Nanotechnology helps for Preparation of Drug for Detection of Brain Tumor

Abstract

Nanotechnology and its applications to the field of medicines and pharmaceuticals has emerged a new area for diagnosis of diseases. The inefficacy of conventional methods has led to the development of new strategies and the significant progress of nanotechnology in recent years. The advent of nanotechnology would greatly facilitate the early detection and treatment of brain tumors. This paper will discuss how nanoparticles in the form drug can detection of brain tumor using nanotechnology.

Keywords: Brain tumor; Antisense; Sclerosis; Nanoparticles; Interference

Sudipta Roy[1] and Samir Kumar Bandyopadhyay[2]*

[1]Department of Computer Science and Engineering, Institute of Computer Technology (UVPCE), Ganpat University, India
[2]Advisor to Chancellor, JIS University, India

*Corresponding author: Samir Kumar Bandyopadhyay, Advisor to Chancellor, JIS University, India, Email: 1954samir@gmail.com

Abbreviations: RNAi: RNA interference; ASO: Antisense Oligonucleotides; MS: Multiple Sclerosis; CAD: Computer-Aided Diagnosis

Introduction

High grade gliomas are some of the deadliest human tumours. Conventional treatments such as surgery, radiotherapy and chemotherapy have only a limited effect. Nowadays, resection is the common treatment of choice and although new approaches, such as perioperative magnetic resonance imaging or fluorescent microscopy have been developed, the survival rate of diagnosed patients is still very low. Amongst the new nanotechnology platforms used for delivery into the brain tissue are: polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbon nanotubes, superparamagnetic nanoparticles and nucleic acid based nanoparticles (DNA, RNA interference [RNAi] and antisense oligonucleotides [ASO]). These nanoparticles have been applied in the delivery of small molecular weight drugs as well as macromolecules – proteins, peptides and genes. The unique properties of these nanoparticles, such as surface charge, particle size, composition and ability to modify their surface with tissue recognition ligands and antibodies, improve their biodistribution and pharmacokinetics. All of the above mentioned characteristics make of nanoplatforms a very suitable tool for its use in targeted, personalized medicine, where they could possibly carry large doses of therapeutic agents specifically into malignant cells while avoiding healthy cells.

Brain tumor, stroke, hemorrhage and multiple sclerosis (MS) disease are the life threatening diseases in both male and female. A brain tumor is the most common and widespread disease among these brain diseases. The worldwide cancer incidence of brain tumor is 3.4 per 100,000 people (men: 3.9 per 100,000, women: 3.0 per 100,000. A total of 256,213 affected worldwide (139,608 men and 116,605 women). The trend of new cases is rising and 189,582 sufferers worldwide. Every day about 700 people is diagnosed with a brain tumor [1]. 15 million people are affected by stroke and hemorrhage; of this 5 million die and another 5 million (2002 estimates) are permanently disabled. Today over 2,500,000 people around the world have MS [2].

Early and accurate diagnosis of brain lesion is vital for determining specific treatment and prognosis. However, the diagnosis is a very challenging task and can only be performed by specialists in neuroradiology. There are at least two specialists required to examine and confirm of each medical report on imaging investigations. Any difficulty may necessitate invasive tests such as biopsy and surgery. Currently, the standard lesion pathological classification is based on histological examination of tissue samples through biopsy. Therefore, radiologists are continuously seeking for greater diagnosis accuracy by the modern medical imaging system. According to quantitative analysis of computer-aided diagnosis (CAD), it may aid radiologists in the interpretation of the medical images. Recent studies showed that CAD could help to improve the diagnostic accuracy of radiologists, lighten their increasing workload, reduce misinterpretation due to fatigue or overlooked and improved inter- and intra-reader variability [3].

Automated identification of brain abnormalities in different medical images demands high accuracy since it deals with life. Also, computer assistance is highly sought in medical institutions because it could improve the results of humans in such a domain where the false negative and positive cases must be at a very low rate. It has been proven that double reading of medical images could lead to better abnormal region detection using nanotechnology [4].

Review Methods

The blood-brain barrier regulates the interface between blood, brain, and cerebrospinal fluid (liquor), allowing some substances to migrate in a single or bi-directional manner; in some instances, however, this barrier appears to be almost impermeable to others. The blood-brain barrier ensures an optimal environment for brain functionality, protects it against harmful substances, and allows the supply of nutrients necessary for its metabolism

