

Overcoming the Limitations of Oncolytic Therapy with Cell Carriers

Amir Yousefkhany¹, Seyed Kiarash Aghayan², Mahdiah Farzanehpour^{2*}

¹ Department of Veterinary Medicine, Shabestar Branch, Islamic Azad University, Shabestar, Iran

² Applied Virology Research Center, Biomedicine Technologies Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

*Corresponding Author: Dr. Mahdiah Farzanehpour, Applied Virology Research Center, Biomedicine Technologies Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran. Email: mah_farzanehpour@yahoo.com

Received 2024-09-04; Accepted 2024-10-17 ; Online Published 2025-03-01

Executive Summary

Cancer is one of the biggest health challenges and the third leading cause of death worldwide. Cervical cancer, after breast cancer, is the most common type of cancer in women in many regions. Research has shown that oncolytic viruses, especially those that do not have humans as hosts, have significant anti-cancer effects. One of the challenges of using these viruses is their rapid clearance by the immune system. Therefore, the use of suitable carriers with anti-tumor affinity for delivering these viruses and enhancing their efficacy is essential. The aim of this study is to investigate the therapeutic effects of dendritic cells carrying Newcastle disease virus on the treatment of a mouse model of cervical cancer induced by papillomavirus. This study was conducted under cell culture conditions and mouse modeling. Forty female C57BL/6 mice weighing 20 to 25 grams and aged 6 to 8 weeks were divided into four groups. The groups included mice that were treated with PBS, doxorubicin, dendritic cells with tumor lysate, and dendritic cells carrying Newcastle disease virus, respectively. After observing palpable tumors, the mice were treated with virus-carrying dendritic cells. The results showed that mice receiving virus-carrying dendritic cells had better survival and slower tumor growth compared to the control group. Additionally, this treatment significantly increased nitric oxide and lactate dehydrogenase production while elevating IFN- γ secretion and reducing IL-4, IL-10, and TGF- β secretion.

Keywords: Cancer, Oncolytic viruses, Dendritic cells, Cervical cancer, Therapeutic effects

Citation: Yousefkhany A, Aghayan SK, Farzanehpour M. Overcoming the Limitations of Oncolytic Therapy with Cell Carriers. Int J Travel Med Glob Health, 2025;13(1):70-73. doi: 10.30491/ijtmggh.2025.525477.1485

Introduction

Cancer is defined as a disease in which abnormal cells grow uncontrollably, disrupting normal cellular signaling. Normal cells receive signals for division, differentiation, or death, but specific changes in these cells lead them to become self-sufficient and independent of these signals, resulting in cancerous transformation and excessive proliferation. Cancer cells exhibit characteristics such as defects in cell cycle control, increased mutation rates, genetic instability, independence from mitotic signals, accelerated division rates, loss of differentiation ability, and increased propensity to invade other tissues (metastasis).¹ Cancer arises due to changes in the genes that control cellular growth and differentiation, which include genetic and epigenetic alterations. These changes lead to defects in the regulatory pathways of normal cell proliferation and homeostasis, resulting in a wide range of

physiological changes. Genetic alterations can originate from both endogenous and exogenous sources, causing damage to DNA. Cancer is recognized as both a genetic and an epigenetic disease, influenced by epigenetic control systems such as DNA methylation and histone modifications. These changes disrupt cellular signaling pathways, leading to increased mitogenic signaling and decreased anti-mitogenic signaling. Ultimately, these disruptions result in physiological changes in cancer cells, including self-sufficiency in producing growth signals, insensitivity to growth-inhibitory signals, and the ability to metastasize.² Cervical cancer is the fourth most common cancer and a significant cause of mortality among women worldwide.³ More than 100 different types of human papillomaviruses (HPV) have been identified, primarily infecting epithelial tissues in the genital tract and skin.

