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Potential and Automotive Applications of Nanomaterials in Combating Cancer and Stem cell Therapy: An Informative Overview on Nanotherapeutics

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Abstract

Nanotechnology is the multidisciplinary emerging advanced technology that has vast array and potential to revolutionize the society. In recent years, development of novel nanomaterials and their use in biomedicine proves a potential and automotive tool which includes iron, carbon, gadolinium, gold, silicon mediated nanovectors like nanotubes, nanorods, dendrimers, nanospheres, nanoantennas used for the targeted delivery of anticancer drugs as well as imaging contrast agents in stem cell therapy and cancer therapy too. Advance approach of nanotechnology is the early detection of malignant and precancerous lesions from the biological fluids. It plays important role in detection and differentiation of the stem cells which is also a breakthrough in the field of cancer and stem cell research. Nanoparticles can be used to target antigens or bio-markers that are highly specific to cancer cells and for that antigen binding peptide ligands which are attached to the nanostructure which is the potential basis of effective drug delivery systems and to develop nanoscaffolds in nerve regeneration therapy too.

Keywords: Nanotechnology; Nanorods; Nanospheres; Dendrimers; Nanoantennas; Stem cell, Cancer cell

Introduction

Nanotechnology has potential impact in the field of medicine especially in the treatment of cancer and stem cell therapy along with its interdisciplinary automotive role in various advance sciences such as biology, chemistry, bio-engineering and physics. Nanomaterials have controlled physicochemical property, geometry, bioactive polymers surface tailoring and surface charge due to which nanomaterials are used in successfully improved biocompatible and active tumour tissue targeting. This has led to the development of different kinds of nanomaterials used for detecting cancers, deliver the drugs and then combating tumor cells by a variety of therapeutic techniques. Hence, nanomaterials are being used as advanced device for the detection and treatment of various types of cancer as well as to study the emerging possibilities for its applications in anticancer therapy [1]. The reason why we use nanoparticles for cancer therapy is because 99% of drugs used for administration in chemotherapy do not reach the cancer cells with least site specific drug targeting. Nanostructures like nanotubes, nanorods, dendrimers, nanospheres, nanoantennas using iron, carbon, gadolinium, gold and silicon are being effectively used in cancer therapy. Cancer cells have the property of over-expression and hyper activity of Epidermal Growth Factor Receptor (EGFR) due to which the growth rate of cancer cells increases rapidly and they start intake of abnormal amounts of nutrients such as folic acid. In recent studies, it is shown that a single intravenous injection eradicates tumor cells near infrared light, which is harmless to human and can penetrate up to 1.5 inches into the tissues. Stem-cell-based cell therapy also shows promising results for patients living with serious and currently incurable diseases such as cancer, Parkinson disease, Alzheimer disease and diabetes [2]. This potential of stem cells relies on their undoubtedly remarkable properties of differentiation and self-renewal into diverse specialized cells which may have hope in the field of regeneration of tissues or organs for replacing diseased and damaged areas in the body [3, 4]. In recent studies, combination therapy for

effective cancer treatment has been done by using combination two or more drugs optimize the response against cancer cells and delivered in effective way. More and more therapeutic nanomaterials are being developed which can contain multiple loaded drugs with site specific drug dosage and controlled release of drug profiles to treat various types of cancer. Different nanoparticle platforms are being developed to deliver multiple types of drugs for combination chemotherapy [5]. In traditional chemotherapy, intravenous injection of toxic agents causes threat to healthy tissues as well therefore, it resulted in dose-limiting side effects. Nanoparticles have enhanced permeability and high retention caused by leaky tumor vasculatures for better drug accumulation at the tumor sites [6]. Many nanoparticle based chemotherapeutics have been emerged in market recently examples of which include, Doxil (a ~100-nm liposomal formulation of doxorubicin) [7] and Abraxane (a ~130-nm paclitaxel-bound protein particle) [8], both of them, are routinely administered as first-line treatments in various cancer types. The major challenge for combination therapy is ratiometric drug loading. First the pharmacokinetics of every drug being used should be known and unified by delivering the drugs simultaneously to the target site.

