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A Brief Review of Nanoparticles Drug Delivery System Used in Cervical Cancer

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Abstract

Among cervical tumor-related deaths worldwide, cervical cancer is a major cause. The limitations of traditional methods, such as chemotherapy and radiation therapy, stem from their adverse effects and increased susceptibility to medications. Despite being seen as innovative options, immune checkpoint inhibitors (ICIs) have rather low clinical response rates. Reliable treatments for patients with metastatic or recurring cervical cancer are currently lacking. Lately, nanomaterials including polymers, liposomes, and dendrimers have been identified as promising delivery vehicles due to their advantages in lower toxicity, enhanced biocompatibility, and tumor-specific administration. This article explores the applications of nanoparticles in cervical cancer treatment, drug delivery, and genome editing utilizing CRISPR technology. Nanoparticles offer a versatile platform for addressing the challenges associated with cervical cancer therapies. By facilitating the precise delivery of therapeutic agents, nanoparticles can enhance the efficacy of treatments while minimizing off-target effects. These nanocarriers can encapsulate chemotherapeutic drugs, enabling controlled release and reducing systemic toxicity. Additionally, advancements in genome-editing technologies, such as CRISPR-Cas9, when combined with nanoparticle-mediated delivery systems, open new avenues for targeting oncogenes and correcting genetic mutations associated with cervical cancer. Furthermore, functionalized nanoparticles can be engineered to exploit the tumor microenvironment, enhancing their accumulation at the tumor site and improving therapeutic outcomes. This innovative approach holds promise for overcoming current limitations and improving patient prognosis.

Keywords: Cervical cancer, Liposomes, nanoparticle, chemotheraphy, human papillomavirus

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INTRODUCTION

These days, cervical cancer (CC) remains a major medical concern despite early efforts at identification and treatment. A persistent infection of the cervix with "high-risk" genotypes of human papillomavirus (HPV) is one of the leading causes of precancerous cervical lesions.

If the ongoing illness is not identified and treated promptly, invasive CC may result [1]. The promotion of CC may also be influenced by additional variables, such as immunosuppression, parity, smoking, and oral contraceptive use [2]. The fourth most common cause of death worldwide and the most common cancer among females diagnosed across 23 nations is cervical cancer. The projected number of new cases of CC worldwide in 2020 was 604,000. Conversely, 342,000 female deaths were attributed to CC, with

most of these victims being middle-class and lower-class women. Nonetheless, during the past few decades, the incidence and mortality rates associated with CC have declined due to the availability of widespread screening techniques, the improvement of socioeconomic levels in many areas, and the reduction of HPV persistent infection risks among the population [3].

The accumulation of DNA alterations inside host cell genes is a long-term process that leads from HPV-infected epithelial cells to invasive carcinoma. The HPV infection that damages the epithelial barrier and causes basal layer microtrauma is the first step in the human papillomavirus cycle. A greater number of viral copies replicate and express the L1 and L2 core genes when the epithelial cells begin to differentiate, resulting in additional variation that are released from the epithelial layer. For HPV infection to be persistent, the virus must infect basal layer cells that have stem cell-like properties and the ability to proliferate [4]. Oncoproteins from the human papillomavirus, primarily the E5, E6, and E7 genes, integrate viral DNA into the host's DNA, transforming into a malignant form and eventually to the growth of cancer. Through disrupting multiple intracellular signaling pathways, including the breakdown of the tumor suppressor's p53 and pRB, changes in cell cycle regulation, overexpression of p16, driving Sphase reentry in the upper epithelial layers, or apoptosis resistance, these proteins promote cell proliferation and decrease apoptosis. The overexpression of E6/E7 core genes is a crucial factor that affects tumor suppressor genes, particularly those involved in cell cycle regulation [5, 6].

PATHOPHYSIOLOGY

The DNA virus known as HPV is a member of the recently created *Papillomaviridae* family [7]. Papillomavirus leads to the development of tumors in the skin and internal mucosal tissues. HPVs target genital mucosa, causing benign epithelial growth and accounting for 90% of malignant carcinomas in the genital tract. Among the 200 identified HPV types, HPV 16 and 18 are considered "high risk" and contribute significantly to the development of cervical cancer. HPV functions as a vector, either increasing the risk of neoplastic transmission or directly inducing the transformation of certain infected epithelial cells into a malignant phenotype. This process often begins at the squamocolumnar junction of the cervix. In situ carcinoma refers to a condition where all neoplastic cells within the epithelial layers remain confined to the basement membrane.