About 40 of these types infect genetic regions. HPV16, the most common high-risk type, is responsible for approximately 50-60% of cervical cancers. As a result, significant efforts have been made to develop effective preventive and therapeutic vaccines against this type of cancer.⁴ Papillomaviruses (PVs) are a group of non-enveloped DNA viruses that target epithelial cells. Some members of this family infect mucosal tissues, causing warts, while others infect skin tissues, leading to condylomas. Additionally, some can infect both types of tissues simultaneously.⁵ Some members of the Papillomaviridae family are involved in the progression of epithelial malignancies, particularly cervical cancer and other tumors of the urogenital tract and respiratory system. Since papillomaviruses have been identified as significant contributors to human cancers, studies have led to the development of virus-like particle (VLP) vaccines based on types commonly associated with human cancers.⁶ The aim of the present study was to investigate the therapeutic effects of dendritic cells carrying Newcastle oncolytic virus in the treatment of an experimental model of cervical cancer caused by papillomavirus.

Materials and Methods

In this study, female C57BL/6 mice weighing 20 to 25 grams and aged 6 to 8 weeks were divided into four groups. Group A was treated with PBS, group B with doxorubicin, group C with dendritic cells, and group D with dendritic cells infected with Newcastle virus. Additionally, TC-1 cells were cultured to create a tumor model for cervical cancer, and after subcutaneous injection into the mice, the tumor weights and their lifespans were assessed. Subsequently, dendritic cells were isolated from bone marrow and co-cultured with tumor cell lysates and Newcastle virus. To evaluate cytotoxic effects, various methods such as cell counting with trypan blue, cytokine measurement, and nitric oxide assessment were employed. The results were analyzed using appropriate statistical tests, with a significance level set at 0.05. This study aimed to investigate the effects of different treatments on cancer tumors and immune responses in mice.

Results

In this study, the effects of different MOIs of Newcastle disease virus (NDV) on dendritic cells were investigated. The results showed that MOIs of 5 and 10 reduced the viability of dendritic cells, while MOIs of 0.1 and 1 had no significant effect. Therefore, MOI 1 was used for the infection of dendritic cells. Additionally, a tumor model of cervical cancer was established in C57BL/6 mice, revealing an average tumor onset time of 10 days. Subsequently, the impact of various treatments on splenic

cell proliferation was examined, with results indicating that NDV-carrying dendritic cells had a higher proliferation capacity compared to non-carrying cells. Furthermore, the levels of TGF-Beta, IL-4, IL-10, and IFN-Gamma were assessed in different groups. The findings demonstrated that in the (DCs-NDV) group, TGF-Beta and IL-4 levels significantly decreased, while IFN-Gamma levels increased. Finally, the evaluation of tumor weight and survival rates indicated that the (DCs-NDV), (DCs), and (PC) groups showed a significant reduction in tumor weight and a significant increase in survival rates compared to the tumor group. These results highlight the positive effect of NDV on enhancing immune response and reducing tumors in experimental models.

Discussion and Conclusion

Cervical cancer currently lacks a definitive cure, but various treatment methods such as surgery, radiotherapy, and chemotherapy are used for its management. Additionally, new targeted therapies aimed at reducing side effects and increasing effectiveness are under investigation.⁷ In 1973, dendritic cells were identified as professional antigen-presenting cells in various tissues, and numerous studies have been conducted on their morphology and function.⁸ These cells are recognized as natural allies in activating the immune system due to their unique ability to stimulate and activate naive T cells.⁹ Some researchers proposed that if dendritic cells are exposed to tumor antigens outside the body, they could stimulate an immune response both inside and outside the body due to their release from the tumor-suppressive environment.¹⁰ Oncolytic viruses are non-pathogenic DNA or RNA viruses that can infect and destroy cancer cells without replicating in healthy cells. This selective replication occurs because healthy cells utilize antiviral pathways to prevent viral survival, while cancer cells, due to disruptions in these pathways, allow the virus to persist and lyse them.¹¹ In the treatment of blood cancers with oncolytic viruses, direct cell lysis is used, while solid tumors are targeted through tumor lysis and immune response induction. Viruses like measles, adenovirus, and herpes simplex have shown promising results in treating various solid tumors, and specific drugs such as Rigvir and Oncocorine have been approved for certain cancers.¹² Oncolytic virus therapy is an appealing treatment method that involves genetically or naturally modified strains that selectively infect cancer cells. This approach induces a strong adaptive immune response against tumors without harming normal tissue cells.¹³ In line with our research findings, Zheng and colleagues conducted a study in 2012 on co-culturing apoptotic breast cancer cells with immature dendritic cells, proposing a new approach for dendritic cell-