Types of Biomedical Nanoparticles

Initially nanoparticles were used as a carrier of vaccines, drug delivery and recently, as cancer chemotherapy agents. The most common drug delivery system for chemotherapy includes polymer based nanoparticles and lipid based nanoparticles. Polymer based nanoparticles are more advantageous as compared to lipid based nanoparticle. Because of very small size of nanoparticles, they easily enter inside human body and cross biological membranes to reach targeted cells, tissues and organs as most suitable carriers for intravenous delivery. Nanoparticles are stable solid colloidal particles consisting of biodegradable polymer or lipid materials and range in size from 10 to 1,000 nm. Drugs can be absorbed onto the particle surface and entrapped inside the polymer or lipid which dissolved within the particle matrix [9]. One of the main goal of nanomedicine is to create medically useful nanodevices that can function inside the body. Among the recently developed nanomedicine and nanodevices, quantum dots, nanowires, nanotubes, nanocantilevers, nanopores, nanoshells and nanoparticles are potentially the most useful for treating different types of cancer [10]. Nanoparticles are prepared in the form of nanospheres (matrix systems in which drugs are dispersed throughout the particle) and nanocapsules (where the drug is confined in an aqueous or oily cavity surrounded by a single polymeric membrane) [11]. Dendrimers are used in drug delivery, gene delivery, sensors, and also as nanoparticles. Dendrimers are used in synthesis of metallic nanoparticles called poly(amidoamine) [PAMAM] and in the cancer therapy, dendrimers are used as nanotemplates for carbon nanotube formation. The dimensions and characteristics of dendrimers are suitable and a very efficient tool for cancer cells imaging. Dendrimers are being applied to many cancer therapies to improve safety and efficiency [12]. Nanogels are being used as drug delivery agents in cancer treatment because they effectively encapsulate therapeutics through electrostatic interactions as pH-responsive nanoparticles. Nanodiamond is a non-toxic substance and can be used in labeling and tracking of cancer cells. Quantum dot nanoparticles are used for imaging and tacking multiple tumors [13].

Nanoparticles for Tumor Targeting and Delivery

We have seen how nanoparticles are much more effective in cancer therapy against other traditional therapies that have been in action till date. Nanoparticles are mostly used in therapeutics as site specific drug targeting in the case of liver or other parts of reticuloendothelial system which depends on the varied hydrophobic and hydrophilic interactions found on the surface of nanoparticles. Liver, spleen and lungs are targeted if the surface of particles is hydrophobic. If the nanoparticles are hydrophilic, they must be prepared with 50% of Poly(N-vinylpyrrolidone) PNVP and 50% of N-isopropyl acrylamide for a better intake by liver. We can also target specific tissues, specific proteins using nanoparticles [14]. Cancer nanotherapeutics is being implemented to solve many limitations of drug delivery and targeting. They are able to carry their loaded active drugs to cancer cells by selectively using pathophysiology. For anticancer drugs to be effective they should be able to reach the tumor tissues with minimal loss of blood and after reaching, drugs should have the ability to selectively kill the tumor cells without affection normal cells. Almost all types of nanoparticles including polymeric nanoparticles, nanocrystals, polymeric micelles, dendrimers, carbon nanotubes have been evaluated to be used in vivo imaging and treatment of cancers [15].

Gold Nanoparticles as Novel Agents for Cancer Therapy

Gold metal due to its surface plasmon resonance, is highly effective in cancer diagnosis and therapy. Gold nanoparticles are conjugated with ligands targeted to biomarkers to allow molecular specific imaging and easier detection of cancer. Gold nanoparticles recently have been used as a very promising agent for cancer therapy. They are small and can penetrate widely throughout the body, mainly accumulating at tumor sites owing to the Enhanced Permeability and Retention (EPR) effect. Gold nanoparticles have a high atomic number which leads to greater absorption of kilo voltage X-rays and provide greater contrast than standard agents. When exposed to a light of specific energy, they resonate and produce heat that can be used for tumor selective photo thermal therapy [16]. One of the therapies of cancer is laser photothermal therapy in which gold nanoparticles convert absorbed light in localized light. Cancer cells can be selectively targeted by conjugating gold nanoparticles with antibodies like Folate and gold binds to the surface of cancerous cells much more strongly than noncancerous cells making easier detection and interpretation [17]. Hollow gold nanoparticles have unique characteristics like higher drug load capacity and less toxicity which are 50 times more effective at absorbing light near the infrared as compared to solid gold particles. These hollow gold particles convert light energy into heat energy resulting in an overheated local environment called photothermal effect. Also, targeted delivery of these hollow gold particles increases their ability to enter cancerous cells. The hollow particles act

