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REVOLUTIONIZING CANCER IMMUNOTHERAPY WITH PLANT VIRUS-BASED NANOPARTICLES

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A B S T R A C T

Cancer is a complex disease and is the leading cause of mortality that affects millions of people across the globe. Cancer is challenging to treat, and current treatments including surgery, radiotherapy and systemic treatments have improved significantly over time; however, a better and effective treatment of cancer remains a challenge for patients, wellness professionals, investigators and scientists. Therefore, it is necessary to develop targeted and less toxic therapies for cancer. Recent research has revealed that plant viruses, occurring naturally, can invade a host cell for their replication and reproduction, and thus may have the ability to use as a tool to treat cancer. Plant viruses, occurring naturally, possess a remarkable ability to infiltrate host cells for their replication and propagation. This unique characteristic positions them as potential tools in the fight against cancer. Unlike conventional therapies, plant viruses are harmless to humans and can be engineered to specifically target cancer cells. Furthermore, the size and genome organization of different proteins of plant viruses are very small in diameter, making them an ideal size for transmission in the blood flow and have potential for carrying and discharge of payload to target cancer cells. This inherent capability holds immense potential for developing targeted and less toxic therapies for cancer, offering hope for improved outcomes and quality of life for cancer patients.

Keywords: Plant viruses, nanoparticles, cancer immunotherapy, drug delivery.

INTRODUCTION

Cancer is a leading source of mortality worldwide, with its burden increasing due to factors such as an aging population, societal changes, industrialization, and improved control over other diseases (Sung *et al.,* 2021). A combination of ageing population, societal changes, industrialization, and better control over communicable and some non-communicable disease has led to cancer to become a major challenge for the 21st century. GLOBOCAN estimates that more than 19 million people will be diagnosed with cancer and more than 10 million will die of cancer every year globally (Sung 2021). Significant geographic variation exist in the frequency and mortality rates of various cancer types worldwide, and this seems to be proportional to the human development index Human Development Report 2019 (undp.org). Despite advances in screening and early detection and treatment of cancer, about 2/3rd of the patients in the western hemisphere, and much less in the rest of the world will be cured or their disease. Over the next 15 years, the number of new cases is expected to rise to more than 28 million cases per year, but the gap between incidence and mortality is expected to increase most markedly in countries with a low to medium human development index (Global health estimates: Leading causes of death (who.int); Ferlay *et al.,* 2018). Clearly there is an unmet need to treat the disease globally, and especially in the developing world, where cancer imposes a significant burden, with millions of new cases diagnosed annually and an estimated 70% of cancer-related deaths occurring in the developing regions. The stark reality underscores the urgent need for accessible and effective cancer interventions.

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Application of plant virus nanoparticle in combating cancer cells: Plant virus nanomaterials (PVNs) have recently emerged as an encouraging platform for cancer immunotherapy due to their exclusive properties, including biocompatibility, biodegradability, and capacity to induce strong immune responses. One of the most promising applications of PVNs in cancer immunotherapy is their application as cancer vaccine. PVNs can be engineered to exhibit tumor-specific antigens, which can stimulate an immune response that targets cancer cells. The efficiency of PVNs as cancer vaccines in animal models has been confirmed (Yusibov *et al.,* 2015). Recently, a study showed that *tobacco mosaic virus* (*TMV*) nanoparticle displaying a tumor-specific antigen and it was able to produce a robust immune response and reduce tumor growth in a mouse prodigy (Liu *et al.,* 2020). The application of PVNs in cancer immunotherapy is their use as adjuvants in combination with other cancer treatments. Adjuvants are substances that are added to vaccines or other immunotherapies to improve the immune response (Basuki *et al.,* 2017). PVNs could be highly effective adjuvants in combination with cancer vaccines and other immunotherapies, such as immune checkpoint inhibitors (Narayanan *et al.,* 2018). PVNs can be manipulated to demonstrate specific antigens at their surface, allowing them to be targeted to cancer cells. Once they bind to cancer cells, the nanoparticles (Nps) can trigger an immune reaction that leads to the destruction of cancer cells. In addition to their ability to induce immune responses, they can also be used as to carry drugs into different body parts to cure cancer. They have been shown to effectively deliver chemotherapeutic agents directly to infected cells effectively, thus decreasing the quantity of medicine required and lessening the aftereffects (Narayanan *et al.,* 2018).

