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Mini Review

Mesenchymal Stem Cell Carriers for *Newcastle Oncolytic Viruses*: The New Era in Colorectal Cancer treatment

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Abstract

Colorectal cancer (CRC) is positioned as the third most widespread form of cancer on a global scale, affecting both males and females. Furthermore, it holds the unfortunate title of being the second leading cause of deaths associated with cancer, and it remains the primary contributor to mortality in cases of gastrointestinal cancer. CRC specifically affects the colon and rectum, resulting from the abnormal growth of glandular epithelial cells in the colon. CRC treatment options encompass a range of interventions such as surgical procedures, radiation therapy, chemotherapy, and additional modalities. However, these treatments often come with side effects that can make the patient's journey exhausting. Therefore, there is a pressing need for new treatment approaches that can minimize these side effects. In recent years, oncolytic viruses have gained substantial attention from researchers as a promising approach in the field of cancer treatment. However, there have been obstacles to overcome, such as the immune system's interference, preventing the oncolytic virus from functioning effectively and neutralizing it before it reaches the tumor. To address this challenge, a carrier is required to ensure safe delivery of the virus to the tumor site. Mesenchymal cells have emerged as potential candidates for facilitating virus transmission due to their favorable properties as carriers. In this article, we delve into the application of mesenchymal cells as carriers for Newcastle Oncolytic Virus in the treatment of colorectal cancer. Our objective through this research is to make significant contributions to the advancement of novel and enhanced methodologies in combating this particular disease.

Keywords: Mesenchymal Stem Cell, Carrier, Newcastle Disease Virus, Colorectal Cancer, Oncolytic

Introduction

Colorectal cancer holds the position of being the third most prevalent cancer globally and is responsible for the second highest number of cancer-related deaths. A worrisome surge in the prevalence of early-onset colorectal cancer, noted for its diagnosis in individuals under the age of 50, has been identified in the United States as well as several other nations.[1] Although there have been some advancements in screening and therapy for colorectal cancer (CRC), the rates of incidence, prevalence, and mortality associated with this disease continue to remain high, even in high-income nations.[2] The clinical manifestation comprises various symptoms, including abdominal pain, changes in chronic bowel habits, alterations in bowel movements, unintentional weight loss, nausea, vomiting, malaise, loss of appetite, and abdominal distension.[3] The choice of treatment options is determined by several factors, including the stage of the disease, the performance status of the patient, and, increasingly, the molecular characteristics of the tumor.[4] The majority of colorectal cancers are typically localized, with or without lymph node metastases. Around 20% of patients are diagnosed with metastatic disease, most frequently affecting the liver.[5] Surgical intervention remains the main treatment for localized colorectal cancer, as it aims to remove the tumor and surrounding tissues.[6] In cases where there