as Trojan horse that can load lots of chemotherapy baits [18]. Recently, targeted delivery of gemcitabine using cetuximab as 'targeting agent' and gold particles was coined as a 'delivery vehicle' results in hindrance in growth of tumor in case of pancreatic cancer. Other cancers like breast, ovary, brain and kidney can be targeted using folic acid as well as cancer can be treated with anti-angiogenic agents too. Photodynamic therapy can also be made effective by using nanoparticles as delivery vehicle. Inorganic nanoparticles like CeO2 aid in cancer therapy. Boron and Gadolinium nanoparticles are also known for treating cancer cells with Neuron Capture Therapy (NCT) [19].

Engineered Nanoparticles in Cancer Therapy

Recently, a nanoparticle formulation of paclitaxel bound to albumin was accepted as a therapy for breast cancer. Presently, more than 10 such anticancer formulations have been made with polymetric nanoparticles. Nanoparticle delivery of anticancer drugs to tumor tissues is achieved either by passive targeting or active targeting. Passive targeting enhances drug bioavailability and efficacy by taking advantage of size of the nanoparticles. Active targeting conjugates a targeting ligand or an antibody to nanoparticles to selectively deliver drugs to tumor tissues with greater efficiency [20]. When compared to traditional therapies, the nanoscale of these systems minimizes the irritant reactions at the injection site. Polysaccharides have anticancer properties such as hindering leukemia and solid tumor and increase the immune function. Cisplatin is a widely used antineoplastic alkylating agent for therapy of testicular cancer [21]. Recently, peptides have been used to fabricate multifunctional nanoparticles for targeted cancer imaging and therap. A triggered signal for cancer targeted drug delivery of nanoparticles is generated because of acidic conditions around a tumor caused by hypoxic metabolic state. Greater stability and enhanced lateral bilayer fluidity is provided through nanoporous support, thereby promoting interactions between protocell and cancer cell using a minimum number of targeting peptides. When nanoparticles functionalize with fluorescence dyes such as fluorescein isothiocyanate (FITC), chitosan-coated magnetic nanoparticles are generated which are efficient in cancer cell imaging probes [22]. Multifunctional mesoporous silica nanoparticles for cancer-targeted and controlled drug delivery have three components which are mesoporous silica nanoparticle core, the amino-cyclodextrin, the PEG polymers functionalized with an adamantane(Ad) unit at one end and a folate (FA) unit at the other. A new targeting approach for cancer cells is based on a novel self-assembly process which allows formation of nanoparticle libraries consisting lots of distinct nanoparticle formulations [23].

Applications of Nanoparticles for Diagnosis and Treatment of Lung Cancer

The lung cancer therapeutic agents consist of nanoscale formulations of metal nanoparticles, chemotherapeutic drugs and herbal extract. The most commonly used polymer for lung cancer treatment includes poly caprolactone, polylactic acid, poly-lactide-co-glycolide, alginic acid, gelatin, and chitosan. Chitosan has a cationic nature and is generally used for the delivery to nucleic acids to lung cancer cells. Nucleic acids can also be delivered by means of dendrimers [24]. The major drawback in treatment of lung cancer is lack of tools for early diagnosis of cancer and second major drawback would be creating psychological barriers which hinder the cancer treatment. Future advanced therapies with modifications are going to witness a lot of new and much more effective strategies.

Role of Nanotechnology in Tissue Regeneration Using Stem Cell

Nanotechnology is having various potential uses in nerve and cell regeneration. It has potential to assist in the repair of severed spinal cords via nanostructured scaffolds. Severed spinal cords and subsequently the loss of movement in limbs, is currently incurable. But, nanoscaffolds has been proven to assist repair spinal cord injury in mice in recent research studies. Now, nanocombinatorics are being developed that can be used to analyze stem cells having vast numbers of chemical and physical structures, varying in size. This method used these structures to identify what is required for stem cells to become osteocytes. A similar nanoscale preparation is used for treatment for nerve damage called as silver nanotubes are injected into the brains of mice suffering a stroke and it appears that they are capable of transporting enough oxygen and nutrients to the area to keep the cells alive. This could be used in conjunction with drugs to try and repair or limit the damage of strokes and other forms of nervous system damage.