[5]. The blood-brain barrier can be divided into two major components: (a) Hemato-encephalic barrier makes the boundary-line between the brain capillaries and brain tissue. Movement of the substances is dependent on whether they are fat-soluble or on the transport system. (b) Hemato-liquor barrier separates blood and the cerebrospinal fluid. It is mostly made of the choroid plexuses' epithelium, which produces liquor. Epithelial cells are bound with tight junctions, which are more permeable than those in the brain capillaries. The surface in contact with the liquor contains microvilli, which significantly increases epithelial surface. Another component of the hemato-liquor barrier are the pia mater's capillaries, which are fenestrated and are similar to capillaries in any other region of the body. The hemato-liquor barrier is more permeable and enables the transport of proteins from plasma to liquor by pinocytosis or by specific transport systems. The blood-brain barrier (BBB) enables the transport of a limited number of small hydrophilic molecules (MW < 400 Da). Many anticancer drugs are large hydrophilic molecules, which makes them unable to cross the BBB. A potential possibility regarding the crossing of the BBB is the conjugation of these big molecules with a small nanocarriers, which could help distribute the drug into the brain.

Surgery currently remains as the basic treatment for brain tumours, consisting in the physical removal of the tumour, and the peripheral infiltrating part is often targeted by supplementary treatments. In some cases, surgery becomes unadvisable due to the less than favourable placement of the tumour, e.g. near major blood vessels, or in the brain stem. If surgery becomes impossible, the only viable alternative for the patient are chemotherapy and radiotherapy treatments. Chemotherapy has, on the other hand, a high systemic effect on healthy cells and tissues. In the search for targeted chemotherapy, several nanoparticles have become the main subject of research in this field. Nanoparticles can act as a "postman" in the specific delivery of a chemotherapeutic drug to cancer cells, which will then be eliminated after exposition to this drug. The treatment drugs are usually encapsulated within the nanoparticle, which can be shaped as a cage, shell, bubble etc. However, drug delivery into the tumour cells could also be non-specific. Non-specific delivery is based on the principle that tumours contain leaky capillaries, allowing thus the accumulation of drug loaded nanoparticles within the cancerous tissue [4].

Nanoparticles are promising "theranostic" agents in the treatment of brain tumours. They can be used either as a diagnostic tool, mainly in imaging methods, as well as therapeutically. In clinical practice, there could be less invasive procedures for the patient and could also shorten of the delay between the diagnostic and therapeutic process. The use of nanoparticles to label cancer cells has become a new trend in the diagnostic phase of brain tumours, making them easier to detect earlier by standard imaging methods [5]. The leading imaging methods for brain tumours include computed tomography (CT), and magnetic resonance imaging (MRI). Magnetic resonance commonly employs enhancing agents such as magnetic nanoparticles with advantageous properties such as increased contrast sensitivity, binding avidity, and targeting specificity. Also promising, is the contrasting agent gadolinium conjugated with chitosan and other nanoparticles [6]. These agents can be injected directly into the tumour (stereotactic delivery), or can be applied intravenously and then migrate to the cancerous focus.

Classic contrast agents do not usually cross the BBB because of their high molecular weight so the conjugation with nanoparticles able to cross the barrier seems to be a very elegant solution of this problem. These conjugates can additionally be labelled with specific membrane antibodies, i.e. α-EGFR [7,8]. Polymeric nanoparticles belong to the most powerful nanotechnologic platforms and have been shown as versatile carriers for the targeted distribution of therapeutic cancer drugs [9]. Polymeric nanoparticles are able to carry not only small drug molecules but also macromolecules like genes and proteins [10]. The nanostructure of these particles provides them with good penetrance across cell membranes, stability in the blood stream, and very low toxicity; most importantly, they are easily manufactured. In addition, their surface can be modified into various forms to make them suitable for different medical uses. For their distribution in the central nervous system, they are commonly synthesized using polysaccharides, proteins, amino acids, polyesters, polyethylamins, etc. Recently, specific nanoparticles have been developed that can be degraded in the body via natural metabolic pathways within the organism. This group of nanoparticles includes Polylactides (PLA), Polyglycolides (PGA), Poly (D, Llactic-co-glycolides) acid (PLGA), Polyanhydrides, Polyorthoesters, Polycyanoacrylates, Polyalkylcyanoacrylate, Polycaprolactone etc. [11,12].

Nowadays, there is very broad range of materials and choosing the type depends mainly on the final usage. Liposomal carriers can be used in several chemotherapeutics, such as doxorubicin, dunosome, vincristine etc. Concerning brain tumours, it has been pointed out in a number of studies that doxorubicin has great potential when used clinically against both primary and metastatic brain tumours and that there is an improved survival rate of glioma patients treated by direct intratumoral infusion of doxorubicin, furthermore, doxorubicin is useful against multiple tumour types [13,14]. Glioblastoma multiforme is highly vascularized with a leaky vasculature, and thus may be amenable to liposome-based drug delivery systems that lead to enhanced drug deposition while limiting systemic drug exposure [15]. Receptor-targeted liposomal doxorubicin has been found to be effective in targeting glioma tumours in a brain tumour model [16]. It has been reported that human brain tumour cell lines express high levels of plasma membrane interleukin-4 receptors, so targeting liposomal carriers with interleukin-4 antibodies may be a useful approach for tumour treatment [17]. As a fully synthetic technology, nanoparticles, liposomes, and polymers, have become of great interest for gene delivery into malignant gliomas. There are several types of nanoparticles currently undergoing clinical trials and the tested genetic treatments are similar to those carried by viruses and stem cells [18].

