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Progress and Perspectives on Nanocarrier Mediated Drug Delivery for Brain-Tumor Targeting

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Abstract-

Brain tumors is one of the most dangerous diseases to be diagnosed and treated, primarily due to the difficulty of crossing the blood-brain barrier to the brain with imaging and therapy agents. Nanoparticles have immense potential as an efficient drug delivery system. In this review, I discussed recent developments in nanotechnology for the delivery of drugs. Throughout recent years, nanotechnology has been involved throughout solving the problems of gene supply and drug supply. Nano systems with various compositions and biological properties have been thoroughly studied for drug and gene delivery applications. In order to ensure an efficient supply of medicines, it is necessary to understand the interactions of nanomaterials with the biological environment, aimed at cell surface receptors, the release of medicines, multiple drug use, the stability of therapeutic agents and the molecular signaling mechanisms of the disease under consideration. Nanomaterials, Quantum dots, chitosan, polylactic/glycolic acid (PLGA), and nanoparticle PLGA have been successfully developed for a variety of anti-carcinogenic drugs including paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone. The rational development of nano systems on the basis of their understanding of biological environment interactions, cell target population, cell surface target receptors is an effective approach to achieving effective drug delivery.

Keywords- nanoparticles, anti-carcinogenic, brain tumor, cancer, polymer nanoparticles

1. Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States. In 2020, the diagnosis and treatment of cancer was hampered by the coronavirus disease 2019 (COVID-19) pandemic. An estimated 1,898,160 cancer cases diagnosed in the United States equivalent of 5200 new cases each day and 608,570 Americans will die from cancer in 2021, corresponding to more than 1600 deaths per day [1]. Nervous system tumors are a type of neoplasm that forms a variety of morphological subgroups, comprising about 3% of all cancers in the world and more common among males than females [2]. They are different patterns of behavior as the diagnosis of new cases of brain and CNS cancer was significant [2,3]. The 5-fold variation between the highest (in Europe in particular) and the lowest (in Asia in particular) has been identified [2]. Published reports have shown that the incidence of brain tumors is different globally in counter-tests [4-6]. The rate of neural cancer mortality worldwide is estimated at 3.4 per 100,000 [2]. Eleven cases of brain cancer are diagnosed in England every day, nine of them dead. Tumors in the US nervous system increased from 11.5 in 1994 to 20.1 in 2008. The increasing trend among elderly people may be due to an increase in their life expectancy. The global prevalence of nervous system tumors among males and females was 3.6 or 2.5 per 100,000; this was 5.9 and 4.1 in both males and females, while 2.8 in males and 2 in females were less developed countries [2]. Factors such as higher life expectancy, urbanization, and lifestyle changes are associated with an increased incidence and death of brain tumors in developed countries compared to other countries in the world [3].

The structure, properties, and behavioral analysis of materials below hundreds of nanometers in size is a relatively new field of scientific research. Nanotechnology has attracted significant interest in cancer therapy in recent years due to its enormous potential to offer an innovative way to overcome the problems of existing chemical healing agents [7,8]. For example, a number of nano vehicle platforms (10-200 nm) are ideally suited for intracellular endocytic absorption, high drug burden, and specific tumor targeting. Artificial

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nanomaterials will significantly improve the therapeutic efficacy of chemotherapy drugs used while reducing the toxicity of non-specific drugs, ensuring the safe and effective treatment of cancer. Over the last few days, enormous efforts have also been made to develop multifunctional therapeutic nanosystems for both cancer diagnosis and treatment that can deliver tumor-specific drugs and monitor their therapeutic reactions at the same time through the visualization of tumor legions within the body [9]. There is no doubt in the near future that the convergence of nanotechnology and biotechnology will revolutionize the whole field of cancer medicine [10]. Matrix an architecture consisting of biodegradable and biocompatible polymers of synthetic or natural origin is used in polymer nanoparticles [11-13]. Nanoparticle formulations can result in a significant reduction in unspecified toxicity via passive or active targeting by the release of therapeutic payloads at cancer sites [14]. But, along with the opportunities, there are always challenges. First, nanomedicine can present a myriad of complete characterization challenges. Second, safety and manufacturing concerns should not be overlooked. Amphiphilic biodegradable polymer NPs for diagnosis and cancer therapy are recent advances in pharmacology. For example, synthetic polyesters such as polycyanoacrylates and related polymers (lactide co-glycolides) PLA or poly(lactic acid) have been used in polymer NPs targeted for drug delivery. Natural polymer-based NPs are more advantageous in terms of efficacy and targeted drug delivery than traditional drug delivery systems. The NPs were prepared using a variety of natural polymers such as dextran, gelatin, albumin, chitosan, and alginate [11,12]. In this review, we will be discussing the NPs based drug delivery system for brain cancer.

