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Nanotechnology and Glioblastomas: A Little Fix for a Big Problem

Due to the severity of glioblastomas, recent advances in medical technology have altered the way doctors treat their patients. Nanoparticles, one of these novel technologies, show great promise as an effective treatment and diagnostic tool for brain tumors.

This paper investigates the application of nanomaterials for the detection, diagnosis, and treatment of glioblastomas. After a discussion of background infomation, this work will assess the benefits and drawbacks of the use of various types of nanomaterials, namely metallic nanomaterials, polymeric nanomaterials, and lipid-based nanomaterials. Additionally, the limitations of current treatments will be weighed in comparison to the risk factors of this novel technology. With further research, nanomaterials, particularly those made from metallic, polymeric, or lipid-based materials, can be engineered to act as a more effective treatment and diagnostic tool than those in current use due to their small size, specificity, bioavailability, and their capacity to cross the blood-brain barrier.

Glioblastomas are the most common and most aggressive type of brain tumor. The abnormal growths of cells arise in the glial cells of the cerebrum and have tentacles that extend into surrounding tissues. Some scientists have found links between the occurrence of these tumors and viruses, blood types, and exposure to chemicals, but no definitive cause is known. Glioblastomas occur in .001 percent of the United States population, and most of these patients die within a year of the tumor's development. The rapid growth of these tumors and their destructive nature yields a high mortality rate. The tumors can double in size in one week, increasing the pressure within the skull and causing painful headaches in patients. Other serious symptoms include vomiting, weakness, seizures, and impaired speech, vision, and mental processing (Turkington, 2002). The discovery of an effective novel treatment, such as the use of nanotechnology, is imperative in order to alleviate the impact of the severity of glioblastomas and to improve the quality of life for affected patients.

Current treatments for glioblastoma include surgical resection, chemotherapy, and radiation. The tentacle-like nature of glioblastomas makes surgical removal of the cancerous tissue nearly impossible without damage to normal tissues (Turkington, 2002). Additionally, the invasive nature of the tumors causes cells to migrate throughout the brain, rendering standard treatments of chemotherapy and radiation ineffective since they destroy healthy tissues and are unable to kill all of the cancerous cells (Holland, 2000). These treatments also cause side effects that are detrimental to patients' quality of life, such as fatigue and hair loss.

Nanotechnology, an innovative yet novel treatment, is the utilization of structures built at the atomic and molecular level, or at a range of one to one hundred nanometers. Although nanoparticles are expensive and require extensive research in order to follow advances in other fields, they show promise in applications in the medical field. Nanomedicine applies nanomaterials in a healthcare environment in order to improve the

lives of patients. This budding field will allow doctors to combine knowledge from various disciplines to treat diseases and disorders at the fundamental level. Nanoparticles can be designed to target specific biological molecules, which is particularly advantageous for nanodrugs and drug delivery. For example, antidepressants developed on the nanoscale use nanoparticles to regulate concentrations of neurotransmitters by increasing increasing or decreasing the rate at which the neurotransmitters are digested. This approach has been implemented successfully in a variety of contexts, including AIDS drug therapy. Nanoparticles also have been used in cancer research to improve the efficacy of current treatments such as chemotherapy or radiation (Ratner and Ratner, 2003).

In the context of glioblastomas, nanoparticles can be used to detect tumors, image the affected cells, and deliver drugs. These nanomaterials could be introduced into the body through one of two methods: systemic administration or convection enhanced delivery (Nduom et al, 2012). Systemic administration inserts the materials into the bloodstream orally or through injection or infusion. Convection enhanced delivery involves the direct infusion of the nanoparticles through catheters implanted in the brain (Vogelbaum and Aghi, 2015).

Most current drug treatments are not able to cross the blood brain barrier in sufficient volume and access the target cells. The small size of nanoparticles makes them potentially more effective for drug treatments, as they can penetrate the membranes of cells, including the blood brain barrier. Increasing the amount of drug that crosses the blood brain barrier increases the bioavailability of the drug, which allows the drug to be more effective in the target location. Nanomaterials could transport drugs across the blood brain barrier to targeted areas where the tumor is located, improving the impact of the drug on the cancerous tissue and alleviating negative effects on healthy tissues. The nanomaterials can also protect the drugs from degradation, protect healthy tissues from drug toxicity, and control drug release (Invernici et al, 2011). Scientists have tested a large variety of nanomaterials for use in a biological context. For this study, I will focus on three types of materials: metallic nanoparticles, polymeric nanoparticles, and lipid-based nanoparticles.

