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Nanotechnology Used in Cancer Diagnosis

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ABSTRACT:
In order to fight against cancer, the basic key point is to detect it at it's earliest. But its early detection is stalled by the basic or conventional techniques used in diagnosis of different types of cancers. These techniques have one or the other limitations that on a whole delays the diagnosing process which in turn delays the patient's treatments.
This review summarizes all of the nanotechnological application methods that have been proposed or used in cancer diagnosis. The application of nanotechnology in cancer diagnosis is one of the latest technologies where early detection of cancer cells is possible and carried out at the nanoscale. In the current scenario, early detection is half the battle against cancer. Nanotechnology applications offer world-class sophistication methods for novel molecular agents used to improve bio-sensing and imaging equipment that help in cancer screening, monitoring, and diagnosis, culminating in successful disease therapy. Here is a review of Nano-particles, Gold Nano-particle, Magnetic Nano-particle, Quantum dots, Dendrimers, Nano-hydrogel, Nano-Shells, Nano-Cantilevers, Carbon Nanotubes, Nano-Rods, Nano-Wire, Nano-Codes.
Keywords: Nanoparticles, Quantum dots, dendrimers, Nano-hydrogels, nanowires

INTRODUCTION:

The detection of cancer cells at an early stage is now a primary requirement to treat this potentially fatal disease. In this section, we discussed the application of nanotechnology to detecting and screening the presence of cancer cells in the early stages of cancer[1], [2].
CONVENTIONAL TECHNIQUES:
In present time the, conventional methods that are being used for Cancer detection are:

1.Histopathology and cell-cytology:
To identify cancer at an early stage, cytology and hi stopathology cannot be used efficiently and indepe ndently alone[3], [1].

2. Imaging techniques:
X-rays, magnetic resonance imaging (MRI), computed tomography (CT), endoscopy, and ultrasound, among others, may only identify cancer when an observable alteration in the tissue is present[4], [5].

The diagnostic ability of these techniques is strong; however they have two big drawbacks:
Firstly, these approaches are unable to distinguish between benign and malignant tumors[1], [6]. Hence it becomes really difficult to obtain the proper detection as early as possible.
Secondly, they can only be used when visual changes start to take place in the tissues or cells[3][1] and by that time it gets really late to treat or operate the cancer in patients' body.

As a result, developing methods to identify cancer at an early stage, before it spreads, is a huge issue[1].

It certainly is a big challenge to develop early detection techniques that are accurate, sensitive and very specific in their task.

Therefore much of the research work has been focused on to the better diagnosting techniques for early recognition of cancerous cells in patients. The best emerging field is the NANOTECHNOLOGY.

The conventional diagnosing techniques are either being combined with the nanotechnology to evolve new novel nano-techniques or replaced with various devices of nano range to help in better diagnosis of cancer[7], [8].

Bioconjugated particles and technologies are also being developed for the detection of early cancer in bodily fluids such as blood and serum.[9]These nano-scale devices work by selectively catching cancer cells or target proteins.

Sensors are often used by covering them with a cancer-specific antibody or other bio-recognition ligands[9], allowing capture of certain electrical, mechanical, or optical signal which is produced by a cancer cell or target protein in order to detect[10], [9].

Such nanotechniques are considered to be more sensitive and specific.[2], [11] They help in multiple measurements and hence are useful for detection of extracellular cancer biomarkers and cancer cells, as well as for in vivo imaging[1].

This chapter helps you to develop a good understanding of how application of nanotechnology is helpful in detection of different types of cancers in patients as compared to the conventional as well as current techniques in use[12].
There are many nano-structures as well as nano-devices that help to detect cancer at very early stage[7].
These may include:

1. NANOPARTICLES:

At least half of the particles in the number size distribution must have a particle size of 100 nm or less[9][13]. The majority of nanoparticles are composed of only a few hundred atoms. A nanoparticle is a tiny entity that, in terms of movement and characteristics, behaves like a full unit[12], [14]. With the numerous applications of nanoparticles in diverse sectors, nanoparticle research is now the most researched branch of science[15]. The particles might have a wide range of uses in biological, optical, and electrical domains[2], [9], [16].

