Review Article

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Nanomaterials for Oral Cancer Diagnosis and Therapeutics- Latest Trends

Abstract:

Oral Cancer is one of the leading causes of deaths in India. Despite growing innovations and trends in the field of oral cancer diagnosis and management, the prevalence rate of the deadly disease keeps escalating. Oral cancer is a debilitating disease, and numerous research activities are being pursued worldwide to combat this deleterious process. Nanotechnology is very diverse field that has revolutionized the industry and is setting new trends in the management of oral cancer.Hence, we have presented an elaborated review on types of available nanoparticles and their use in the field of oral cancer diagnosis.

Key-words: Nanoparticles, Oral Cancer Diagnosis, Nanomaterials, Drug Delivery

Introduction:

Nanotechnology is the fastest growing field of science that is being explored intensively for application in cancer diagnosis and management. Regardless of the unceasing efforts by medical researchers and practitioners, cancer still remains the leading cause of mortality worldwide. In 2020, cancer accounted to around 10 million deaths around the globe, out of which, one third of cancer deaths are attributed to tobacco use. According to the key facts presented by World Health Organization (WHO), late stage presentation and limited means of early diagnosis contribute towards large magnitude of death rate. In pathological terms, cancer or neoplasm "is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissue and persists in the same excessive manner after cessation of stimuli which may have evoked the change" [R. A. WILLIS]. Oral Cancer is one of the foremost culprit and is a broad terminology that includes various malignant conditions that present in the oral tissues [Burket's, 12th edition][1,2].

Non-lethal genetic damage lies at the heart of carcinogenesis, and thus, neoplasia could be understood as a disease of progressive genetic dysregulation. Cells accumulate mutations to become neoplastic and are characterized by six hallmarks viz: evasion of growth suppressors, resistance to cell death, induction of angiogenesis, sustainment of proliferative signaling, activating invasion and metastasis and enabling replicative immortality. Despite, continuous advancements in diagnostic field and in therapeutic methods such as CT, MRI, PET, SPECT, radiotherapy, chemotherapy etc., they still remain deficient in early diagnosis and management at cellular level. Thus, in order to conquer shortcomings of conventional diagnosis and treatment modalities, nanotechnology is being researched and

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implemented, marking a quantum leap in cancer detection and management.[3]

Norio Taniguchi of the Tokyo Science University in a 1974 paper, first time described "nanotechnology" as a process of separation, deformation and consolidation of materials by one atom or molecule. In simpler terms, nanotechnology is processing of matter at molecular and cellular levels and is one of the most rapidly growing fields of development inmedical research. Nanotechnology acquire its name from a Greek word that means "dwarf" and thus involves dealing and tailoring structures in size range of 1-100nm or smaller.[4]

Owing to the smaller size, these materials can infiltrate cells and modify their functioning. Basic units of life such as DNA, protein molecules etc are of nano-dimension and physiological processes of living organisms take place at nano-scale. Therefore, tools of less than 50nm can effortlessly enter the living cell and those smaller than 20nm can move in and out of blood vessels (in turn participating in circulation). Moreover, as size diminishes distinctive magnetic, optical and electric properties materializes differentiating nonmaterial from conventional macromolecules. Due to the ability of nanotechnology to manipulate physiogical and pathological processes at the subatomic level, it influences the key challenges of cancer diagnosis and management. Moreover, another outstanding capability of nanotechnology over conventional cancer treatment modalities is its potential to amalgamate multiple functions. According to the analyzed literature, few nanosystems are designed to by-pass drug resistance by controlling its vital mechanism, such as, the efflux of P-glycoprotein, thus introducing a novel hope for cancer treatment. Similarly, evolution of nanosized probes is revolutionizing the field of early identification of malignancy. [4]

This chapter aims to review the field of nanotechnology and nanomaterials and their application in revolutionizing oral cancer detection, management and prognosis.