Tracking of Stem Cell in Stem Cell Therapy

Traditionally, the transplanted stem cells are studied through the histological analysis, which is largely invasive at pre-determined time points after transplant [25]. Thus non-invasive imaging methods are highly needed to monitor transplanted stem cells both qualitatively and quantitatively. By this the prediction of treatment efficacy is predicted, and optimal transplantation conditions are revealed and allowing the determination of delivery route, cell dosage and timing of transplantations [26]. Host tissue administered cells are identified from the contrast agents that are required in cell labelling. Contrast agents such as fluorescent proteins, endogenous biomolecules, organic dyes, and fluorescent lanthanide chelates which suffer from photo-bleaching effects and in which in-vivo chemical and metabolic degradation for optical imaging was included [27]. These shortcomings hinder the efforts to track transplanted stem cell in vivo. The development of optically active nanoparticles provides hope in addressing this challenge [28]. One promising agent is the semi- conductor nanocrystals or quantum dots (QDs), which has non-bleachable fluorescence with controllable wavelength ranging from visible to near infrared [29].

Nanomaterials Aided Fluorescence Imaging

Fluorescent imaging is found to be attractive when it comes in terms of sensitivity, accessibility and cost. Before the cell administration they are pre-labelled with fluorescent nanoparticles. Considering the quantum yield, brightness and

stability issues, fluorescent nanoparticles for stem cell tracking mainly involves quantum dots (QDs), fluorescent polymer nanoparticles and fluorescent silica nanoparticles. Quantum dots (QDs) are highly fluorescent semiconductor nanoparticles with tuneable emissions, high extinction coefficients, sharp emission bandwidths, and good photo stability [30]. The tuneable emission especially at the near infrared region (> ~800 nm) avoids the background signal of auto fluorescence of the animal tissues (emissions are mainly at the visible region, ~300-550 nm). For the long- term tracking of stem cells good photostability is allowed by quantum dots [31]. One major concern of quantum dots for stem cell labelling is their cytotoxicity [32]. To address this issue, inert materials like silica have been used as the coating of quantum dots to add extra functionalities and to decrease their cytotoxicity. [33]. Researchers have designed biocompatible silica and polymeric nanaoparticles containing fluorescent dyes [34]. The biocompatible shell (polymer or silica) prevents organic dyes from oxidation or decomposition and strong fluorescence is generated by concentrating the dyes. Fluorescent silica NPs are mainly Cornell dots (C-dots) [35]. C-dots possess enhanced brightness, photo-stability and versatile surface functionalities which are biocompatible too. Besides C-dots and another type of silica nanoparticles are cyanine dye-doped silica nanoparticles which were synthesized using a reverse microemulsion method and could allow the discrimination between live and early-stage apoptotic stem cells through the different surface distribution. Besides silica nanoparticles, fluorescent polymeric nanoparticles like polystyrene nanoparticles are another popular choice for advanced therapeutics with clinical excellence in cancer treatment and stem cell therapy due to their variety of functional groups [36]. A powerful technique for the high-resolution imaging is the fluorescence imaging with multiphoton excitation. In this technique, noble metal nanoparticles like gold nanoparticles are excited to a high energy state by two or more photons of red or near infrared light simultaneously. Compared with the traditional ultraviolet-visible excitation, near infrared provided relatively higher depth of tissue penetration and minimized the interference of background fluorescence from the biological samples. In addition, gold nanoparticles are generally considered biocompatible compared to other conventionally prepared nanoparticles [37].

Advanced Aspect of Upconversion Nanoparticles

Upconversion is a process in which the sequential absorption of two or more photons leads to the emission of light at shorter wavelength. The most efficient upconversion materials are formed by solid state materials doped with rare-earth ions. In the nanoscale, nanoparticles made of upconversion materials, term coined as upconversion nanoparticles (UCNPs), are utilized as contrast agents in molecular imaging. Imaging with upconversion nanoparticles provides higher sensitivity (lack of auto fluorescence background), less toxic components as compared to quantum dots, high penetration depths (excitation with NIR light) and good photostability (no photobleaching) [38]. While unique, upconversion nanoparticles have certain disadvantages as contrast agents for fluorescence imaging. The upconversion efficiencies have been relatively low usually less than 1%. The excitation thresholds are quite high and the investigated phosphors (generally fluorides) often presented poor chemical stability [39]. A thorough and systematic investigation is still highly needed to reveal their biocompatibility and biostability.