It typically takes 10–20 years for intraepithelial cancer to progress to an advanced stage. Eighty to ninety percent of cancers have a squamous histology [8]. The primary method of HPV transmission is skin-to-skin contact through mild abrasion or micro-shock of the epidermis. The HPV replication cycle is believed to initiate when the virus infects the basal cells of stratified squamous epithelium, where the replication of HPV DNA occurs [9]. Within the basal layer, viral replication is considered non-productive, as the virus establishes itself as a low copy episome. It utilizes the host's DNA replication machinery to replicate its DNA in differentiated keratinocytes. Subsequently, the virus transitions to a rolling-circle mechanism of DNA replication, amplifying its DNA to a high copy number, synthesizing capsid proteins, and enabling viral assembly [10].

Transmission

Skin-to-skin contact is the main way that HPV is spread. HPV first infects the basal cells of the stratified squamous epithelium. It seems that other cell types are more resilient. The HPV replication cycle begins when the virus enters the basal layer of the epithelium. For HPV to infect the basal layer, there must be a mild abrasion or micro trauma to the epidermis. Viral DNA replicates once it enters the host cell. The virus's reproduction in basal cells is thought to be ineffective. Typically, the virus replicates its DNA once every cell cycle using the host's DNA replication machinery. In the keratinocytes of the epithelium's suprabasal layer, the virus produces many copies of its DNA during replication, and capsid proteins are produced to facilitate viral assembly (Figure 1).

Mechanism

There is extra-chromosomal viral DNA in the nucleus of benign HPV lesions. HPV-DNA enters the host genome during invasive cancers. The loss of expression in the E2 region is caused by breakage or

loss of the area due to viral DNA integration. This results in an increase in the expression of the E6 and E7 genes by interfering with E2, which typically down-regulates the transcription of these genes. During a productive HPV infection, the E6 and E7 proteins facilitate viral replication by interfering with the regulatory mechanisms that control cell growth and modify the cellular environment. These proteins achieve this by binding to and inactivating two tumor suppressor proteins, thereby disrupting the host cell's growth cycle.

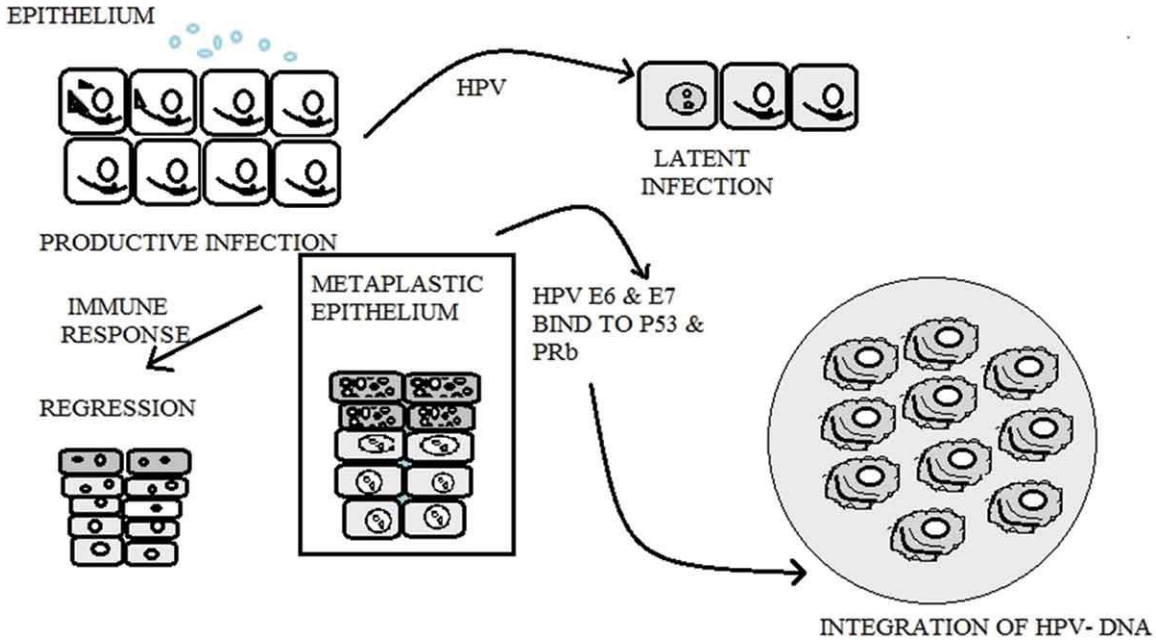

Figure 1. HPV virus productive phase, latent infection phase, regression phase, and integration of virus into host DNA [11].