are lymph node metastases, adjuvant chemotherapy is often recommended. This additional treatment helps to target any remaining cancer cells and reduce the risk of recurrence. Surgery is considered a standard treatment modality for CRC, particularly for patients in stage 0 to stage II. In addition to surgery, radiation therapy, chemotherapy, and targeted therapy play essential roles in the treatment of rectal cancer.[7,8] Given the inherent limitations of the aforementioned treatment methods, there has been a growing interest in the utilization of immunotherapy as a promising alternative for managing colorectal cancer (CRC). Immunotherapy harnesses the power of the body's immune system to identify and combat cancer cells.[9] By stimulating or enhancing the immune response, this approach holds great potential in effectively targeting and eliminating cancer cells in CRC. This approach has shown considerable potential in improving patient outcomes and has opened up new avenues for the treatment of CRC.[10] Due to the constraints and adverse effects associated with existing treatment options, As the need for a safer and more effective treatment for this aggressive form of cancer grows, researchers are exploring alternative therapeutic interventions.[11] Immuno-oncolytic or oncolytic virotherapy has emerged as a promising potential alternative. This innovative approach utilizes viruses that are modified to selectively target and destroy cancer cells, while also stimulating the immune system's response against the tumor.[12] By harnessing the power of viruses, immuno-oncolytic or oncolytic virotherapy aims to provide a safer and more effective treatment option for this malignant carcinoma. Numerous oncolytic viruses have undergone testing for the treatment of colorectal cancer, both in preclinical and clinical trials, yielding promising outcomes.[13] Oncolytic viruses (OVs) can be divided into two primary categories: naturally occurring viruses and genetically modified viruses. Naturally occurring OVs, including Newcastle disease virus (NDV), reovirus, measles virus (MV), and enteroviruses, have been utilized in their original forms. On the other hand, human pathogenic viruses like herpes simplex virus (HSV) and adenovirus have undergone genetic modifications to restrict their replication to tumor cells. This modification allows for their selective targeting and replication specifically within tumor cells.[14,15] Research conducted both in preclinical and clinical settings, as early as the 1950s, has provided evidence that NDV possesses oncolytic properties and has demonstrated the capability to stimulate robust immune responses against tumors. NDV is a naturally occurring RNA virus that has shown promise as an effective oncolytic agent.[16] Upon infecting tumor cells, NDV initiates an immune response through the activation of its envelope protein and intracellular factors. This immune response proves to be highly effective in eliminating the tumor cells, while ensuring the protection of normal cells from any harm or damage. This selective targeting mechanism holds great potential for the development of targeted and less toxic cancer therapies.[17,18] Oncolytic viruses function as biotherapeutic agents that have the ability to cause tumor cell lysis, trigger local immune responses, and enhance systemic anti-tumor immunity. This unique immune stimulatory property of oncolytic viruses offers significant potential in overcoming cancer.[19] In recent years, remarkable advancements have been made in the field of oncolytic viruses. Both genetically engineered and naturally occurring oncolytic viruses have demonstrated promising outcomes in preclinical models and clinical trials. These breakthroughs hold immense potential in the development of ground-breaking and efficient cancer treatments.[20] Oncolytic viruses (OVs) have two main ways of achieving their anti-tumor effects: directly infecting and destroying tumor cells, and activating the immune system to generate an immune response against the tumor. These combined functionalities offer two potential approaches for enhancing therapy.[21] Firstly, there is the possibility of improving the tumor specificity of OVs by utilizing promoters specific to tumors, employing techniques to knock out viral genes, and even modifying the viral capsid. These strategies aim to increase the effectiveness of OV infection in tumor tissue and reduce any harmful effects on normal tissue.[22] Another method involves arming the virus with immune system-activating substances like antibodies, costimulatory molecules, and cytokines. This can potentially counteract the immunosuppressive tumor microenvironment, leading to an improved immune response against the tumor.[23] Furthermore, the localized and concentrated effects of immune system-activating agents produced by OVs can reduce apparent side effects compared to traditional administration routes. While OVs show promise in virotherapy, there are certain limitations that must be addressed to enhance their effectiveness.[24] These limitations include viral tropism (ability to target specific

cells), delivery platforms, viral distribution within the body, dosing strategies, antiviral immune responses, and the ability of OVs to effectively destroy tumor cells. By addressing these factors, the efficacy of OVs in virotherapy can be improved.[25] OVs can induce a strong innate immune response through interactions with antigen-presenting cells (APCs) and other components of the immune system. The presence of preexisting circulating antiviral immunity, blood factors, and antibodies, can contribute to the clearance of OVs by the host's immune system. As a result, it becomes challenging to ensure that an adequate number of OVs reach the tumor site for effective therapeutic action. Efforts to overcome these limitations are crucial in maximizing the therapeutic potential of OVs.[25,26] Although oncolytic viruses (OVs) show great promise in preclinical studies, The clinical assessments of OVs for cancer therapy have underscored the significance of improving delivery and targeting strategies.[27] Mesenchymal stromal cells (MSCs) have emerged as a promising choice for OVs delivery due to their ability to target tumors specifically and their low immunogenicity.[28] MSCs play a vital role in enhancing OV delivery by protecting the viruses from quick clearance and efficiently directing them to the tumor site. This, in turn, enhances the therapeutic potential of OVs in cancer treatment. MSCs can act as "biological factories," allowing the OVs to replicate within the cells and promote tumor lysis upon their arrival at the tumor site.[29] Utilizing MSCs as vehicles for cancer therapeutic agents, including OVs, is a highly promising strategy. MSCs possess tumor-homing properties and limited immunogenicity, making them suitable for delivering therapeutic payloads to solid tumors. Their ability to home to tumors is attributed to the resemblance of the tumor microenvironment to that of non-healing wounds. By leveraging the unique properties of MSCs, the targeted and efficient delivery of OVs to tumors can be achieved, potentially improving the overall efficacy of cancer therapy.[30,31]

Search Methods

The research methodology employed in this study involved the use of a narrative review to examine the reported articles and their narrative results. Due to the wide variability in both the primary and secondary outcomes, as well as the methodologies utilized, conducting a meta-analysis was not feasible. The study was conducted over a period of one year, from July 2022 to July 2023.

