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Medical nanotechnology and the development of methods for the diagnosis and treatment of cancer

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Abstract

Nanotechnology is the design and assembly of submicroscopic devices called nanoparticles, which are 1–100 nm in diameter. The application of nanotechnology for the diagnosis and treatment of human disease has been a growing interest in nanomedicine. In recent review, nanoscale differnt platforms has been present for being used as tools for different application including cancer diagnosis and treatment, detection of tumor angiogenesis, nanoimaging, blood-brain barrier, and drug delivery. Nanoscale platforms is including polymeric nanoparticles, polymeric nanoconjugates, carbon nanotubes, peptides and proteins, superparamagnetic iron oxide nanoparticles, endohedral metallofullerene nanoparticles, fullerenes, nanodiamonds, micelles, and dendrimers. In total, nanoscale platforms present unique same properties including biocompatible, biodegradable, functionalization and alteration of surface chemistry, chemically stable in environment, less immunogenic, effective permeation through cell membranes, a long shelf life, little toxicity, delivering optimal drug concentrations to the site of treatment, reduce adverse effects on healthy tissue, dissolving a broad variety of poorly soluble pharmaceuticals, and specifically interacting with certain receptors overexpressed by cancer cells as targeting molecules for drug delivery. The information provided in this review is important in regards to the safe and widespread use of nanoscale platforms particularly in the biomedicine field.

Keywords: Nanotechnology; Nanoparticles; Nanomedicine; Biomedicine; Drug delivery

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1. Introduction

Nanotechnology is the study of functional systems at the molecular level on nanoscale dimensions and it is one of the fast growing areas of research in many scientific disciplines[1]. Modern medicine is not only the product of our greater understanding of biological processes but is also largely dependent on technology to uncover and exploit this deeper understanding.

Nanotechnology takes this enterprise to the submicroscopic level, with tools, such as nanoparticles, being developed at the subcellular level (Size<100 nm) [2].

Nanomedicine refers to the use of nanostructures for the diagnosis and treatment of medical diseases. Nanostructures have the potential to play a critical role in the future of medicine by serving as carriers for drugs, genes, and imaging agents that will bind to targets on injured or neoplastic tissue. Organic

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and inorganic nanostructures that interface with biological systems have attracted widespread interest in the fields of biology and medicine. For instance, nanoparticles that are novel intravascular or cellular probes are being developed for diagnostic (imaging) and therapeutic (drug/gene delivery) purposes (Figure 1).

This article provides an overview of nanoscale differnt platforms and use as tools for different application including cancer diagnosis and treatment, detection of tumor angiogenesis, nanoimaging, blood barrier, and drug delivery.

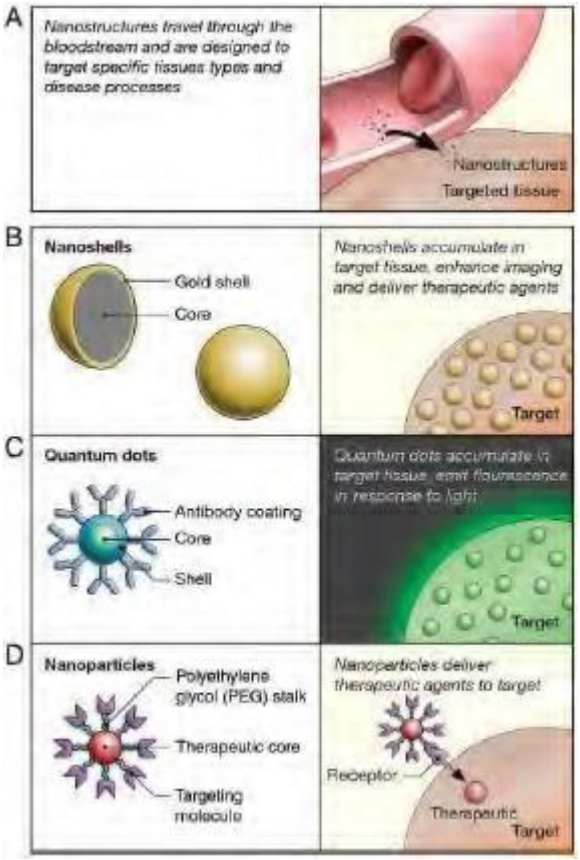

Figure 1. (A) One pathway for nanostructures to reach target tissues is via the bloodstream. (B) Nanoshells can be used in imaging, as well as drug delivery. (C) This schematic shows a quantum dot-based structure with an antibody coating. (D) This shows a nanoparticle functionalized with a targeting molecule interacting with a receptor at the target site.