Besides PVNs, plant viruses can also be used to trigger the immune system to treat cancer. For instance, noninfectious plant based virus-like particles (VLPs), such as, *potato virus X* (*PVX*) and *turnip yellow mosaic virus* (*TYMV*) were shown to trigger an immune response against cancer cells. These VLPs can be further manipulated to demonstrate specific antigens, expressed on the surface of cancer cells. In a study conducted on mice, *PVX VLPs* displaying a tumor antigen were shown to persuade an immune reaction against cancer growth (Figure 1).

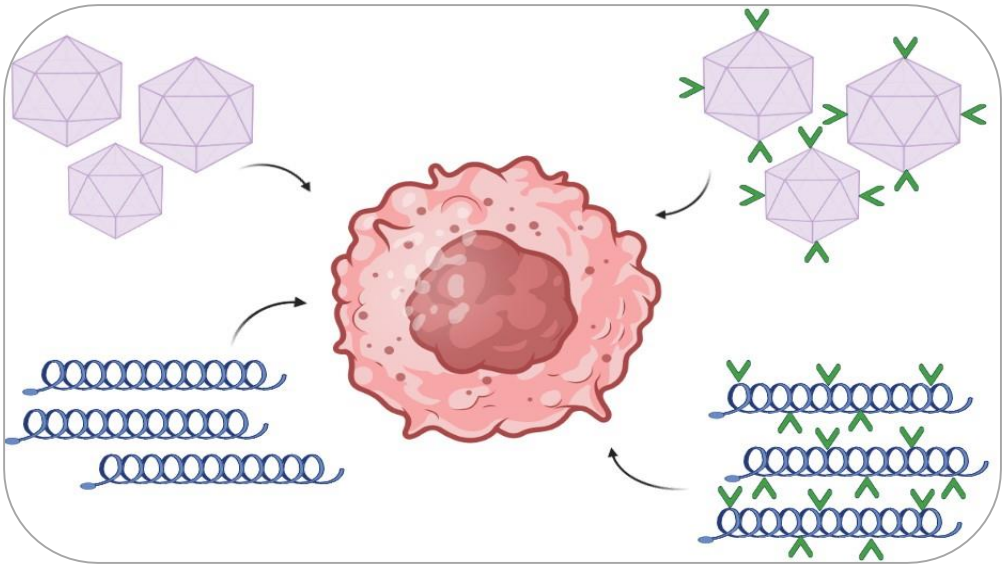

Figure 1. Schematic presentation of cancer cell (center) targeted by plant virus nanomaterials in cancer immunotherapy. Empty VLPs (top left/icosahedra and bottom left/ rod-shaped), virus particles with highly functionalized (Nps) (top right and bottom right) can be used to trigger an immune response and/or drug delivery payload to the infected cells.

The plant virus based vector system has numerous benefits due to their small genome size, non-infectious nature, ease of manipulation and multiplication, and the potential to target particular cells. They act as carrier that can transport a therapeutic agent to a precise location, such as a cancer cell. One such plant virus-based vector is *Cowpea mosaic virus* (*CPMV*), which has been shown to be non-toxic to humans and has successfully been engineered and tested to deliver anti-cancer drugs directed at cancer cells (Zhang *et al.,* 2019). Similarly, *CPMV* and *Papaya mosaic* (*PapMV*) based nanomaterials have been generated that can carry therapeutic agents to the infectious cells (Lizotte

et al., 2016). These nanomaterials are designed to deliver the drug specifically to cancer cells, decreasing the toxicity to normal cells (Table 1). Likewise, *Sesbania mosaic virus* (*SeMV*) and *Tobacco mosaic virus* (*TMV*) based nanomaterials transport small interfering RNA (siRNA) to cancer cells. siRNA can silence explicit genes involved in cancer cell development as well as to be effective in preventing development of lung cancer (Lan *et al.,* 2020; Bruckman *et al.,* 2018). Moreover, *TMV*-NPs can reduce tumour size, reduction in cellularity and evident nuclear condensation resulting in apoptosis (Czapar *et al.,* 2016) (Table 1).

