

Oncolytic Bacteria and Viruses: A Novel Approach for the Treatment of Colorectal Cancer

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Executive Summary

This study investigates the effect of mesenchymal stem cells (MSCs) carrying Newcastle oncolytic virus, treated with the probiotic *Lactobacillus casei*, in the treatment of colorectal cancer in a mouse model. Colorectal cancer is a significant health issue and the third leading cause of death worldwide. The results showed that mice receiving MSCs carrying the virus had better survival rates and slower tumor growth compared to the control group. Additionally, this treatment increased nitric oxide and IFN- γ production while decreasing IL-4, IL-10, and TGF- β secretion. However, treatment with *Lactobacillus casei* extract did not show a significant difference compared to the untreated group. The overall conclusion is that using MSCs carrying Newcastle oncolytic virus is beneficial in treating colorectal cancer.

Keywords: Colorectal cancer, *Lactobacillus casei* probiotic, mesenchymal stem cells, Newcastle oncolytic virus

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Introduction

Cancer is one of the major health challenges and the third leading cause of death worldwide. Colorectal cancer is the third most common cancer globally, accounting for 10% of cancer-related deaths.¹ Colorectal cancer develops in the colon and rectum, categorized together due to their shared characteristics. It begins in the innermost mucosal layer and can spread to other layers, allowing cancer cells to grow in blood vessels or lymphatics and spread to nearby or distant lymph nodes. The progression from abnormal cell growth to colorectal cancer typically takes 10 to 15 years, making regular screening essential for prevention and reducing mortality.² The World Health Organization predicts a 7% increase in new colorectal cancer diagnoses and an 80% rise in mortality due to the disease by 2030.³ Although surgery is one of the effective treatment methods, recurrence is observed in about 30 to 40 percent of patients after surgery.⁴ Probiotics are beneficial live microorganisms that, when consumed by humans or animals, positively impact health by influencing the body's microbial flora, primarily consisting of key bacteria in the

human gut.⁵ The most common probiotic microorganisms are divided into two groups: bacteria and fungi, with selected strains of *Lactobacillus* and *Bifidobacterium* being prominent, while *Enterococcus*, *Streptococcus*, and *Escherichia coli* are also used. Yeasts like *Saccharomyces cerevisiae*, *Saccharomyces boulardii*, and *Candida antarctica* are also considered probiotics. Most *Lactobacillus* and *Bifidobacterium* bacteria are deemed safe, and except for *Streptococcus* and *Enterococcus*, other lactic acid bacteria are rarely pathogenic to humans and animals, with their use in food production proven safe over time.⁶ The Newcastle disease virus (NDV) is an RNA virus belonging to the *Paramyxoviridae* family and is recognized as a strong inducer of cell death in malignant cell lines.⁷ As an oncolytic virus, NDV is a potential tool for cancer treatment, proven to be a safe and effective anti-tumor agent that enhances anti-tumor immune responses by increasing cytokine production, especially interferon (IFN), and inducing cell death in cancer cells.⁸ In the present study, our aim is to enhance the viability and

therapeutic potential of mesenchymal stem cells carrying the Newcastle oncolytic virus in the treatment of colorectal cancer.

Materials and Methods

This study was conducted on female BALB/c mice weighing between 20 to 25 grams and aged 6 to 8 weeks. The mice were divided into four experimental groups: the control group, which received 100 microliters of PBS daily; the group that received mesenchymal stem cells infected with Newcastle virus (MOI 20); the group that received both the infected mesenchymal stem cells and *Lactobacillus casei* extract; and the group that was treated with 5-FU. To create a tumor model, CT26.WT cancer cells were obtained from the cell bank of the Pasteur Institute of Iran and injected into the mice. These mice were kept in environmental conditions for two weeks to acclimate, after which 5×10^6 CT26 cells were injected subcutaneously. After 18 days, a palpable tumor was observed, and treatments began. Mesenchymal stem cells were extracted from the bones of the mice and infected with the Newcastle virus. Additionally, to evaluate the effects of the treatments, tumor volume, mouse lifespan, and various assays, including cytokine measurements and nitric oxide levels, were conducted. Finally, statistical analysis was performed using SPSS and Excel software, with a significance level set at 0.05. These steps were meticulously designed to investigate the effects of different treatments on the tumor and the immune system of the mice.