NANOPARTICLES ARE USED IN BIOLOGY AND MEDICINE FOR A VARIETY OF REASONS:

- Developing fluorescent biological labels for essential biological markers and substances used in disease research and diagnostics[17].
- Drug administration systems[18][3].
- In gene therapy, gene delivery techniques are used using nanoparticles[4], [19].
- For the biological identification and diagnosis of disease-causing organisms[20], [21].
- Protein detection[5], [11]
- In researches related to biological substances and tumor cell isolation and purification[22].
- DNA structure investigation in relation to cancer[23], [24].
- Tissue and genetic engineering[9], [23].
- Tumors are destroyed using medications or heat[4].
- In MRI research[4], [5].
- In pharmacokinetic research area[25], [26].

Nanoparticles are being used in cancer detection to collect biomarkers such as cancer-associated proteins, circulating tumour DNA, circulating tumour cells, and exosomes[27][1]. One significant advantage of using nanoparticles for cancer detection is their high surface area to volume ratio in comparison to other heavy materials[1], [28]. Because of this feature, antibodies, small molecules, peptides, aptamers, and other moieties can be thickly coated on nanoparticle surfaces but with special care to still maintain their sizes in nano ranges[5], [9], [11]. These target recognizing components when added with nano size particles have the ability to attach to and identify certain cancer molecules[9], [17]. Multiplicative effects can be obtained by providing multiple bindings of ligands to cancer cells, which further increases the specificity and sensitivity of such nano particles[1].These nanoparticles can be made up of various kinds of materials (metals) corresponding to formation of different types of nanoparticles like gold, silver, magnetic and etc.

a. GOLD-Nanoparticles

Because of their tiny size, strong biocompatibility, and high atomic number, gold nanoparticles are a suitable contrasting agent[5], [28], [17]. They target cells in both active and passive ways as illustrated according to researches[2], [15], [25]. Because of the permeability tension effect (EPR) in tumor tissues, the principle of passive targeting is guided by a collecting of gold nanoparticles to increase imaging[1], [25]. Gold-nanoparticles active targeting of tumor cells is achieved by combining these nanoparticles with tumor-killing targeted medicines, such as EGFR monoclonal antibodies[7], [9], [1].

b. MAGNETIC-Nanoparticles

Over recent decades, a variety of narrow size distribution magnetic nanoparticle preparations have been created[5], [11]. The particles are prepared from gold and iron oxide which help to incorporate magnetic properties in them[9], [17]. These are small size particles that respond to the magnetic field and hence can easily be used for diagnostic purposes not only in cancer but also in other disorders[26].

Magnetic nanoparticles play a major role in cancer treatments by helping in early detection of tumors and cancerous cellsin the body fluids[29], [26], [30]. These nanoparticles are conjugated with the peptides and made more advantageous for helpful[5], [7]. They are used for angiogenesis imaging, cancer staging, immune cell tracking (cells such as monocytes/macrophages, T cells), and molecular and cellular targeting[18], [23]. Such particles represent high degree of biocompatible nature as well as low toxicity[31], [32].

2. QUANTUM DOTS:

Quantum dots are nano sized crystalline particles, more appropriately known as nanocrystals. They are made up of semiconductor materials as a basic component that entraps an inorganic element at its centre and a metal forms a shell around them. QDs have sizes ranging from 2 to10 nm. Quantum dot's size and composition may be varied between 400 and 2,000 nm (1).they have the property of showing various colors in presence of different wavelengths. Hence using varying wavelengths, quantum dots may be tuned to any hue, allowing for the detection and tracking of differently labelled biomarkers with a single light source emitting different wavelengths.[5], [33].Spectral imaging techniques have been used to separate signals from various fluorescent markers in cells or tissues, but the inability of visible spectrum imaging to penetrate things restricts its application[26], [17]. To address this issue, quantum dots that produce fluorescence in the near. Infrared range starting from 700nm to 1000nm have been developed, making them more suited for imaging colorectal cancer,.livercancer,. Pancreaticcancer,. and lymphoma[34], [26],[35]. To improve cancer imaging, a subsequent near-infrared (NIR) window "NIR-ii", ranging from 900-1700 nm with greater tissue incursion power and superior spatial and temporal resolution has been created[26].

Silver rich quantum dots including a sulphur source has been made and have reported to enable for the observation of higher spatial resolution pictures throughout a broad infrared spectrum[26].In the context of multi-photon microscopy, fluorescence tagged quantum dots provide multicolor bright imaging in live tissues[20].

Quantum dots show attractive properties which adds to the advantages for their utilization such as:

- On simple excitation they show stable fluorescence
- Can easily be tuned to multiple spectra's.
- High sensitivity and specificity
- Absence of the need for lasers.