Table 1. Different plant viruses used for delivery of different protein in cancer immunotherapy

Virus*	Genome	Symmetry	Family	Delivery	Application	Reference
PhMV	(+)ssRNA	Icosahedral	*Tymoviridae*	Stacking interactions	Breast cancer	Hu and Steinmetz (2020)
TMV	(+)ssRNA	Rod-like	*Tombusviridae*	Electrostatic interaction	Ovarian cancer	Franke *et al.* (2018)
CPMV	(+)ssRNA	Icosahedral	*Secoviridae*	Infusion process	Brain tumors	Lam *et al.* (2018)
PVX	(+)ssRNA	Rod-like	*Potexviridae*	Covalently attached cysteine	B cell malignancies	Shukla *et al.* (2020)
TMV	(+)ssRNA	Rod-like	*Tombusviridae*	Electrostatic entrapment	Breast cancer	Czapar *et al.* (2016)
PapMV	(+)ssRNA	Rod-like	*Alphaflexiviridae*	Attachment to C-end of the coat protein	HCV treated	Denis *et al.* (2007)
CCMV	(+)ssRNA	icosahedral	*Bromoviridae*	Self-assembly	Colon cancer	Cai *et al.* (2020)
Jg*CSMV*	(+)ssRNA	icosahedral	*Tombusviridae*	Covalent attachment	mild leukopenia and Breast cancer	Alemzadeh *et al.* (2019)
SeMV	(+)ssRNA	Icosahedral	*Solemoviridae*	Blood, liver and spleen	mild leukopenia	Vishnu Vardhan *et al.* (2016)
TBSV	(+)ssRNA	Icosahedral	*Tombusviridae*	Blood, liver and spleen	Non-toxic	Blandino *et al.* (2015)

*Plant virus acronyms: *Cowpea chlorotic mottle virus* (*CCMV*), *Cowpea mosaic virus* (CPMV), *Johnson grass chlorotic stripe mosaic virus* (*JgCSMV*), Papaya mosaic virus (*PapMV*), *Physalis mottle virus* (*PhMV*), *Potato virus X* (*PVX*), *Sesbania mosaic virus* (*SeMV*), *Tobacco mosaic virus* (*TMV*), *Tomato bushy stunt virus* (*TBSV*).

These plant-based viruses have also previously been employed for vaccine production, and therefore can contribute an important substitute tool for medicine distribution (Koprowski and Yusibov 2001). Examples are, *Hibiscus chlorotic ringspot* (*HCRSV*), *Red clover necrotic mosaic virus (RCNMV), Cowpea chlorotic mottle virus* (*CCMV*), *Johnson grass chlorotic stripe mosaic virus* (*JgCSMV*), *Physalis mottle virus* (*PhMV*) and Tomato bushy stunt virus ((Ren *et al.,* 2007; 2010; Steinmetz *et al.,* 2009; Miermont *et al.,* 2008; Nkanga and Steinmetz 2021) displayed promising application in cancer treatment.

Major challenges: Despite the promising outcomes of preclinical trials, there are numerous challenges that need to be overcome before PVNs can be applied in clinical settings. One challenge is the requirement for large-scale production of nanoparticles (Nps). Although several approaches for producing PVNs have been established, including plant-based expression systems and bacterial expression systems (Lee *et al.,* 2017), however, these approaches need to be augmented for large-scale production. In addition, there are also safety concerns. Although PVNs are generally considered harmless, there is a need for rigorous safety studies to confirm that they will not cause unacceptable side effects (such as Severe pain and discomfort, Debilitating fatigue and weakness, Nausea, vomiting, and loss of appetite, Hair loss (alopecia), Cognitive impairment or "chemo brain" affecting memory, concentration, and decision-making abilities, Emotional distress, anxiety, and depression, Immune suppression, increasing susceptibility to infections and other illnesses, Disfigurement or loss of function, long-term complications such as organ damage, infertility etc.) in human beings. Furthermore, the potential for immune tolerance need to be explored.

CONCLUSION

In conclusion, PVNs offer a promising platform for cancer immunotherapy due to their unique properties and potential

versatility in treatment design. Continued research into PVNs and their potential for cancer therapy is likely to lead to new, effective treatments for cancer. Additionally, the safety and efficacy of these approaches need to be tested in clinical experiments. Future directions in the field of cancer immunotherapy with plant virus-based nanoparticles may involve optimizing delivery systems for enhanced targeting of specific cancer cells and exploring combination therapies to maximize treatment efficacy while minimizing side effects. Additionally, research may focus on developing personalized approaches by tailoring nanoparticle design to individual patient characteristics for improved therapeutic outcomes.

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Muhammad S. Shahid	:	Writing of the original manuscript.
Ikram A. Burney	:	Reviewing and editing of the manuscript.