The retinal tumors gene product (pRb) and the tumor suppressor protein (p53) are examples. After binding to p53, the HPV E6 gene product directs its quick destruction. This results in the disruption of p53's regular functions, which control DNA repair, a process called and G1 arrest.

As seen in Figure 2, low-risk HPV E6 proteins do not bind p53 at amounts that can be detected or affect the stability of p53 in vitro [10].

Nano-Drug Delivery Systems

Drug delivery systems are cutting-edge medication administration methods that focus on organelle locations to reduce systemic toxicity and increase bioavailability. Every drug delivery system is different, with variations in morphology, chemistry, and physical characteristics. Moreover, they are compatible with a range of agent polarities due to specific chemical or physical interactions. Drug delivery methods are both systemic and localized, depending on the mode of administration. Because of this, the systemic drug delivery pathways use nanoparticles with unique surface properties, like dendrimers, liposomes, and micelles, to help identify the intended location. [11, 12].

They are intended to lessen medication concentration shifts inside the body, systemic side effects brought on by their target, and the frequency and dosage of the agent. The coupling of nanocarriers to diverse ligands that have a high affinity for damaged cell locations, including tumor cells, results in the achievement of target specificity. As a result, the drugs or molecules can be built within the structure of the nanoparticles, or they can be established on the outside. Conversely, the medicine's systemic toxicity is limited by the localized delivery channels, which release the drug directly to the tumor location (Figure 3). When treating cervical cancer, the delivery system is positioned either directly on the tumor or close to the cancer site [13, 14].