based vaccination in cervical cancer. Their results indicated that matured dendritic cells with apoptotic cancer cells enhanced the proliferation and secretion of IFN-Gamma from T lymphocytes, which aligns with our study showing a significant increase in IFN-Gamma levels in the (DCs-NDV) group compared to the tumor group ($P \leq 0.001$).¹⁴ Shevchenko and colleagues conducted a review study in 2020 on autologous dendritic cells and activated cytotoxic T cells as a combination therapy for cervical cancer. They concluded that the investigated cellular immunotherapy is safe for breast cancer, reduces the risk of recurrence and metastasis, and improves immunity by decreasing regulatory T cells, suggesting it may be a new approach to combat distant metastases in cervical cancer.¹⁵ Ilett and colleagues conducted a study in 2011 on the internalization of oncolytic reovirus by human dendritic cell carriers, demonstrating that this process protects the virus from neutralization. The results indicated that the anticancer capability of dendritic cells infected with reovirus was enhanced compared to free reovirus, and electron microscopy showed that dendritic cells protect the virus from neutralizing antibodies, suggesting that reovirus delivery via dendritic cells could be a promising new approach for combining systemic viral therapy with the induction of tumor-specific immune responses.¹⁶ In line with our research findings, a study was conducted in 2020 on the anticancer effects of mesenchymal stem cells carrying Newcastle oncolytic virus. They reported that these stem cells possess both migration capacity and tumor tissue homing ability, significantly reducing tumor growth and enhancing specific lymphocyte proliferation, CD8+ T cell cytolytic responses, and splenic responses of IFN-Gamma, IL-4, and IL-10 compared to control groups.¹⁷ The results regarding tumor weight in the groups (DCs-NDV, DCs, PC) compared to the tumor group indicate that the tumor weight in the DCs-NDV group showed a greater reduction, highlighting the positive effect of using dendritic cells carrying Newcastle oncolytic virus. Additionally, a 2020 study demonstrated that oncolytic viruses can induce apoptosis in human cervical cancer cell lines, effectively eliminating these tumor cells.¹⁸

Conflicts of Interest Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent For Publication