Metallic nanoparticles fall under the category of inorganic nanomaterials, which are particles made of mineral compounds. Commonly made from gold, silver, copper, zinc, or iron, metals have emerged as the nanomaterial most commonly applied in a biomedical context. The ability of metal nanoparticles to be modified through the addition of functional groups allows for scientists to use them in a wide variety of fields and to design them with specific applications in mind. Additionally, their size and shape can be manipulated in order to control toxicity and improve their stability within the bloodstream (Zhang et al, 2016). One subsection of metals, known as magnetic particles, shows promise for use as a diagnostic tool for glioblastomas. These particles, often manufactured from iron or gadolinium, exhibit a quality known as paramagnetism, meaning that they have unpaired electrons. Paramagnetic nanoparticles are MRI contrast agents, which improve the sensitivity of the MRI's readings. Infusing paramagnetic nanoparticles into the brain that are designed to target tumors could allow doctors to gain more accurate information on the severity of neural abnormalities without an invasive diagnostic process (Mody et al, 2010). Additionally, studies have found metal nanoparticles to have anti-angiogenic properties and to be toxic to cancer cells. For

instance, a group of doctors at Auburn University found in a 2016 study that zinc and copper nanoparticles induced cell death among rat brain glioma cells, but did not affect the noncancerous cells. Scientists hypothesize that these nanoparticles kill the cancerous cells by moving through and destroying the nuclear membrane, but more research is needed in order to fully understand why metal nanoparticles act as apoptotic agents (Vodyanoy et al, 2016).

Polymeric nanoparticles are manufactured from synthetic polymers. These particles can be divided into two subcategories: biodegradable and non-biodegradable (Pourgholi et al, 2015). Biodegradable polymers show the most promise for use in drug delivery because they can penetrate the blood brain barrier, shield drugs from deterioration, and allow for targeted delivery. When synthesizing polymeric nanoparticles, scientists include a targeting molecule that can bind to a receptor on the blood brain barrier and then prompt the transfer of the particle through the barrier by endocytosis (Constantino and Boraschi, 2012). Polymers penetrate the blood brain barrier more effectively than other nanomaterials and do not damage the barrier when moving through it. Furthermore, scientists intentionally design the particles so that drugs are not vulnerable to the negative effects of excretion or digestion during transport (Invernici et al, 2011). The synthesis of polymers is a long and detailed process that results in a polymer shell that has an anti-cancer drug enclosed within. The polymers often act as "amphiphilic drug delivery systems" that involve a hydrophobic inner section and a hydrophilic outer casing. As the polymer travels to the tumor, enzymes break down the outer shell hydrolytically. The polymer uses an active targeting system of ligands to find and enter the cancerous cells through receptor-mediated endocytosis. The low toxicity and the biocompatibility of polymers towards brain tissues reinforce their promise as an effective drug delivery and treatment tool for glioblastomas (Masood, 2016).

Lipid-based nanoparticles are comprised of a vesicle surrounded by a phospholipid membrane (Pourgholi et al, 2015). One prominent type of lipid-based nanoparticle is the liposome, which is comprised of a water-based core encased by at least one phospholipid bilayer. Liposomes are particularly advantageous as a drug transport tool because of their versatility. They can carry hydrophilic drug molecules within the aqueous center or hydrophobic drug molecules within the phospholipid bilayers. The size and number of bilayers in each liposome can be engineered depending on what best suits the drug being transported. Liposomes can also decrease drug toxicity and improve the effectiveness of the drug. Therefore, they decrease the drug's damage to healthy tissue and increase its damage to cancerous tissues. They can move through the blood brain barrier using a method similar to that of polymeric nanoparticles (using receptors). In order to optimize the specificity of the liposome, scientists use the active targeting system, in which they attach target ligands to the outside of the phospholipid bilayer (Karim et al, 2016). This method was tested in a 2000 study performed in Greece in which ten patients with metastatic brain tumors and five patients with glioblastomas were treated with doxorubicin enclosed in liposomes. The scientists found that in the glioblastomas, the liposomes were able to selectively penetrate the blood-brain barrier and accumulate within the cancerous cells at a concentration thirteen to nineteen times higher than the concentration within healthy cells (Koukourakis et al, 2000). Since this study was performed, more research has been conducted that supports these results and further highlights liposomes as an effective drug delivery tool for glioblastomas.

Although nanotechnology shows great promise as a diagnostic and treatment tool for malignant tumors within the brain, it is important to acknowledge the potential challenges and risks that accompany its use. The flexibility in design of the nanoparticles can be beneficial in tailoring them for drug specificity, but the need for precision at such a small scale and the large range of variability in chemical properties makes effective nanoparticles difficult to reproduce. This barrier hinders replication and in turn, hinders the progress towards commercialization and widespread use of nanoparticles. Additionally, the small size of the nanoparticles allows them to overcome barriers faced by conventional treatments but also greatly limits the carrying capacity of particles used as drug transport tools. The higher concentration of nanoparticles required in order for the patient to receive an adequate dosage of drug raises questions about toxicity and the impact of large amounts of nanoparticles on healthy cells. Finally, due to the fact that nanomedicine is still an emerging field, there is a lack of official and specific regulatory guidelines regarding their implementation. The absence of clear guidelines for the manufacturing of nanoparticles creates a lengthy approval process, slowing the progress of research and preventing patients from receiving care in a timely manner (Wicki et al, 2015). Nevertheless, the benefits of nanotechology outweigh its risks and justify the need for additional research.

Nanotechnology has the potential to revolutionize the detection, diagnosis, and treatment of glioblastomas, tumors that are currently viewed as incurable. With the correct implementation, nanoparticles could both greatly improve the quality of life for affected patients and improve the disease's survival rate. In order to make nanotechnology a standard treatment for brain tumors, more research must be conducted, especially in humans, to alleviate related risks and to ensure that it is safe to use in clinical cancer care.

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