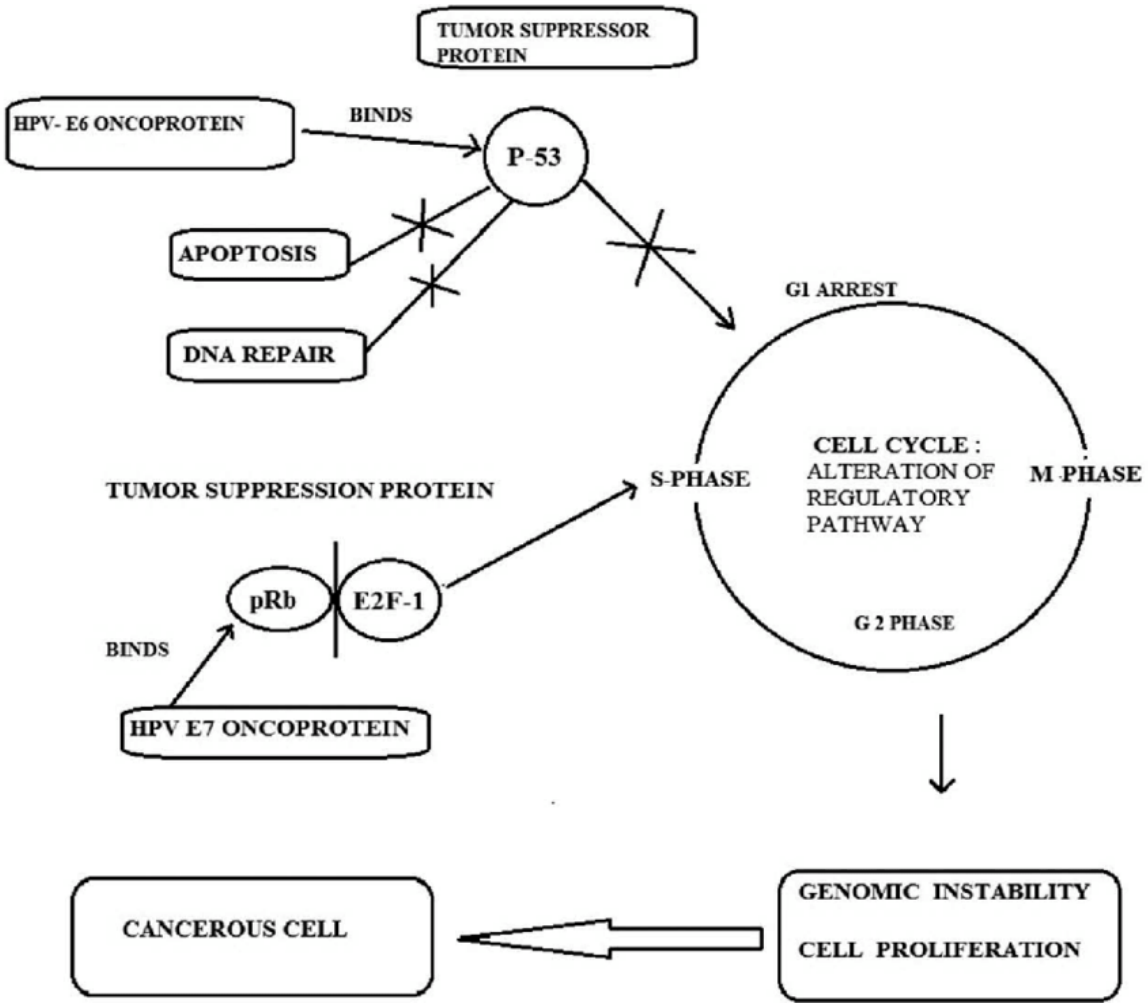

Figure 2. Schematic representation of the molecular mechanisms of oncogenic HPV infection, binding of E6 and E7 on coprotien to the p53 and pRb genes and blocking of apoptosis; G1 arrest which leads to genomic instability and neoplasia [6, 10].

Drug Delivery for Cervical Cancer Via Nanomaterials

The aim of sustained drug release, systemic distribution, and constant absorption efficiency has resulted in a great deal of research into nanocarrier-based delivery systems in recent years as seen in Figure 3, these drug-administration-friendly vehicles fall into several categories, including liposomes, polymers, dendrimers, and inorganic compounds (metallic or nonmetallic).

Liposome-Based Nanoparticle

Amphoteric liposomes' flexible characteristics, such as their zeta potential, particle length, and controlled-release ratio, enable them to get across membrane-mediated barriers for the delivery of chemotherapy medicines. Due to their lipophilicity/hydrophilicity and EPR impact, lipid carriers are superior in terms of enhancing drug penetration and reducing the amount of time required for systemic delivery [15]. As mentioned before, cisplatin is a successful first-line chemotherapy medication for cervical cancer [16].

Developing a liposome- and polylactic-co-glycolic acid (PLGA)-based cisplatin-related carrier using a double emulsion solvent evaporation technique, the drug Avast, an antiangiogenic medication, was also coupled to the lipid system. The 3D cell and tumor tests showed greater cellular uptake potential and stronger binding capability of the L-PLGA-Cis-Avastin combination. An additional group created a type of compound that included CD59, miRNA1284, and cisplatin (CDDP), and then

liposomes were added. In comparison to cisplatin or miR-1284 alone, this co-delivery system notably enhanced the apoptosis rate in cervical cancer cells (60% versus 20% and 12%, respectively). It also showed stronger anticancer effects. Additionally, the clearance rate decreased by eight times while the maintenance of the encapsulated drug in blood circulation showed a 6.9-fold higher than that of the cisplatin group [17].

Polymeric Nanoparticles

PNPs are particles that range in size between 1 to 100 nm [18]. PNPs can be created from polymers, such as polyacrylamide and polyacrylate, and they are classified as nanospheres and small capsules [19]. PNPs were used in the treatment of cervical cancer as chemotherapeutics and antibacterials. Polyethylene glycol (PEG) is used as a stabilizing agent and chitosan-graft-poly (acrylamide) as a reducing agent in the aqueous dispersion of silver nanoparticles. The human cervical HeLa tumor cells treated with the synthesized nanoparticles exhibited significant cytotoxicity, with the 50% inhibitory concentration (IC50) calculated to be 8 μg/mL [20]. Polymer nanoparticles are sustainable structures with excellent preservation against degradation caused by chemicals or enzymes, as well as a high penetration rate and controlled release within cancerous cells. They can encapsulate antibodies, DNA, or RNA, allowing for targeted interactions with different substrates [21].

Dendrimer Conjugates as Nanocarriers

Dendrimers have been the subject of much research due to their unique branching structure that has cavities and a core. This structure allows for the formation of precise molecular structures and high geometric symmetry in nanocarriers. Functional groups abound on the surface of dendrimers, which can be altered by a variety of small-molecule medications or conjugate with small molecules through hydrophobic and electrostatic interactions [22]. A new kind of non-toxic surface coating was created to reduce the cytotoxicity of surface groups on dendrimers. The components of the unique surface were phosphoryl choline hexanamide and 6- hydroxyhexanoyl/oxy-hexanamide. According to Svenningsen et al. (2016), the specifically designed dendrimers significantly reduced the toxicities in cervical cancer cells compared to traditional PAMAM-dendrimers [23].