2. Aim and Objectives

Under this section, the objectives of the study to achieve the ultimate aim of the study will be highlighted. Following will be the objectives pertaining to the study:

- To demonstrate the current status of brain cancer and available methods
- To review the advantages of nanotechnology with a special focus on polymer-based nanoparticles being utilized for target-specific deliveries of anti-cancer drugs.
- To review future prospects of polymer-based nanoparticles as drug delivery agents in brain tumors.

3. Recent advancement with NPs and brain tumor

Brain tumors are more likely to occur in the West than in the East and are also higher in developed countries than in developing countries. The age-standardized distribution of these diseases in Australia, North America, and North Europe is equally different worldwide, with the lowest incidence in Africa. The influence of the Caucasians is much greater than that of African Americans. According to the latest National Vital Statistics Systems (NVSS) report, the number of deaths among men between 1975 and 2016 was higher among older individuals and higher among whites than among other races [2, 3]. For those over 65 years of age, the mortality rate for all tumors has increased significantly, while for those over 20 years, there have been no major moral changes. This study tracks the revised mortality rates for malignant brain tumors by histology, age, race, and sex. There have been no significant changes in overall death due to these tumors from 1975 to 2016. Mortality has increased significantly in elderly people (aged 65 + years), particularly those aged 75–84 years [4,5,15].

Increased imagery, such as radioisotope imaging, increased the rate of tumor detection in the nervous system. Early diagnosis and development of therapeutic methods would also increase the survival rate of such patients and increase the likelihood of increased brain metastases in these patients. Brain metastases are one of the most common forms of brain tumors and are associated with significant mortality and morbidity. Age-standardized incidence rates range from 4.3 to 18.6 per thousand years for primary brain tumors [2,16]. Brain tumors are a mixed primary and metastatic group with varying degrees of malignancy. Malignancies are relatively rare, but the incidence of malignancies in highly developed, industrialized countries has increased rapidly. Primary malignant tumors have not only received considerable attention due to their poor

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pronouncements but also due to their direct effects on neurological function, psychological health, and quality of life [3]. These nanostructures acquire unique physical and chemical properties on a nanoscale that cannot be seen in their macroscale due to quantum effects. In addition, thanks to their molecular scale, they can interact with biological systems at the cellular level [12].

New technologies are currently focusing on the design and development of new pharmaceutical formulations or drug carriers, both size-specific and locally-oriented to the specific delivery of active drugs to the tumor site and re-cutting of the reticuloendothelial system [11]. In the last few decades, different nanocarriers [Fig 1] have been developed to be used for drug delivery for the treatment of various neurological disorders by the direct nose to brain targeting [17]. This helps in enhancing the bioavailability of the therapeutic agents at the site of action. Most of these nanocarriers are polymers like ethylene glycol [18-24] lactic-co-glycolic acid [25,26] and chitosan [27-34]. Biodegradable polymers are a useful option for the use of cancer medications. Polymer nanoparticles are solid carriers with a diameter of 10 to 1000 nm, which are made of natural and artificial polymers that are usually biodegradable by simple ester or amide bonding that is hydrating in therapy and in which therapeutic drugs may be adsorbed, dissolved, enclosed, encapsulated and covalently bound to the polymer backbone (Figure 2)[12]. In addition to the most thoroughly studied synthetic polymers, including poly(lactic acid)(PLA), poly(glycolic acid)(PGA) [11], poly(ethylene glycol)(PEG), and their copolymers, due to their biocompatibility, biodegradability and regulatory acceptance. Derived polymers have also been extensively tested for chitosan, alginate, and gelatin [12]. The development of a variety of nanostructured materials for therapeutic and medical applications has contributed to developments in nanotechnology and medicine. Nano-scale drug delivery systems based on polymer micelles, liposomes, and inorganic nanoparticles have undergone extensive research over the last decades due to their therapeutic potential for cancer control. Such nanomaterials offer some unique advantages that other modern cancer therapies cannot achieve. First, nanomaterials have a small number of macromolecules, such as peptides, proteins, and nucleic acids, similar to biologics [13]. In general, they are 10 nanometers in diameter and 100-1000 times smaller than the size of a single cancer cell. Due to the small size and dimensional similarity of the biomolecules, nanomaterials have a much higher intracellular absorption compared to micron particles, which makes them excellent candidates for cancer-driven drug use [35].

