Nanomaterials for Head/Neck Cancers

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Early diagnosis of head and neck cancer (HNC) is a significant clinical concern and, due to a lack of signs, just one-third of HNC patients are diagnosed at an early stage. Functional nanomaterials are appearing as versatile systems in nanomedicine, particularly in the field of biomedical imaging and treatment. Various surface chemistries, peculiar magnetic properties, tunable excitation and fluorescence properties, and recent developments in the design and synthesis of different nanoparticles indicate their high potential.

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1. Introduction

It houses and protects important sense organs such as eyes, nose, ears, tongue, and related structures [1]. Besides the regular arrangement of different components between the head and neck, diseases produced in these vital structures and organs may threaten the health of a person [2]. Head and neck cancer (HNC) comprises a group of various malignant tumors that grow in the throat, larynx, mouth, sinuses, and nose [3]. HNC squamous cell carcinomas (HNSCCs), which arise from the mucosal surfaces of the oral cavity, oropharynx, and larynx, include 90% of head and neck cancers cases [4].

Traditionally, tumors are classified by stage and anatomic site of origin. Within the head and neck, these sites are classified based on established anatomic parameters. Beyond the upper aerodigestive tract, the paranasal sinuses, skull base, salivary glands, endocrine glands, skin, ear, and temporal bones are other possible sites where primary HNSCCs may arise. While HNSCC has traditionally been categorized by its anatomic site of occurrence, other factors may also be important in determining prognosis.

It was reported that consumption of alcohol and tobacco can increase the risk of this type of cancer by up to 80% [5]. Due to this, India, Bangladesh, and Pakistan are among the highest-risk countries. In the northern regions of America and Europe, HNSCCs include 5–10% of all new cancer cases. In the United States, 53,600 patients are diagnosed yearly and 11,500 deaths are recorded annually as associated with these types of cancer [6][7].

Most of HNCs can be developed in the flat squamous cells that create a thin layer of tissue on the surface of the head and neck. So, the main methods for the treatment of HNC are surgery, radiation, chemotherapy, and antibody-blocking therapy [8][9][10]. Surgical methods are the standard route for patients diagnosed with early-stage disease. The majority of patients, however, face advanced-stage disease that precludes surgery.

It is important to determine the stage of cancer and the resectability of the tumors for a better treatment approach. In many clinical outcome studies, stage remains one of the only valuable prognostic parameters. Intermediate-stage tumors, i.e., infiltrative tumors, poor-prognosis T2 tumors, or exophytic T3 N0–N1 tumors, may benefit from a combined-modality approach. Patients with locally advanced tumors are best treated with concurrent chemoradiation if the tumor is unresectable, or if it is resectable but organ preservation is desired, or else if patients are receiving postoperative adjuvant radiation with concurrent cisplatin [11][12].

The molecular structures (receptors) and genetic change (biomarkers) that happen in head and neck cancer have allowed the detection of candidate routes for effective “targeted” approaches to therapy. Advances in the understanding of the molecular basis of HNC should help in the identification of new markers that could be used for the diagnosis, prognosis and treatment of the disease. Cancer is a genetic disease but does not imply inheritance; rather, the agents that bring about malignant transformation of a cell in the foundational step of tumorigenesis do so by inducing change in the tumor DNA. This may be by alteration in the base sequence (through mutation, deletion, insertion, or rearrangement), change in copy number of a chromosomal segment (through duplication, larger segment deletion, and loss of heterozygosity), alterations in the level at which a gene is transcribed through rearrangements that bring the gene into new association with promoter regions, or through epigenetic events including (hypermethylation of promoter regions) that block expression of mRNA into protein [13][14].

Multiple signaling pathways involved in the invasion process are influenced by genetic alterations in the development of head and neck cancer. Conventionally available methods for HNC treatment suffer some major restrictions. The mainstays of medical imaging for detection of HNC patients are magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET). Furthermore, interpretation of imaging results can be complicated by difficult anatomy, edema or inflammation, scarring from prior treatment, and loss of detail changes because of patient’s movement [15].

Nanotechnology is expected to develop a wide range of instruments for detection and treatment of sickness in medicine [16][17][18][19][20][21]. Nanostructures with small particle size distributions are well applied to interact with biological molecules and diverse structures developed inside living cells [22][23][24][25]. The capacity to effectively control the nanosized nature of surface chemistry allows interacting at molecular levels [1displays the application of some nanostructured devices for the detection and treatment of HNC.

