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(REVIEW ARTICLE)

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mRNA vaccines in cancer clinical trials: HPV16 tumor-derived antigens (e6 and e7 oncoproteins) associated with head and neck squamous cell carcinoma (HNSCC), oropharyngeal and cervical cancers

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Abstract

Human papillomavirus (HPV) induces the most common sexually transmitted disease and has been classified in the *Alphapapillomavirus* genus, *Papillomaviridae* family. They are non–enveloped viruses presenting a closed circular double–stranded non–segmented DNA genome of approximately 8 kb that infect the anogenital epithelium causing cervical cancer, anal and penis cancer. There are viral groups based on their oncogenic activity as high–risk types, low–risk types and types of undetermined–risk. mRNA vaccines are being evaluated in people with HPV-related cancers. This study described how mRNA cancer vaccines work and their applications recruiting several strategies for HPV cancer immunotherapy. Several biopharmaceuticals are developing mRNA vaccines encoding neoepitopes that can induce immune responses against target tumors. One trial is testing a personalized mRNA vaccine in combination with an immune checkpoint inhibitor in patients with advanced head and neck cancer. The production of therapeutic mRNA proteins for development of vaccine cancer have been manufactured by upstream and downstream methods. Several stages are processed in bioreactors using input and output parameters to measure the quality control of purified substance. Thus, novel technologies using different mRNA delivery system can be able to be integrated in clinical trials of HPV16 tumor-derived antigens associated cervical intraepithelial lesions of different stages until head and neck squamous cell carcinoma, oropharyngeal and cervical cancers.

Keywords: mRNA vaccine; HPV; cancer immunotherapy; oncoproteins

1 Introduction

Human papillomavirus (HPV) induces the most common sexually transmitted disease and has been classified in the *Alphapapillomavirus* genus, *Papillomaviridae* family [1]. They are non–enveloped viruses presenting a closed circular double–stranded non–segmented DNA genome of approximately 8 kb that infect the anogenital epithelium causing cervical cancer, anal and penis cancer. There are viral groups based on their oncogenic activity as high–risk types, low–risk types and types of undetermined–risk [1]. Baculovirus and yeast (*Saccharomyces cerevisiae*) were the target as an expression system for licensed HPV recombinant vaccines [1].

A cross-sectional design study demonstrated into several predictor factors for cervical cancer associated with sociodemographic, psychosocial and psychosexual variables linked with percentage distribution age group HPV-positive [2]. Papillomaviruses can be used as viral vectors in the gene therapy. An overview of the several classic technological platforms (inactive viruses, attenuated viruses, subunit protein vaccines and virus-like particle - VLP)

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vaccines; and new generation of vaccine platforms (replicating and non-replicating viral vectors, nucleic acid vaccines – DNA and RNA and antigen-presenting cells) have been described [3].

According to the central dogma of molecular biology, RNAs are responsible for mediating the transfer of genetic information from the nucleus (genes) to the cytoplasm through proteins. Several advances in the genomics era and the development of new technological tools for next-generation sequencing have revealed that approximately 98% of RNAs are not translated into proteins. In 1995, fundamental research demonstrated that an intramuscular injection of Nu RNA, which encodes carcinoembryonic antigens, could elicit antigen-specific antibody responses in mice. The following year, a separate study showed that mRNA-transfected dendritic cells injected into tumor-bearing mice induced T-cell immune responses and inhibited the growth of the tumors. This study paved the way for numerous studies exploring the feasibility, efficacy, and safety of mRNA-based technologies. However, instability, innate immunogenicity and inefficient *in vivo* delivery still limit mRNA vaccine and therapeutic applications. One of the main challenges researchers faced was how to get the mRNA to where it needed to go; an mRNA sequence injected into the body without some form of protection would be recognized as a foreign substance and would be destroyed.

Among the numerous RNAs, messenger RNA (mRNA) stands out, as "messenger" molecule that allows genetic information stored in the cell nucleus DNA to be transported to the ribosomes for protein synthesis. Thus, two scientists – Hungarian biochemist Katalin Karikó and American doctor Drew Weissman – had been beginning research using the *in vitro* synthetic mRNA platform in the 1990s, when they worked together at the Pennsylvania University. Recently these researchers were awarded the Nobel Prize in Medicine in 2023 for their innovative discoveries in the development of mRNA vaccines, key role in combating the Covid-19 pandemic. Some biopharmaceutical companies from Pfizer and its partner BioNTech and the Moderna mRNA-1273 vaccine have successfully used the new technological platform [3].