In addition, internal nanomaterials can interact with biomolecules in different intracellular compartments, likely influencing the target signal pathways involved in cancer survival and spread. Very precisely, nanomaterials often have enticing ways to overcome the technological obstacles and processes of biological defense of the body. For example, macrophages are easily absorbed in micro-particles whose sizes are comparable to microbial ones. This results in the accelerated elimination of microparticles from the bloodstream of the reticuloendothelial defense system [35,36]. In view of the fact that very small capillaries with a diameter of approximately 2.3 micrometers had been served, well-designed nanomaterials with a controlled size range (sub-200 nm) could be accessed to several areas of the body via the circulating system [37]. Second, due to their vast surface area relative to their total volume, nanomaterials can carry a large number of imaging and/or therapeutic agents. For example, a polymer nanoparticle with an average diameter of 70 nm would contain around 2,000 drug molecules, whereas only nine drug molecules per molecule carry the polymer-drug conjugate. This high nanomaterial loading capacity is very beneficial for the achievement of significant therapeutic efficacy in cancer medicine. They also offer the possibility to enhance the surface of other specific sections for the effective treatment of cancer (such as small molecules, peptides, or antibodies) [37].

Finally, nanomaterials have great potential to overcome many of their limitations. In general, most chemotherapy agents are not readily resolved in aqueous solutions. Paclitaxel is a good example of antifungal drugs that are insoluble in water. Because of its strong apoptotic effects on cancer cells, paclitaxel has been extensively used in the treatment of ovarian, breast, and other cancers[37].Concurrent cellular resistance to multiple lipophilic medicines is a major problem in cancer chemotherapy. This drug resistance may occur

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clinically either as a decrease in tumor size or as a clinical recurrence following an initial positive response to antitumor therapy. Resistance mechanisms may either be directly linked to specific tumor tissue-developed mechanisms or may be linked to a more general problem involving the disbursement of a drug to its specific tissue [38]. Nano-size injectable carriers (5–250 nm) are used in anti-cancer drugs for the targeted brain supply of drugs. These polymer nanoparticles (Np) have been studied since 1995, but only five of them have recently begun phase I clinical studies. Drug trials have been started to date in the treatment of brain tumors for the delivery of macromolecular and nanocarrier systems to the brain [39-44]]. The small, customized surface area of nanoparticles, improved solubility, and multiple functionalities will continue to open many doors to new biomedical applications. In fact, the novel properties of nanoparticles allow them to interact with complex cellular functions in a new way. In this rapidly growing field, cross-disciplinary research is needed and multifunctional devices that can target, diagnose, and treat devastating diseases, such as cancer, can be developed and produced [45,46].

Despite recent changes in surgery and multimodal adjuvant therapy, treatment for brain cancer remains a challenge. Due to the blood-brain barrier and the lack of specificity of potentially harmful drugs, brain cancer drug therapy has been particularly ineffective. Nanoparticles have emerged to solve the problems of current approaches as a possible vector for brain delivery. Multifunctionality can also be designed into a single nanoplatform to provide specific tumor detection, treatment, and follow-up surveillance. Such multitasking is not possible with conventional technologies [14,47]. De Solvation has been used to produce human serum albumin (HSA) nanoparticles. The SNS-PEG-MAL-5000 crosslinker was covalently coupled with HSA-nanoparticles by transferrin or transferrin receptor monoclonal antibodies (OX26 or R17217). As a model drug, loperamide did not normally cross the Blood-Brain (BBB) barrier and was absorbed into the nanoparticles [48-49]. HSA nanoparticles loaded with loperamide or OX26 and R17217 were found in a tail-flick test for intravenous mice (CD-1) showing significant anti-nociceptive effects after injection that loperamide and possibly other drugs can be transported through BBB via transferrin or these antibodies covalently combined with HSA nanoparticles. HSA Nanoparticles with IgG2a antibodies loaded with loperamide regulation had minimal effects [50].