Information Sources and Search Strategy

To identify literature relevant to the topic, a comprehensive search was undertaken in two electronic databases, namely MEDLINE/PubMed (https://www.ncbi.nlm.nih.gov) and Google Scholar (https://scholar.google.com). This search included both pre-print and published literature, covering the time frame from January 1, 2002, to April 31, 2023. The goal was to gather a wide range of sources for comprehensive analysis and examination. The initial field search incorporated a combination of the following terms: "Colorectal cancer", "Colorectal cancer treatments", "CRC treatment challenges", "Oncolytic Viruses", "Newcastle disease Virus", "Newcastle Oncolytic Viruses", "OVs delivery challenges", "OVs carriers", "Mesenchymal Stem Cell", "MSC therapeutic potentials", "MSC as a carrier", and "MSC in cancer treatments". These terms were utilized to narrow down the search and focus on the specific areas of interest within the field of study. Boolean operators, specifically "AND" and "OR," were utilized during the search process in the selected search engines. To enhance precision, stop words such as adverbs, prepositions, and conjunctions were excluded from the search terms. Furthermore, the reference lists of the indexed articles obtained through the electronic database search were manually examined to identify any additional relevant articles. The database search was conducted in two distinct phases. The initial phase took place in July 2022, during which a search strategy was developed and an initial analysis was performed. The final phase was conducted in July 2023 and involved searching for articles identified through both forward and backward reference searches, as well as recent publications. This comprehensive two-phase approach ensured the compilation of a comprehensive and up-to-date collection of relevant literature.

Colorectal Cancer

Colorectal cancer (CRC), which refers to cancer occurring in the colon or rectum, has been on the rise for over four decades, particularly in developed nations where it ranks among the top cancer sites. It is a significant contributor to cancer-related mortality globally.[32] In developed countries, the implementation

of screening programs has played a significant role in enhancing the early detection of colorectal cancer (CRC), resulting in improved 5-year survival rates.[33] However, despite these advancements, approximately 25% of patients still present with stage 4 disease, indicating advanced metastasis at the time of diagnosis. Additionally, a substantial proportion of patients (ranging from 25% to 50%) initially present with early-stage disease but later develop metastatic disease.[34] This highlights the need for further research and interventions to better understand the mechanisms underlying disease progression in CRC and to develop effective treatments for metastatic disease.[35] In 2017, the global incidence of colorectal cancer reached 1.8 million cases, with an age-standardized rate of 23.2 per 100,000 person-years. This represented a 9.5% increase from 1990 to 2017. Additionally, colorectal cancer caused 896,000 deaths worldwide in the same year.[36] Among countries, Slovakia, the Netherlands, and New Zealand had the highest incidence rates, while Greenland, Hungary, and Slovakia had the highest mortality rates for this disease. The number of cases and deaths were higher in men compared to women, particularly in the age group 80-84 and above. In 2018, there were 1,849,518 colorectal cancer cases, accounting for 10.2% of all cancer cases worldwide, and causing 880,792 deaths, which represents 9.2% of all cancer-related deaths According to estimates, it is projected that in 2020, there will be around 1.93 million new cases of colorectal cancer diagnosed, resulting in approximately 0.94 million deaths worldwide. These numbers account for approximately 10% of the total cancer incidence and 9.4% of all cancer-related deaths.[32] Surgical intervention continues to be the primary approach for achieving a cure in the treatment of colorectal cancer.[37] Despite the presence of advanced diagnostic and treatment options such as chemotherapy, radiotherapy, and immunotherapy, the average 5-year survival rate for patients with colon cancer remains below 60%.[38] The current standard protocols for treating invasive cancers involve a combination of radiation, surgery, and chemotherapy.[39] However, these treatments often face challenges such as limited public accessibility and high costs. Additionally, these methods are invasive and can result in various side effects. It is important to note that these treatment options are not always completely successful on their own, necessitating the use of complementary approaches.[40]

MSC as a Carrier for Oncolytic Viruses

MSC Cells

MSCs, derived from adult bone marrow, have the ability to undergo cell division and their offspring can differentiate into various mesenchymal cell types. These include osteoblasts (cells responsible for bone formation), chondrocytes (cells that form cartilage), myocytes (muscle cells), marrow stromal cells, tendon-ligament fibroblasts, and adipocytes (fat cells).[41] In 1970, Alexander Friedenstein first described mesenchymal stromal cells (MSCs) as a group of cells found in the bone marrow that have the capacity to differentiate into mesodermal cell types and provide nourishment for hematopoiesis, the process of blood cell formation.[42] In 2006, the International Society of Cellular Therapy (ISCT) established three criteria to define MSCs: (1) MSCs should possess the ability to attach to plastic surfaces in standard tissue culture conditions; (2) They should exhibit the presence of specific cell surface markers, such as CD73, CD90, and CD105, while lacking the expression of other markers like CD11b, CD14, CD19, CD34, CD45, CD79a, and HLA DR surface molecules; (3) MSCs should demonstrate the capability to differentiate into osteoblasts, adipocytes, and chondroblasts when cultured *in vitro*.[43,44]