Significant challenges in the development of vaccines based on mRNA had been recorded that, after experimental trials involving inoculated laboratory animals, showed inflammatory reactions with the production of cytokines in which the immune system recognized the mRNA produced *in vitro* as an antigen. Therefore, the need to modify the nitrogenous bases of mRNA proven by clinical trials, scientists replaced the nitrogenous base uridine with a similar molecule called pseudouridine. Additionally, the mRNA was absorbed by cells without provoking an unwanted inflammatory response, increasing the production of the target protein of interest.

Future mRNA vaccines and new mRNA-based medicines are the potential of the future. Some laboratories have been already carried out immunization tests against all types of coronaviruses and for the prevention of viral and non-viral infectious diseases. This biotechnological strategy may also be applicable to autoimmune diseases and degenerative pathologies such as Alzheimer's.

Biopharmaceutical companies are developing mRNA drugs with applicability for different types of solid tumors, as melanoma and HPV. Furthermore, there is the development of mRNA vaccines in phase 2 clinical trials for cancer of different types: the melanoma, colorectal cancer, head and neck carcinoma, prostate cancer, and lung cancer, recruiting the immune system of how mRNA cancer vaccines work. The applications of mRNA in cancer vaccines are broad, with researchers exploring several strategies for cancer immunotherapy (figure 1).

- Antigen presentation: mRNA vaccine delivery cancer antigens to antigen-presenting cells (APCs) for presentation to major histocompatibility complex classes I and II;
- Adjuvant function: mRNA stimulates activation by binding to pattern recognition receptors expressed by APCs;
- Antigen receptors: mRNA introduces antigen receptors such as chimeric antigen receptors (CARs) and T cell receptors into lymphocytes;
- Protein production: mRNA allows the expression of immunomodulatory proteins, including toll-like receptors, chemokine receptors, co-stimulatory ligands, cytokines, chemokines and different formats of monoclonal antibodies in various cell subsets.

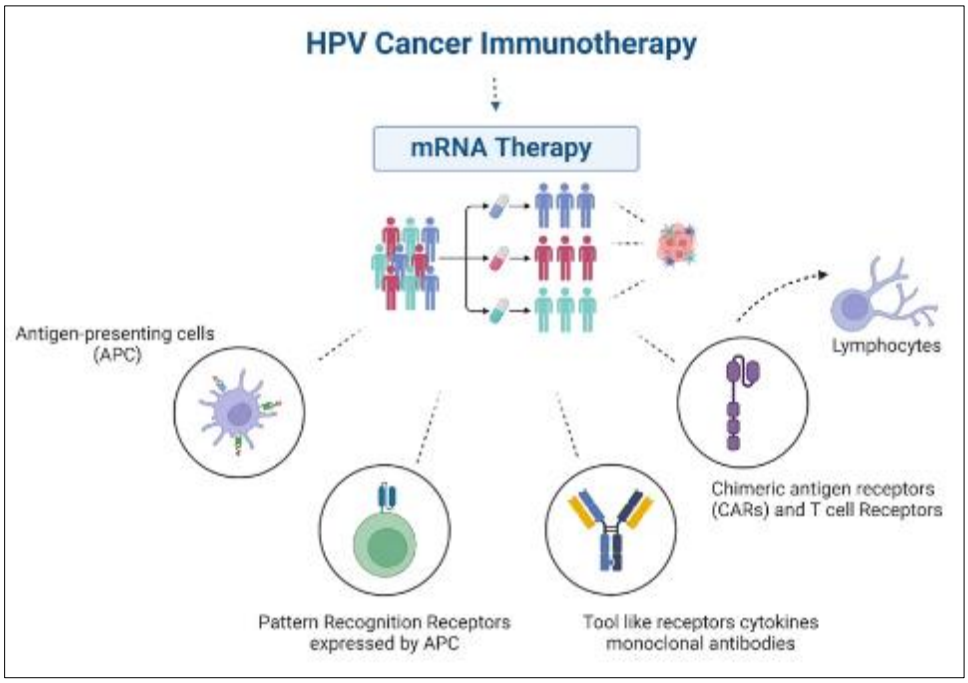

Figure 1 Strategies for cancer immunotherapy. This figure was created and designed by the author using scientific image and illustration software with publication license into journals.

Several biopharmaceuticals are developing mRNA vaccines encoding neoepitopes that can induce immune responses against target tumors. Clinical trials are testing mRNA vaccines as monotherapies or as part of a combination treatment in people with several types of cancer, including head and neck cancer. Most oncology research has focused on mRNA therapies, with a wide variety of candidates entering clinical development trials.

