REVIEW

Demystifying oral squamous cell carcinoma with nanotechnology

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ABSTRACT

Nanodentistry in the form of nanomaterials, nanodiagnostics, nanorobots and nanoparticles has the potential to revolutionize oral cancer diagnosis and treatment. Oral cancer claims approximately 40% of cancer cases of which the majority belong to Oral Squamous Cell Carcinoma (OSCC). Early diagnosis of OSCC is of utmost importance due to the high mortality rate of the disease when detected at a later stage. Nanodiagnostics contribute significantly towards improved diagnosis, which is rapid and has greater sensitivity. The drawbacks of conventional treatment modalities such as inability of targeted destruction of cancerous cells can be overcome with nanotechnology in the form of nanoparticles and drug carrier systems. The aim of this review is to explore and discuss up-to-date literature on OSCC diagnosis and efficient treatment.

KEYWORDS: Oral Squamous Cell Carcinoma, Nanocarriers, Nanodentistry, Nano diagnostics Nanotechnology

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INTRODUCTION

The insatiable inquisitiveness and impulse towards cognition of humans has led to the genesis of Nanotechnology, a multidisciplinary field encompassing myriad of fields such as applied physics, materials science, colloidal science, device physics, supra-molecular chemistry, and even mechanical and electrical engineering. The word 'nano' is derived from the Greek word 'nano' meaning 'dwarf'. One-billionth of a metre is a nanometer, which is ten times the diameter of a hydrogen atom, so miniscule that it goes beyond the capacity of a naked human eye, or even a light microscope and requires a special tool called electron microscope (EM) or scanning probe microscope (SEM).

The inception of nanoscience and nanotechnology happened at a talk titled "There's Plenty of Room at the Bottom" by physicist Richard Feynman at an American Physical Society meeting on December 29, 1959 where he talked about a process wherein scientists would be able to manipulate and control individual atoms and molecules. More than a decade later, Professor Norio Taniguchi coined the term nanotechnology and was not until 1981, with the development of the scanning tunnelling microscope individual atoms could be seen and modern nanotechnology truly began.

Today, Nanotechnology influences every facet of life from agriculture to electronics with tremendous potential and relevance in the field of medical science and healthcare, including dentistry. Nanodentistry incorporates the nanotechnology in the form of nanomaterials, nanodiagnostics, nanorobots and nanoparticles. When dental structures are viewed with an electron microscope, on a nanoscale, a completely new perspective is presented which provides not only an enhanced understanding about their structure but also the physiological relationship of the dental surfaces. (Tomsia et al., 2011) Oral diseases such as dental caries, dental hypersensitivity and oral cancer can be quantified on the basis of morphological, biophysical and biochemical nanoscale properties of the tooth surface, dental materials and oral fluids such as saliva (Kanaparthy et al., 2011; Poonia et al, 2017) Advanced oral cancer prevention, diagnosis and treatment are possible with nanotechnology. (Satyanarayana et al., 2011; Lainovic et al., 2012)

ORAL SQUAMOUS CELL CARCINOMA

Oral cancer is a common and aggressive cancer with high morbidity, mortality, and recurrence rate globally, which presents to be a huge burden to society. The incidence and mortality rates have been reported to show a steady increase worldwide with around 575,000 new cases and 320,000 deaths annually. (Gaphor et al., 2014). In India, oral cancer is the most common type of cancer, accounting for up to 40% of all cancers. Moreover, several epidemiological studies and cancer society's reports have anticipated that caseload would further increase from 1 million in 2012 to 1.7 million in 2035, which could be attributed to most cases being diagnosed at advanced stages. Further studies have shown that Oral Squamous Cell Carcinoma (OSCC) accounts for the majority of cases among these oral cancer cases with incidence rates of 12.8 and 7.5/100,000 in men and women, respectively. (Varshitha, 2015; Gupta et al., 2012; Byakodi et al., 2020)

The mainstay of treatment for OSCC remains to be surgical re-sectioning. Adjuvant chemoradiotherapy or adjuvant radiotherapy is advised for locally advanced disease (pT3-4, pN2-3); positive surgical margins, perineural invasion and lymphovascular invasion (Adelstein et al., 2017). In spite of advanced treatment modalities, less invasive surgical techniques, new reconstructive modalities and the intensity-modulated RT technique this standard multimodal approach can result in significant morbidity. (Felice et al., 2016; Felice et al., 2018) Cancer nanotechnology shows promising and novel possibilities and opportunities in the OSCC scenario right from diagnosis to treatment.