The abundance of research has led to an understanding of genetic, molecular, and cell cancer that provides an avenue for methods that increase the antitumor efficacy of pharmaceuticals while at the same time reducing systemic side effects. Nanoparticle technology is particularly instrumental in the development of a new generation of cancer therapies that are more effective in overcoming the many biological, biophysical, and biomedical barriers to standard body operations. Due to their small size and modifiability, nanoparticles show significant promise in cancer therapy through selective tumor access. Nanoparticles are formulated from a range of substances and developed for controlled and targeted transport of a range of substances. Nanoparticles are ready to use basic cancer morphology and developmental modes, such as rapid cell proliferation, antigen expression, and leaky tumors. Many of the targeted functions of chemotherapy, radiotherapy, immunotherapy, immune detection, thermotherapy, imaging, photodynamic therapy, and anti-angiogenesis are used in the treatment of cancer and the detection of nanoparticles. Modifiers not only help target tumors more precisely, but they also help overcome biophysical barriers, such as the existing blood-brain barrier, by reducing peripheral effects and increasing the relative number of drugs that reach the brain. In addition, many tasks are carried out simultaneously by multifunctional nanoparticles, such as the targeted provision of powerful cancer drugs and imaging material to visualize the efficacy of drugs for follow-up therapy. This review includes the development and modification of nanoparticles for the detection, analysis, and treatment of cancer by a number of recent US and World patents [45].

Improved cancer chemotherapy is promising as a drug delivery system using solid lipid nanoparticles (SLNs). Various barriers that often occur to compounds such as natural tissue toxicity, low specificity and stability, and high drug-resistant tumor cells are partially addressed by the use of SLN. The development of new SLN forms such as polymer lipid hybrid nanoparticles, nanostructured lipid transport, and long-circulation SLN can further enhance this versatile drug carrier's role in cancer treatment.Several obstacles

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frequently encountered with anticancer therapeutics, such as toxicity by healthy cells, lower specificity and stability and a high chance of drug-resistant tumor cells, are at least partially overcome by delivering them using SLN [45]. Brain capillary cells denote BBB (Blood-Brain Barrier) and combine nanoparticles with antibodies that can facilitate their upload and transmission to the brain by targeting molecules expressed by these endothelial cells. Magnetic nanoparticles, such as siRNA, cDNA, and polypeptides, can be enclosed in liposomes and hold large therapeutic molecules. The use of an extracranially distributed magnetic force is another method to improve the transport of magnetic nanoparticles through the BBB. Specific antibodies conjugated nanoparticles targeted to molecules expressed by brain capillary endothelial cells of BBB enhance uptake and transport of drug molecules [46]. Innovative products will be developed as targeted drug supply strategies with novel nanomedicine technologies. The primary areas of research in which nanomedicine plays a key role and needs are targeted drug delivery of various drugs for cancer, AIDS, and brain disorders. The study covers emerging targeted nanomedicines (polymer nanoparticles, solid lipid nanoparticles, polymeric micelle, and liposomes), multifunctional carriers capable of combining target drug delivery and pharmaceutical imagery (polymeric micelle, diarrhea, and magnetic nanoparticles) [49]. In order to be effective, interactions between nanomaterials and the biological environment must be understood, focusing on cell-to-surface receptors, drug releases, multiple drug administration, therapeutic stability, and the molecular signaling mechanisms involved in pathobiology. Several anticancer drugs have been successfully formulated using nanomaterials, including paclitaxel, doxorubicin, 5-fluorouracil, and dexamethasone. In vitro RNAi delivery also included Quantum Point, Chitosan, Polylactic / Glycolic acid (PLGA), and PLGA nanoparticles. Brain cancer is one of the most dangerous diseases to be diagnosed and treated, primarily due to the difficulty of crossing the blood-brain barrier to the brain with imaging and therapy agents. Anti-cancer drugs such as loperamide and doxorubicin, packaged in nanomaterials, crossed the intact blood-brain barrier and released at safe doses in the brain. Nanomaterials, including peptide nanotubes, are a new approach to disease progression control with the aim of focusing on the endothelial receptor and cell adhesion molecules such as integrins, cadherins, and selectins [49].