Nanoporous materials also have appealing properties, including uniform pore morphology, high surface area, and small particle size distribution, and have been applied in different areas, such as medical applications [26][27][28][29][30]. Just to provide some examples, magnetic nanostructures were widely utilized due to their unique features such as magnetic susceptibility and stability. Li et al. developed methotrexate-conjugated and hyperbranched polyglycerol-grafted Fe3O4magnetic nanoparticles for targeted anticancer effects in HNC. used fibrous nanostructures with high physicochemical properties for cancer detection and treatment by local anticancer therapy.

2. Metallic and Metal Oxide Nanoparticles

Different metallic and metal oxide nanoparticles with a size of 1–100 nm have emerged as potential “weapons” for treating HNC, including cerium oxide, gadolinium, gold, iron oxide, and silver, which are synthetized mainly for amplifying radiation effects [31][32][33] due to their high X-ray absorption and ability to emit secondary energy in form of photoelectrons, auger electrons, and X-rays into the surrounding tissue [34][35][36][37]. Moreover, metallic and metal oxide nanoparticles provide a versatile platform for surface modification through covalent bonds, complexation, or coupling to the capping agents [38][39][40][41].

Gold (Au) nanoparticles exhibit two main mechanisms for treating HNC: photothermal therapies of malignant tumors and radiosensitization of the cancer cells [42], based on their unique physicochemical properties, including biocompatibility, preferential accumulation in tumors, photostability, photothermal conversion, and optical and multifunctionalization features [43].

Photothermal ablation is a mechanism for treating malignant tumors by using a photothermal agent to produce an intense and highly localized hyperthermic effect [44]. Au NPs exhibit unique surface plasmon resonance (SPR) properties, in which gold electrons resonate in response to incoming radiation, promoting the absorption and light scattering to obtain localized heating [33]. This efficient conversion of light is achieved at the near-infrared (NIR) wavelength range, 700–1000 nm, and is suitable because the electron–photon interaction at this wavelength presents low scattering and low absorption by blood and soft tissues [45][46]. It is worth highlighting that gold nanorods or gold nanostars are more convenient for photothermal therapies based on their higher efficiency in the absorption of near-infrared light [47].

On the other hand, Au NPs are very attractive radiosensitizers that intensify the radiation dosage through a strong X-ray absorption followed by the emission of secondary electrons [48] which stimulates the radiolysis of intracellular water, a high production of free radicals, a radiation-induced reactive oxygen species (ROS) generation, oxidative stress, DNA damage, and interferences in the cell cycle that are associated with increased necrotic and apoptotic cell death [49][50], triggering cytotoxic effects in tumoral cells [42].

In addition, Au NPs can be coated with targeting ligands and surface-engineered with anticancer drugs for combining radiotherapy with chemotherapy [51], in order to improve the outcomes through a synergistic effect in which the nanoparticles act simultaneously as a radiosensitizer and as a targeted carrier of chemotherapeutic agents [34].

Gadolinium (Gd) is a lanthanide whose potential radioenhancing properties have been widely explored, despite the fact that, unlike other metallic nanoparticles, Gd NPs are not metal-core particles, thus they typically refer to Gd chelates or Gd-based nanoparticles [52]. Therefore, Gd chelates or Gd-based nanoparticles are used for enhancing radiation dose during radiotherapy by inducing the activation of an autophagy pathway when the tumoral cells are exposed to X-rays, which improves the effectiveness of radiotherapy while reducing collateral damage [53]. In the same way, the radiosensitizing properties of Gd NPs stimulate photocytotoxic effects through the production of extra ROS and water radiolysis products [54]. Furthermore, Gd NPs exhibit some advantages during HNC

treatments such as low toxicity, enabled renal elimination, and preferential uptake in tumors through an EPR effect [31].

Iron oxide (Fe3O4) nanoparticles have been approved by FDA as a photothermal agent for application in cancer treatments due to their broad absorption in the near-infrared (NIR) range [55]. Moreover, superparamagnetic Fe3O4NPs can exhibit magnetic hyperthermia by converting an external high-frequency field energy into thermal energy, which produces thermal ablation when the temperature raises over 50 °C to cause irreversible cell damage, inhibition of tumor growth, and necrosis of tumoral cells in HNC [56][57]. Nonetheless, Fe3O4NPs are easily recognized by the innate immune system as invaders, so they are rapidly cleared from the systemic circulation by the reticuloendothelial system (RES) [58]. Another main problem during cancer treatments is the low targeting properties of superparamagnetic Fe3O4NPs, which results in lower efficacy and greater side effects [59].