2. Nanoscale Platforms

2.1. Polymeric Nanoparticles

Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective permeation through cell membranes and stability in the blood stream [3]. Polymers are being developed to create delivery systems with excellent drug and protein loading and release properties, a long shelf life, and little toxicity [4].

Polymers, such as poly-lactic acid (PLA), polyglycolic acid (PGA), poly-lactic glycolic acid (PLGA), poly(ε-caprolactone), polyglutamic acid, and polymalic acid, and their copolymers have been the most extensively studied. These polymers have been used in surgery for 30 years and have proven biocompatibility [5].

Polymers can also be used to coat other types of nanoparticles. Polyethylene glycol (PEG) is a hydrophilic polymer that has been used to coat the surface of nanoparticles, which allows them to avoid clearance by the reticuloendothelial system, reach the central nervous system, and cross the BBB (CNS) [6].

2.2 . Pplymeric Nanoconjugates

These agents bear numerous functional groups (eg. like–OH,–COOH, or –NH2) that are available for covalent binding to a variety of biochemically active groups, which direct them to malignant tumors where they can deliver functional drugs acting on several tumor targets.

Nanoconjugates that carry more than one functional group provide the capability to simultaneously inhibit several tumor pathways, deliver optimal drug concentrations to the site of treatment, and reduce adverse effects on healthy tissue [7].

Nanoconjugate delivery systems are chemical entities unlike unconjugated nanodelivery vehicles (micelles, liposomes, etc.), which are physical but not chemical entities of drug, targeting, and/ or other functional molecules [8]. Nanoconjugates are also smaller in size than micelles and liposomes, less immunogenic, and chemically more stable in plasma
[8].

By virtue of their high molecular weight (m.w.), this class accumulates at the tumor site and has slower clearance than smaller molecules [7]. Particularly relevant to anti-cancer therapy is the need to reduce side effects that arise from drug toxicity to normal cells and to minimize cancer drug resistance.

Polycefin is polymeric nanoconjugates which provides the capability to attach various inhibitors of multiple molecular targets to the same nanoconjugate platform, providing combination therapy with one “superdrug”(Fig.2).

2.3. Carbon Nanotubes

Carbon nanotubes (CNTs) are synthesized by rolling sheets of carbon into hollow tubes that are singlewalled (0.4- to 2-nm diameter), double-walled (1- to 3.5-nm diameter), or multi-walled (2- to 100-nm diameter). Functionalization and alteration of CNT and other graphite nanoplatfom surface chemistry can make the CNTs more

biocompatiable[9].One way to significantly enhance biocompatibility of CNT is by heparinizing the nanotubes [10].

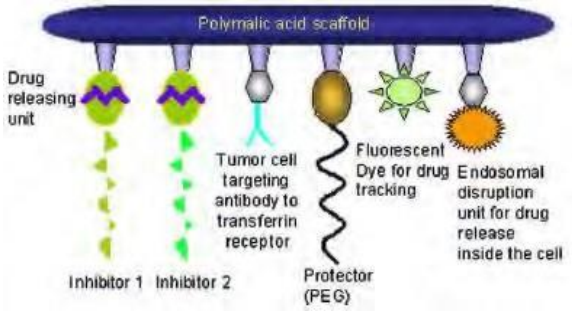

Figure 2. Schematic view of Polycefin with several with the functional modules.

Although CNT toxicity is not fully understood and toxicity study results are conflicting, it is important to be aware of potential complications. Systemic application of CNT can result in oxidative stress in end organs[11] and inhalational exposure of CNT can result in acute lung injury, inflammation, and fibrosis [12].

