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Targeted Therapy in Chronic Diseases Treatment by Nanomaterial Based Drug Delivery

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Abstract: *The application of nanomedicines is increasing rapidly with the promise of targeted and efficient drug delivery. Nanomedicines address the shortcomings of conventional therapy, as evidenced by several preclinical and clinical investigations indicating site-specific drug delivery, reduced side effects, and better treatment outcome. The development of suitable and biocompatible drug delivery vehicles is a prerequisite that has been successfully achieved by using simple and functionalized liposomes, nanoparticles, hydrogels, micelles, dendrimers, and mesoporous particles. A variety of drug delivery vehicles have been established for the targeted and controlled delivery of therapeutic agents in a wide range of chronic diseases, such as diabetes, cancer, atherosclerosis, myocardial ischemia, asthma, pulmonary tuberculosis, Parkinson's disease, and Alzheimer's disease. Understanding of the characteristics of nanoparticles and their interactions with the biological environment will enable us to establish novel strategies for the treatment, prevention, and diagnosis in many diseases, particularly untreatable ones.*

Keywords: Targeted therapy, Nano-material, chronic Diseases.

I. Introduction

Nanomedicine is an emerging approach for the implementation of nanotechnological systems in disease diagnosis and therapy. This branch of nanotechnology can be classified in two main categories: nanodevices and nanomaterials. Nanodevices are miniature devices at nanoscale including microarrays [1, 2] and some intelligent machines like respirocytes [3]. Nanomaterials contain particles smaller than 100 nanometers (nm) in at least one dimension. Recent explorations of biomedical science resulted in the successful improvement of therapeutic agents' design in disease treatment. However, there is a major obstacle before the treatment efficiency of various diseases, which is the delivery of therapeutic agents to the target area. The application of conventional therapeutic agents has limitations such as non-selectivity, undesirable side effects, low efficiency, and poor biodistribution [4]. Therefore, the focus of current research activities is to design well-controlled and multifunctional delivery systems. Association of therapeutic agents with nanoparticles exhibiting unique physicochemical and biological properties and designing their pathways for suitable targeting is a promising approach in delivering a wide range of molecules to certain locations in the body [5]. However, toxicity issues warrant extensive research to ensure high safety for the implementation of these medicines in clinical settings. Considering the promise of nanotechnology in the therapy of human diseases, this review aims to cover various nanomaterial-based drug delivery systems, their applications in the diagnosis and therapeutics of chronic diseases, and other associated challenges.

II. Designing Nanoparticles for Therapeutics

Targeted therapy in disease treatment is the approach of delivering appropriate amounts of therapeutic agent for a prolonged period to the affected area within the body. To achieve this, development of safer and more effective therapeutic nanoparticles is crucial and one of the ultimate goals of nanomedicine. Most of the nanoparticles are taken up within the cells by endocytosis through either clathrin- or caveolae-dependent mechanisms [6-7]. The shape of nanoparticles is also critical for biodistribution due to their internalization by the targeted cells. For instance, rod-

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shaped cationic nanoparticles are easier targets for endosomal uptake than cationic nanoparticles of other shapes, suggesting that these nanoparticles may be comprehended by immune system cells as rod-shaped bacteria [8]. Surface modification of nanoparticles with long-chain polymers such as polyethylene glycol (PEG) was shown to minimize non-specific protein absorption onto the nanoparticle surface. Due to its intrinsic physicochemical properties, PEG is a favorable polymer for therapeutic nanoparticles, which decreases their phagocytic uptake and reduces their accumulation in non-target organs [9].

III. Application of Various Nanocarriers for Diagnosis and Treatment [10-13]

The nanocarriers discussed above are being used for diagnosis and disease control. Various diseases that can be detected and subsequently treated using nanomedicines are discussed below.

3.1 Nanomedicines in Diabetes Management

In the last few decades, diabetes mellitus (DM) has become a chronic metabolic disorder that has impacted the lifestyle of billons of peoples throughout the world. DM ranks among the top five reasons for death in most developed and developing countries. According to the International Diabetes Federation, the number of people affected with diabetes worldwide is 382 million, which has been estimated to reach 592 million in 2035.However, the treatment of DM using nanoparticle-based vehicles is quite effective compared to conventional treatment because of sustained drug release from the vehicle.

3.2 Neurological Disease Control using Nanomaterials

Globally, the most common neurodegenerative diseases include Alzheimer's disease (AD) and Parkinson's disease (PD). The common clinical hallmark of AD is the extracellular deposition of amyloid beta (Aβ) peptide along with phosphorylated tau protein, which leads to irreversible neuronal loss and thereby to loss of memory and decision-making power. Furthermore, the degeneration of dopaminergic neurons of the brain followed by the inhibition of dopamine leads to PD. Bradykinesia, postural instability, rigidity, and resting tremor are the most common clinical symptoms that characterize the disease.

3.3 Nano Drug Delivery System for Alzheimer's Disease

Serious efforts have been made by the scientific community to develop potent molecules and compounds that could mitigate the progression of neurodegenerative diseases. The inability or limited ability to cross the blood–brain barrier (BBB) is the major reason for the limited therapeutic effects of the currently available drug molecules. However, nanomedicines are emerging as a novel strategy to overcome the BBB and to provide the advantage of targeted and sustained release. Additionally, bioavailability for longer durations limits the frequency of dosing and minimizes possible side effects. In preclinical studies, RT-loaded poly(lactide-co-gycolide) (PLGA) and polysorbate 80 (PBCA-80)-coated poly(n-butylcyanoacrylate) nanoparticles have shown potential in brain targeting [12-14].

