Nano-Drug Delivery Systems in Oral Cancer Therapy

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Oral cancer (OC), characterized by malignant tumors in the mouth, is one of the most prevalent malignancies worldwide. Chemotherapy is a commonly used treatment for OC; however, it often leads to severe side effects on human bodies. Nanotechnology has emerged as a promising solution for managing OC using nanomaterials and nanoparticles (NPs). Nano-drug delivery systems (nano-DDSs) that employ various NPs as nanocarriers have been extensively developed to enhance current OC therapies by achieving controlled drug release and targeted drug delivery.

Keywords: oral cancer ; nanomaterial ; nanoparticle ; nano-drug delivery system ; targeting

1. Introduction

Oral cancer (OC), explicitly affecting the oral cavity and oropharynx, is classified as a subtype of head and neck cancer. It is characterized by the presence of malignant tumors in various tissues, including the lips, tongue, palate, floor of the mouth, hypopharynx, oropharynx, larynx, alveolar mucosa, buccal mucosa, gingiva, or a combination of these [1][2][3][4][5][6]. The most frequently occurring OC cases are lip and oral cavity cancers. Oral squamous cell carcinoma (OSCC) is the predominant type of OC, accounting for 90% of OC cases and ranking among the 15 most common cancers worldwide. OSCC is highly dangerous, with a high morbidity rate, malignancy, and poor prognosis. Treating OSCC is challenging due to its high recurrence rate and tendency for lymph node metastasis [3].

Excessive alcohol and tobacco use, biological factors such as human papillomavirus (HPV), syphilis, oro-dental factors, betel chewing, nutritional deficits, and viruses are potential risk factors for OC. Patients with OC may experience early symptoms such as non-healing ulcers, intraoral bleeding, leukoplakia, erythroplakia, oral submucous fibrosis, and abnormal lumps in the mouth [4]. However, during the early stages of OC, many patients may not experience noticeable symptoms or signs of deterioration. This can lead to a delayed diagnosis and, in some cases, may result in the cancer progressing to an advanced, incurable stage, ultimately leading to increased medical expenses for the patient [5][6]. Globally, the survival rates for OC patients over five years range from 45% to 72% [1][2]. The survival rates gradually decrease with the delay of disease detection, with the five-year survival rate approaching 80% when OC is detected at an early stage but dropping to less than 20% when it is diagnosed at a late stage [7].

For several decades, the primary treatments for OC have been surgery, chemotherapy, radiation therapy (RT), and combination therapy. However, these treatments often have severe side effects and toxicity [8][9][10]. OC surgery can result in impairment or changes in breathing, swallowing, speaking, and other functions due to the removal of some oral tissues. It can also cause pain, swelling, bruising, xerostomia, infection, and bumps or scars on the face or neck [11]. RT can lead to side effects, such as oral mucosal inflammation, hypofunction of salivary glands, dysphagia, oral infections, nausea, vomiting, and skin reaction [12]. Chemotherapy involves the use of highly toxic drugs like cisplatin (CDDP), paclitaxel (PTX), 5-fluorouracil (5-FU), doxorubicin (DOX), methotrexate, cetuximab, and docetaxel (DTX), which can cause ulcers, mucositis, xerostomia, and damage to the skin, hair, blood, and kidneys [13][14][15][16][17][18][19]. Although low-toxic therapies, such as light stimulus-responsive therapies, including photodynamic therapy (PDT) and photothermal therapy (PTT) [20][21], as well as immunotherapy [22][23], have been studied for OC treatment, they have not been mature in clinical practice.

The clinical manifestations and treatment effects on OC patients can cause severe impacts on their lives, including adverse psychosocial effects from various aspects, the decline and loss of aesthetic and oral function, and the ensuing physical changes. Moreover, the economic cost of cancer treatment can increase the burden of OC patients and significantly impact their quality of life [24]. Therefore, there is an urgent need for innovative therapeutic strategies that prioritize bioavailability and precise drug delivery while minimizing harm to healthy cells or tissues [25].

