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REVIEW ARTICLE

NANOTECHNOLOGY IN CANCER THERAPY

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ABSTRACT

Cancer is caused by damage of genes which control the growth and division of cells. Detection/diagnose/treatment is possible by confirming the growth of the cells and treated by rectifying the damaging mechanism of the genes or by stopping the blood supply to the cells or by destroying it. The application of nanotechnology for cancer therapy has received considerable attention in recent years. Cancer nanotechnology (an interdisciplinary area of research in science, engineering and medicine) is an upcoming field with extensive applications. Recent developments in nanotechnology have provided researchers with new tools for cancer imaging and treatment. This technology has enabled the development of nanoscale devices that can be conjugated with several functional molecules simultaneously, including tumour-specific ligands, antibodies, anticancer drugs, and imaging probes. Since these nanodevices are 100 to 1,000-fold smaller than cancer cells, they can be easily transferred through leaky blood vessels and interact with targeted tumour-specific proteins both on the surface of and inside cancer cells.
Keywords: tumour, chemotherapy, liposomes, nanoparticles, treatment

INTRODUCTION

Cancer is one of the major causes of mortality. The worldwide incidence of cancer continues to increase. Cancer is known to develop via a multistep carcinogenesis process entailing numerous cellular physiological systems such as cell signalling and apoptosis, making it a highly incomprehensible and complex disease. The most common cancer treatments are limited to chemotherapy, radiation, and surgery.

Greater targeting selectivity and better delivery efficiency are the 2 major goals in the development of therapeutic agents or imaging contrast formulations. At present, non-invasive imaging approaches, including x-ray–based computer-assisted tomography (CT), positron emission tomography (PET), single-photon emission tomography, and magnetic resonance imaging (MRI), are used as important tools for detection of human cancer.[1-2]

The development of tumour-targeted contrast agents based on a nanoparticle formulation may offer enhanced sensitivity and specificity for in vivo tumour imaging using currently available clinical imaging modalities.[3]

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. By creating nanometres-scale structures, it is possible to control fundamental characteristics of a material, including its melting point, magnetic properties, and even color, without changing the material's chemical composition.

The theme of nanotechnology is the control of material on a scale of 1 to 100 nanometres and fabricates the devices on this scale of length. On nano scale, there is vastly increase in ratio of surface area to volume. Due to this, materials at nano scale show very different properties compared to what they exhibit on a micro scale, enabling unique applications. For instance,

• Opaque substances become transparent (copper),

• Inert material becomes catalysts (platinum),

• Stable material turn combustible (aluminium),

• Solids turn into liquids at room temperature (gold),

• Insulator becomes conductors (silicon).[4]

By applying a vast and diverse array of nanoparticles, whose design derives from the engineering, chemistry, and medicine fields, to molecular imaging and targeted therapy, cancer nanotechnology promises solutions to several of the current obstacles facing cancer therapies. Nanotechnology is a "disruptive technology" which drives a new generation of cancer preventive, diagnostic, and therapeutic products, resulting in dramatically improved cancer outcomes. Nanoparticle drug delivery using biodegradable polymers is expected to provide a more efficient way to overcome some of these problems.

Nanoparticles:

Nanoparticles have a mesoscopic size range of 5 to 200 nm, allowing their unique interaction with biological systems at the molecular level. As a result of their material composition, nanoparticles are capable of self-assembly and maintaining stability and specificity, which are crucial to drug encapsulation and biocompatibility. Recent progress in cancer nanotechnology raises exciting opportunities for personalized oncology in which diagnosis and treatment are based on the molecular profiles of individual patients.

In this, we will address first the types and characteristics of nanoparticles; second, how nanoparticles can be used as drug delivery systems and imaging devices to increase the efficacy per dose of therapeutic or imaging contrast agents; and last, how nanoparticles will be further developed to improve their functionality in cancer treatment and imaging.[5-7]

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Nanocarriers can offer many advantages over free drugs. They:

• protect the drug from premature degradation;

• prevent drugs from prematurely interacting with the biological environment;

• enhance absorption of the drugs into a selected tissue (For example, solid tumour);

• control the pharmacokinetic and drug tissue distribution profile;

• improve intracellular penetration.