2.4 . Peptides and Proteins

Peptides and proteins have better defined chemical compositions and molecular weights than most nanomaterials. Peptides interact nonspecifically with cell membrane components and specifically with various cellular receptors. Peptides that specifically interact with certain receptors overexpressed by cancer cells have been successfully developed as targeting molecules for drug delivery and in vivo imaging [13]. Proteins (antibodies in particular) generally have better receptor-mediated targeting than peptides and more specific interaction with receptors. They are widely used for drug delivery and imaging [13]. Multicolored fluorescent proteins highlight angiogenesis within tumors [14]. Multifunctional nanoscale proteins serve for iron oxide loading and cell-specific targeting [15].

2.5. Superparamagnetic Iron Oxide Nanoparticle

Superparamagnetic iron oxide nanoparticles can selectively image proliferating cells in vivo which can provide critically important insights into tumor growth rate, degree of tumor angiogenesis, effectiveness of treatment, and vigor of normal cells. Superparamagnetic iron oxide (SPIO) nanoparticles can be used to image neovasculature in glioma animal models and to image stem cells in vivo and in vitro [16,17].

The signal intensity of these nanoparticles is related to the size of the particle, its position, its concentration, the magnetic field, and dosage of the SPIO [18].

2.6. Endohedral Metallofullerene

Nanoparticle

Metal fullerene cages solubilize metallic agents and prepare them for use in MRI applications [19].One group developed a nanoparticle (gadolinium nitride PEGylated-hydroxylated endohedral metallofullerene) consisting of gadoliniumcontaining metalofullerene (tri-,Gd3N@C80), which was functionalized with polyethylene glycol (PEG) and multihydroxyl groups to significantly increase water solubility and distribution. In vitro experiments showed that the nanoparticle-based contrast agent produced as much contrast as the control clinical agent but at much lower concentrations. The highly stable carbon cage of the nanoparticle prevents the release of toxic metal ions from the metalofullerene core and prevents water molecules from interacting with the metal atoms [20].

2.7. Fullerenes

Well-defined fullerene containing polymers and stimuli-sensitive amphiphilic systems can be readily synthesized [21]. The most common form is C60 and its variations is including C70, C20 (the smallest member), carbon nanotubes (elongated, tubestructured fullerene), carbon nano-onions, and nano buds [22].Fullerenes have the ability to assume different forms and to encage compounds. The unique physical, chemical, electrical, and optical properties of fullerenes and their derivatives have led to their incorporation into new or improved devices and materials and to advancements in engineering, industry, and science [23]. Hydrated fullerenes are radioprotective. Hydrated C(60) fullerene protects against damage from X-ray irradiation (7 Gy) in vitro and in vivo[24].

2.8. Nanodiamonds

Nanodiamonds (NDs) are attractive agents for use in biological and medical applications largely due to their greater biocompatibility than other carbon nanomaterials, stable photoluminescence, ease of purification, commercial availability, and minimal cytotoxicity [25]. Nanodiamonds can be functionalized and conjugated to a variety of molecules for the purpose of cell labeling and drug delivery.The variety of functionalizations that can be attached to nanodiamonds broadens the scope of their potential diagnostic and therapeutic applications.

Nanodiamonds are suitable for controlled drug delivery applications because of their capability to release drug slowly and consistently and their abundant capacity for drug loading due to their large surface area-to-volume ratio

[26].Nanodiamonds have also been used to solubilize and efficiently deliver water-insoluble chemotherapeutic agents to breast and liver tumor cells [26].Nanodiamonds have successfully been used as biomarkers or tracers to label or trace HeLa cells, lung cancer cells, and murine fibroblasts[27]. NDs have a tendency to form agglomerates. Research is ongoing to determine the long-term cytotoxicity and stability of functionalized NDs.

2.9. Micelles

Micelles are amphiphilic spherical structures composed of a hydrophobic core and a hydrophilic shell [28]. Due to their nanoscale dimensions (diameter less than 50 nm) [29] and their hydrophilic shell, polymeric micelles resist elimination by the reticuloendothelial system, which increases their circulation time and ability to deliver drug to the target. Polymeric micelles are highly stable in vitro and in vivo, are very biocompatible, and can dissolve a broad variety of poorly soluble pharmaceuticals.

2.10. Dendrimers

Dendrimers are highly complexmolecules with a core, branches, and endgroups (Fig. 3). The generation (shell) number and the chemical composition of the core, branches, and surface functional groups determine the size, shape, and reactivity of dendrimers. The ability to precisely control their size, shape, and surface functionality during synthesis makes dendrimers one of the most versatile and customizable nanotechnologies.