In recent years, nanotechnology has played a crucial role in this regard. Various nanoparticles (NPs) have been developed to detect, diagnose, and treat OC [26][27] while minimizing damage to healthy cells during treatment [1][28][29][30].

Nanomaterials have emerged as vital tools in the development of new and effective therapies for OC [29] since they can be directly used as antitumor drugs [3][31][32][33][34][35][36][37] or utilized to form nano-drug delivery systems (nano-DDSs) for the administration of antitumor drugs.

DDSs are commonly used to address issues such as low solubility, poor absorption, poor permeability, inappropriate size, instability, and first-pass metabolism of chemotherapy drugs. Conventional DDSs like oral tablets, capsules, and injections, have been widely used in clinical settings to control drug release and ensure targeted delivery, resulting in improved pharmacokinetics, sustained bioavailability, and enhanced distribution at the primary tumor site [1][5][38][39][40]. In addition, the manufacturing process for conventional DDSs is well-established and cost-effective. However, many conventional DDSs lack the ability to specifically target diseased cells or tissues, leading to potential off-target effects and low accumulation at the desired sites. Individual differences in absorption and metabolism can also affect the bioavailability of drugs in conventional DDSs, resulting in inconsistent treatment outcomes. Additionally, the poor solubility of certain drugs poses challenges in formulating them into effective conventional DDSs. In contrast, nano-DDSs offer various advantages over conventional DDSs. They can be designed to target specific cells or tissues, increase drug delivery efficiency, minimize off-target effects, and can also improve the solubility of poorly water-soluble drugs, enabling the delivery of a wider range of therapeutic compounds [30][41][42]. In addition, due to the high permeability of micro-vessels in tumor tissues and the poor lymphatic drainage, NPs can take advantage of the enhanced permeability and retention (EPR) effects, swiftly entering tumor tissues and accumulating at tumor sites, allowing for sustained and controlled release [43]. Despite their benefits, some nanomaterials used in nano-DDSs may have toxicity issues, and their effective clearance and biodegradation in the body may present challenges, potentially leading to long-term accumulation and effects. Therefore, a comprehensive safety assessment is required. Furthermore, the manufacturing and scaling of nano-DDSs are technically challenging and require specialized equipment and expertise. So far, many NPs have been utilized as carriers for antitumor chemotherapy drugs and other therapeutic agents.

Targeted nano-drug delivery systems (nano-DDS) is a technology that allows drugs to be delivered precisely to the targeted organs, cells, or molecules [44], thereby safeguarding healthy cells and minimizing the side effects of loaded drugs, making it a practical approach for treating OC. Targeted drug delivery can be categorized as passive, active, immune, and magnetic targeting based on the targeting methods.

2. Passive Targeting

Passive targeting relies on the EPR effect of tumor tissue. The neovascularization in tumor tissue allows small-diameter nanocarriers to easily pass through the blood vessel wall and reach the tumor tissue with higher permeability compared to normal tissue. Nanocarriers are modified and assembled with drugs to increase their stability in plasma and extend their circulation time in the blood. This increases the chances of the nanocarriers aggregating in tumor tissues. The drugs are then delivered to the tumor cells through extracellular diffusion, which enhances the distribution and retention time of the drugs [44].

To achieve a better EPR effect, the nano-DDS must maintain stability in plasma without leakage and have a long blood circulation time to increase the chance of aggregation in tumor tissues [45] while also being able to penetrate deeply into the tumor. However, achieving long blood circulation and deep penetration into the tumor can be challenging, as these requirements may contradict each other. To achieve long circulation in the blood, the nano-DDS must possess a slightly larger particle size (such as 50~200 nm, preferably ca. 100 nm) [46] with a hydrophilic modification on the surface and be negatively charged [47]. On the other hand, for optimal uptake by tumor cells and deep penetration into the tumor tissue, nano-DDS should have a smaller size (such as <50 nm) and a positively charged surface after diffusion from capillaries to the tumor site [48]. In addition, the shape of the nano-DDS also plays a role in enhancing the EPR effect. By rationally designing the nano-DDS through size variation [49][50], shape modification [51], surface charge reversion [52], and other factors, the EPR effect can be improved.