Additionally, it should be noted that the markers present on MSCs may vary between different species. Furthermore, there is an overlap in the expression of certain markers between hematopoietic stem cells and mesenchymal-derived cells, which can lead to incorrect characterization of cells if solely relying on marker expression.[45] Perivascular MSCs play a crucial role in responding to external stimuli and collaborating with the vascular and immune systems to facilitate wound healing. Interestingly, the changes observed in MSCs during cancer development mirror the wound healing response. Consequently, MSCs are now acknowledged as significant contributors at various stages of tumorigenesis.[46] MSCs have sparked considerable interest due to their involvement in various physiological and pathological processes, such as development, tissue repair, organ transplantation, autoimmunity, and cancer. Additionally, their elusive nature and characteristics have contributed to the intrigue surrounding MSCs.[47] MSCs have the ability to engage with cells of both the innate and adaptive immune systems, resulting in the modulation of various effector functions. When administered *in vivo*,

MSCs can promote peripheral tolerance and migrate to injured tissues. In these tissues, MSCs can suppress the release of pro-inflammatory cytokines and support the survival of damaged cells.[48] Mesenchymal stem cells are being recognized as crucial cellular components that have a significant impact on tumor progression and drug sensitivity. Their interactions with tumor cells and the surrounding stromal cells can influence various aspects of tumor development, including promoting tumor growth, angiogenesis, and metastasis.[49]

Additionally, mesenchymal stem cells have the ability to affect the response of tumor cells to anticancer treatments, potentially leading to alterations in drug sensitivity and resistance. Their role in the tumor microenvironment provides potential targets for therapeutic interventions aimed at modulating tumor progression and enhancing treatment efficacy.[50] scientists have successfully devised a therapeutic approach that utilizes mesenchymal stem cells (MSCs) as carriers to deliver specific biologic agents directly to tumors.[51] Through this strategy, it is possible to precisely target the tumor site and use the ability of MSCs to produce therapeutic agents locally.This approach allows for targeted delivery of biologic agents, improving efficacy and minimizing off-target effects, ultimately leading to enhanced treatment outcomes.[52]

MSCs as a Carrier

Recently, there has been an increasing interest in utilizing mesenchymal stem cells (MSCs) as a potential approach for delivering anti-tumor drugs. This interest stems from the innate ability of MSCs to specifically target tumors.[53] MSCs have the unique ability to migrate directly to tumor or inflammatory sites. Recent research has indicated that advanced modifications can be made to MSCs in order to enhance their therapeutic potential and effectively inhibit tumor growth. This approach holds great promise in the field of cancer treatment.[54] There is a growing body of evidence suggesting that MSCs have the potential to serve as an ideal delivery vehicle for antitumor biologics such as cytokines, chemotherapeutic agents, and oncolytic viruses. The primary factors contributing to this interest are as follows: (1) Prolonged expression: MSCs that express transgenes have the capability to sustain their expression within the body for an extended period. This is attributed to their low immunogenic properties and the production of immunosuppressive molecules, which enable them to evade detection and clearance by the immune system.[55] (2) Tumor tropism: MSCs possess a natural ability to specifically target tumors. They exhibit a strong attraction to tumor sites, allowing for enhanced delivery of therapeutic agents directly to the tumor microenvironment.[56] (3) Ethical advantages, accessibility, and rapid proliferation: MSCs can be obtained from various ethical sources, such as bone marrow or adipose tissue, without raising significant ethical concerns. Additionally, they are easily accessible and rapidly proliferate, making them viable candidates for therapeutic applications.[57] They are also readily accessible and can be easily isolated and expanded in large quantities for therapeutic purposes. These characteristics make MSCs a promising candidate as a carrier for antitumor biologics, offering potential advantages in terms of their long-term expression, tumor-targeting ability, and practicality in clinical applications.[58] When injury occurs, inflammatory cells release chemo-attractant molecules that create a chemical gradient, drawing MSCs to the site of injury. Once at the site, local factors such as hypoxia (low oxygen levels), cytokines, and Toll-like receptor ligands stimulate the recruited MSCs to undergo proliferation.[59] These activated MSCs then express and release growth factors that promote tissue regeneration and accelerate the healing process. The innate capacity of MSCs to respond to injuries allows them to play a crucial role in the process of tissue repair and regeneration.[60] Mesenchymal stem cells (MSCs) have distinct characteristics that make them promising candidates for cancer therapy. They have been shown to have low immunogenicity, making them less likely to provoke an immune response. MSCs have also demonstrated positive safety profiles in clinical trials, further supporting their potential as therapeutic carriers.[61] Additionally, MSCs have the ability to selectively home to inflammation and tumor sites, allowing for targeted delivery of anticancer agents. These properties make MSCs an attractive option for developing innovative and effective cancer treatment strategies.[62] Recent experimental studies have revealed that MSCs have the ability to not only shield pre-loaded oncolytic viruses (OVs) from immune cells during their transportation to the tumor site but also possess immunosuppressive properties.[63] This dual function of MSCs allows for the protection of OVs from immune recognition and clearance, while simultaneously