Dendrimers have myriad applications, including solubility enhancement [30], gene therapy [31], drug delivery [32], nanocomposites [33], bioimaging and cancer treatment [34]. Biocompatible dendrimers have been used as delivery systems for potent drugs, such as cisplatin and doxorubicin, in cancer treatment [35].

Dendrimers can be complexed to metal nanoparticles, but toxicity has been reported with some of these complexes, reducing their attractiveness as imaging agents. Coating the surface of dendrimer–metal nanoparticles with gold has been reported to greatly reduce their toxicity without significantly altering their size and to provide an anchor for attachment of targeting molecules with high affinity to tumor cells [36].

3. Applications

3.1. Cancer Diagnosis and Treatment

Immunoassays that detect the presence of tumor markers are one application of nanotechnology in oncology.

Mechanisms of multiple drug resistance may render conventional chemotherapy ineffective. Cancer chemotherapy also is non-specific in that it kills rapidly dividing cells not only within the tumor but also in normal tissue.

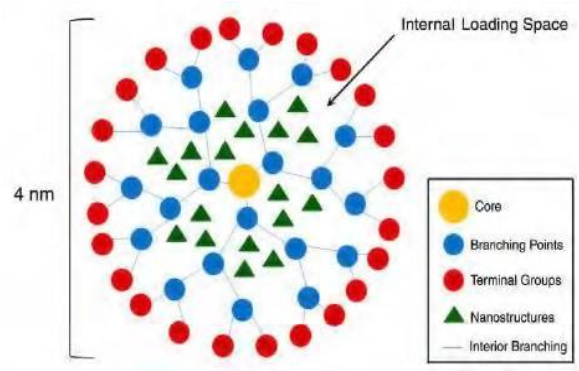

Figure 3. This is a schematic of a third-generation (three shells, G3) dendrimer.

Dendrimers can range from 1 to 10 nm, depending on the number of generations and properties of the terminal groups.

Nanoconjugates can surmount these drawbacks of classical chemotherapy because they can be designed for (1) sustained release of drug, (2) passive enhanced permeability (EPR) effect-based targeting of macromolecules to tumor tissue, (3) ligandbased targeting of cell surface antigens (Fig.4) and modules active in endosomal uptake and membrane disruption, (4) drug release into the cytoplasm, and (5) protection from enzymatic degradation [37].

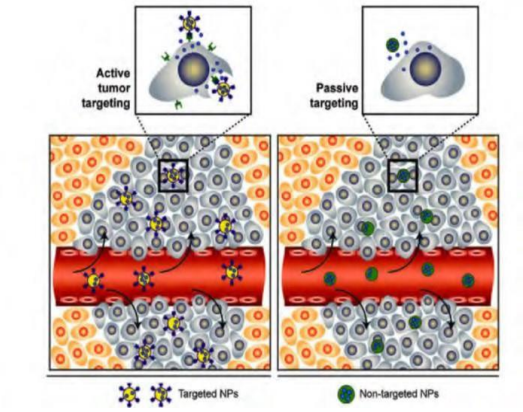

Figure 4. General macromolecular targeting of tumor tissue "passive"(EPR effect) (right), and site-specific targeting of cell surface molecules and receptors "active"(left).

3.2. Detection of Tumor Angiogenesis

Angiogenesis is required for the growth of solid tumors and antagonism of angiogenesis can slow tumor growth. Nanotechnology is being used to identify mechanisms of tumor angiogenesis. To explore the contribution of endothelial precursor cells to the neovascularization of certain tumors,

endothelial precursor cells (EPC) of hematopoietic stem cell origin were labeled with FDAapproved dextran-coated superparamagnetic iron oxide (SPIO) nanoparticles [38]. The labeled cells were injected intravenously into mice and then monitored by MRI for migration and incorporation into growing tumor. This study suggests that nanoparticle-loaded EPC might be used clinically to detect sites of tumor angiogenesis.