1.1 Making mRNA cancer vaccines a reality

In recent years, high advances in cancer mRNA biotechnology have been documented but otherwise some challenges remain are still a barrier to be overcome. Firstly, mRNA cancer vaccines require specific packaging and delivery systems with a suitable affinity for the target tissue and/or organ as association of organ-targeted fragments to oligonucleotides. Although lipid nanoparticles (LNPs) are the most studied vehicles for mRNA delivery, their clinical application has been impeded by concerns about cytotoxicity and relatively short circulation time. Therefore, several alternative smart delivery systems (e.g., exosomes) to improve the bioavailability, loading, and release of mRNA are under evaluation.

Successful delivery of the mRNA is not enough. To ensure maximum effectiveness, researchers have investigated approaches to increase protein expression in vivo. All parts of the mRNA—cap, 5′ and 3′ regions, open reading frame, and polyadenylated tail—can be optimized to increase protein expression.

Self-amplifying and circular mRNAs are being explored as strategies to extend RNA lifetime and increase total protein yield. Immunotherapies such as checkpoint inhibitors have been shown to be a critical advance in cancer treatment. Not all tumor types respond to immunotherapeutic agents and resistance mechanisms can lead to immune tumor escape and growth. Morphological alterations occurring inside HPV-positive cervical carcinoma SiHa (HPV-16) and HeLa (HPV-18) cell lines ($3x10^6$ cells) were detected by transmission electron microscopy and suggested the oncoproteins pathways to produce virions as mechanism of differentiation of keratinocytes in the epithelial layers [4].

Tumor-associated antigens (TAAs), tumor-specific antigens (TSAs), or immunomodulators are currently being investigated to clinical applications of mRNA cancer vaccines and cancer immunotherapy using several mRNA delivery systems as polymer bound mRNA, liposomal formulation, lipoplex (LPX), lipopolyplex (LPP), virus-like particles (VLPs), dendritic cell (DC), and lipid nanoparticles (LNPs) [5] (figure 2). For illustrated highlighted HPV-16 oncoproteins, RNA-LPX immunization induces a strong antigen-specific effector and memory CD8+ T cell response in murine models experimentally testing [6].

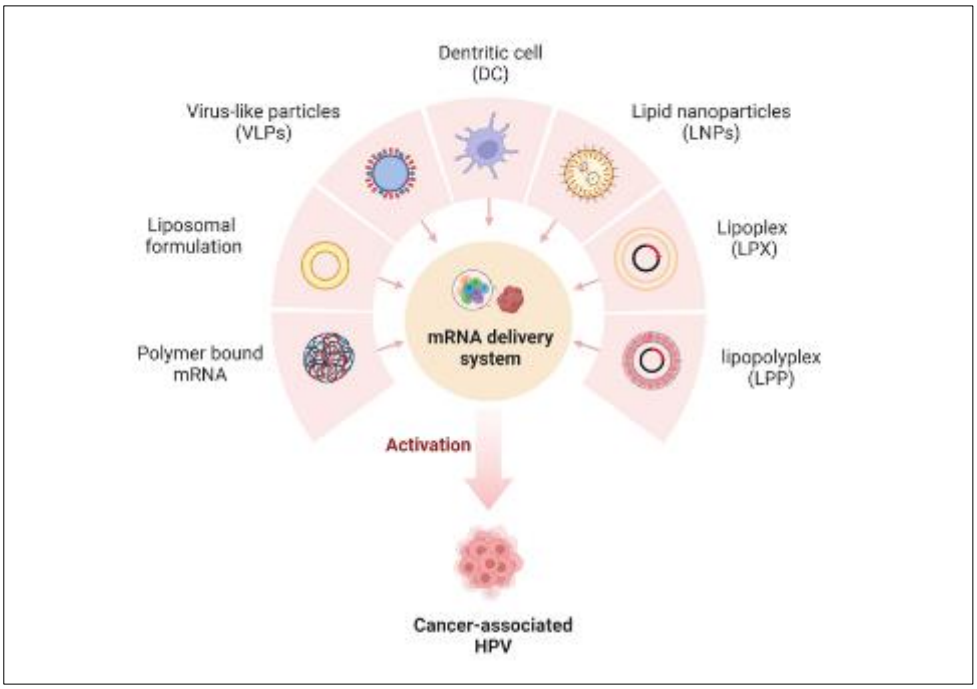

Figure 2 Schematic representation of mRNA delivery system - Cancer immunotherapy using several mRNA delivery systems as polymer bound mRNA, liposomal formulation, lipoplex (LPX), lipopolyplex (LPP), virus-like particles (VLPs), dendritic cell (DC), and lipid nanoparticles (LNPs). This figure was created and designed by the author using scientific image and illustration software with publication license into journals.