dampening the immune response. By evading immune surveillance and modulating the immune system, MSCs effectively enhance the therapeutic efficacy of OVs in cancer treatment. These findings contribute to the growing understanding of the multifaceted role of MSCs in cancer immunotherapy.[64] Numerous studies have provided evidence that tumor cells within the tumor microenvironment can produce elevated levels of cytokines. These cytokines act as signaling molecules that facilitate the migration of MSCs to the tumor tissue. Once present, MSCs actively contribute to the construction and modulation of the tumor micro-environment.[65] Through their interactions with tumor cells and other components of the microenvironment, MSCs help create a favorable environment for tumor growth, invasion, and metastasis. The complex interaction between tumor cells and MSCs emphasizes the important role that MSCs play in influencing the tumor microenvironment.[66] Besides their function in aiding OV delivery, MSCs have also shown immunosuppressive properties. They are capable of inhibiting the proliferation, cytokine production, and cytotoxicity of natural killer (NK) cells and can suppress the differentiation and function of dendritic cells (DCs).[67] MSCs also have the ability to induce the emergence of regulatory T cells, which further contribute to immune suppression. These immunosuppressive features of MSCs make them highly desirable candidates for the delivery of oncolytic viruses (OVs), as they can not only protect OVs from immune clearance but also contribute to creating an immune- suppressive environment that favors effective viral replication and antitumor activity (Figure 1).[68]

Why Do We Use Carriers?

Recently, there has been a growing interest in utilizing oncolytic virotherapy as a promising treatment method for human tumors. However, the *in vivo* administration of oncolytic viruses faces significant impediments that greatly curtail their effectiveness. The immune response mounted against the viruses hampers the therapeutic effect, while the inherent inability of the viruses to efficiently infect micrometastatic lesions reduces the effective viral dosage.[69] Unsurprisingly, researchers have actively pursued strategies to surmount these limitations and enhance the outcomes of oncolytic virotherapy. Several research groups commenced investigating the feasibility of utilizing cells as alternative carriers to circumvent these challenges years ago.[70] The effectiveness of systemic oncolytic virus (OV) administration is frequently hindered by the host's immune defenses, which clear the virus and the inadvertent targeting of non-cancerous tissues through the bloodstream.[71] The concept of intravenous administration of antitumoral drugs holds great promise in targeting not only the primary tumor but also systemic metastases and undetectable micrometastases. However, despite its potential, there are significant limitations associated with systemic injection of oncolytic viruses (OVs). Foremost among these challenges is the formidable presence of the immune system, which poses a constant threat to the viability of attenuated OVs. Its vigilant nature often results in the removal or neutralization of OVs before they can effectively reach the intended tumor site. In addition to safety concerns, this immune response remains a key obstacle to successful systemic OV therapy.[72] Pattern recognition receptors, like toll-like receptors (TLRs), have a vital function in distinguishing viral proteins and nucleic acids from cellular counterparts. These receptors are present in the cytoplasm or on the surface of cells. When they interact with viral components, they activate the production of inflammatory cytokines such as interferon IFN-α, -β, -γ, tumor necrosis factor TNF-α, IL-6, and IL-12.[73] Subsequently, these cytokines bind to receptors on other cells, triggering the synthesis of antiviral genes and the mobilization of immune cells.[74] The use of cell-mediated oncolytic virus (OV) delivery presents an opportunity to evade host defenses and specifically target tumors. Mesenchymal and neural stem cells have been recognized for their unique ability to both home to tumor sites and effectively deliver OVs. By harnessing their tumor-targeting capabilities, these specialized cells can serve as carriers for OVs, ensuring their delivery directly to the tumor microenvironment while evading detection and elimination by the immune system.[71] By loading carrier cells with OVs ex vivo and subsequently administering them intravenously, the OVs can be shielded from antibody-mediated neutralization and nonspecific uptake. Animal models have demonstrated the effectiveness of this approach, which significantly improves the biodistribution of OVs and has the potential to enhance safety. The reduced systemic doses required to achieve a therapeutic dose of virus specifically delivered to the tumor make this strategy highly advantageous.[72]