Inorganic Nanocarriers

Nonmetallic materials like graphene oxide (GO), silica, or carbon, as well as metallic vehicles like gold and copper, can be categorized as inorganic nanocarriers. Many inorganic materials with increased dispersion and more efficient cellular absorption have been employed as gene or medication vectors [24]. However, the properties of poor degradation rates and possible toxicity are also significant issues, and structural modification is required to guarantee safe internal degradation and clearance.

A ring of carbon oxide atoms makes up the single-atomic-layered material class known as GO. GO materials have been applied to many different areas, including cancer vaccination and gene delivery [25]. Primary GO cannot be used for gene delivery due to the challenge of loading dsDNA. This led to the creation of the GO nano-vehicles coated with 1, 2-dioleoyl-3- trimethylammonium-propane (DOTAP) (GOCL), a cationic liposome. GOCL nanocarriers showed suitable physical and chemical properties for DNA payload through investigation of their size and surface charge [26]. Drug reservoirs can also be generated using silica vectors. Recently, Duo et al. used mesoporous silica nanoparticles, or MSNs, to encase CX-5461, an inhibitor that specifically targets RNA polymerase and induces tumor cell autophagy. The MSNs were then loaded with polydopamine (PDA), PEG, and AS-1411. PDA prevented CX-5461 from seeping into the system, PEG enhanced stability and biocompatibility, and AS-1411 accelerated nucleolar aggregation. This nanoplatform's size, potential, and encapsulation were examined without showing any overt harm to the mice's viscera. In Hela xenograft models, reconstructed MSNs-CX-5461 demonstrated improved dispersion and growth inhibition in addition to increased cytotoxicity, as predicted [27].

Multifunctional Nanoparticles

Nanoparticle-based medication delivery has not yet found considerable clinical use. The fundamental reason is that the previously described single nano-platform can only partially address the challenges associated with in vivo drug administration, such as restricted targeting, low biocompatibility, and brief circulation times. Creating multifunctional nanoparticles is one of the most effective strategies to address these challenges. NPs with multiple functions made up of two or more different nanoparticles (NPs) with similar or contrasting compositions have been used in a variety of anti-cancer applications, such as delivering chemotherapy medications, triggering the death of cancer cells, and working in concert with photodynamic therapy (PDT) [28]. Chemothermal therapy is a new approach to treating cervical cancer. A particular type of multifunctional FePt-Fe_3O_4 NPs (CNAs) was created to increase the tumor-killing efficiency. The multifunctional nanoparticles (NPs) had a high loading ability of 90% and were highly water-stable and carboxyl-enriched. In addition to demonstrating a pH-responsive release capacity, CNAs loaded with DOX also demonstrated the ability of alternating current magnetic field to improve drug release. With the aid of hydrogen peroxide in cancer cells and Fe and Pt in the NPs, CNAs were able to create ROS. By utilizing DOX delivery and ROS production, this multifunctional nanoplatform precisely destroyed tumor cells while having no effect on normal cells [29].