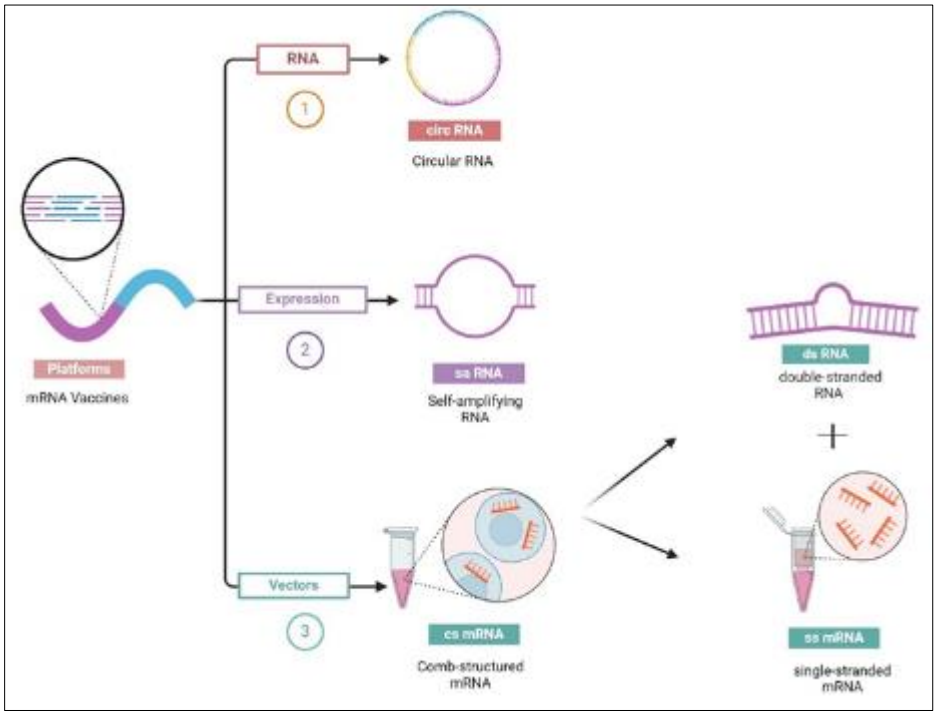

Figure 3 Schematic representation of three types of RNA expression vectors used in mRNA cancer vaccines. This figure was created and designed by the author using scientific image and illustration software with publication license into journals.

The self-amplification RNA (saRNA) targeting the human papillomavirus (HPV) exhibited high antitumor effects [5]. There are different types of RNA expression vectors used in mRNA cancer vaccines as circular RNA (circ RNA), self-

amplifying RNA and comb-structured mRNA involved hybridizing short double-stranded RNA (dsRNA) with single-stranded mRNA as vaccine platforms [5] (figure 3).

DNA-based vaccines, recombinant proteins, nanoparticles, synthetic peptides, viral and non-viral vectors may be novel therapeutic targets to HPV vaccination [7]. So, mRNA vaccines encoding tumor-associated antigens (TAA) as CEA (Carcinoembryonic Antigen), HER2/neu, MUC1 (Mucin 1), NY-ESO-1 associated colorectal and other adenocarcinomas, gastric cancer, colorectal cancer, epithelial cancers, esophageal cancer, respectively [5]. One clinical trial, for example, is testing a personalized mRNA vaccine in combination with an immune checkpoint inhibitor in patients with advanced head and neck cancer (Figure 4).