OSCC DIAGNOSIS

The diagnosis of OSCC is of paramount importance due to the high mortality rates of late-stage disease. Therefore, early and accurate recognition and diagnosis of OSCC might improve patient survival and reduce treatment-related morbidity. (Brocklehurst et al., 2010; Brocklehurst et al., 2015; Garg et al., 2012)

At present, the protocol for detection of OSCC remains to be a combination of the conventional oral cavity examination which involves visual inspection of the oral cavity and tactile examination of head and neck lymph nodes and other supplementary techniques such as incisional or excisional biopsies, cytological techniques, vital staining, auto-fluorescence, chemiluminescence, imaging diagnostic techniques [Magnetic resonance imaging (MRI) with and contrast-enhanced computed tomography (CT) of chest, Positron Emission Tomography(PET) & Optical Coherence Tomography(OCT)] and the more advanced molecular analysis entailing detection of genetic alterations and tumor markers.(Carreras-Torras et al., 2015; Marur et al., 2016) The criteria for suspicion of OSCC are the changes seen in surface texture, loss of surface integrity, colour, size, contour deviation or mobility of intraoral or extra-oral structures and radiological diagnosis.

Nano diagnostics

On a nanoscale, a single cancer cell sizes up to approximately 104 nanometres while the nanorobots measure up to 0.5x 104 to 3 x 104 nm and nanomaterials are 0-100nm. With their nanoscopic dimensions, these have revolutionized cancer diagnosis with detection of even a single in-vivo cancer cell and drug delivery to cancerous cells possible. The use of nanotechnology in the imaging of oral cancer is illustrated in Figure 1. (Kah et al., 2007; Chen et al., 2018) Various ways this technology facilitates cancer diagnosis is as follows:

Magnetic resonance imaging

Magnetic resonance imaging (MRI) helps in the assessment of the primary tumour, its bone invasion and mapping of the actual tumour borders during surgery. Nano-contrast agents are utilized for cancer screening because of their ability to recognize unique cell surface markers. They also have prolonged blood circulation half-life and exhibit better contrast properties than the usually used contrast agents. Magnetic PLGA nanoparticles with their surface modified with folatechitosan conjugate 'shell', shorten the overall T2 relaxation time thereby enhancing the nanoparticle relaxivity to provide better in vitro MR imaging and Gd3+ doped amorphous TiO2 nanoparticles conjugated with folic acid enhance the agent biocompatibility and image contrast for the molecular receptor. These nanoparticles have been used for oral cancer screenings. (Shanavas et al., 2017)

Optical coherence tomography

Spherical Au nanoparticles, conjugated with anti-EGFR monoclonal antibodies and PEG, enhance the contrast by approximately 150% as well as increase the penetration depth in vivo OCT image. These nanoparticles are also biocompatible. (Kim et al., 2009; Kim et al, 2010)

Photoacoustic imaging

Plasmonic nanosensors, conjugated with anti-EGFR monoclonal antibodies and PEG, noninvasively identify micrometastases by producing large photoacoustic signals. (Luke et al., 2014).

Surface plasmon resonance scattering

Colloidal gold nanoparticles which may either be conjugated or unconjugated with anti-EGFR monoclonal antibodies due to their surface plasma oscillation resonantly scatter visible and near infrared light, and thus help in finding specific molecular biosensor techniques for the diagnosis of oral epithelial living cancer cells both in vivo and in vitro. However, the stability of these nanoparticles is difficult to control. (El-Sayed et al., 2015; Kah et al., 2007)

Surface-enhanced Raman spectroscopy

Colloidal gold nanoparticles, conjugated with anti-EGFR monoclonal antibodies, can be utilized for preparing highly sensitive SERS-based saliva assay which is simple and cost-effective. It uses nanorods with large aspect ratios which can provide near-infrared region plasmon wavelengths and high index sensitivity. (Kah et al., 2007; Singh et al, 2018)