Nano-CRISPR System for Cervical Cancer Treatment

The combination of nanoparticles with recently developed genome-editing techniques, such as CRISPR (clustered regularly interspaced short palindromic repeats), has led to success in targeted cervical cancer therapy. The CRISPR system, which is derived from the adaptive immunological response mechanism of bacteria and archaea, includes single-guide RNA (s) and Cas9 endonuclease [30]. Three systems can be used to achieve CRISPR-dependent editing processes: plasmid, mRNA system, and gRNA ribonucleoprotein (RNP) [31]. The most popular RNP technique assists with editing processes by eliminating transcription and translation, but it may also result in endotoxin contamination and decreased delivery efficiency. Although the plasmid method is more cost-effective and stable than the RNP system, plasmid distribution and targeting are still somewhat hampered by its size. While the mRNA system is a solution for reducing the off-target ratio, its inherent instability [32]. Despite the effectiveness of both physical and viral delivery methods in reducing degradation and ensuring accurate targeting, the use of viral vectors has been restricted due to their high immunogenicity, heightened risk of certain cancers, and complex procedures. Conversely, non-viral delivery methods including lipidic and inorganic nano vehicles are gaining a lot of attention [33]. Liposome's can also offer nonviral genome editing platforms. CRISPR has recently been successfully delivered via self-assembled cationic lipid nanoparticles or CL-NPs. This complex showed outstanding efficiency in both tumor-specific targeting and gene knockout, and it was pH-responsive. Because CL- NPs inactivated the E6/E7 genes in vitro, they significantly reduced cell survival in cervical cancer and increased cell death. They also further inhibited the formation of HPV-positive tumors. shown the ability of the lipofectamine-coated CRISPR system to selectively inhibit the development of E7-transformed cells. Additionally, recent research details the first instance of utilizing stealth liposomes to deliver the CRISPR system to a cervical xenografted tumor. confirmed the reach and safety of EGylated lipid carriers in vivo. The PEGylated lipid complex (LCas-E6/E7), measuring an average size of 210 nm with a zeta potential of +45 mV, encapsulated gRNAs and the Cas9 endonuclease. For up to six hours in serum, plasmid DNA could not degrade thanks to PEGylated lipids. By upregulating the expression of activated caspase-3 protein, the LCas-E6/E7 system effectively reduced tumor growth and encouraged cell apoptosis. Furthermore, as demonstrated in Figure 3, stromal cells took the place of the tumor regression remnants, as confirmed by p16 IHC labeling. Therefore, the lipid-CRISPR platforms are useful for in vivo genome editing. But the important things to remember are that CRISPR-Cas9 might result in unfavorable Cancer outcomes including chromosome abnormalities and nontarget genomic cleavages in humans [33].

Immunotherapy and Cervical Cancer

Immunotherapy stimulates and develops the body's immune system using immunological concepts and techniques. Immunotherapy can improve the immune system's capacity to identify, fight, and

eliminate malignant cells, which will stop the growth of tumors. In Figure 3, the mechanisms behind adoptive cell therapy and therapeutic vaccinations are displayed. The E6 and E7 viral cancer-causing proteins, which are constantly produced by HPV-infected host cells, are the ideal antigens for cervical cancer therapeutic vaccines. Antigen-present cells (APCs) may absorb infections and display harmful peptides on their surfaces after being exposed to costimulatory molecules. The major histocompatibility complex (MHC) can then identify these peptides on APCs' surfaces. Live-vector vaccines are very immunogenic. Samples of these include the bacterial vectors Lactobacillus plantarum, Lactobacillus monocytogenes (Lm), Lactococcus lactis, and Lactobacillus casei [34].

The following features of peptide/protein-based vaccines are present: ease of manufacture, good safety profiles, and stability in storage. According to phase II clinical trials, the SGN-00101 vaccine, which combines Mycobacterium bovis heat shock protein and HPV 16 E7, can cause grade II and III cervical intraepithelial neoplasia to decrease. Protein-based vaccinations, as opposed to peptide-based vaccinations, contain all antigens regions of E6 and E7, which are not bound by MHC class I restrictions. But in vivo stability and immunogenicity are low for both vaccinations. To improve their immune-boosting effectiveness, lipids or other adjuvants ought to be added [34].