Not applicable

References

- Hanahan D. Hallmarks of cancer: new dimensions. *Cancer discovery*. 2022 Jan 1;12(1):31-46. [Doi: 10.1158/2159-8290.CD-21-1059](https://doi.org/10.1158/2159-8290.CD-21-1059)
- Goggins S, Marsh BJ, Lubben AT, Frost CG. Signal transduction and amplification through enzyme-triggered ligand release and accelerated catalysis. *Chemical Science*. 2019;6(8):4978-85. [Doi: 10.1039/C5SC01588J](https://doi.org/10.1039/C5SC01588J)
- Fazeli M SH, Dadashzadeh S. . Further Stimulation of Cellular Immune Responses through Association of HPV-16 E6, E7 and L1 Genes in order to produce more Effective Therapeutic DNA Vaccines in Cervical Cancer Model. *Iranian journal of cancerprevention* 2020;8(1):18.
- Cho H LH-J, Heo Y-K, Cho Y, Gwon Y-D, Kim M-G, et al. Immunogenicity of a Trivalent Human Papillomavirus L1 DNA-Encapsidated, Non-Replicable Baculovirus Nanovaccine. *PLoS ONE*. 2019 Apr 23;9(4):e95961. [Doi: 10.1371/journal.pone.0095961](https://doi.org/10.1371/journal.pone.0095961)
- Nguyen HP R-FM, Rady PL. . The Biology of Human Papillomaviruses. . 2020;45:19-32. [Doi: 10.1159/000355959](https://doi.org/10.1159/000355959)
- Lowy D.R. HP, Papillomaviruses. 2019. In: Knipe DM, Howley PM, editors. *Fields virology*. Vol 2, 5th edition, 2231-2264.
- Diamantopoulou Z, Castro-Giner F, Schwab FD, Foerster C, Saini M, Budinjas S, .4 728. Strittmatter K, Krol I, Seifert B, Heinzlmann-Schwarz V, Kurzeder C. The metastatic spread of Kvedaraite E, Ginhoux F. . breast cancer accelerates during sleep. *Nature*. 2022 Jun 22:1-7. [Doi: 10.1038/s41586-022-04875-y](https://doi.org/10.1038/s41586-022-04875-y)
- Murphy, Human dendritic cells in cancer. *Science Immunology*. 2022 Apr 1;7(70):eabm9409. [Doi: 10.1126/sciimmunol.abm9409](https://doi.org/10.1126/sciimmunol.abm9409)
- Meunier, L., Bata-Csorgo, Z. and Cooper, K.D., 1995. In human dermis, ultraviolet radiation induces expansion of a CD36+ CD11b+ CD1-macrophage subset by infiltration and proliferation; CD1+ Langerhans-like dendritic antigen-presenting cells are concomitantly depleted. *Journal of investigative dermatology*, 105(6), pp.782-788. [Doi: 10.1111/1523-1747.ep12326032](https://doi.org/10.1111/1523-1747.ep12326032)
- Nathan C, Srimal S, Farber C, Sanchez E, Kabbash L, Asch A, Gailit J, Wright SD. Cytokine-induced respiratory burst of human neutrophils: dependence on extracellular matrix proteins and CD11/CD18 integrins. *The Journal of cell biology*. 1989 Sep 1;109(3):1341-9. [Doi: 10.1083/jcb.109.3.1341](https://doi.org/10.1083/jcb.109.3.1341)
- Lawler SE, Speranza MC, Cho CF, Chiocca EA. Oncolytic viruses in cancer treatment: a review. *JAMA oncology*. 2017 Jun 1;3(6):841-9. [Doi: 10.1001/jamaoncol.2016.2064](https://doi.org/10.1001/jamaoncol.2016.2064)
- Hong J, Yun CO. Overcoming the limitations of locally administered oncolytic virotherapy. *BMC Biomedical Engineering*. 2019 Dec;1:1-1. [Doi: 10.1186/s42490-019-0016-x](https://doi.org/10.1186/s42490-019-0016-x)
- Raja J, Ludwig JM, Gettinger SN, Schalper KA, Kim HS. Oncolytic virus immunotherapy: future prospects for oncology. *Journal for immunotherapy of cancer*. 2018 Dec;6(1):1-3. [Doi: 10.1186/s40425-018-0458-z](https://doi.org/10.1186/s40425-018-0458-z)

14. Zheng J, Liu Q, Yang J, Ren Q, Cao W, Yang J, Yu Z, Yu F, Wu Y, Shi H, Liu W. Co-culture of apoptotic breast cancer cells with immature dendritic cells: a novel approach for DC-based vaccination in breast cancer. *Brazilian Journal of Medical and Biological Research*. 2012;45:510-5.
15. Shevchenko JA, Khristin AA, Kurilin VV, Kuznetsova MS, Blinova DD, Starostina NM, Sidorov SV, Sennikov SV. Autologous dendritic cells and activated cytotoxic T cells as combination therapy for breast cancer. *Oncology reports*. 2020 Feb 1;43(2):671-80.
16. Ilett EJ, Bárcena M, Errington-Mais F, Griffin S, Harrington KJ, Pandha HS, Coffey M, Selby PJ, Limpens RW, Mommaas M, Hoeben RC. Internalization of oncolytic reovirus by human dendritic cell carriers protects the virus from neutralization. *Clinical Cancer Research*. 2011 May 1;17(9):2767-76. [Doi: 10.1158/1078-0432.CCR-10-3266](https://doi.org/10.1158/1078-0432.CCR-10-3266)
17. Delirez N, Moazzeni SM, Shokri F, Shokrgozar MA, Atri M, Kokhaei P. Autologous dendritic cells loaded with apoptotic tumor cells induce T cell-mediated immune responses against breast cancer in vitro. *Cellular immunology*. 2009 Jan 1;257(1-2):23-31. [Doi: 10.1016/j.cellimm.2009.02.002](https://doi.org/10.1016/j.cellimm.2009.02.002)
18. Castle PE, Maza M. Prophylactic HPV vaccination: past, present, and future. *Epidemiology & Infection*. 2016 Feb;144(3):449-68. [Doi: 10.1017/S0950268815002198](https://doi.org/10.1017/S0950268815002198)