Different types of coating and surface functionalization have been studied for countering the rapid clearance of Fe3O4NPs and for stimulating their accumulation in cancer cells through the EPR effect [60]. The novel approaches for coating magnetic Fe3O4NPs include cell-membrane coating and anti-CD44 antibodies, both with the purpose of targeting the overexpressed CD44 receptors in cancer stem cells and the evasion of immune system [55][59] to their specific cell killing potential without damaging the surrounding healthy tissue [56].

In addition, magnetic drug targeting has been explored for guiding and inducing the accumulation of superparamagnetic Fe3O4NPs into a specific site (commonly tumors) by strong external magnetic field gradient [61] [56]. This approach is mainly used when superparamagnetic Fe3O4NPs are employed as nanocarriers by functionalizing their surface for delivering chemotherapeutic agents in order to increase the efficacy of cancer treatments [60]. However, superparamagnetic iron oxide NPs can also be crosslinked with different polymeric matrixes, such as cellulose nanocrystals, to form hierarchically organized networks similar to “nanocages” with the objective of capturing circulating tumor cells in the blood during HNC treatments [62].

Silver (Ag) nanoparticles have demonstrated some antiproliferative properties against cancer cells by inducing cellular cytotoxicity in cancer cells through different mechanisms such as generating ROS and free radicals, genomic instability, DNA fragmentation, disruption of calcium (Ca2+) homeostasis, cytoskeletal weakening, damage of intracellular organelles, and interruption of some intracellular signal transduction pathways, which results in cancer cell apoptosis [63][64]. Therefore, Ag NPs show great potential for new therapeutic approaches by improving the sensitivity of current therapies [65]. Ag NPs can even act as cell sensitizers for photothermal therapy, whereas they provide different alternatives for delivery of chemotherapeutic drugs through their surface functionalization and conjugation in a clearly synergistic effect which can enhance the efficacy of the treatment [44]. Recent studies have demonstrated that Ag NPs ingestion is safe and could be associated with a complete and sustained regression of HNC, including metastases to other organs such as the liver or the lungs [66].

Cerium oxide (CeO2) nanoparticles have attracted a special interest due to their dual radioenhancing and radioprotective properties based on their redox-modulatory activities, which are related to an antioxidant/pro-oxidant reversal property that is useful for sensitizing cancer cells and protecting normal cells from ROS during

radiation therapy [52][67]. conditions, CeO2NPs adopt an enzymatic defense mechanism similar to superoxide dismutase, catalase, peroxidase, and oxidase activities [68], in which CeO2NPs mimic superoxide dismutase activity by converting Ce3+to Ce4+and diminishing the levels of superoxide and free radicals such as nitric oxide, hydroxyl, and hydrogen peroxide [69], followed by catalase activity stimulated by the reconversion of Ce4+into Ce3+, in which the hydrogen peroxide is decomposed into water and hydrogen molecules [70]. Otherwise, the antioxidant activity of CeO2NPs is significantly reduced at low pH, suggesting that under acidic environments of highly glycolytic tumors their catalase activity is reduced, inducing oxidative stress and cytotoxicity in cancer cells that results in apoptosis of cancer cells and inhibition of tumor metastasis [71].

3. Polymeric Nanoparticles

Polymeric nanoparticles are colloidal particles with a mean diameter between 100 and 300 nm that are prepared with biocompatible polymers for controlled and targeted transport of drugs [72][73]. They represent a great and versatile platform for improving HNC therapy due to their high encapsulation efficiency of hydrophobic anticancer drugs, which usually exhibit poor pharmacokinetics and inappropriate biodistribution [74]. Furthermore, polymeric nanoparticles promote the accumulation of encapsulated drugs inside tumor tissues through the EPR effect [75][76] with a subsequent controlled release to increase its antitumoral efficacy [77][78]. In the same way, polymeric nanoparticles can be loaded with radiosensitizing drugs for countering radiotherapy resistance and reducing side effects [79].

Additionally, polymeric nanoparticles allow the delivery of a combination of therapeutic agents with a reduced intensity of side effects. The surface of polymeric nanoparticles can be modified for triggering an efficient cell-membrane penetration and cellular internalization in the acidic environment of tumoral cells, as compared to the neutral pH of healthy cells [80].

Otherwise, polymeric nanoparticles are divided into nanocapsules and nanospheres, based on their morphology. A nanocapsule refers to a polymeric shell that surrounds an aqueous or oily core in which the active compound is confined (usually dissolved), whereas nanospheres are a polymeric network in which the active compound and the polymer are uniformly dispersed [73][81].

Natural (e.g., chitosan and hyaluronic acid) and synthetic (e.g., poly(lactide-co-glycolide) and polyethylene glycol) polymers have been studied for administering chemotherapeutic drugs and radiosensitizers based on their biocompatibility and biodegradability [38][72]. After drug release, the polymeric matrix is usually degraded into innocuous molecules such as water and hydrogen-

However, natural polymeric systems present variability between batches, irregular release kinetics, and mild immunogenicity, which sometimes restrict their use as vehicles for anticancer molecules [38] in comparison with synthetic polymers that offer the additional advantages of high purity, reproducibility, and well-known chemical composition [82].

Chitosan is a natural cationic polymer that exhibits high biocompatibility, biodegradability, reduced toxicity, low cost of preparation, high encapsulation rate, controllable drug release kinetics, and targeting properties at specific tissues [83]. In addition, chitosan NPs provide drug stability, reduce adverse reactions, present facilitated transmucosal drug delivery, and have mucoadhesive features, which make them appropriate nanocarriers for delivering entrapped chemotherapeutic agents during HNC treatments [84]. For instance, oxaliplatin (OXPt) has been successfully incorporated in chitosan NPs to interact with the mucosa for a prolonged time, leading to an initial drug burst effect followed by a long-term sustained release with the opportunity to accumulate in the tumor tissue in a more concentrated way, thus increasing the rate of apoptosis in oral tumors [85]. Moreover, the controlled release from chitosan nanovehicles is associated with reduced kidney toxicity and decreased inflammatory response, without affecting their anticancer activity [86].

In the same way, chitosan has a pKa value around 6.5, which plays a key role in its drug-releasing and mucoadhesive properties, with a positive charge at low pH due to amino group protonation that allows interaction with negatively charged components of mucus [82]. Therefore, chitosan NPs can be engineered to develop a pH-sensitive tumor-targeting property under the acidic conditions of the tumor microenvironment, followed by an enhanced mucoadhesive activity that stimulates NP internalization by endocytosis to reduce chemotherapy-induced damage in healthy tissues [83]. For that reason, chitosan NPs are used in novel mucoadhesive topical formulations to deliver anticancer agents through iontophoresis, in which a small electric current is applied to transport hydrophilic anticancer molecules (i.e., drug-loaded chitosan NPs) for treating oral tumors through rapid penetration of the NPs into the mucosa [85].

Otherwise, the functional groups on the surface of chitosan, i.e., hydroxyl (-OH) and amine (-NH2), are highly reactive, allowing the easy modification of their surface through different chemical reactions [82], which make it an appropriate compound to administer drugs such as cisplatin, by coordinating bonds between the carboxylic moieties available in the polymer backbone and the center of the drug [86]. Moreover, specialized ligands can be conjugated with chitosan functional groups for interacting with specific cell surface receptors leading to NP endocytosis. The most common targeted receptors in cancer cells are the folate receptor, CD44 receptor, EGFR, low-density lipoprotein receptors, and integrins [84].

Hyaluronic acid (HA) is a natural glycosaminoglycan polysaccharide that has been extensively studied as a safe carrier or coating material for the delivery of anticancer agents, based on its unique properties [87]. Since HA represents an extracellular matrix constituent of connective tissues, it exhibits biodegradability, biocompatibility, nonimmunogenic properties, and specific binding ability with the overexpressed surface receptors in tumoral cells: CD44 and receptor for hyaluronan mediated motility (RHAMM) [88][89].

For these reasons, HA is not commonly used alone for preparing nanoparticles, but it can be applied as a protective layer with the capability of improving drug pharmacokinetic properties [90]. Nevertheless, HA conjugation has been demonstrated to increase drug solubility, stability under biological conditions, a prolonged time in blood circulation that leads to a higher passive targeting, and a specific affinity for some overexpressed cellular receptors [91]. Therefore, HA is usually conjugated with hydrophobic and amphiphilic chemotherapeutical drugs that are

required to overcome multidrug resistance (MDR) by actively targeting CD44 receptors, facilitating antitumor drug entrance into the tumor cells via receptor-mediated endocytosis with reduced toxic side effects and an enhanced efficacy at lower doses [92]. For example, HA–cisplatin nanoconjugates have been developed for local therapies of HNC, in which the conjugate stabilizes the cisplatin in the bloodstream and targets CD44 receptors of tumoral cells, followed by an accumulation of drug at tumor area based on an EPR effect to improve their therapeutic effect [88].