3.3. Nano-Imaging

Interest in nano-imaging has grown due to its potential to detectand diagnose cancer and other human diseases at an earlier stage than with current imaging methods. Nanoparticles have been developed with better body compartment distribution and tissue targeting than standard contrast agents [39]. Talanov et al. [40] synthesized a dendrimer-based nanoprobe for dual modality magnetic resonance and fluorescence imaging. Another tumor-detecting nanoprobe was constructed using an ultra-sensitive metal-doped magnetism-engineered iron oxide (MEIO) particle conjugated with Herceptin which be used for detecting small tumors in breast and ovarian cancer [41].

3.4. Blood-Brain Barrier

Drug delivery to the brain continues to be one of the most significant challenges of modern neuromedicine. For drugs to reverse pathologic changes in the CNS, they must be able to traverse the nearly impervious blood–brain barrier (BBB). Unlike other capillaries in the body, the capillaries of the BBB are extraordinarily selective inpermeability; only hydrophobic, nontoxic, and uncharged molecules can pass through the BBB along a diffusion gradient [42]. A nanoparticle drug complex could be effective against CNS disease if it could pass through the blood–brain barrier, find the CNS lesion, target tumor cells specifically, and release a payload of therapeutic agent without altering the vital functions of the CNS. To deliver molecules across the BBB, a few invasive and noninvasive methods have been developed and studied, but their clinicaleffectiveness has not exceeded that of current treatment methods. These methods include lipidization, temporary alteration of the BBB,invasive delivery, convection-enhanced delivery (CED), and active/ facilitated cell transport. Nanotechnology may offer solutions to CNS drug delivery problems because (1) the size of the molecular cargo and the carrying complex can easily be controlled and optimized for drug delivery to the CNS; (2) nanoscale technologies offer specificity to site of action, creating drug targeting that is precise enough to avoid damage to the delicate CNS structures; and (3) the requirement of lipid solubility can be circumvented by using microemulsions of nanoparticle complexes in oil that can cross the BBB [6].

3.5. Drug Delivery

In medicine, the major thrust for nanotechnology has arisen from a need to improve drug delivery, and this effort has led to rapid growth in this sector of the pharmaceutical industry. While nanodelivery of drugs is the most obvious application of nanomedicine, it is certainly not the only application, nor the most powerful and paradigmshifting in terms of medicine and health care. By adding molecular biosensor switches to control drug delivery we can gain sophisticated control over the many steps of drug delivery[2].

Since well-targeted drug delivery is a multistep procedure, the more sophisticated nanomedical systems will have a general strategy that at least conceptually consists of a multilayered and multicomponent approach mirroring the multistep delivery process with antibody or peptide targeting, as shown in Figure 5.

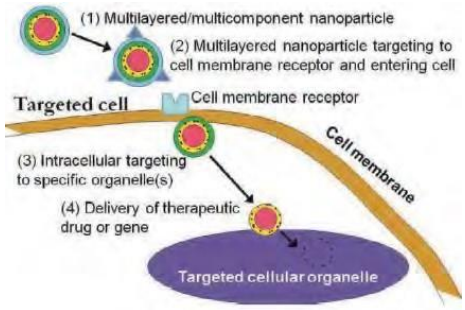

Figure 5. Multi-step targeting and drug delivery with multilayered/multi-component nanomedical devices.

4. Conclusion

Nanovectors, nanostructures, nanoplatforms, and nanoscale objects hold the potential to bring about less invasive and more selective treatment of brain tumors and other CNS diseases. Reaching this potential will requiremore research and the development of nanovectors that are less toxic, more versatile, and more biodegradable that current ones. Poor water solubility of some nanoplatforms must be overcome before they can be utilized in the development of nanodrugs. Many groups have functionalized very stable nanoplatforms such as CNT and gold nanoparticles in order to achieve solubility. Others have designed soluble nanoplatforms such as poly(malic acid) nanoconjugates, which contain various antibodies and oligonucleotides formultitargeted drug delivery . A new generation of nanovectors could incorporate multi-functional compounds and allow multistage, complex delivery of therapeutic compounds and augmented cellular therapies. The

fields of nanomedicine, image-guided drug delivery and therapy, and gene therapy will inevitably converge further and to enable personalized medicine and targeted disease therapy. Advances in each field will drive the development of synergistic, more effective, and less toxic therapies for presently incurable neoplastic and non-neoplastic diseases of the CNS.

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