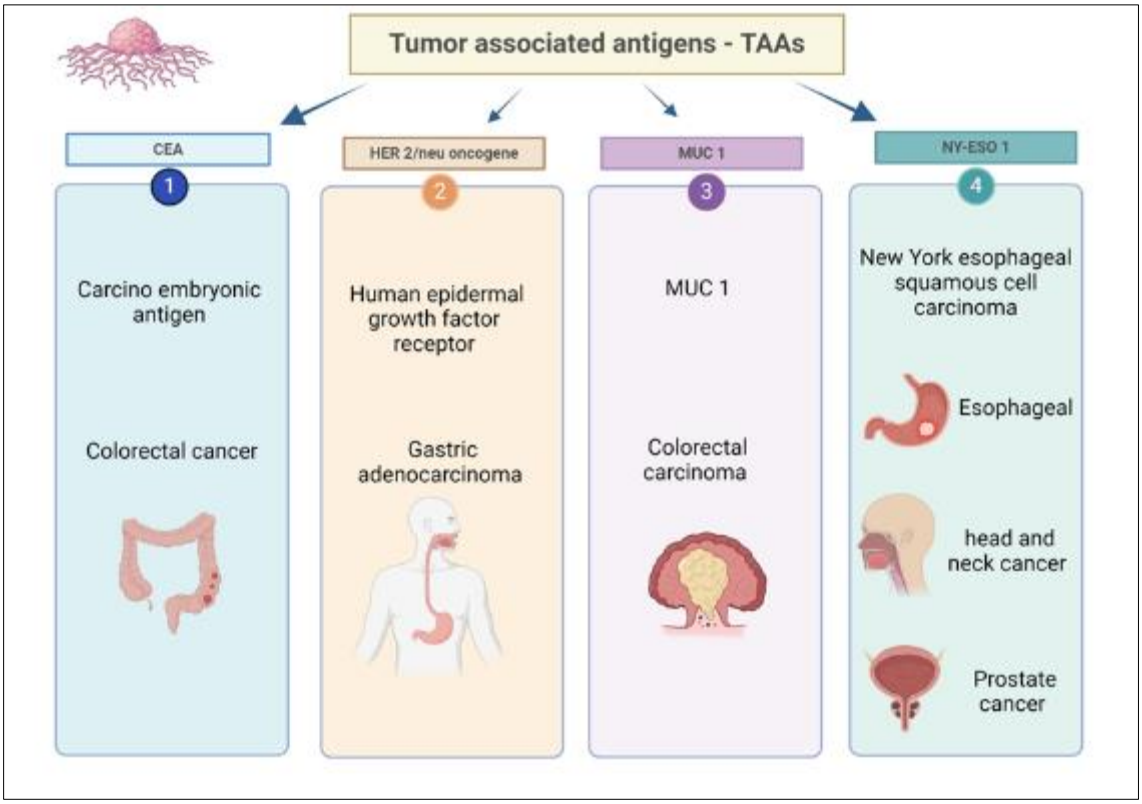

Figure 4 Biomarkers tumour associated antigens (TAAs). This figure was created and designed by the author using scientific image and illustration software with publication license into journals.

Another trial is evaluating a different mRNA vaccine against HPV-related head and neck cancer. This study will combine the vaccine - BNT113 - with the immune checkpoint inhibitor. The combination therapy of mRNA-4157 and pembrolizumab has advanced to Phase III clinical trials (NCT05933577), after reduced the risk of recurrence or death marking it as the first mRNA cancer vaccine [5].

Moreover, chimeric protein derived from the fusion of the HPV-16 E7 oncoprotein and the herpes simplex virus type 1 glycoprotein D (gDE7), mRNA vaccines induced activation of E7-specific memory $CD8^+$ T cells gDE7 mRNA associated lipid nanoparticle (LNP)-encapsulated self-amplifying mRNA vaccines showed better potential therapeutic to recombinant protein vaccines in experimental comparative studies [8].

2 Discussion

Several potential benefits of mRNA-based vaccine may be mitigating risks in HPV related diseases as cancer anus-genital, head and neck cancer, colorectal tumors, cancer penile and recurring respiratory papillomatosis. VLPs are non–infectious bionanoparticles composed of structural proteins capable of self–assembly in viral capsid mimicking epitopes of antigens presented by tumor cells [1,4]. The production of therapeutic mRNA proteins for development of vaccine cancer have been manufactured by upstream and downstream methods. Several stages are processed in bioreactors using input and output parameters to measure the quality control of purified substance. Thus, novel technologies using different mRNA delivery system can be able to be integrated in clinical trials of HPV16 tumor-derived antigens

associated cervical intraepithelial lesions of different stages until head and neck squamous cell carcinoma, oropharyngeal and cervical cancers.

3 Conclusion

Several mRNA delivery systems as polymer bound mRNA, liposomal formulation, lipoplex (LPX), lipopolyplex (LPP), virus-like particles (VLPs), dendritic cell (DC), and lipid nanoparticles (LNPs) had been documented for cancer immunotherapy using types of RNA expression vectors. So, the biomarkers tumour associated antigens (TAAs) and a personalized mRNA vaccine in combination with an immune checkpoint inhibitors in patients with advanced head and neck cancer, gastric cancer, cervical cancer, colorectal, adenocarcinomas and others are mRNA-based medicines how the potential vaccine of the HPV future.

Compliance with ethical standards

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Disclosure of conflict of interest

No potential conflict of interest relevant to this article was reported.

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