Photoacoustic Imaging of Nanomaterials

Photoacoustic imaging, also called optoacoustic imaging is a biomedical imaging modality based on photoacoustic effect in which absorbed energy from the light is transformed into kinetic energy of the sample through energy exchange processes. It is a hybrid modality, combining high-contrast and spectroscopic-based specificity of optical imaging with the high spatial resolution of ultrasound imaging in which contrast depends on the optical absorption of samples. Thus biological tissues with optical properties such as haemoglobin could be visualized with photoacoustic imaging. As stem cells are usually labelled with biocompatible materials with optical properties such as gold nanoparticles or gold nanorods [40].

Raman Or Surface Enhanced Raman Spectroscopy Of Nanomaterials

Spontaneous Raman spectroscopy has been widely used for monitoring the differentiation of human embryonic stem cells (hESC), adult stem cells, and neural stem cells due to the spectral characteristics of different types of cells. Raman spectroscopy provides an alternative method allowing screening of cultured stem cells from abnormalities (abnormal and trans- formed stem cells) prior to cell transplantation [41]. Raman imaging does not suffer from photobleaching and autofluorescence background interference once near infrared excitation is used. Among various nanoparticles based contrast agents, single-walled carbon nano-tubes showed an intense intrinsic Raman peak (G band at 1593 cm-1) produced by the strong electron photon coupling that causes efficient excitation of tangential vibration in the nanotubes quasi one-dimensional structure upon light exposure [42]. Strong and narrow signal of single-walled carbon nano-tubes, not only enables fast mapping (with integration time of 0.1 s for each mapping point) but also provides easy differentiation from the tissue autofluoresence.

Magnetic Resonance Imaging of Nanomaterials

Magnetic Resonance Imaging (MRI) is a popular non-invasive, non-ionizing imaging technique that can be used to differentiate between pathological and healthy tissues. Magnetic Resonance Imaging (MRI) uses superparamagenetic nanoparticles (SPIONs) are a form of iron oxide nanoparticle that exhibit superparamagnetism[43]. Several forms of iron oxide are their but, magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) SPIONs are used in common. It is a powerful imaging method capable of providing insight into anatomical, physiological, and molecular processes, and it is often used for the diagnosis of diseases, the study of biological functions, and to identify cancer metastasis and inflammation [44]. Optimizing scanner parameters or using MRI contrast agents can enhance contrast between tissues of interest, allowing for clearer imaging of

specific molecules, cells, or tissues. MRI resolution is mostly insufficient at a molecular and cellular scale, unless magnetic contrast agents are employed. SPIONs have been shown to be more efficient and longer lasting than many other agents, and they importantly exhibit long blood retention times, biodegradability, and low toxicity. The magnetic properties of SPIONs can be manipulated by controlling the size of their core and coatings [45]. Labelling stem or progenitor cells with SPIONs allow their migration pattern to be non-invasively monitored in vivo with MRI. This has the possibility to help monitor stem cell therapy in the treatment of diseases such as myocardial infarctions, neurological diseases, and cancer. Success has recently been reported in a rat model of Huntington's disease [46]. Scientists and clinicians have put tremendous efforts to develop new therapeutics that are based on stem-cell. Some of the greatest approaches include bone marrow derived mesenchymal stem cell for graft-versus-host disease [47].

Conclusion

By the means of nanotechnology, cancer and stem cell therapies are taken to a new step of advancement raising hopes for the future advanced and most effective medication. Nanoparticles are now being modified day by day, in such a way that we may get controlled drug delivery through the vehicles or carriers that are biocompatible and non-allergic too [48]. The achievement includes the detection of the cancer to the target drug delivery and finally the controlled release of the drug from biocompatible nanoparticles for cancer treatment too. The nanoparticles also helpful in the detection of the stem cells and its trafficking which by this, providing ease for the technology used in the stem cell therapy. Many researches are still working in this advanced field of nanotechnology with few more advancement in the formulation and preparation of various nanomaterials to make the use of nanotechnology as advanced and crucial mode to cure cancer and tissue regeneration using the stem cell research by increasing its nanotherapeutics aspects [48].

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