4. Conclusions and Recommendations

Nano drug delivery systems are apparently very likely to overcome certain barriers to effective inflammation and cancer targeting of cells and molecules. There is also an exciting opportunity to address drug resistance issues in target cells and to make drug movement easier across barriers such as those in the brain. However, the challenge remains to recognize and ensure that these molecules are only released in the target organs in order to prevent healthy tissues. Second, the fate of drugs once delivered to the nucleus and other sensitive organelles are important for understanding. In addition, because nanosystems increase the efficacy of drug delivery, re-calibration of doses may be necessary. The future, however, is exciting and broadly open.

Conflict of interest

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Contributions

RNM conceived the idea and wrote the first draft as well as the final version of the manuscript.

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Figure :

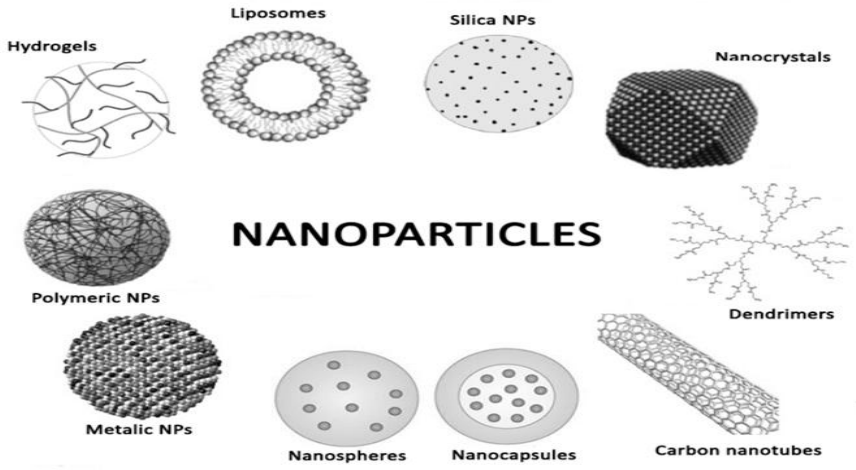

Fig 1: Schematic view of different types of nanoparticulate drug delivery systems

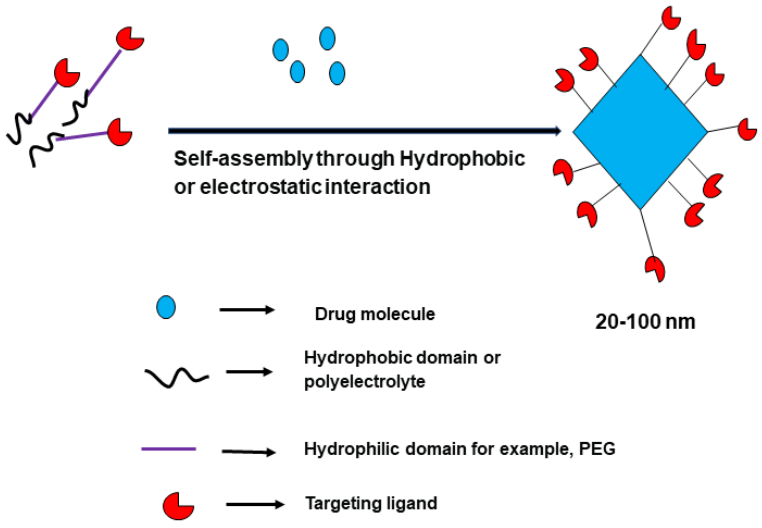

Figure 2. Shows the NPs drug encapsulation. (reproduced from [15])