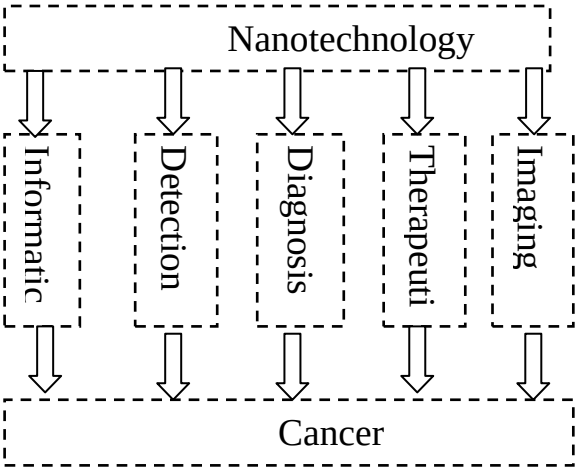

Figure 1: Schematics diagram showing nanotechnology applications in cancer

NANOPARTICLES FOR TUMOUR TARGETING AND DELIVERY:

Types of Nanoparticles as Drug Delivery Systems:

1. Liposomes
2. Polymeric Nanoparticles (Nano spheres and Nano capsules)
3. Solid lipid particles
4. Nano crystals
5. Polymer Therapeutics such as dendrimers, fullerenes.
6. Inorganic Nanoparticles (e.g. Gold & Magnetic Nano particles)

Liposomes and Other Lipid-based Nanoparticles

Liposomes are the small vesicle of spherical shape that can be produced from cholesterols, non toxic surfactants, sphingolipids, glycolipids, long chain fatty acids and even membrane proteins. Liposomes are the most studied formulation of nanoparticle for drug delivery. Several types of anticancer drugs have been developed as lipid-based systems by using a variety of preparation methods. Liposomal formulations have shown an ability to improve the pharmacokinetics and pharmacodynamics of associated drugs. Liposome-based formulations of several anticancer agents (Stealth liposomal doxorubicin [Doxil], liposomal doxorubicin [Myocet], and liposomal daunorubicin [DaunoXome]) have been approved for the treatment of metastatic breast cancer and Kaposi's sarcoma. [8-14]

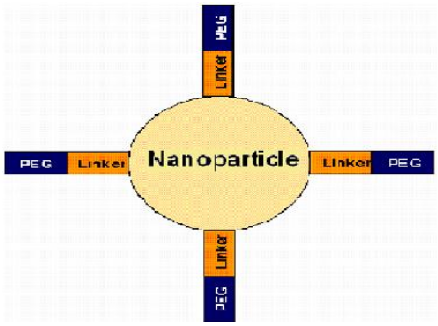

Figure 2: Structure of Lipid-based Nanoparticle

First generation liposomes have an unmodified phospholipid surface that can attract plasma proteins, which in turn trigger recognition and uptake of the liposomes by the mononuclear phagocytic system (MPS), which is synonymous with the reticuloendothelial system, resulting in their rapid clearance from the circulation. The Surface-modified liposomes (Stealth) have hydrophilic carbohydrates or polymers, which usually are lipid derivatives of polyethylene glycol (PEG) grafted to the liposome surface. While this surface modification has solved the problem of fast clearance from the circulation, yielding liposomes with a significantly increased half-life in the blood, the challenge remains to attain preferential accumulation of liposomes in tumour tissues. One strategy to achieve tumour-specific targeting is to conjugate a targeting moiety on the outer surface of the lipid bilayer of the liposome that selectively delivers drug to the desired site of action. For example, an immunoliposome has antibodies or antibody fragments conjugated on its outer surface, usually at the terminus of PEG. Several studies have documented improved therapeutic efficacy of immunoliposomes targeted to internalizing antigens or receptors compared with that of nontargeted liposomes.[15-20]

Polymeric Nanoparticles

To reach the targeted tumour tissue, nanoparticles must be able to stay in the bloodstream for considerable lengths of time without being eliminated. Nanoparticles with no surface modification are usually caught by the MPS, primarily the liver and spleen, during circulation, depending on their size and surface characteristics.[21]

To overcome this problem, nanoparticles can be coated with hydrophilic polymers. Coating can efficiently protect nanoparticles from capture by macrophages.[22-24] The increased hydration also helps nanoparticles to be more water soluble and less sensitive to enzymatic degradation, therefore enhancing biocompatibility.[25-26] Recently, a nanoparticle formulation of paclitaxel bound to albumin (Abraxane or ABI-007) was approved for the treatment of metastatic breast cancer. In a Phase III clinical trial, ABI-

007 showed greater therapeutic efficacy and increased response compared with free paclitaxel. Currently, more than 10 formulations of anticancer polymeric nanoparticles have entered clinical development, including paclitaxel poliglumex (Xyotax) N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer-camptothecin (MAG-CPT) and HPMA-DOX (PK1)[27-29]

Multifunctional nanoparticles for tumour imaging

Tumour imaging plays a key role in clinical oncology, with radiological examinations able to detect solid tumours, determine recurrence, and monitor therapeutic responses. Conventional tumour imaging approaches such as CT and MRI focus mainly on delineating morphological features of the tumour, tissue, and organs, such as the anatomic location, extent, and size of the tumour, at various levels of spatial resolution and contrast.