3. Active Targeting

For active targeting, the surface of nanocarriers is typically modified with specific ligands, such as aptamers, peptide chains, and antibodies. By recognizing and binding to receptors on tumor cells and in the tumor microenvironment (TME), the nanocarriers deliver drugs to the intended sites, effectively enhancing the precision and efficacy of drugs and minimizing toxic side effects of drugs on normal tissues [44][53][54].

In targeted tumor therapy for OC, various sites such as tumor vessels, interstitial fluid and extracellular matrix, tumor matrix cells, tumor cells, related dendritic synaptic cells, and tumor stem cells can be targeted using nano-DDSs [28].

Depending on the characteristics of the tumors, different target sites can be selected in clinical treatment and nanocarriers can be modified accordingly. The identified overexpressed receptors in OC cells are listed in **Table 1**.

Table 1. Summary of ligands and targeted receptors overexpressed in OC cells.

Ligand	Target Receptor	Ref.
Folic acid (FA)	**FA receptor**	[55][56][57][58][59][60][61]
Protein corona-modulating Tf2 peptide	**Transferrin receptor (TfR)**	[62]
HN-1, a 12-amino acid peptide	**HN-1 receptor**	[63][64]
Anti Programmed death-ligand 1 (PD-L1) antibody	**PD-L1**	[65][66]
α-tocopherol	**α-tocopherol receptor**	[67]
Fucoidan	**Scavenger-A receptors (SR-A), L-selectin, Toll-like receptors, and PD-L1**	[68]
Antibodies specific for matrix metalloproteinase-1 (MMP-1)	**MMP-1**	[69]
pH-sensitive H-peptide	**Epidermal growth factor receptor (EGFR)**	[70]
Anti-Her-2 (human epidermal growth factor receptor 2) nanobody	**Her-2**	[71]
Dental pulp mesenchymal stem cell (DPSC), which expresses the CXCL8 binding receptor, CXCR2	**Chemokine CXCL8**	[72]
Chemokine SDF-1	**CXC chemokine receptor 4 (CXCR4)**	[73]
Shiga Toxin-B	**Globotriaosylceramide receptor (GB3)**	[74]
Fibroblast activation protein (FAP)-targeted peptide chains	**FAP**	[75]
AE105 (H-Asp-Cha-Phe-(d)Ser-(d)Arg-Tyr-Leu-Trp-SerOH) peptide	**Urokinase plasminogen activator receptor (uPAR)**	[76]

4. Immune Targeting

Cancer cells have developed various strategies to evade the immune system, such as reducing the expression of cell surface antigens, secreting antigens that inactivate the immune system, and stimulating the TME to release immune-suppressing chemicals that promote tumor growth. Cancer immune targeting is a treatment method that aims to activate the host's immune system using foreign materials, including both active and passive immunity approaches. Active immunotherapy involves stimulating the production of antibodies that specifically target and eliminate tumor cells by administering vaccines containing tumor antigens into the patient's body. On the other hand, passive immunity involves using highly specific antibodies as carriers to introduce foreign substances with antitumor effects into the body. These antibodies target specific receptors on the surface of tumor cells, thereby enhancing the immune response. Nano-DDSs offer a promising approach in the field of OC immunotherapy, directly targeting cancer cells and helping facilitate the intracellular penetration of therapeutic agents, potentially minimizing autoimmune side effects and reducing treatment costs [77][78][79].

5. Magnetic Targeting

Magnetic NPs are inorganic materials that can be easily manipulated using external magnetic field gradients, allowing for precise targeting of desired sites [80][81]. Magnetic targeting is a technique used in cancer therapy where magnetic NPs are delivered to tumor cells and concentrated in the lesion area using external magnets. This method enhances the effectiveness of chemotherapy drugs that are administered along with magnetic NPs. Furthermore, magnetic NPs also possess magnetic hyperthermia properties, which can be utilized in an alternating magnetic field (AMF) to kill tumor cells.

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