3.4 Nano Drug Delivery System for Parkinson's Disease

Dopamine (DA) and DA agonists are the most frequent treatment strategies in PD patients. However, limited permeability across the BBB restricts the therapeutic potential of these dopaminergic molecules. Furthermore, frequent doses are necessary to ensure high bioavailability, which eventually leads to systemic side effects such as nausea and dyskinesias.Nano drug delivery systems are quite promising to overcome these limitations, as confirmed by several studies. DA-loaded chitosan NPs facilitate transport across the BBB and minimize the cytotoxicity. A dose-dependent increase in dopamine level was observed after the administration of these NPs [15]. Furthermore, intracranial implantation of scaffolds embedded with DA-loaded cellulose acetate phthalate NPs resulted in sustained drug delivery. The maximum DA entrapment efficiency was 63%, and the DA peak was reported to be highest at day 3 in both the cerebrospinal fluid and plasma of rats while maintaining an adequate level up to 30 days compared to inherent DA levels[16].

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3.5 Targeted Delivery Applications of Therapeutic Nanoparticles

Targeted delivery refers to the successful direction of therapeutic agent and its dominant accumulation within a desirable site. For the efficient targeted delivery, the agent-loaded system should be retained in the physiological system for the preferable time, evade the immunological system, target specific cell/tissue, and release the loaded therapeutic agent [17]. Currently, targeted delivery of nanoparticles is widely studied in cancer treatment. Over 20% of the therapeutic nanoparticles already in clinics or under clinical evaluation were developed for anti-cancer applications. In addition, related research has focused on nanoparticle-mediated therapy for some other diseases, such as neurodegenerative, infectious, autoimmune, etc. diseases.

Active targeting refers to ligand-receptor interaction after nanoparticles reach the targeted site via systemic circulation. Ligand-receptor interaction is possible only if the two components are in close proximity (< 0.5 nm). Active targeting in tumors can be achieved by functionalizing the nanoparticles with proteins, peptides, nucleic acid aptamers, carbohydrates, and other small molecules. Several classes of materials have been developed to date for targeted therapy, including biodegradable polymers, liposomes, dendrimers, nanoshells and nucleic acid-based NPs. In cancer therapy, biodegradable nanoparticles are extensively utilized due to their high biocompatibility. In targeted delivery, sustained release and site-specific delivery are the prime requirements. Another important factor is the stability of nanoparticles for longer retention in blood circulation and finally accumulation in tumors.

IV. Cancer and Challenges in its Therapy

Cancer, usually termed malignant tumors, encompasses a large number of diseases where mutations in the genetic material of the cell are responsible for uncontrolled growth. The impact of cancer and the dismal prognosis for patients include a high mortality rate, poor quality of life and expensive therapy. Much technological development and much research have been undertaken to fight against cancer, such as chemotherapy, injections of micro/nanoparticles, immunotherapy, and radiation therapy. However, these technologies possess some defects associated with systemic delivery, such as poor/low drug concentration at the tumor site, nonselectivity towards cells or tissues leading to toxicity, and the low efficacy of the drugs due their short half-life. In local delivery systems, the drug is delivered directly at the targeted site via implantation.

Currently, the majority of FDA-approved therapeutic nanoparticles are developed as a re-formulation of chemotherapeutic drugs combinations with polymeric nanoparticles. The first nano-drug for cancer treatment was a PEGylated liposomal formulation of doxorubicin (Doxil®, Caelyx®). Doxil is formulated with sterically stabilized liposomes composed of phospholipids, cholesterol, and a lipopolymer (PEG) to achieve extended circulation time and eliminate RES. It is less than 120 nm and thus takes the advantage of EPR in accumulation in the tumor and in resulting in decreased cardiotoxicity [18-20].

V. Conclusion

During the last decade, development of nanoparticle-based therapeutic agents has been extensively studied, and nano-delivery systems are the area of prime importance for specifically targeting the desired area in the treatment of many diseases. Currently, the majority of nanoparticles used for the targeting delivery approach are made of polymers or lipids. Even though polymeric nanoparticles demonstrate great advantages in disease therapy, they also present disadvantages such as difficulties in scaling up, usage of organic solvents in their fabrication process, biocompatibility, cytotoxicity, and immunogenicity. On the other hand, lipid-based nanoparticles exhibit the ability to cross hard-to-reach sites, even without any surface functionalization, because of their similarity to cell membrane. Thus, lipid-based nano-delivery systems are considered as the next generation of therapeutics. The application of nanomedicines has witnessed an unprecedented increase during the last decade. The rationale for developing nanotechnology-based drugs includes factors, such as the need for improved versions of current drugs, site-specific or targeted drug delivery and eventually better patient compliance. Nanotechnology-based diagnosis and treatment strategies have been successfully delivered in both preclinical and clinical trials. The advantage of nanomedicines over conventional treatment includes minimum toxicity and maximum efficacy as a result of controlled drug release and improved pharmacokinetics and

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pharmacodynamics. hus, addressing these aspects is necessary to ensure the safety and utility of nanomedicines in clinics. Additionally, further research is required for the development of synthesis protocols, as for large-scale production, preparation methods should be simple, cost effective and have high batch-to-batch reproducibility. Considering nanotechnology as the most promising area for diagnosis and therapy, additional clinical trials must come from all over the world.

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