Conclusion

These relatively new technologies derive their benefits from the unique properties of nanoparticles and their complexes with cytostatics, virostatics, antibiotics and other agents. They enables the delivery of therapeutic drugs across the blood-brain barrier and, at the same time, diminishes the dangerous side effects of

the treatment, thus eliminating the manifestation of acute and chronic toxicity. The use of nanotechnology enables a more efficient targeted therapy against cancer cells than casual non-specific chemotherapy. Such effect could be amplified by the use of liposomal nanoparticles as carriers along with other active molecules directed to specific molecular pathways regulating cell proliferation and survival. The enhancement of these treatments is important in dealing with "residual disease", metastasis, and delay the development of therapy resistance mechanisms of cancer cells. Experimental, as well as clinical trials have already proved that molecular interactions can be specifically targeted ensuring their expression only in cancer cells, sparing healthy cells from the negative effects of the treatment.

Acknowledgment

None.

Conflicts of Interest

None.

References

1. IARC: GLOBOCAN (2012) Estimated Cancer Incidence, Mortality and Prevalence Worldwide.

2. The Multiple Sclerosis International Federation (MSIF).

3. Ei Sayed Ahmed EI Dahshan, Tamer Hosny, Abdel Badeeh M Salem (2010) Hybrid intelligent techniques for MRI brain images classification. Digital Signal Processing 20(2): 433-441.

4. Invernici G, Cristini S, Alessandri G (2011) Nanotechnology advances in brain tumors: The state of the art. Recent Patents on Anti-Cancer Drug Discovery 6: 58-69.

5. Kateb B, Chiu K, Black KL, Yamamoto V, Khalsa B, et al. (2011) Nanoplatforms For Constructing New Approaches To Cancer Treatment, Imaging, And Drug Delivery: What Should Be The Policy? Neuroimage 54(Suppl 1): 106S-124S.

6. Reardon DA, Wen PY, Mellinghoff IK (2014) Targeted molecular therapies against epidermal growth factor receptor: Past experiences and challenges. Neuro Oncol 16(Suppl 8): 7-13.

7. Zhang L, Liu Y, Yu D, Zhangl N (2013) Gadolinium-loaded chitosan nanoparticles as magnetic resonance imaging contrast agents for the diagnosis of tumor. J Biomed Nanotechnol 9(5): 863-869.

8. Sahay G, Kim JO, Kabanov AV, Bronich TK (2010) The exploitation of differential endocytic pathways in normal and tumor cells in the selective targeting of nanoparticulate chemotherapeutic agents. J Biomaterials 31(5): 923-933.

9. Miki K, Oride K, Inoue S, Kuramochi Y, Nayak R, et al. (2010) RRing-opening metathesi polymerization-based synthesis of polymeric nanoparticles for enhanced tumor imaging *in vivo*: synergistic effect of folate-receptor targeting and pegylation. J Biomaterials 31(5): 934-42.

10. Walter KA, Tamargo RJ, Olivi A, Burger PC, Brem H (1995) Intratumoral chemotherapy. Neurosurgery 37: 1128-1145.

11. Cummings J, McArdle CS (1986) Studies on the *in vivo* disposition of adriamycin in human tumours which exhibit different responses to the drug. Br J Cancer 53: 835-838.

12. Allen TM, Cullis PR (2004) Drug delivery systems: Entering the mainstream. Science 303(5665): 1818-1822.

13. Madhankumar AB, Slagle-Webb B, Wang X, Yang QX, Antonetti DA, et al. (2009) Efficacy of interleukin-13 receptor-targeted liposomal doxorubicin in the intracranial brain tumor model. Mol Cancer Ther 8: 648-654.

14. Hong HY, Lee HY, Kwak W, Yoo J, Na MH, et al. (2008) Phage display selection of peptides that home to atherosclerotic plaques: Il-4 receptor as a candidate target in atherosclerosis. J Cell Mol Med 12: 2003-2014.

15. Verrecchia T, Spenlehauer G, Bazile DV (1995) Non-Stealth (poly (lactic acid/albumin)) and stealth (poly(lactic acid-polyethylene glycol)) nanoparticles as injectable drug carriers J Control Rel 36: 49-61.

16. Kwiatkowsk A, Nandhu MS, Behera P, Chiocca EA, Viapiano MS, et al. (2013) Strategies in Gene Therapy for Glioblastoma Cancers 5(4): 1271-1305.