Quantum dots' red/infrared hues allow for whole blood tests. However, one issue with imaging normal healthy tissue in the past has been that it frequently shows auto-fluorescence, which interferes with the signal from malignant cells. Quantum dots have been made to exhibit fluorescent characteristics in the NIR spectrum, allowing them to reduce this interference to a large extent[20], [36]. Another issue with employing quantum dots in vivo is whether or not injection provides a hazardous danger. To reduce potential toxicity, changes have been made[20].

3. DENDRIMERS:

Dendrimers are engineered complex nanostructures with branched concentric layers encompassing an inward center. The shape, measure, surface functionalities and branching length of a dendrimer may be controlled to perform distinctive capacities[37], [38]. The breadths of dendrimers run between 1nm to 10 nm. Dendrimers are demonstrating to be especially proficient at serving as a flexible measured quality able of identifying a number of proteins, which are right now identified by performing person's ELISA testing. In expansion, dendrimer nanoparticles have been made, which may be dually utilized for imaging utilizing MRI or NIR fluorescent modalities in a single test[39]. This process has been utilized in the research works and has appeared to be successful in mouse for mapping using soli-lipid nanoparticles[20].

Dendrimers show various advantagessuch as:

- Simplicity and ease of synthesis.
- Show excellent drug loading capacity[40].
- Show superb bio-degradable property[40].
- Transepithelial transport is improved[41].
- Gastrointestinal toxicity can easily be minimized.

Certain research studies have shown that in case of colorectal cancer cells, SN38(an antineoplastic agent) conjugated dendrimers had shown improved transepithelial transfer of anti cancerous drugs with much lower colon and rectum toxicity to a large extent, suggesting that dendrimers have significant promise as carriers in the transport of anticancer medicines[20], [42]. (They have also shown the results of increased oral bioavailability when used for delivery of anti-tumor drugs[43]. Various researchers have shown through their studies that polypropylenimine dendrimers can efficiently deliver tumor necrosis factor α-gene into colorectal adenocarcinoma cells to restrain the development of colorectal malignancy without causing toxic effects in the animals, signifying that dendrimers are an encouraging carrier for the delivery of target focused anti-tumor genes in treatment of cancer[44], [20].

4. NANO-HYDROGELS:

Hydrogels are the nano-sized networks having the property of swelling.They are created via non-covalent interactions or covalent cross-linking of polymer chains intonano-sized hydrogels also known as nano-gels[45]. Nano-gels have piqued attention in medicine as imaging labels and targeted medication release while lowering systemic adverse effects because to their huge surface area to volume ratio, size tunability, regulated drug release profile, superior drug loading facility, and accessibility to environmental stimuli[45], [20].

Nano-hydrogels can be used for a variety of purposes, including:

- They have a lot of consistency.
- They have a high level of blood compatibility[46].
- They are simple to link to targeted agents.
- Low cytotoxicity is demonstrated[20], [46].
- When used as gene carriers, they perform admirably[20].
- Have the potential to be used in controlled delivery systems that are taken orally[20].

5. NANO-SHELLS:

Another widely used nanotechnology in cancer is nano-shells. Nano-shells are dielectric cores with diameters ranging from 10nm to 300 nm. They are frequently made of silicon and topped with a thin metal casing usually of gold[47], [26]. Using UV-infrared emission/absorption arrays, these nano-shells convert plasma-mediated electrical energy into light energy signals that could easily be detected. Nano-shells are required because their imaging is devoid of heavy metal toxicity, despite their large size limiting their applicability[48].Gold-coated nano-shells with a dimension of 120nm were employed by Rice University researchers to remove cancer tumors in mice. Nano-shells may be designed to attach to malignant cells found everywhere in the live body by attaching antibodies or peptides to their surfaces. By irradiating the location of the carcinoma clusters with an infrared laser beam, which penetrates through tissue without heating them helps in killing those cells perfectly. The gold metal coated on the nano-shells is sufficiently heated to kill cancer cells when such nano-shells are bombarded on them[30].

6. NANO-CANTILEVERS:

On the nanoscale, cantilevers are microscopic flexible beams that are stacked in a row. Biosensing is possible with cantilevers because these tiny probes vibrate spontaneously at a frequency dictated by mechanics and mass characteristics. When a biological molecule bonds to this nanoscale probe, it alters the baseline probe frequency, which is normally measured by a change in the probe's light deflection pattern easily detected by the detectors or by other electrical means[49]. Cantilever vibrations are predominantly deflected in atomic force microscopy (AFM) force feedback mode to generate real-time pictures[20], [49].

