, increasing their susceptibility to immune checkpoint blockade. Further, NDV-induced release of tumor antigens can broaden the range of immune targets for immune checkpoint inhibitors, enhancing their effectiveness (Burman et al., 2020; Chiu et al., 2020).

It has also been shown that NDV can be used in conjunction with adoptive cell therapies, like Chimeric Antigen Receptor (CAR) T-cell (Bahmanyar et al., 2022). Infection with NDV can increase the expression of tumor-associated antigens on cancer cells, making them more recognizable and susceptible to CAR T-cell therapy (Mardi et al., 2022). Furthermore, NDV can induce immunogenic cell death, causing a pro-inflammatory microenvironment supporting adopting T cells' activation and persistence (Ajina and Maher, 2017; Rezaei et al., 2022).

Combination with targeted therapies

By combining NDV with targeted cancer treatments, such as monoclonal antibodies and tyrosine kinase inhibitors (TKIs), more effective treatment can be achieved (Zhu et al., 2021). Targeted therapies can specifically inhibit molecular targets or aberrant signaling pathways that contribute to tumor growth and survival.

Preclinical studies have demonstrated several mechanisms demonstrating how NDV can enhance targeted therapies' anti-tumor effects. Signaling pathways such as VEGF, HER2, or EGFR can be modulated by NDV infection (Howells et al., 2017; Ali et al., 2021). These pathways are commonly targeted by TKIs or monoclonal antibodies. With targeted therapies, NDV

inhibits tumor cell proliferation, induces apoptosis, and suppresses angiogenesis (Zhang and Cheng, 2020; Tian et al., 2022).

In combination with targeted therapies, NDV has demonstrated acceptable results in cancer types, including melanoma, breast cancer, and colorectal cancer (Markman and Shiao, 2015). It is essential to study the safety profiles of treatment options, determine the most beneficial treatments, and determine the most appropriate treatment schedule (Figure 3).

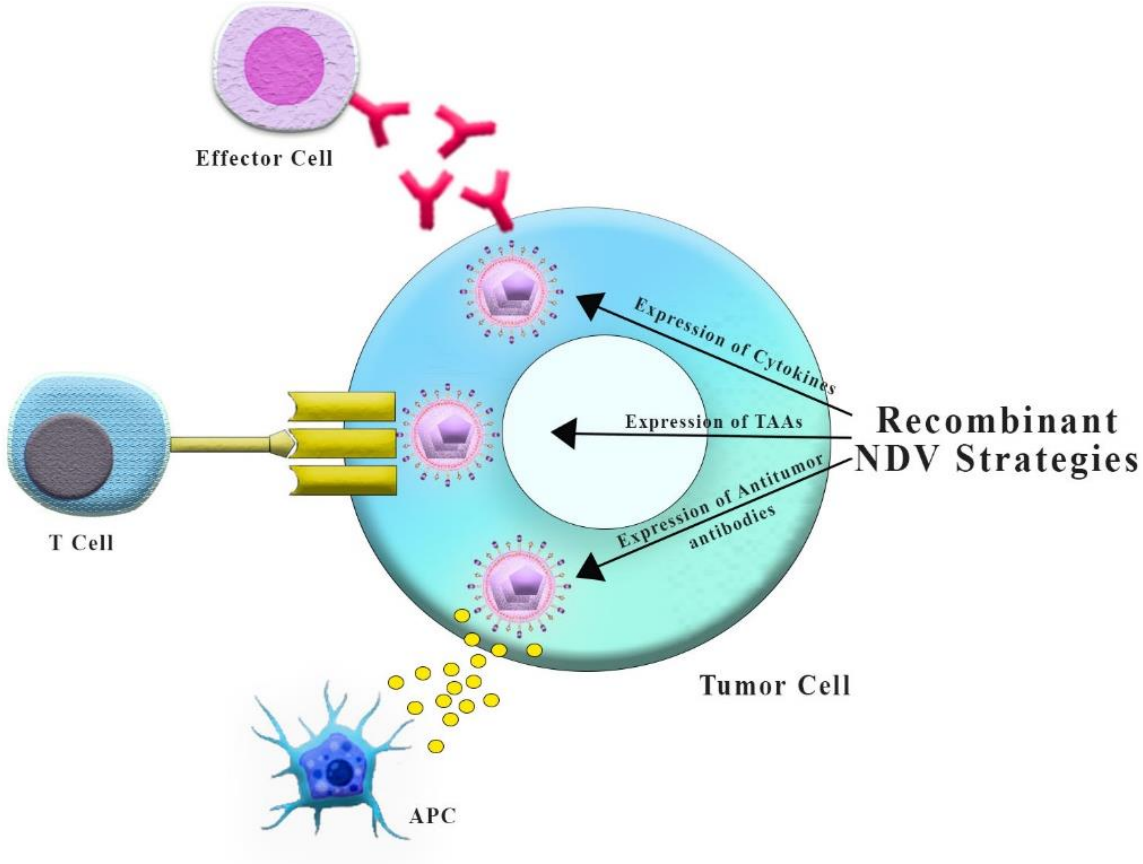

Figure 3. Recombinant Newcastle disease virus is a modified form of the Newcastle disease virus that has been engineered for various therapeutic and immunotherapeutic applications. It is known to activate cytotoxic T cells and induce the secretion of cytokines and chemokines from antigen-presenting cells, such as dendritic cells.