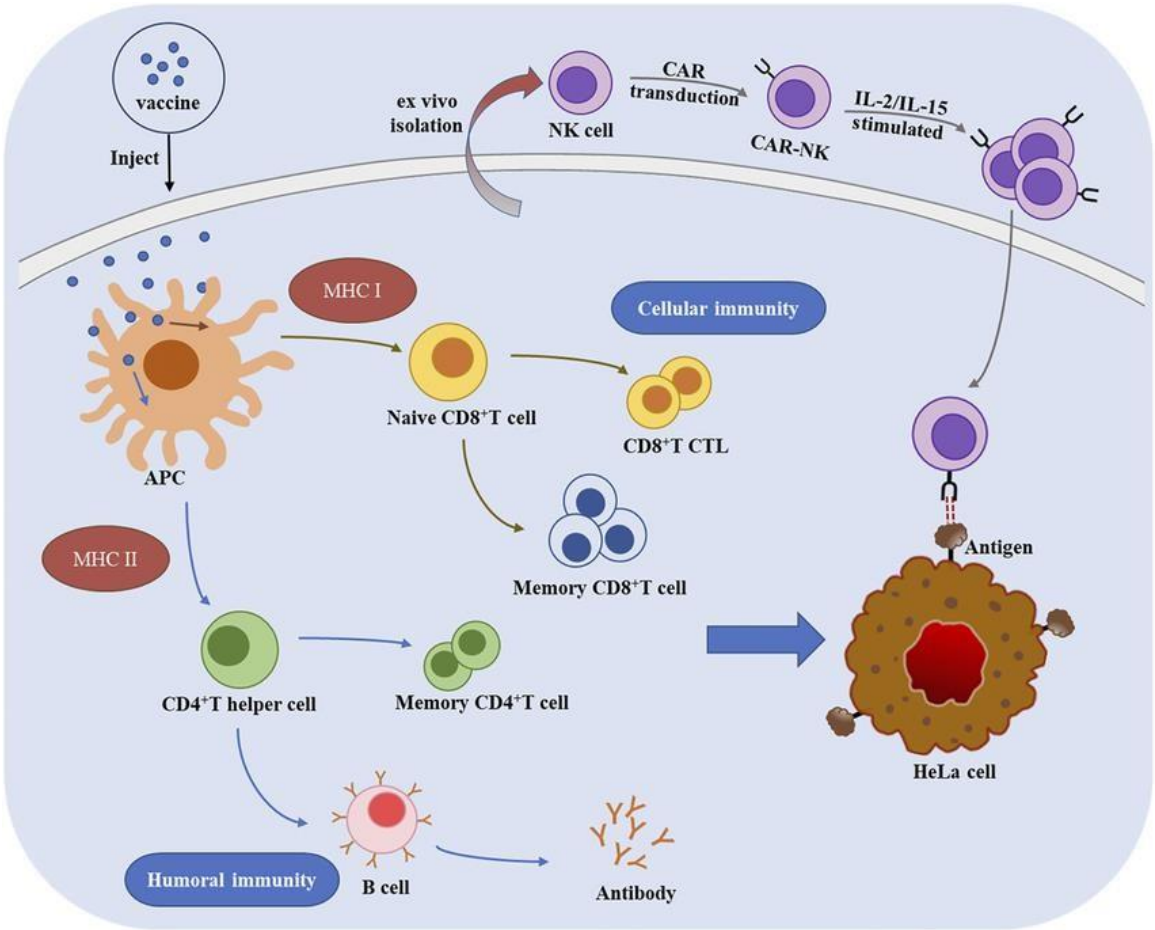

Figure 3. The mechanisms of therapeutic vaccines and adoptive cell therapy for cervical cancer [34].

Chemotherapy of Anticancer Drug Effective Cervical Cancer

Several studies have demonstrated how NPs increase the activity of well-known anticancer medications and natural products as well as their in vitro efficiency against cervical cancer cell lines. Nonetheless, there are still few in vivo investigations on these NPs' efficacy. The antibacterial, anti-inflammatory, and anticancer properties of silver nanoparticles have been demonstrated, as shown by Al-Sheddi and colleagues. aqueous extracts of the plant *Nepeta deflersiana* were used to create silver

nanoparticles (NPs), which were then shown to have anticancer activity in HeLa cells by promoting ROS, lipid peroxidation, and subG1 cell cycle arrest. Yuan and colleagues investigated the combined effects of silver nanoparticles and camptothecin, a topoisomerase inhibitor with strong anticancer action, on HeLa cells that had been cultivated for cervical cancer. This combination changed the permeability of the mitochondrial membrane, increased the production of ROS, and activated caspases 9, 6, and 3 to help treat cervical cancer. Therefore, combining NPs with anticancer drugs is an option in the field of cancer research. As for other nanomaterials, Luo and others synthesized biotin-modified polylactic-co-glycolic acid NPs and showed that they could enhance the antiproliferative effects of 15, 16dihydrotanshinone I in HeLa cells by reducing the formation of intracellular ROS. Transferrin is a commonly utilized drug that targets cancer cells because cancer cells overexpress the transferrin receptor compared to normal cells. Boondireke and his partners. enhanced the cytotoxicity of saw palmetto palm monomyristin, a monoacylglycerol, in HeLa cells by encasing it in polylactide nanoparticles coated in dextran and linked to transferrin. Encapsulation and transferrin receptor targeting worked in concert to increase monomyristin's water solubility and anticancer activity. The use of cisplatin (also known as CDDP), an effective anticancer medication, has been restricted due to its lack of selectivity for cervical cancer tissue. Thus, through tumoral acidic pH responses, Cheng and coworkers added CDDP to fluorescein PEG amine grafted-aldehyde HA (Cy5.5-PEG-g-A-HA) NPs to boost their selectivity for cervical cancer. Even though HA is a targeting agent in nanocarriers, a significant portion of it may accumulate and be quickly removed from the liver. This problem appears to have been lessened using aldehyde HA (A-HA) in this investigation.