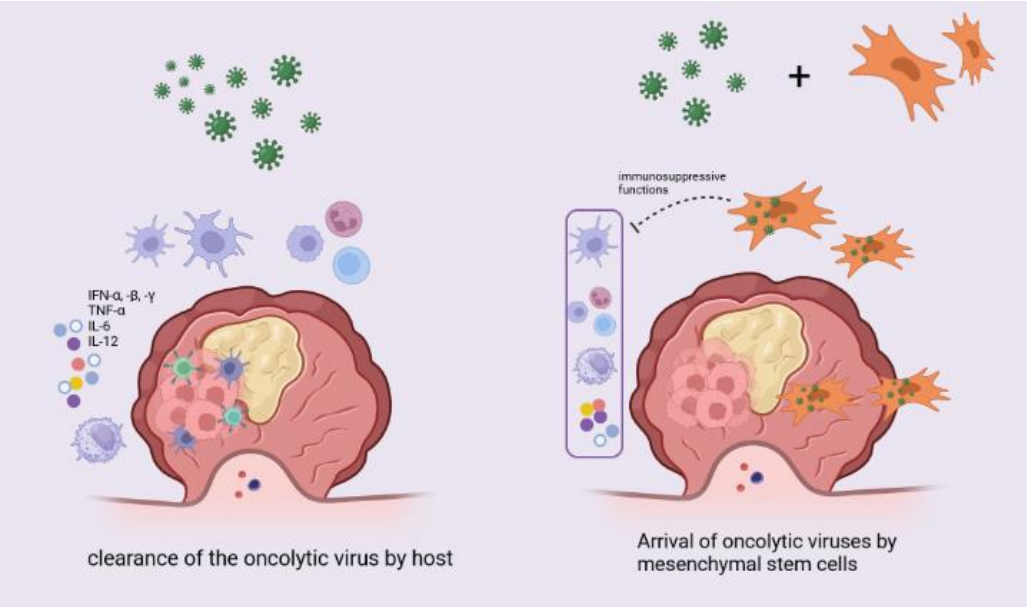

Figure 1. Illustrates the contrast between using a carrier to facilitate the delivery of the virus to the tumor site versus the absence of a carrier. It highlights the significance of utilizing mesenchymal cells as carriers due to their immune system inhibitory properties and their capacity to infiltrate the tumor region. Without these carrier cells, there is a potential risk of oncolytic viruses being cleared by the immune system, thus impeding their successful arrival at the tumor site.

Oncolytic Viruses

Oncolytic viruses (OVs) are specially designed to precisely target and eradicate cancer cells, leaving normal cells unharmed. The infection and subsequent elimination of cancer cells by OVs trigger the activation of immune responses against tumors.[75] This immune reaction not only enhances the killing of cancer cells but also contributes to the modulation of the tumor microenvironment, shifting it towards a less immune-suppressive phenotype. By promoting an immune response against the tumor, OVs can enhance the overall effectiveness of cancer treatment and potentially improve patient outcomes.[76] The primary mode of action for oncolytic viruses (OVs) involves their ability to penetrate tumor cells, establish a lytic cycle, and subsequently activate cell death pathways.[77] While certain OVs naturally possess the ability to infect specific tumors through receptor-mediated internalization, Most oncolytic viruses (OVs) have undergone genetic modifications to improve their ability to specifically target tumor cells and decrease their harmful effects on normal cells. This targeted approach aims to maximize the therapeutic efficacy of OVs while minimizing potential harm to healthy cells.[78] Indeed, oncolytic DNA viruses such as adenoviruses, herpes simplex virus (HSV), parvoviruses, vaccinia virus (VACV), and myxoma virus (MYXV) have shown promise as therapeutic agents. These viruses offer benefits such as high genome stability and the ability to accommodate larger transgenes without compromising their infectivity and replication. In addition, oncolytic RNA viruses have shown promise in the field of cancer therapy.[79] RNA viruses including Newcastle disease virus (NDV), Maraba virus, measles virus (MV), Coxsackie virus, poliovirus, Seneca Valley virus (SVV), reovirus, retroviruses, Semliki Forest virus (SFV), vesicular stomatitis virus (VSV), and Sindbis virus (SBV) possess the capability to specifically target and destroy cancer cells.[SEP]Both oncolytic DNA and RNA viruses offer unique advantages and have been extensively studied for their application in oncolytic virotherapy (Figure 2).[80]

The antitumor activity of oncolytic viruses (OVs) relies on two crucial mechanisms: direct destruction of malignant cells and the stimulation of systemic antitumor immunity. During the lysis of infected cells, viral antigens and cellular components are released into the cancer microenvironment. This results in the release of damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and cytokines.[81] These molecules facilitate the maturation of antigen-presenting cells (APCs), particularly dendritic cells (DCs). As a result, tumor cells that previously evaded immune detection are now recognized and targeted. The activation of pattern recognition

receptors (PRRs) on immune cells, including DCs, occurs when they encounter PAMPs and DAMPs produced as a consequence of oncolytic virus (OV) infection within the tumor. The subsequent activation of APCs enables the recruitment of CD4+ and CD8+ cells, which are essential for destroying tumor cells expressing viral antigens. This recognition of tumor antigens by the immune system is crucial for the destruction of tumors at distant sites that were not directly infected with the OV.[82,83]

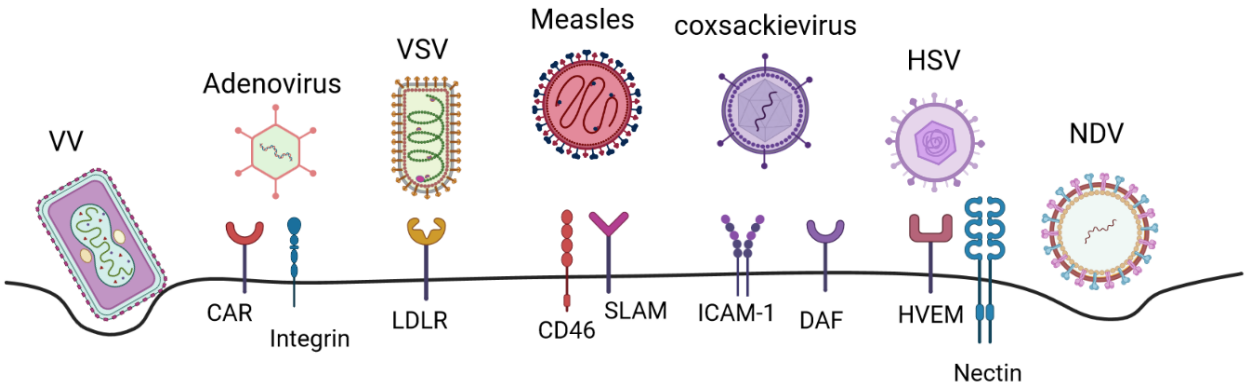

Figure 2. A number of oncolytic viruses and how they enter the cell by a series of surface receptors. VV; vaccinia virus, VSV; Vesicular stomatitis virus, HSV; Herpes simplex virus, NDV; Newcastle disease virus.

Newcastle Virus as a Colorectal Cancer Treatment

Newcastle Viruses Biology

Proteins: hemagglutinin-neuraminidase (HN), matrix protein (M), nucleocapsid protein (NP), NDV, a type I avian paramyxovirus in the Paramyxoviridae family, has a genome of 15186 nucleotides that encodes six structural phosphoprotein (P), RNA-dependent RNA polymerase (L), and fusion protein (F). The three pathotypes of NDV in birds are lentogenic (avirulent), mesogenic (intermediate), and velogenic (highly virulent). The virulence of NDV is primarily determined by variations in the F gene sequence, which affects the cleavage efficiency of the F protein (Figure 3). Mesogenic strains such as PV701, MTH-68/H, 73T, Italien, Beaudette C, and AF2240, and lentogenic strains such as Ulster, HUJ, LaSota, Hitchner B1, and V40-UPM are commonly studied in preclinical research. The lentogenic LaSota strain is widely used in the poultry industry as a live attenuated vaccine and a safe vaccine vector.[18,84-86]

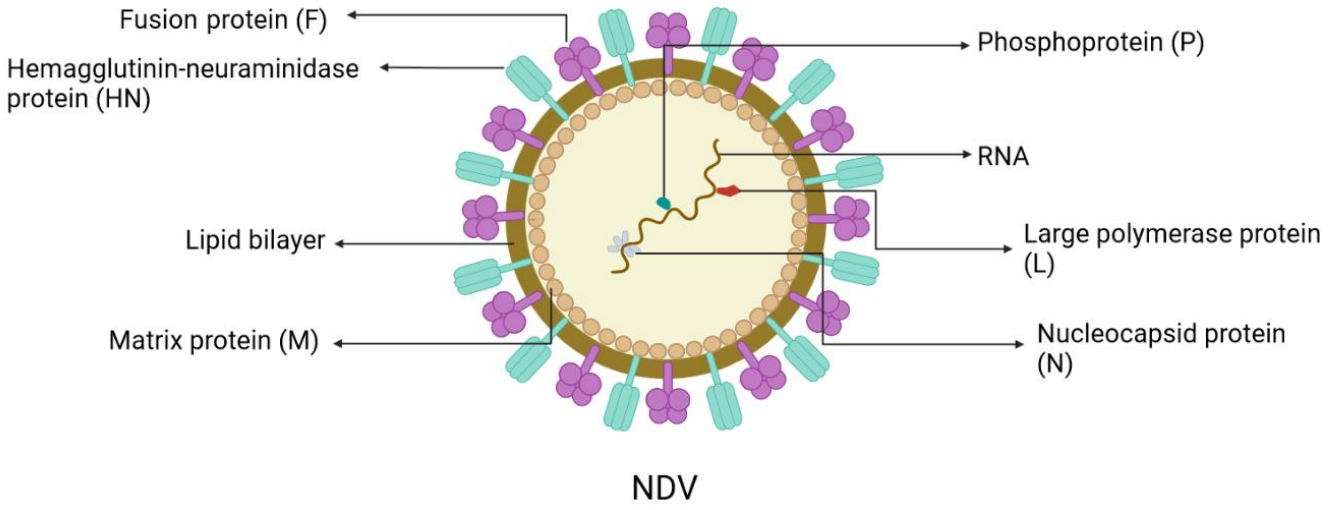

Figure 3. showing the schematic shape of Newcastle disease virus and its proteins such as: Nucleocapsid (N), Matrix protein (M), Phosphoprotein (P), Fusion protein (F), Hemagglutinin-neuraminidase protein (HN), and Large polymerase protein (L).

NDV causes severe infections in birds, but it does not typically cause significant symptoms in humans. This is because the virus has a limited host range and humans do not possess pre-existing antibodies against NDV.[87] Furthermore, NDV exhibits antigenic differences compared to common human pathogens. An important feature of NDV is its ability to preferentially replicate in tumor cells instead of normal cells, highlighting its potential as an oncolytic agent. Its oncolytic properties are dependent on its ability to induce apoptosis, or programmed cell death, in infected cancer cells.[84,88]

Anticancer Effects

Colon cancer is considered an ideal example of a solid tumor that relies on angiogenesis for its growth and progression. The enhanced manifestation of vascular endothelial growth factor (VEGF) occurs within tumor cells due to the activation of oncogenes and the deactivation of tumor suppressor genes.[89] Excessive production of VEGF leads to the formation of abnormal tumor vessels characterized by distortion, fragmentation, and a lack of pericytes. The presence of these abnormal blood vessels in the tumor tissue environment obstructs the efficient transportation of anti-tumor medications to their designated targets, thereby impeding their effectiveness.[84] NDV has shown sensitivity to various human tumors such as liver cancer, glioblastoma, and lymphoma. Unlike other viruses, NDV exhibits a unique characteristic where its RNA transcription and translation processes are not dependent on cell proliferation. As a result, NDV has the capability to target various types of tumor cells including tumor stem cells, dormant tumor cells, and X-ray-irradiated vaccine tumor cells.[90] The oncolytic mechanism of NDV involves multiple key factors. Firstly, the virus selectively infects and replicates within tumor cells. Additionally, the innate and adaptive immune responses of the host indirectly contribute to the antitumor effect, as natural killer (NK) cells and cytotoxic T lymphocytes recognize and attack the viral antigen. The envelope protein of NDV also aids in facilitating the oncolytic effect. Furthermore, the activation of the apoptotic pathway plays a role in promoting the oncolytic effect.[91] Notably, the process of virus-induced oncolysis not only leads to the release of tumor-associated antigens (TAAs), pathogen-associated molecular patterns (PAMPs), and danger-associated molecular patterns (DAMPs), but also has the capacity to activate antigen-presenting cells (APCs) such as dendritic cells (DCs), which are proficient in presenting antigens efficiently.[92] The activation of APCs, in turn, stimulates the immune cells, ultimately giving rise to the production of CD4+ T cells, CD8+ T cells, and NK cells that specifically target the antigens associated with both the tumor and the virus. NDV has been observed to trigger immunogenic cell death (ICD), which involves processes such as necrosis, pyroptosis, and immunogenic apoptosis. During this process, the synthesis of proteins is halted, and the cells are exposed to calreticulin, heat shock proteins, and viral proteins HN and F.[93] Following NDV infection, the accumulation of HN and F proteins on the surface of host cells induces the formation of cell syncytia, which results in the fusion of adjacent cells. This, in turn, initiates necrosis, leading to the breakdown of syncytia, the release of cellular contents, and the activation of an inflammatory response. Additionally, the activation of caspase 8 through cellular TLR and the TNF family also contributes to the induction of cell necrosis. Overall, NDV's potential as an oncolytic virus lies in its selective replication within tumor cells, its interaction with the immune system, its induction of apoptosis, and its ability to stimulate immunogenic cell death.[17,94-96]

Conclusion

In summary, extensive exploration and research have provided a better understanding of how oncolytic viruses (OVs) kill tumors, leading to the initiation of clinical trials. Extensive research has been conducted on the introduction, integration, and enhancement of NDV anti-CRC therapy, with promising results demonstrated in animal experiments and clinical trials. OVs hold immense potential and market value as a treatment modality, although there are still limitations in their clinical application. The *in vivo* administration of oncolytic viruses has important limitations that significantly reduce their effectiveness. The unique migratory abilities of stem cells have provided potential opportunities for their utilization as carriers or vectors to target metastatic cancer. Promising results have been obtained through the combination of stem cells and oncolytic viruses in the treatment of metastatic cancer. However, thorough research is required to assess the safety and effectiveness of using MSCs as carriers and incorporating NDV into CRC therapy, both in preclinical studies and clinical trials.

Ethics approval

The ethics committee of the Baqiyatallah university of medical sciences, Tehran, Iran (IR.BMSU.REC. 1399.507) reviewed and approved the study protocol.

Conflict of Interest

The authors declare no conflicts of interest.

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