Results

In the conducted research, the results show that all treatment groups significantly increased spleen cell proliferation and nitric oxide production compared to the control group. Additionally, lactate dehydrogenase release also increased significantly in all groups. Regarding cytokines, the treatments elevated IFN- γ levels while reducing IL-4, TGF- β , and IL-10 cytokines; however, no significant difference was observed between the MSC-NDV and MSC-NDV-L.casei groups. In the tumor volume assessment, the results indicated that the groups treated with MSC-NDV, MSC-NDV-L.casei, and 5-FU significantly reduced tumor volume. Furthermore, in evaluating the lifespan of tumor model mice, after 30 days of treatment, 40% of mice in the MSC-NDV and MSC-NDV-L.casei groups and 60% in the 5-FU group survived, while all mice in the control group perished. Again, no significant difference was observed between the MSC-NDV and MSC-NDV-L.casei groups.

Discussion

NDV is an RNA virus belonging to the Paramyxoviridae family and is recognized as a potent inducer of cell death in malignant cell lines.⁹ As an oncolytic virus, NDV is a potential tool for cancer treatment and has proven to be a safe and effective anti-tumor agent. It has been shown that NDV can directly enhance anti-tumor immune responses by increasing cytokine production, particularly interferon (IFN), and inducing the death of cancer cells.¹⁰ One of the main obstacles in using naked viruses for cancer virotherapy is the host immune system, which reduces the treatment's effectiveness through antibody-dependent neutralization via complement.¹¹ To protect oncolytic viruses from adverse effects of immune-mediated clearance or neutralization, the use of cellular carriers has been proposed as a new approach. Additionally, employing cells with inherent ability to migrate within the tumor microenvironment enhances the effectiveness of cancer treatment.¹² Previous studies have evaluated several candidate carrier cells, including monocytes, dendritic cells, mesenchymal stem cells (MSCs), and tumor cells.¹³ In the present study, our goal is to enhance the viability and therapeutic potential of mesenchymal stem cells carrying Newcastle disease virus for the treatment of colorectal cancer.

In 2020, a study by Keshavarz and colleagues titled *Oncolytic Newcastle Disease Virus Delivered by Engineered Mesenchymal Stem Cells Enhances Therapeutic Effects in Modifying Tumor Microenvironment* was conducted. The results showed that mesenchymal stem cells carrying the virus increased survival, reduced tumor volume, and elevated levels of cytokines IL-12 and IFN- γ , as well as lactate dehydrogenase compared to the untreated control group.¹⁴ In 2021, Babaei and colleagues conducted a study titled *Mesenchymal Stem Cells Loaded with Oncolytic Reovirus Enhance Antitumor Activity in Colorectal Cancer Mouse Models*. The results indicated that mesenchymal stem cells carrying the virus increased survival, reduced tumor volume, and enhanced cellular immune responses compared to the untreated control group.¹⁵ In 2020, Ahadi and colleagues conducted a study titled *Investigating the Effects of Lactobacillus Extract on the Viability of Mesenchymal Stem Cells*. The results showed that *Lactobacillus* extract has protective effects against oxidative stress on mesenchymal stem cells. The researchers also suggested that the simultaneous use of mesenchymal stem cells treated with *Lactobacillus* probiotic extract could enhance their efficacy in cell therapy.¹⁶ In 2020, Hassan and colleagues demonstrated that the LaSota strain exhibited significant antitumor activity against AMN3 mouse adenocarcinoma breast cells, inducing cytolysis and apoptosis through the intrinsic

(mitochondrial) pathway. This effect was determined by the increased percentage of caspase-9 expression compared to caspase-8.¹⁷ In 2019, Zahiah and colleagues reported that intratumoral viral therapy increases virus dissemination to the tumor site, leading to the generation of natural killer cells and cytotoxic T lymphocytes against viral antigens in infected tumor cells, aiding in oncolytic activity. The MTT cytotoxicity method also showed that rAF-IL12 selectively induces cytotoxic effects (IC50) in chicken and human breast cancer cell lines, with no significant toxicity against the normal MCF10A cell line, making it an ideal therapeutic agent.¹⁸ In 2022, Jalali Kondori and colleagues evaluated the anticancer effects of combined treatments with copper nanoparticles, Newcastle oncolytic virus, heat, and radiation on colorectal cancer cells. MTT and apoptosis tests indicated that these treatments inhibited the proliferation of the cancer cells and induced apoptosis.¹⁹

Conclusion

The present study indicates that treatment of colorectal cancer using stem cells carrying Newcastle oncolytic virus is effective; however, the *Lactobacillus casei* probiotic extract does not have a significant impact on the anti-tumor response of these stem cells. Additionally, the results suggest that the beneficial effects of this treatment may be partly due to a shift in immune responses from producing anti-inflammatory cytokines to pro-inflammatory cytokines and the activation of innate immunity. Furthermore, the increase in lactate dehydrogenase and nitric oxide as representatives of the innate immune system indicates that both arms of the immune system are activated in this treatment approach.

Conflicts of Interest Disclosures

The author 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

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