A recent work described the creation of a folic acid-decorated pH-sensitive lipid polymer conjugate NP surface for the targeted administration of carboplatin and paclitaxel to cervical malignancy. By means of pH-responsive drug release and receptor recognition, the dual functionalized nanoparticles led to increased cellular uptake of the loaded medicines in cervical cancer cells as well as tumor inhibition. In contrast, a different recent work described the use of multifunctional, layer-by-layer controlled, released mesoporous $CaCO_3$ nanoparticles (NPs) to deliver doxorubicin to cervical cancer cells. Chitosan and sodium alginate were used as substitute materials, folic acid was used as a ligand to target cancer cells, and layer-by-layer construction was used as a pH-responsive method to create the intelligent NPs.

THERAPEUTIC VACCINES FOR CERVICAL CANCER NANOPARTICLES-BASED THERAPY

Components of Therapeutic Cancer Vaccines

Although cervical cancer preventative vaccines are frequently administered, pre-existing tumor cells cannot be eradicated by them. Consequently, the development of a therapeutic vaccination to prevent cervical cancer is important. Not like therapeutic cancer vaccines, which transport tumor-specific antigens to the lymphatic system and activate antigen-presenting cells, are intended to elicit strong and long-lasting immune responses. Prophylactic vaccinations generate antibodies that protect against diseases. Therapeutic cancer vaccines generally consist of four essential elements: delivery vehicles, adjuvants, different formulations, and cancer antigens. It is most likely imperative to identify tumor antigens, which can be further divided into tumor-specific and tumor-associated antigens.

Nanocarriers in Therapeutic Vaccines of Cervical Cancer

There are several types of therapeutic vaccines against HPV antigens, including bacterial or viral vectors, proteins and polypeptides, dendritic cell types (DCs), and adoptive cells. When it comes to cervical cancer, the DNA therapeutic vaccine has received the most research. According to a phase IIb study, VGX-3100, the first DNA vaccine that targets both the E6 and E7 fragments of HPV16/18, can treat women with cervical intraepithelial neoplasia 2/3 (CIN2/3). The ratio of histopathological regression increased by almost 19% in VGX-3100 compared to a placebo. Treatments and nanoscale carriers have been trying to improve the cytotoxicity of therapeutic vaccinations against cervical

cancer to get around the aforementioned challenges. Adjuvant CpG/GPI- 0100 in conjunction with TVGV-1 (an exotoxin-based vaccine based on pseudomonas and HPV16 E7), for example, may induce strong immunoreactions. IFNc was secreted by CpG-TVGV-1 conjugates, which also improved high immunogenicity. The poor absorption and fundamental instability in vivo of mRNA vaccines have caused them to lag the development of DNA vaccines. mRNA vaccines have demonstrated remarkable forefront for treatment with the development of novel delivery materials like cationic liposomes and improved methods of preparation. The mRNA vaccines have several clear advantages over other vaccinations, such as cost-effective manufacture, numerous tumor antigens encoding simultaneously, low vector-related immunogenicity, and genomic nonintegrating. The fact that mRNA therapeutic vaccines have just recently shown promise in a phase I clinical trial is especially remarkable.

CONCLUSION AND FUTURE PERSPECTIVE

There is an urgent need for the development of targeted treatments for cervical cancer that are specific to tumor types and have minimal side effects. While nanocarriers, such as liposomes, polymers, dendrimers, and inorganic materials have shown significant potential for clinical application, it is nearly impossible for one type of nanoparticle to overcome all challenges, including dose-dependent toxicity, drug biocompatibility, and controlled release in vivo drug delivery. Therefore, developing the best multifunctional materials could be a viable option for the efficient delivery of chemotherapy drugs that exactly target the cervical cancer apoptotic pathway to either cause cell death or prevent cell proliferation. Given the critical role that radiation plays in the treatment of cervical cancer, it is clinically significant to create a nanoparticle-based radiosensitizer soon that is paired with either newly discovered tumor neo-antigens or HPV antigens. Lipidic nanocarriers' efficacy in the CRISPRE6/E7 editing system has been successfully validated in a mouse model; the next steps will be to determine whether the technology is as safe and effective in patients with cervical cancer as it is in those with lung cancer. Therapeutic DNA vaccines that target HPV E6/E7 are effective in treating precancers, but they are not able to treat cervical cancer that has already progressed to a clinical stage. Considering this, stronger mRNA vaccines should be developed because their shortcomings – such as single-stranded instability and ineffective delivery – have been addressed by improved production processes and suitable nanocarriers.

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