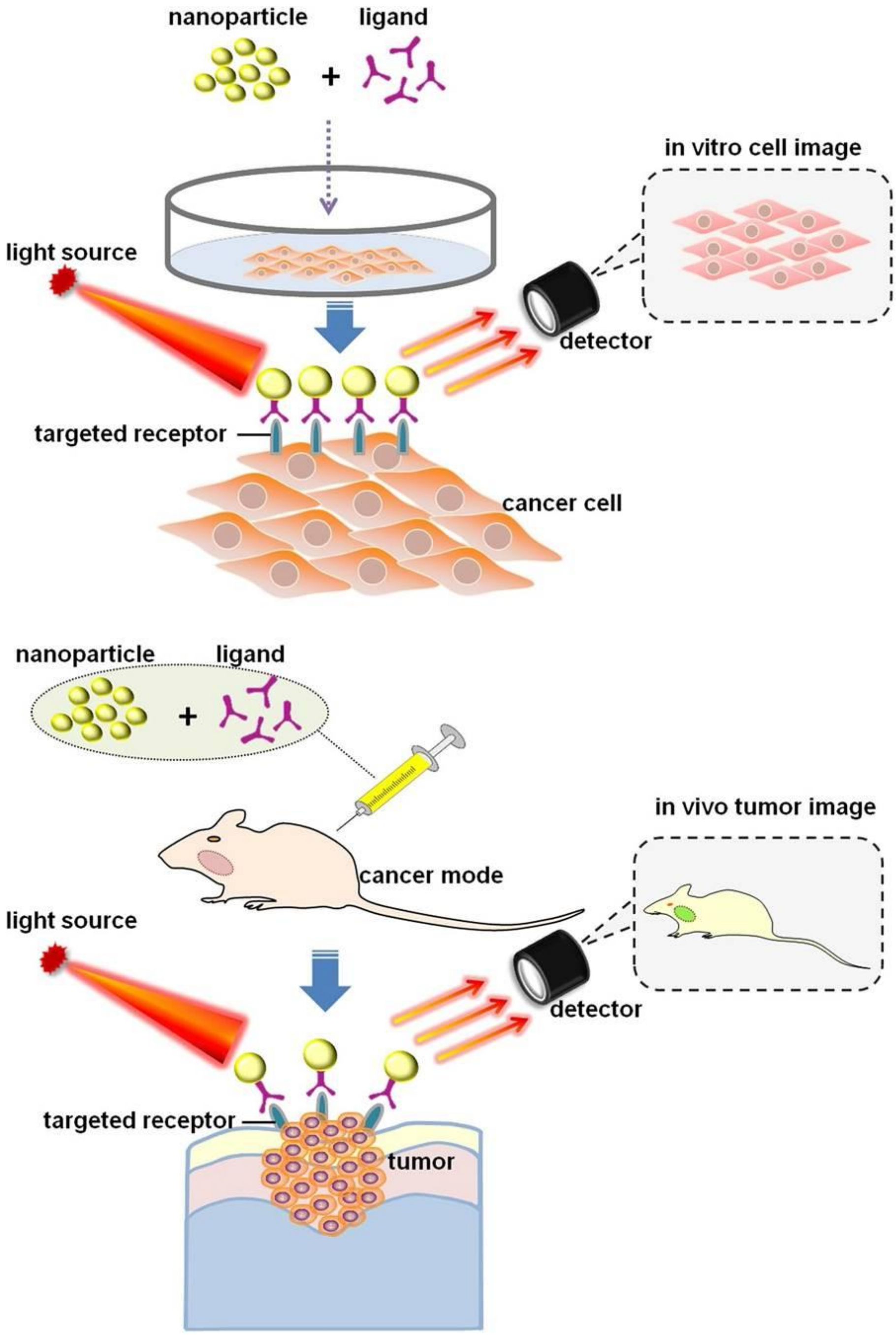

Figure 1: Nanotechnology in imaging of oral cancer: in-vitro and in-vivo (Chen et al. 2018).

Diffusion reflection imaging

GNRs, conjugated with anti-EGFR monoclonal antibodies, present to be a promising tool for screening of malignant lesion and to detect the residual disease during surgery. Their main characteristic is the ability to map tumour margins in OSCC with high resolution and depth of penetration. (Fixler et al., 2014)

Quantum dots imaging

It utilizes water-soluble quantum dots, conjugated with biotin and PEG and binds to the proteins related to the cancer cells and fluoresce when illuminated by ultraviolet light. The advantages of quantum dots are that they have high fluorescence intensity, low non-specific binding and have good stability against photo-bleaching. However, their biodegradability and cytotoxicity present to be a problem. (Li et al., 2006; Kumari et al., 2018)

Nano-based ultrasensitive biomarker detection

Nanotechnology may assist in the detection sensitivity for biomarkers with low concentrations in the tissue samples or body fluids. Saliva peptide finger print analysis helps in the prediction of potential biomarkers for OSCC diagnosis. Gold nanoarray, binded to the Fc region of the TNF-α capture antibody, detects TNF-α. Nano-bio-chip, labelled with anti-EGFR monoclonal antibodies enables rapid detection and quantitation of EGFR biomarker. Gold nano-beads, coated with antiCD63 IgG secondary antibody, explore quantitative approaches to biochemical characterization of exosomes. (Sharma et al., 2010; Chen et al., 2018)

Nanoscale cantilevers

These are flexible electric beams resembling rows of divided boards, which are used to attach to cancer-linked molecules. They bind to the altered DNA sequences or proteins related to certain types of cancers. When these molecules bind to the cantilevers, the cantilevers bend due to the change in the surface tension and this can be monitored to identify these molecules. These make cancer tests faster and more efficient.