Recent advances have stimulated the emergence of the new field of "molecular imaging," which focuses on visualizing or imaging biological events and processes in living systems, including patients. [30]

Current molecular imaging approaches, including PET, single-photon emission tomography, and optical imaging including fluorescence-mediated tomography and near-infrared fluorescence reflectance (NIRF) imaging, have shown a high sensitivity in non-invasive tumour imaging. [31-33]

A commonly used PET imaging probe, F-labeled fluorodeoxyglucose (FDG), can only localize tumours by identifying cells in the body that have increased glucose uptake and metabolism, allowing for the detection of those tumours. However, it is not suitable for tumour types with a low glucose uptake. It is well recognized that the development of novel approaches for early cancer detection and effective therapy will significantly contribute to the improvement of patient survival. The development of nanoparticles as imaging contrast agents also makes it possible for the production of multifunctional nanoparticles with the capacity of targeted tumour imaging and delivery of therapeutic agents. In comparison with radioactive probes (i.e., F-labeled FDG) used for PET imaging, nanoparticles have both greater surface areas and more functional groups that can be linked with multiple diagnostic and therapeutic agents.[34-38]

Advances in nanotechnology have shown the promise of nanoparticles for tumour-targeted drug delivery and non-invasive tumour imaging. With unique pharmacokinetics, nanoparticles with sizes between 10 to 100 nm have a prolonged circulation time since they are usually not taken up by the MPS within the liver or excreted by the kidney, common limitations to the delivery of small molecular imaging agents or drugs. Such nanoparticles can navigate the vasculature and cross barriers through small capillaries into tumour cells. Nanoparticles of specific sizes can be synthesized under controlled conditions to obtain the desired optical and magnetic properties and levels of therapeutic agents attached to the particles. These properties offer the opportunity to design "smart" nanoparticles, including target-specific contrast agents, multimodality imaging probes, or even multifunctional reagents for simultaneous imaging and treatment. [39-43]

Quantum Dot Nanoparticles

Semiconductor quantum dots (QDs) are nanometre-scale, light-emitting particles with unique optical and electronic properties such as size-tunable light emission, improved signal brightness, enhanced stability of the fluorescent signal, and the ability to simultaneously excite multiple fluorescent colors.[44]

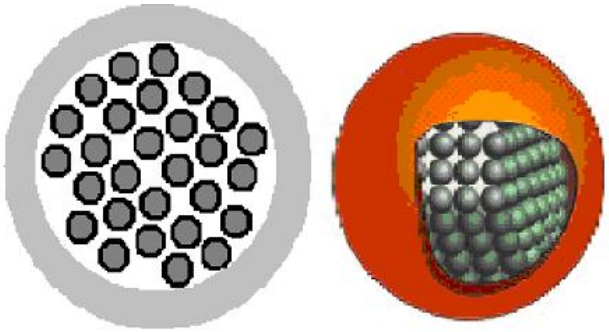

Figure 4: Structure of Quantum Dot Nanoparticles

These properties are most promising for improving the sensitivity of molecular imaging and quantitative cellular analysis by 1 to 2 orders of magnitude.[45] Recently QDs producing NIRF signals have been developed. NIRF light penetrates much more deeply into tissues compared with visible fluorescence and allows for the detection of signals inside animals, as compared with visible fluorescent signals, which can only pass through several millimetres in the tissues. A major advantage of NIRF QDs is that their emission is well beyond the spectral range of the fluorescence signal produced by blood and tissues (autofluorscence), resulting in imaging with a high signal-to-background ratio.[46]

Magnetic Iron Oxide Nanoparticles

Super paramagnetic iron oxide (SPIO) or iron oxide (IO) nanoparticles are becoming increasingly attractive as the precursor for the development of a target-specific MRI contrast agent. IO nanoparticles have unique paramagnetic properties, which generate significant susceptibility effects resulting in strong T2 and T*2 contrast, as well as T1 effects at very low concentrations.[47-50]