FUTURE DIRECTIONS AND CHALLENGES

Emerging research and novel applications

NDV investigation is being carried out to discover new applications for this virus and examine its potential in cancer therapy. Incorporating newly developed targeted therapies, radiotherapy, and epigenetic modulators into NDV is being studied (de Graaf et al., 2018). It is possible to enhance the anti-tumor effects of NDV through these combinations so as to circumvent potential resistance mechanisms and further improve its effectiveness (Oladejo et al., 2022). Using genetic engineering methods, NDVs with enhanced therapeutic properties are created (Everts and van der Poel, 2005; Kaufman et al., 2015). Therefore, it is possible to modify NDV so that tumor selectivity is improved, replication efficiency increases or therapeutic components are included to enhance anti-cancer activity (Howells et al., 2017; Zhu et al., 2021). It is modifying immune responses to enhance anti-tumor immunity triggered by NDV. It is necessary to boost the immune system in order to overcome immunosuppression caused by tumor microenvironment using cytokines, immune checkpoint inhibitors, or other immunomodulators in conjunction with NDV (Locy et al., 2018; Vijayakumar et al., 2020).

Facilitating the delivery of NDV directly to tumor cells while minimizing adverse effects (Raja et al., 2018; Scott et al., 2018). For instance, viral vectors, nanoparticles, and specific targeting ligands are capable of improving therapeutic performance and tumor targeting (Kontermann et al., 2021).

Addressing limitations

Achieving optimal results of NDV-based therapeutic plans calls for dealing with several limitations and challenges.÷ Optimizing NDV-based therapies with consideration of tumor heterogeneity as well as individualized patient profiles. Discovering and disabling immune evasion pathways cancer cells use to escape NDV-induced immune reactions (Twumasi-Boateng et al., 2018; Abdou et al., 2022). NDV can be combined with immune checkpoint inhibitors, immune stimulators, or innovative immunotherapeutic methods to increase the immune response against cancer (Moehler et al., 2016; Shaver et al., 2021). They establish the most appropriate dose, timetable, and delivery method for NDV-based treatments. Several factors are considered, such as the dose of the virus, the type and stage of the disease, the frequency with which the drug is administered, and the possibility of drug interactions (Farkona et al., 2016; Schirrmacher, 2020). They assess NDV's safety parameters across different patient groups and consider possible concerns like systemic toxicity, viral shedding, and long-term consequences (Vile et al., 2002). The monitoring and reporting of adverse reactions are essential to evaluating the safety of therapeutic interventions based on NDVs and complying with regulations and guidelines to receive approval for NDV-based medical applications (Jafari et al., 2022). Maintain compliance with regulatory requirements for NDV-based therapies, as well as facilitating their translation into standard clinical practice through awareness of the regulatory framework (Ricca et al., 2018; Burke et al., 2020; Svensson-Arvelund et al., 2022). Having a strategy for commercializing and an analysis of the economic feasibility is also imperative for NDV-based treatments to be widely adopted and accessible. Challenges such as these must be overcome, and research in these areas must progress in order for NDV-based therapies to become a mainstream treatment option for cancer and provide better results for patients. In order to overcome these challenges, collaboration is required among clinicians, scientists, regulatory authorities, and industry constituencies.

CONCLUSION

This review highlights the growing prominence of oncolytic virotherapy utilizing NDV in cancer treatment, underscoring its ability to replicate within tumor cells selectively, trigger immunogenic cell death, and influence oncogenic signaling pathways, as supported by various *in vivo* and *in vitro* studies.

Numerous clinical trials have been undertaken at the NDV site, assessing its safety, effectiveness, and use in combined strategies for cancer treatment. Although these advances have been made, several challenges remain, including immune escape mechanisms, tumor heterogeneity, and tailoring treatment options according to tumor traits. In addition, treatments based on NDV require careful consideration of both regulatory and commercialization issues in order for them to become widely available and accepted. The potential of NDV in cancer therapy is considerable. A combination of oncolytic virotherapy, cell death induced by immunogenic factors, and alteration of oncogenic signaling pathways is at the core of this innovative approach. However, it's crucial to acknowledge that the clinical translation of NDV-based oncolytic virotherapy may face challenges such as optimizing delivery methods, addressing potential off-target effects, and ensuring its safety and efficacy in human subjects, which require further research and development. NDV-based treatments are expected to revolutionize cancer treatment, improve patient outcomes, and allow for more individualized and precise cancer treatments by conducting further research, collaborating, and addressing challenges in the future.

DECLARATIONS

Authors' contribution

Alireza Omranzadeh conceptualized the study, while all authors contributed to the methodology, formal analysis, and investigation. The original draft was a collaborative effort, with all authors involved in writing, reviewing, and editing. All authors approved the final version of the manuscript for publication in the journal.

Ethical consideration

Ethical issues, such as data fabrication, double publication and submission, redundancy, plagiarism, consent to publish, and misconduct, have been checked by all the authors before publication in this journal.

Availability of data and materials

The datasets generated during the current study, on a reasonable request, are available from the corresponding author.

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Conflict of interests

All of the authors declare no conflict of interest.

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