The following are some of the stated benefits of employing nanoscale cantilever devices in cancer detection:

- They don't need to be labelled with fluorescent or radioactive materials.
- They're capable of detecting cancer in liquid samples[20].
- The technology can readily be transferred to “chips” to be utilized in test facilities helping in cancer providing cancer diagnosis [50]
- Because of their cheaper cost in terms of sample preparation, time, and materials, they've also been labelled a "simple replacement" for polymerase chain reaction techniques and detection technologies.
- Nanometre cantilever devices, in which cantilevers are coated with specialized receptors, might be utilised to detect disease-specific molecules like DNA or protein in a very sensitive and rapid way[51], [20]. (17)

7. CARBON NANO-TUBES:

Carbon nanotubes are yet another type of nanodevice that may be used to locate biomarkers related to cancer[9], [52].Researchers have routinely put polymer coatings on the exterior of carbon nanotubes to make them biocompatible in their attempt to turn them into nanoscale wonders. They have been studied as clinically useful drug delivery and imaging agents. Carbon nanotubes maintain their potential to bind exceptionally to high number of therapeutic and imaging molecules in a secure yet reversible way, according to Stanford University researchers[30].Researchers have used single-walled carbon nano-tubes as high-resolution atomic force microscopy (AFM) tips to show that specific kilobase-size DNA configurations may be seen, particularly from single-base mismatch sequential patterns[9], [52].

The researchers also discovered that when the carbon nano-tubes were dissolved in normal physiological buffer and blood serum, the therapeutic payload was preserved, but the drug was released fast from the nano-tubes in the acidic environment. This makes them useful in killing cancer cells as the tumor cells also have an acidic environment hence the drug from nano-tubes is easily released in them. The researchers also demonstrated that tumor-targeting chemicals and imaging contrast agents could be fastened to nano-tubes, paving the way for multipurpose nanodevice that can both detect and treat cancers in a living body[30].

8. NANO-RODS:

Nano-rods completely covered with cetyltrimethylammonium bromide which is a cationic surface active agent used in various synthesis are internalised into cells via a nonspecific uptake pathway within hours, whereas careful removal of cetyltrimethylammonium bromide from nano-rods which are already functionalized with folate causes their accumulation on the cell surface over the same time period. Hence, when irradiated at the nanorods' longitudinal plasmon resonance, the nano-rods render tumor cells more vulnerable to photothermal damage in either scenario, resulting in considerable blebbing of the cell membrane[53], [30].

A rising amount of research has shown that gold nanorods may be used to create extraordinarily brilliant imaging agents.Researchers at Georgia Institute of Technology discovered that by linking gold nanorods to an antibody that binds to tumour cells, gold nanorods will align themselves in an ordered fashion on the surface of cancer cells, further intensifying the optical signal produced by the nanorods and providing a unique optical signature for tumour cells[30].

9. NANO-WIRES:

Nanowires are another form of nanodevice used in cancer diagnostics. They may be produced from a variety of materials, including semiconducting, metallic, and magnetic materials, as well as oxides and polymers of various compositions. In order to employ nanowires as target-focused materials, they are coated with ligands. The particular interaction between the target and its capture molecules causes a change in charge density, which is turned into measurable data in the electric field of the nano-wire devices, enabling very efficient detection of biological targets.Silicon nanowires have been produced for the detection of specific DNAs. Silicon nano-wire FETs with various surface receptors have been designed and connected into arrays, resulting in nano-wire arrays that are ideally suited for selective, highly sensitive, multiplexed, and label-free biomarker assays.

The incorporated control nano-wires may help to limit the number of false positive outcomes even further. Nucleic acid receptors integrated into arrays may enable real-time telomerase activity studies utilizing samples collected from only 10 tumor cells without the use of repetitive amplification procedures.

10. NANO-BARCODES:

Mirkin and colleagues[24], [54]described a novel technique to protein and nucleic acid detection based on biobarcode-amplification (BCA). This method employs both colloidal gold nanoparticles and magnetic microbeads, with gold nanoparticles being modified with both target capture strands and bar code strands, which are then hybridised to bar code DNA, and magnetic microparticles being changed with target capture strands. In the presence of target DNA, gold nanoparticles and magnetic microbeads create sandwich structures that are magnetically separated from solution and washed to remove unhybridized bar code DNA. A colorimetric approach is used to detect the barcodes (hundreds to thousands per target). This combined capture and detection approach is four to six orders of magnitude more sensitive than typical ELISA (enzyme-linked immunosorbent test) for proteins, with equivalent sensitivities to PCR.

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