In addition to the previously described unique properties and advantages of nanomaterials, IO nanoparticles have a long blood-retention time and are generally biodegradable and considered to have low toxicity. Several forms of IO nanoparticles have been used in clinical settings and have proven to be safe for human use. Some recent studies have demonstrated that IO nanoparticles can be internalized by various cell lines, which allows for magnetic labelling of the targeted cells. These features give IO nanoparticles great advantages for in vivo tumour imaging and drug delivery compared with other types of nanoparticles. [51-56] Recent efforts also focus on the development of ultrasensitive magnetic nanoprobes for tumour imaging. Using magnetism-engineered iron oxide nanoprobes that are conjugated with HER-2 antibodies, Lee et al showed an enhanced sensitivity of MRI for the detection of HER-2 expressing cancer in an animal model compared with that of commonly used SPIO probes. This new generation of magnetic nanoparticles should provide us with a powerful contrast agent for cancer detection.[57]

 ISSN: 2250-1177 CODEN (USA): JDDTAO

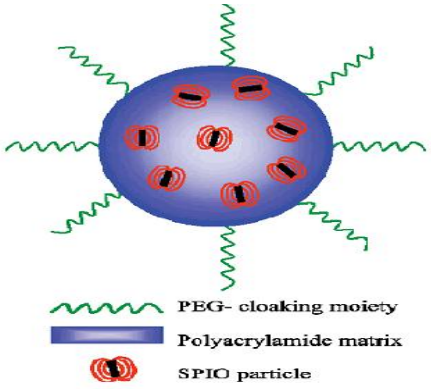

Figure 2: Structure of a Superparamagnetic Iron Oxide (SPIO) Poly Acryl amide Magnetic (PAM)

8. Dendrimers

Dendrimers are a unique group of nanoparticles that are highly suitable for effective delivery of drugs, particularly for cancer treatment. Dendrimers can be synthesized by controlled, repeated polymerization reactions to engineer a desired shape and size. The main advantage of dendrimers is their exclusive branching point that is available for conjugation to multiple entities , including targeting proteins, treatment moieties, and even apoptosis factor ligands . Chemotherapy drugs, when incorporated into the core of the dendrimer, do not affect healthy cells. Antibody-dendrimer conjugates have been used for radiolabeling with minimal loss of immunoreactivity. Some research shows that the anti-PSMA antibody J591 when conjugated to a dendrimer containing a fluorochrome, can be used for targeting prostate cancer and has potential as an efficient delivery system for therapeutics and imaging agents The dendrimer can be engineered so that when it gets into the target tumor cell, it can change its conformation, allowing the incorporated moiety to be released to the tumor site, efficiently suppressing tumor growth. The size, tenability, and multifunctional capability to enhance multiple drug interactions to deliver a chemotherapeutic agent to the specific tumor site make dendrimers an excellent nano-carrier for tumor targeting and therapy.[58]

Gold Nanoshells

Gold nanoshells are useful in detecting tumors and metastasis in many solid tumors. The main advantage of the gold is its potential for cancer detection and treatment of cancers using near-infrared light. In a study where silica/gold nanoshells were used to treat breast cancer in vivo, the nanoshells were injected into the tumor site and irradiated with 820 nm, light pulses. The tumor site increased in temperature when irradiated with light, and thus this system had the ability to destroy the tumor cells without causing any harm to the surrounding, normal cells. In another step forward, gold nanoshells were conjugated with ligands for specific accumulation in oral squamous carcinoma cell lines (HSC 313 and HOC 3 Clone 8) . Furthermore, these kinds of nanoshells have been used for targeted delivery and therapy of many cancers, including breast and prostate cancers. [59]

Carbon Nanotubes

Another type of nano device for biomarker detection is carbon nanotubes (CNTs).Using single-walled carbon nanotubes as high-resolution atomic force microscopy (AFM) tips, Woolley et al. Showed that specific sequences of kilo base-size DNA can be selectively detected from single-base mismatch sequences. Specifically, target DNA fragments were first hybridized with labeled (for instance, strepavidin-labeled) oligonucleotides, and then AFM was used to directly detect the presence and special location of the labels. This technique enabled the simple and direct detection of specific heliotypes that code for genetic disorders such as cancer. CNT-modified electrodes can amplify the electrochemical signal of guanuine bases, which has been used for label-free electrochemical detection of DNA at nanomolar concentrations. More recent work has utilized CNTs as nanoscale carriers for imaging and therapeutic agent delivery.[60]

Nanowires

Nanowires are available in metallic, semiconductor, magnetic, oxide, and polymer compositions and are promising as ultra small chemical and biological sensors. Functionalized nanowires are coated with capture ligands such as antibodies. For personal use only.oligonucleotides. In the presence of target molecules, the specific binding between target molecule and capture molecule generates an immediate conductivity change within the nanowire that can be measured.[61]