Nanomaterials for Oral Cancer And Therapeutics:

National Nanotechnology Initiative described nanomaterials should be 1-100nm at least in one dimension and might include atoms, clusters, films or combinations of these. Classic nanomaterials are characterized by following properties:

a. High surface to volume ratio
b. Enhanced electrical conductivity
c. Super paramagnetic behavior
d. Spectral shift of optical absorption
e. Unique fluorescence properties
f. Increased permeability

These properties determine that nano-materials implied in favor of their role in cancer therapeutics.[5]

Nano Drug Delivery System:

A relatively latest but fast evolving science is of nanomaterials and nano-drug delivery system(NDSS), where nano sized materials serve as diagnostic means and as vehicle for drug delivery. Nano-drug delivery system are of four types viz: i) Active targeting (enables drugs to achieve specific tumor sites through modification and adjustment of nanocarriers) ii) Passive targeting(It modifies the surface of the carrier by specific ligands) iii)Immune targeting (involves active and passive immunity) iv) Magnetic targeting (deliver magnetic nanoparticles with chemotherapy drugs to tumor cells).[6,7]

Currently, the literature describes two main approaches for manufacturing nanomaterials which are:

Bottom-Up approaches:

This is referred to the process where smaller fragments are put together to fabricate complex structures utilizing the strong covalent bonds. "Nano diagnostics", "Anaesthetic agents", "local drug delivery systems" are manufactured using this approach.[8]

Bottom-down approach:

This is a process where larger particles are used to create smaller components. Devices such as NEMS (Nanoelectromechanical systems) used for cancer diagnosis are assembled using bottom down approach. [8]

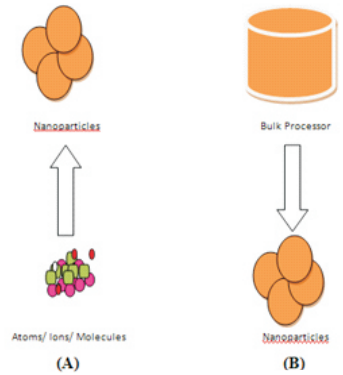

Figure 1: A) Bottoms up B) Bottoms down

Generations Of Nanotechnolgy

Literature classifies nanotechnology into 6 generations in a sequential manner, where one generation evolves from the previous one: [9]

1st Generation: Passive nanostructures: depicts basic understanding of nanotechnology

2nd Generation : Nanostructures are active with the potential of altering specific properties

3rd Generation: Nanostructure work together to unravel problems

4th Generation: Heterogeneous molecular nanosystem is the perfection of nanotechnology which fully control molecules with in nanoscale

5th , 6th generations and nano-bio-info-cogno (NBIC) : Creates spin-off nano-platforms in medicine, and health care services and nanosystem convergence networks which includes networks of foundational technologies platforms (NBIC) and their spin-offs.

Nanomaterials for Oral Cancer Diagnosis And Therapeutics:

Primary objective of an oral health worker is early diagnosis and timely management of signs and symptoms of oral cancer. Although, many diagnostic tools are available for the same but advancements are still in demand. Nanotechnology is currently a hot spot for researchers to achieve satisfactory ways of cancer diagnosis and therapeutics. However, continuous efforts are required for its application from bench side to bed side.

Number of distinctive Nanomaterials are available drug and gene delivery, probing DNA structures, etc.,They include: [7,9]

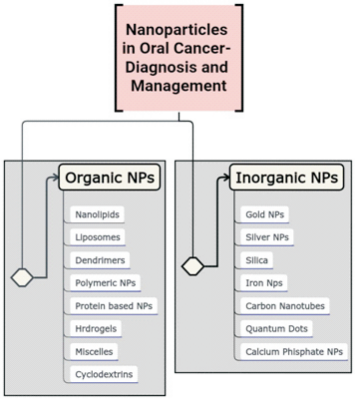

Figure 2: Types of Nanoparticles in Oral Cancer Diagnosis and Management

Nanolipids for Cancer Diagnosis and Management:

Solid lipid nanoparticles(SLN) have a lipodial matrix core that dissolves lipophilic drugs and belong to a size range of 50-1000 nm. Lipid matrix of these nanomaterials constitutes lipids like monoglycerides (glycids (stearic acid), steroids (cholesterol), and waxes (cetylpalmitate). According to a review published by Gharat et al (2021), the limitations posed by SLNs such as low drug-loading capacity, drug degradation due to high-pressure homogenization, leaching out of the drug due to modifications in the lipids, and nonuniform kinetics of the distribution process, Nanolipids Carriers (NLCs) developed.[10, 11]

Liposomes for Cancer Diagnosis and Management:

These are formed from lipid layers, usually phospholipids and cholesterol (ampiphillic outer layer) that surround aqueous zones(hydrophilic centre). These are structurally configured in unilamellar or multilamellar fashion

Liposomes are one of the most widely applied nanomaterial for cancer research and are transported to target tumor site via passive targeting utilizing enhanced permeability and retention effect. Further, to enhance their susceptibility, liposomal surfaces are sensitized by attachment of ligands. Depending upon their configuration and properties, different liposomes are applied for oral cancer diagnosis and therapeutics. [12]

Polymeric Nanoparticles for cancer Diagnosis and Management:

Nanocapsules and nanoparticles are two types of polymeric nanopaticles that enclose cancertherapeutic medicines using synthetic or natural polymeric shells. Such polymeric particles are broadly used in nanotechnology because of their convinient features when it comes to parameters as elaboration and design, biocompatibility, structural variation. Yang et al conducted a research to scrutinize the effectivity of polymeric nanoparticles in oral cancer eary diagnosis and reported high efficiency of these particles in fluoroscent endoscopic detection of oral cancer. [10]

Dendrimers for Cancer Diagnosis and Therapy:

Dendrimers are tree-like multibranched 3D structures composed of a central core, repeated branches and terminal functional group [13]

All the three parts depicted in the figure can be customized for desired function such as imaging, targeted drug delivery, enzyme function etc. These nanomaterials are synthesized via two processes such as :i) Divergent method and ii) Convergent method.

Dendimers are desired choice for oral cancer diagnosis and had been developed by researchers to determine biomarkers such as interleukin-8 RNA, interleukin-8 protein, interleukin-1β protein with better sensitivity and specificity and even more bioaffinity.

Protein Based Nps for Cancerdiagnosis and Therapy:

Because of the tremendous biocompatibility of albumin in physiologic system, it is the most widely accepted member of protein family that present as an alternative biomaterial for carrier. Plant proteins such as legumin and gliadin have also been tried in development of Nanoparticles for drug delivery in oral cancer.[14]. Easy preparation of PNPs, low immunogenicity, non-toxicity, biodegradable, biocompatibility and a long plasma half-life are few advantages of protein based nanomaterials.[15] Kumar S et al in 2016, reported high sensitivity , wide linear detection range and a faster response rate (15 min) of protein functionalized nanostructured hafnium oxide based biosensing platform for non-invasive oral cancer detection.[16]

Hydrogels for Cancer Diagnosis and Therapy:

Hydrogels are three dimensional web of hydrophilic fibres containing large amount of water or biological fluids and act as localized target delivery systems by providing sustained delivery of both hydrophilic and hydrophobic drugs. They can also manage the release of therapeutic agent for short and long periods (upto several months) by modifying the density of nanofibres. Other advantage of hydrogel over other nano-materials is its ability to allow co-administration of different drugs with synergistic anti-tumor effects and decreased drug resistance.[17,18] In a study done by Li J et al in 2012, intra-tumoral administration of poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG, PECE) hydrogel was done in a mouse with OSCC, and as a result sustained release of loaded SAHA and DDP for more than 14 days, with enhanced therapeutic effects, and reduced side effects. [19]

Gold Nanoparticles for Cancer Diagnosis and Treatment:

Excellent biocompatibility, ready bioconjugation and enhanced tissue permeability are few properties that make gold nanoparticles interesting and sort after modality in biomedicine. Moreover, they also have precisely controllable size, high colloidal stability, and tunable optical properties, and are available in varied sizes & the geometric shapes such as nanospheres, rods, cages, prisms, shells etc. [30]These can also be fabricated in short or long chains of spherical particles with needed optical properties depending on the size of chain, and depending on their surface ligands, their properties vary(fig 4)

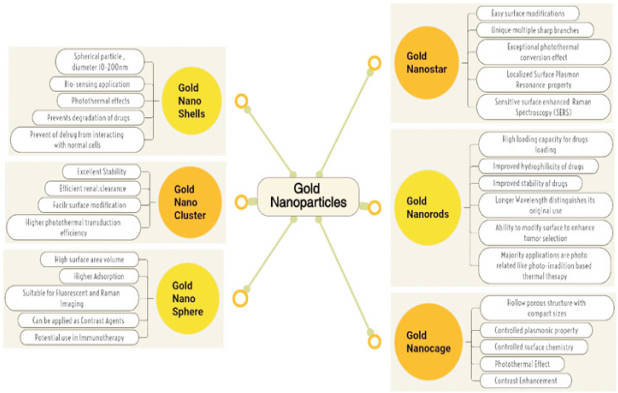

Fig 3: The most common gold nanoparticle assemblies and their characteristic features

Calcium Phosphate NPS (capnps) for Cancer Diagnosis and Therapy:

As per the review presented by Lin Y et al in 2017, calcium phosphate nanoparticles are the most promising nonmaterial as they had already been utilized therapeutics and diagnostics, such as bone/tooth repair, imaging, and DNA transfection. Their wide range of application could be attributed to their properties such as effective biocompatibility, biodegradability and stability in colloidal solutions.[20,21] In an another study done by Mohiyuddin S et al in 2018, the potential of inorganic calcium phosphate nanomaterial enhanced the therapeutic ability of antiproliferative drugs due to their excellent loading efficiency, biodegradable nature and controlled-release behavior.[22] Moreover, calcium phosphate nanoparticles are great delivery vehicle for nucleic acids, drugs, proteins, and enzymes into tumor cells, as therapeutic agents.

Possible Risk for Human Health and Ethical Issues:

Although nanomaterials have a numerous advantages such as high optical and flourescenece properties, smaller size, varied morphological shapes, biocompatibility etc. that make this technology apt and demanding. However, enough information was not found regarding the toxic effects of nanoparticles . Toxic properties of nanomaterials vary depending both on the size as well as the chemical formulations of the materials used in synthesizing the nanoparticle, and thus, nanoformulations require evaluation before application in the field of nanotechnology. According to the studies done so far, the biodegradable nanoparticles decompose and waste products are excreted through intestine and kidney. However, some proportion gets accumulated in different organs, such as inliver. Toxicity and side effects produced by this residue is not yet studied. [23,24]

Ethical and moral concerns also need to be addressed in parallel with the new developments in some areas, for example, neuroethics need to be investigated before brain and neural system research.

Conclusion:

The contribution of nanomaterials and nanotechnology in the field of science is impeccable. It has revolutionized the landscape of cancer diagnosis and treatment. Owing to its multifunctionality and controlled size nanotechnology has gained popularity over traditional techniques. [25]Faster advancements and improvisations are continuously taking place to fabricate more efficient nanosystems that could deliver precise diagnostic details regarding tumor growth and propogation and also helps in target therapeutics that helps in achieving better prognosis. Although, the bedside to benchside transformation of nanomedicines and technology have introduced new era in oncology, however, despite promising future, intensive and in-depth research is still needed to analyze the toxic effects related to nanomaterials. Therefore, it could be easily concluded that introduction of nanoparticles have opened doors for intensive research that could be a game changer in field of oncology.

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