On the other hand, HA can be conjugated on the surface of metallic NPs through covalent amide bonds to improve their targeting and stability properties with the purpose of maximizing their anticancer effects in radio- and phototherapies. For instance, HA-coated Fe3O4NPs represent a promising multifunctional platform for magnetic hyperthermia therapy due to their good colloidal stability, biocompatibility, high heating efficacy, and specific interaction with overexpressed receptors in HNC cells [89]. Furthermore, HA offers interesting coating features for mesoporous NPs, such as mesoporous silica, in three main aspects: (1) acting as a barrier that prevents drug release through the NP pores, (2) protecting drugs from the harsh conditions in the bloodstream, and (3) targeting specific receptors to promote an effective internalization of mesoporous NPs [90].

(PLGA) is a biocompatible copolymer approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) and is widely used in the fabrication of nanoparticles for encapsulating and enhancing the properties of hydrophobic chemotherapeutic drugs, which results in a controlled drug release, lower dosage requirement, and reduced side effects [93]. PLGA properties can be tuned by modifying the molecular weight and changing the ratio of lactic to glycolic acid, in order to control the release rate of a drug or the biodegradability of the nanoparticle [94]. Another significant advantage of PLGA NPs as drug delivery vehicles is their property of being easily endocytosed by tumor cells, where they are transported into acidic endolysosomal compartments. These attractive features of PLGA-based NPs make them promising delivery vehicles for chemotherapeutic drugs such as docetaxel (DTX), which has shown a localized in situ delivery to the tumor site and an increased antiproliferative efficiency compared with free DTX in a dose-dependent manner [95].

Furthermore, PLGA NPs have been developed for the successful encapsulation and administration of photosensitizers, considering that most of them are hydrophobic and need to maintain their stability for a prolonged circulation in the blood in order to reach an appropriate accumulation in tumor tissues. One good example is the encapsulation of pheophorbide (Pba), which has shown stability after one week, prolonged blood circulation, and a faster uptake on cancer cell lines, with an effective killing of tumoral cells in mice by photodynamic effect [96]. However, PLGA NPs show some disadvantages, such as initial burst, incomplete release, and limited surface functionalization. It is worth highlighting that PLGA exhibits some angiogenic properties that could interfere with the anticancer effects of the therapeutical molecules or, in the case of diabetic patients, accelerate wound healing [97].

Polyethylene glycol (PEG) is an amphiphilic, nontoxic, biodegradable polymer that offers biocompatibility, stability, and prolonged blood circulation time for different drugs while promoting the accumulation at tumor sites, which results in the introduction of a therapeutic agent with a minimally invasive approach [98]. PEG incorporation into an NP structure promotes water solubility of poorly soluble drugs, inhibits aggregation, decreases serum protein adsorption, and reduces capture rate by the reticuloendothelial system. However, PEG concentration is

fundamental for determining the therapeutic effect of drugs because an increasing PEG concentration decreases the drug release rate that could increase the therapeutic effect and minimize the drug side effects. Moreover, PEG can diminish the initial burst that triggers an overmedication in conventional drug delivery systems [99].

Cationic nanocomplexes can be PEGylated for improving their stability by shielding their charge in order to prevent protein adhesion, aggregation with red blood cells, or activation of the immune system, which limits their potential clinical applications [100]. In the same way, polymer–lipid–PEG hybrid nanoparticle systems have emerged as a novel design for encapsulating anticancer drugs and photosensitizers to exhibit higher cytotoxicity in tumor tissues due to an increased drug loading and a reduced aggregation of the photosensitizer in aqueous solution, which promotes a faster cellular uptake [101]. PEG can be mixed with other polymers to prepare nanoparticles that reduce undesirable toxicity to healthy tissues and improve the pharmacokinetic properties of loaded anticancer molecules, such as PLA–PEG NPs [102].

Additionally, PEG can be modified to be pH-sensitive for promoting nanoparticle permeability in tumoral cells with the objective of decreasing noncancerous cellular uptake by releasing the radiosensitizer or chemotherapeutic drug inside the low-pH microenvironment of HNC cells [103]. Moreover, PEG can be conjugated with specific antibodies such as low-density lipoprotein receptor (LDLR) to target the tumor hypoxic region, which is the main contributor to chemoresistance. Thus, PEG could represent a useful nanocarrier for treating cancer by co-delivering a chemotherapeutic (cisplatin) and a chemosensitizer (metformin) into the hypoxia core area of tumors in a very promising strategy for treating HNC [104].

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