Nanopores

These are perforated surfaces which act as filters for DNA due to the nano dimensions of the holes through which only single strands of DNA can pass through, thus efficient DNA sequencing is possible. As the DNA strand passes through, the electrical properties and genetic codes can be encoded and detection of any errors due to cancer can be deciphered.

Nanotubes

These nanosized carbon rods which measure to about half the diameter of a DNA molecule not only identify altered genes but also pinpoint their exact location. Specific tags are designed which identify specific DNA mutations and bind to them. Nanotips are then used to trace the exact shape of the DNA and pinpoint the mutation regions. Nanomap identifying the shape of the DNA molecule and the tags is created by the nanotubes.

Nanodiamonds

They do not interpose cell division or differentiation, have minimal cytotoxicity, and can be easily functionalized with proteins and other markers for targeting purposes. Hence, they can be used for cell labelling and tracing. They have been successfully used as biomarkers or tracers to label or trace HeLa cells, lung cancer cells, and murine fibroblasts. (Bharadwaj et al., 2014; Alkahtani, 2018)

TREATMENT AND DRUG DELIVERY

Treatment of OSCC consists of treatment modalities like chemotherapy and radiation therapy. These treatment modalities are unable to selectively destruct the cancerous cells, posing danger of impairment of vital organs and thus

OSCC treatment is a challenge. The advent of nanotechnology and its incorporation in medicine presents a solution to the aforementioned limitations of conventional treatments. The nanoscopic targeted drug-delivery specifically to the cancerous cells, constant and uniform delivery of drug at the cancer lesion; thus, increasing drug penetration into the tumour gives these treatment modalities an edge over the others. Some of the ways in which nanotechnology can be incorporated in OSCC treatment is as follows:

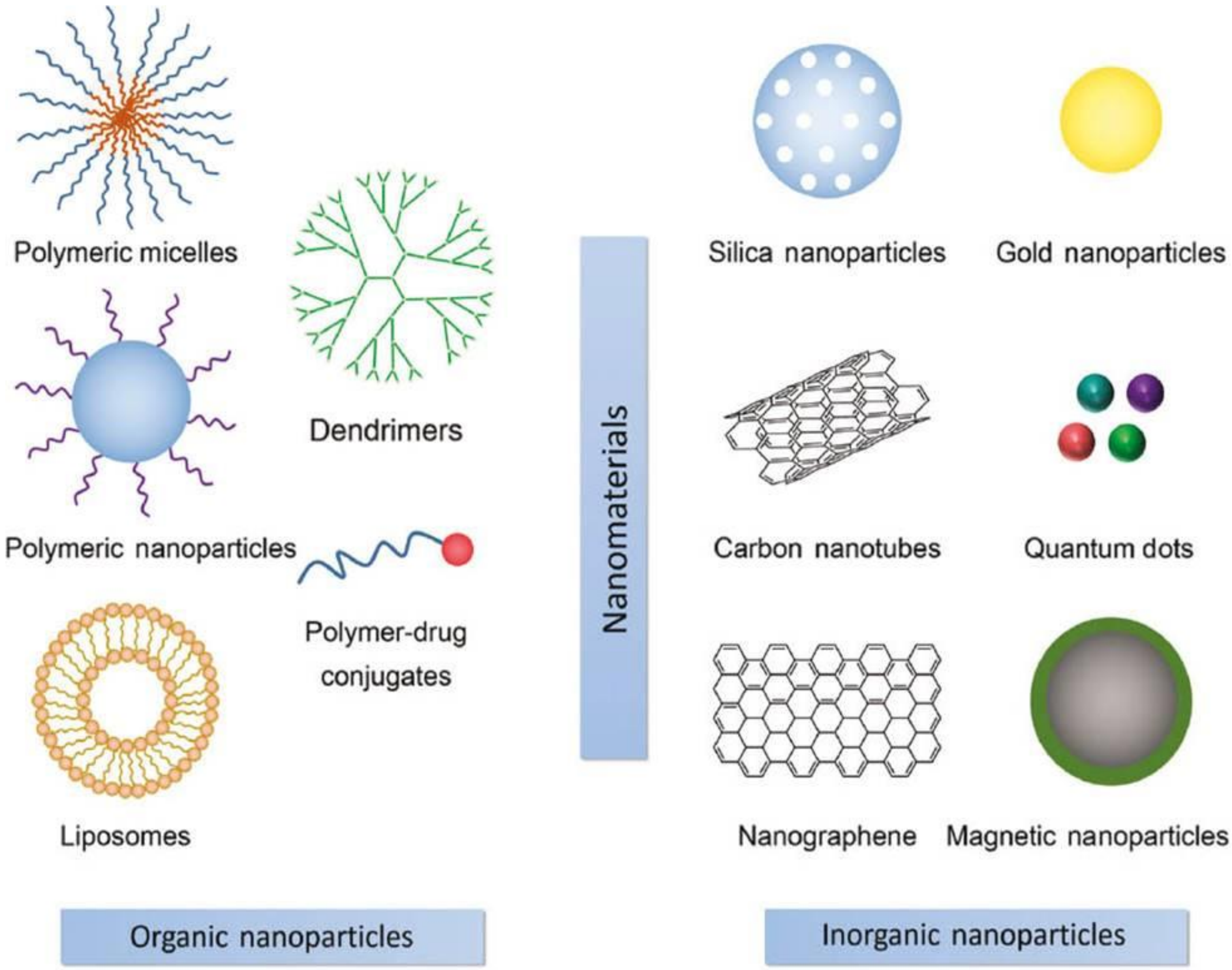

Figure 2: Different nanoparticles used for diagnosis and treatment (Zhou et al. 2017).

Nanoshells

These round gold-coated silica nanoparticles selectively absorb infrared frequency and release heat which is lethal for the cancerous cells. Antibodies too can be attached to these which then identify and target cancer cells. These enhance chemical sensors and each nanoshell as a Raman scattering enhancer.

Nanowires

Nanowires can link together tiny components into extremely small circuits, deliver and receive electrical impulses and monitor brain electrical activity without using brain probes which violate the brain parenchyma.

Nanosponges

Nanosponges are like a three-dimensional network containing spherically shaped particles with cavities in which drug molecules can be stored and then injected into the body. Nanosponges have several advantages over direct injection like being three to five times more effective at reducing tumour growth and in targeted drug delivery.

Dendrimers

Dendrimers are highly complex molecules with a core, branched and end groups and have been used for targeting and delivering the potent therapeutic drugs namely cisplatin and doxorubicin which are utilized in cancer treatment and contrast agents for MRI. (Poonia et al., 2017) Drug-delivery is possible with dendrimers by three methods, firstly, in the form of dendrimer pro-drug wherein the drug is covalently attached to the periphery of the dendrimer; secondly, with the help of ionic interactions the drug is coordinated to the outer functional groups and thirdly, the drug acts as a uni-molecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug super-molecular assembly.

Nanotechnology-based drug delivery systems

Nanoparticles

They are composed of polysaccharides, proteins and biocompatible/biodegradable polymers. Their physical stability, excellent tolerability and controlled release are of great significance. They protect the incorporated labile drugs from degradation. The various nanoparticles are illustrated in Figure 2. (Zhou et al., 2017)

Liposomes

They are being studied for chemotherapeutic drug delivery for better therapeutic efficacy and less toxicity to normal cells. Synthetic cationic liposomal-DNA called lipoplexes which are liposome-based formulations for gene therapy has potential for oral cancer treatment.

Hydrogels

These are meshes of hydrophilic polymeric chains dispersed in water that swell and release drugs for dissolution and disintegration through the spaces in their mesh and can be used for drugs including paclitaxel, doxorubicin, DTX, tamoxifen and cisplatin. Studies have reported that the SAHA-cisplatin/PECE hydrogel system with direct intratumoral injections may be a useful method for the treatment of oral cancer.

Liquid crystals

These are material in mesophase state that is they demonstrate a property between a solid and a liquid. They change the drug release profile; reduce the toxicity of drugs and improve clinical efficiency. (Patra et al., 2018)

CONCLUSION

Nanotechnology is undeniably promising treatment modality to bring about a paradigm shift in the way oral squamous cell carcinoma is being diagnosed and treated and its complete potential still remains to be explored. With early detection and targeted drug efficiency and delivery the nanoparticulate systems have potential of improving the patient's quality of life and lowering mortality rate.

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The author has declared that no competing or conflict of interest exists.

Author's contributions

Conception and design: Atre, Jain, Kumar. Acquisition of data: Atre, Shah. Analysis and interpretation of data: Jain, Bhanushali. Drafting the article: Atre, Mandal, Kumar. Critically revising the article: Jain, Bhanushali, Kumar, Mandal. Reviewed submitted version of manuscript: Atre, Kumar. Approved the final version of the manuscript on behalf of all authors: Atre. Study supervision: Jain.

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Declaration of originality

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