Implications and future directions

Cancer is known to develop via a multistep carcinogenesis process and to progress using several complex survival mechanisms, such as self-sufficiency in growth signalling, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tumour invasion and metastasis.[62]

Molecularly targeted therapy is a recent introduction acknowledging our increased understanding of these cancer behaviours at the molecular level. Success of targeted therapies depends on expression of the targeted molecules, which can also serve as cancer-specific biomarkers. [63]

The development of multifunctional nanoparticles may contribute significantly to the realization of individualized therapy for cancer. Ideally, for constructing multifunctional nanoparticles, an appropriate combination of agents (therapeutic agent and targeting moiety) will be chosen based on accurate biological information within the tumour (molecular biomarker profiling of the patient) with imaging material attached on the nanoparticle surface. Nanoparticles may eventually be capable of detecting malignant cells (active-targeting moiety), pinpointing and visualizing their location in the body (real-time in vivo imaging), killing the cancer cells with minimal side effects by sparing normal cells (active targeting and controlled drug-releasing system), and reporting back that their payload has accomplished its mission (monitoring treatment effects in real time).[64]

Detection and diagnosis through nanotechnology

Another important issue to be addressed is cancer diagnosis through nanotechnology. In order to provide early and thus more effective cancer treatment, early

detection of the disease is crucial. Two approaches to cancer detection may be envisioned and they include

• In vitro (laboratory-based) diagnostics

• In vivo diagnostics.

In vitro (laboratory-based) diagnostics

Laboratory-based (in vitro) nanotechnology methods are based on the concept of computer chips. For example, with the use of some recent discoveries in nanoarrays, we can now detect multiple biomolecular markers at very low concentrations in various biological fluids. There are currently two equally effective nanoarray methods.

The first method involves nanowires (Figure 20) connected to a high-sensitivity electronic ammeter. Each nanowire is designed to be a good binding site for a specific bio molecule. The bio fluid under study is passed through a channel where it is allowed to come into direct contact with the wire array. The conductance of the wires changes as the molecules bind, and detection is made possible by measuring the conductance in real time. [65]

***In-vivo* diagnostics.**

The second method involves a nanoarray of Atomic Force Microscope (AFM) cantilevers which are equipped with antibodies specific to selected molecules. The array is submerged in a biofluid where the molecules that are present are allowed to bind to the antibodies. As they bind, they cause the levers to deflect, and the deflection is measured by a combination of a highly focused laser beam and sensitive photo detectors, with a technique similar to that used in AFM. Both methods can yield data that are highly accurate, even with concentrations in the range of parts per million. Some promising in vivo techniques are currently under development. One method is to use nanoarrays similar to those described above. However, due to conditions that are much more adverse in a living patient, significantly higher concentrations of the desired molecules are necessary for accurate detection. Another method is to implant biosensors directly into the patient and to have them relay gathered information to an external data collector. The major problem with these methods that still remains unresolved is bio fouling or the nonspecific adoption of serum proteins to the sensors.[66] Since serum proteins are present in healthy as well as malignant environments, the accuracy of the measurements can be greatly impaired. This problem has been in the way of effective in vivo detection for quite some time.

CONCLUSION

Cancer nanotechnology field has the potential to better monitor therapeutic efficacy, provide novel methods for detecting and profiling early stage cancers, and for enabling surgeons to delineate tumour margins and sentinel lymph nodes. Nanomaterials have unique features that are attractive, and can be applied to bio sensing. An important aspect of cancer treatment is its early detection. There have been significant improvements largely due to breakthroughs, both, in the bottom-up and in the top-down nanotechnology. A nanoparticle holds new promise as means for earlier detection and better treatment of cancer. Imagine a future where nanoparticles can help detect cancer before it even has a chance to manifest, and selectively destroy cancer cells while leaving the normal cells unharmed. Cancer, in such a circumstance, could become a highly manageable condition. However, despite our current research there is much we still do not understand. Nanoparticles offer a new avenue to tackle these challenges. More research is needed in this promising and dynamic field of cancer therapeutics.

Developments in such areas as in nanoarrays, nanosensors, liposomes, monoclonal antibodies, improved nanoparticles (dendrimers, diamondoids, gold-based nanoparticles, magnetic nanoparticles, and quantum dots) and nanoelectronics are making early detection, prevention and treatment with a high degree of accuracy and ease possible. Also other recent discoveries and inventions in nanotechnology are suggesting that a safe and effective cure for cancer is just around the corner. Of course the hope is to turn cancer into a manageable ailment that we can treat and we can live with.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO