The Uses Of Nanotechnology To Diagnose And Treat Cancerous Brain Tumours

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Abstract

This research paper will inform on what nanotechnology is and cover some of the ways in which it can impact medical science. There are many innovative possibilities that it can create in the intense field of medicine, including new diagnostic techniques and medical procedures that can be performed. The main research of this paper will cover the potential of using nanotechnology based techniques and treatments in the field of oncology (cancer), with cancerous brain tumours being the main focus. Current methods of diagnosis and prognosis of brain tumours will be covered and research in the use of nanotechnology to improve and provide an alternate option in the diagnosis and treatment of brain tumours will be discussed.

Introduction

What is nanotechnology?

Nanotechnology is the scientifical study of utilising matter on a nanometre (nm) scale. A nanometre is one billionth (10^{-9}) of a metre, which is the same as the length of 10 hydrogen atoms. Nanotechnology can be applied to a wide variety of professional fields such as medicine, cosmetics, home economics and manufacture. It can be difficult to imagine exactly how this greater understanding of the world of atoms and molecules has and will affect the everyday objects we see around us, but it is apparent that our increased knowledge on how things work at a nanoscale will aid us in our way of life.

Scientists had been researching and working with nanoparticles for centuries, but the effectiveness of their work was held back by their inability to see the structure of nanoparticles. However, due to recent advancements in technology, the progress of microscopes capable of displaying particles as small as atoms has allowed scientists to see what they are working with. Our ability to see nano-sized materials has opened up a world of possibilities in a variety of industries and scientific accomplishments, and in this paper the focus will be on the application of these possibilities to cancer, specifically of the brain.

Why are techniques using nanoparticles are vital part of medical research?

Nanoparticles play a very important role in medical research. The size of nanoparticles gives them a key advantage over other larger sized particles. They are usually very stable and solid particles consisting of a biodegradable polymer or lipid and range in size from 5 to 1000 nanometers. Nanoparticles are extremely tiny in size so therefore can be easily absorbed by the human body and are able to cross cell membranes and access areas of the body that larger sized particles can't, or have difficulty in accessing. Their large surface area to volume ratio means that they can easily diffuse to areas of the body, and also means that the increased surface area gives a greater space for chemical reactions to happen on. Nanoparticles are reactive due to the presence of large numbers of chemical bonds on their particle surface, so could be effective in destroying cancer cells(see Figure 1) Drugs can be absorbed onto the particle surface, entrapped inside the particle structure, or dissolved within the particle matrix.

What are the key developments in nanotechnology relating to cancer?

Medical Treatments:

Nanoshells may be used to concentrate the heat from infrared light to kill cancer cells with minimal damage to surrounding healthy body cells. A nanoshell consists of a gold coated metal shell and a non-conducting silica centre and the shell is able to absorb nearby infrared laser energy emitted by a source. The nanoparticles are injected into the bloodstream where they travel to the cancerous growth. Nanospectra Biosciences has developed such a treatment using nanoshells illuminated by an infrared laser that has been approved for a pilot trial with human patients. The advantage of using nanoshells to treat cancerous tumours is that they can destroy cancerous cells but do not excessively damage normal cells in the process (see Figure 1).There is an advantage over chemotherapy, which destroys both cancerous and normal cells. The drugs used in chemotherapy are nt able to target the cancerous growth specifically, and the damage of healthy body cells can result in secondary conditions such as immune system suppression and hair loss, whereas nanoparticles have the potential to be able to target only the cancer cells, so prove to be a more harmless treatment. Another advantage is that this procedure is much less invasive than current common treatments such as surgically resecting the tumour.

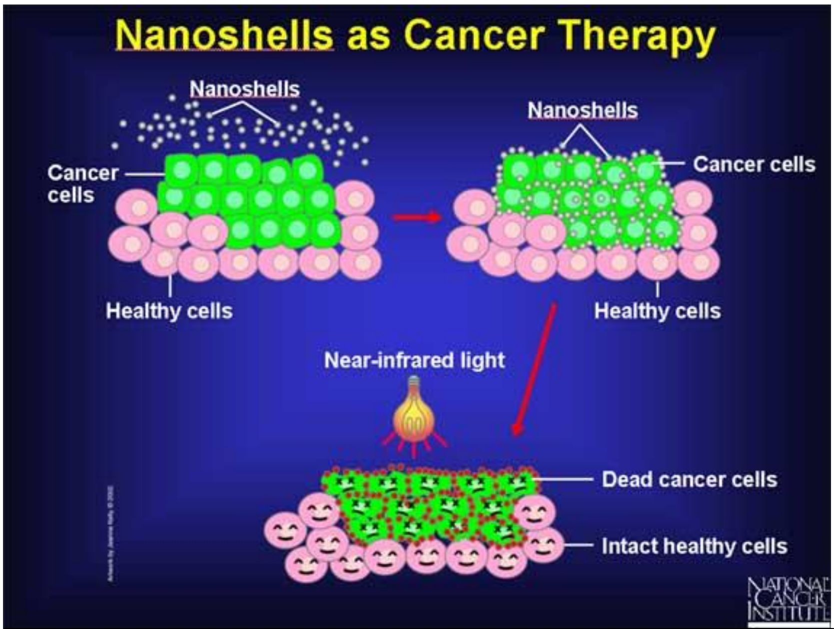

Figure 1 the process of nanoshells in cancer destruction.

Medical Diagnosis:

Quantum Dots may be used in the future for locating cancer tumours in patients. Current testing has been done on mice, where the quantum dots have been observed to give off a detectable fluorescence when stimulated by UV light, hence indicating the position of the tumour. By combining different sized quantum dots within individual granules, granules that release distinctive colours and intensities of light, after stimulation by UV light, can be created. The large variety of quantum dots can give scientists the potential to make them into many different granules so high numbers of DNA sections can be coded for and recognized. Cancerous tumours contain many different types of mutating DNA, so therefore quantum dots can be used to identify different kinds of cancer, reducing the requirement for an invasive biopsy which can be uncomfortable for the patient, especially when brain tumours are concerned and a craniotomy has to be performed with the patient under a general anaesthetic.

Scientists have experimented by injecting PEG coated quantum dots in to the bloodstream of a mouse and the effect of the surface coating on the length of time of circulation in the blood was observed. It was found that the circulation time was much longer in comparison to organic dyes which had a short half life. Organic dyes also can only come in certain amount of colours and are susceptible to photo bleaching so therefore cannot always be reliable. However, quantum dots are highly resilient against photo bleaching and come in a diverse range of colour shades(once activated by UV light), allowing a great range of cells to be identified (see Figure 2). The quantum dots also have high contrast which makes them able to recognize the smallest of tumours, allowing early detection whereas currently used radioactive markers have low specificity meaning that they cannot always detect small areas of affected tissue. The long circulation feature can be explained by the unique structure of the quantum dots, as they are large enough to avoid renal filtration by the kidneys, but small and hydrophilic enough to slow down non specific binding of proteins.

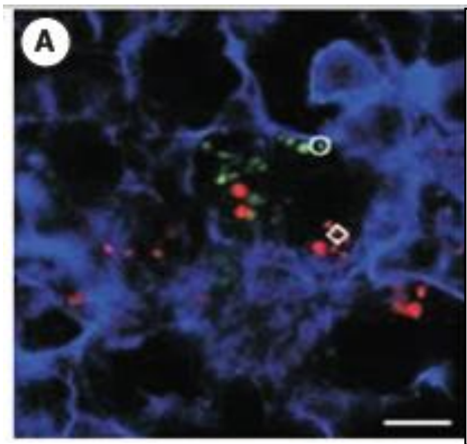

Figure 2 Quantum dot labelled cancer cells trapped in a mouse's lung.

Discussion

What is a brain tumour?

A brain tumour can be either benign or malignant (cancerous). Benign tumours are those which remain in the part of the brain in which they started and don't spread into and destroy other areas of the brain or body. Benign tumours are usually surgically removed. However, sometimes it's difficult to remove the tumour because of its position within the brain, or because the surrounding brain tissue could be damaged by surgery. Some benign tumours have the tendency regrow slowly and, if this happens, treatment with radiotherapy, chemotherapy or further surgery may be needed in order to remove the tumour. Malignant tumours grow faster than benign tumours and spread aggressively to other parts of the brain or body, overpowering healthy cells by taking their space, blood, and nutrients. This is a problem because there is a space restriction due to the skullso therefore an increase in brain size due to the rapid growth of a cancerous tumour can cause raised intracranial pressure and damage surrounding brain tissue causing it to malfunction.

Primary brain tumours originate in the brain and can be benign or malignant. They are most commonly located in the posterior cranial fossa in children, and in the cerebral hemispheres in adults. The different types of brain cancers are usually named after the part of the brain which they locate in. In the UK, the breakdown of primary brain tumour types is: glioma 45%, meningioma 15%, acoustic neuroma 8%, pituitary adenoma and craniopharyngioma 8%. Other rarer forms of primary brain tumours account for up to 10% of the total. Secondary brain tumours are those which have spread to the brain from a different area of the human anatomy through the bloodstream. The most common cancers that spread to the brain are from the lung, breast or kidney. The cells spread to the brain from another tumour in a process called metastasis where cancer cells leave the primary cancer tissue and enter either the lymphatic system to reach the blood or the bloodstream directly. The cancer cells reach the brain and form tumours. Metastatic brain tumours are more common than primary brain tumours. 85% locate in the cerebrum (the largest portion of the brain, located in the upper part of the skull cavity).

The risk of developing a brain tumour can be increased by exposure to:

- HIV infection
- Radiation to the head
- Genetic inheritance
- Cigarette Smoking
- Environmental toxins

How do brain tumours form?

Carcinogenesis is the process in which normal body cells become cancerous cells (see Figure 3). Primary brain cancers form when cells of the brain undergo a mutation in their genetic make up causing the cell to reprogram and begin to uncontrollably divide at a rapid rate and become a malignant mass of cells which damages healthy cells as it grows, pushing them out of the way in order to make room for the cancer. As cell replication continues, a tumour eventually forms, which develops its own blood supply and vessels, supplying it with blood and nutrients to enable its growth.

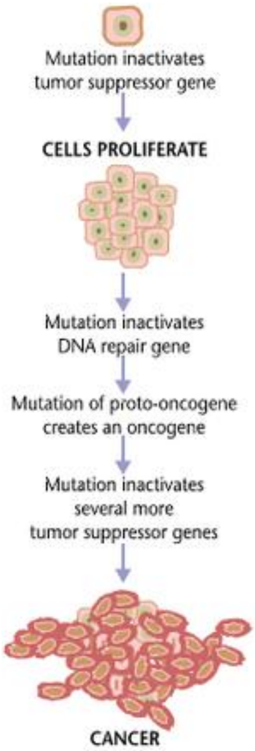

Figure 3 the process of carcinogenesis.

Diagnosis of brain tumours:

There are a variety of different signs and symptoms for the different kinds of brain tumours, so there is no single symptom specific to the presence of a brain tumour, but a combination of symptoms may be an indicator to undergo a diagnostic investigation to the direction of a brain tumour. Some possible symptoms include double vision, an obstruction in the passage of cerebrospinal fluid leading to raised intracranial pressure, headaches, vomiting and epileptic seizures that can be detected by abnormal spikes in an electroencephalogram(EEG).

Currently, one efficient way of confirming the presence of a brain tumour is through a CT(computed tomography) scan. Figure 4 shows a CT scan of the brain, indicating a glioma brain tumour which appears to be more darkly coloured (as it is denser)and bordered with whiter edges than surrounding brain tissue. A CT scan works by sending x-ray beams through the body and then using a computer to work out the relative densities of the tissues penetrated by the x-rays. Cross sections ('slices') through the body are taken.

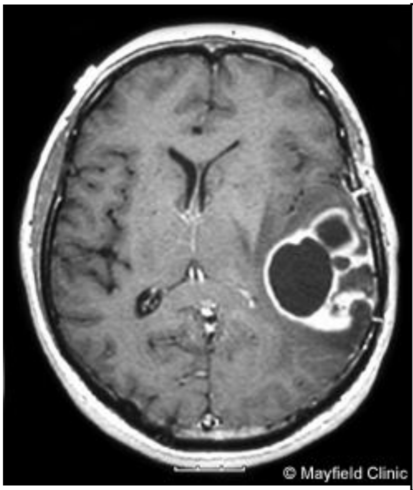

Figure 4 – a CT scan of the brain showing a glioma tumour.

Another common method of diagnosing brain cancer is by using an MRI scan. Figure 5 shows a preoperative MRI brain contrast images showing a large posterior fossa tumour with obstructive hydrocephalus. A MRI scan works by sending magnetic radiowaves through the body, causing the nuclei of the hydrogen atoms (in water) to vibrate and give out radiowaves of their own. These radiowaves are detected by a scanner and turned into an image by a computer. No exposure to damaging radiation is involved.

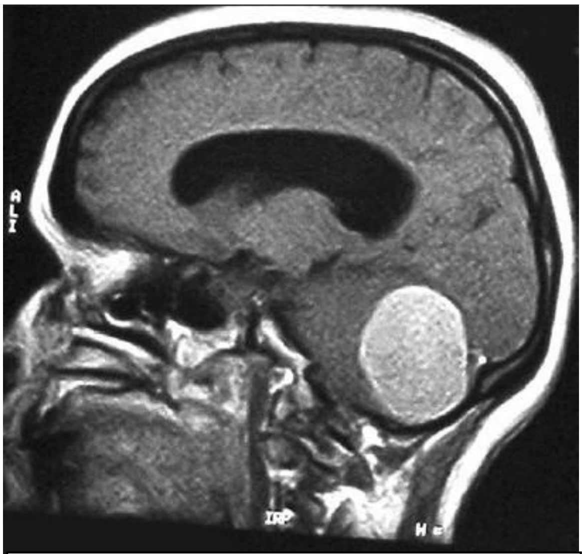

Figure 5 – a MRI image showing a posterior fossa tumour.

What nanotechnology involving diagnostic methods are there for brain cancers?

MRI Detection of Brain Tumours by Chlorotoxin-Conjugated Superparamagnetic Nanoprobes

Currently, gadolinium chelate contrast-enhanced MRI imaging is the main method of detection and diagnosis of pre-operative brain tumours due to the fact that it is not invasive and has high resolution and contrast. However, the imaging quality may still be seen as limited in its ability to accurately indicate the boundaries and distinctions between the tumour cells and healthy brain cells, and give a very accurate idea of the volume taken up by the tumour, due to surrounding edema (tissues swelling from an excessive accumulation of fluid) and diffusion of contrast agents from the tumour cells. Therefore, it may be said that a patient's recovery is sometimes hindered by the inability to accurately locate tumour cells and distinguish them from healthy tissue. During surgery, it may be difficult to resect the entire tumour, if it is tough to distinguish between cancer cells and normal cells.

Scientists have done research into using superparamagnetic iron oxide nanoparticles as MRI contrast agents in order to increase the visual distinction between cancer and normal brain tissue. The nanoprobe is made of up an iron oxide core, coated with PEG (polyethylene glycol), and joined together with the targeting agent chlorotoxin (see Figure 6). Chlorotoxin is a scorpion derived 36 amino acid peptide, which has high selectivity for gliomas and other brain cancers, once it has been injected into the bloodstream. It has also been show to be able to bind to medullablastoma (another brain cancer type), prostatecancer and intestinal cancer. Non targeting nanoparticles are those which do not contain agents which are able to specifically target and bind to the cancer cells, but chlorotoxin is able to bind to cancer cells and therefore offer better contrast MRI imaging and enhance the quality, due to the fact that the chlorotoxin is able to recognise the molecular markers present in cancer cells. The magnetic property of iron oxide enhances the images from the MRI scan, allowing areas of different densities to be more clearly differentiated between and giving an advantageous increased sensibility in the ability of MRI scans to detect small tumours. This gives the opportunity for a better identification of brain tumours and also gives neurosurgeons more information regarding the tumour so that they are able to perform a more thorough resection of the cancer. It reduces the chances of damage to surrounding tissue which is a benefit and research done on mice shows that there are no acute toxic side effects of the particles. The advantages of this nanoparticle based technique is that the agents offer a longer circulatory time in the brain compared to gadolinium chelate, and give an improved visual of the brain tumour margins and boundaries, due to increased cellular internalization. This gives the potential to lead on to significant improvements in tumour detection and localization by exploitation of the unique molecular build up of cancer cells.

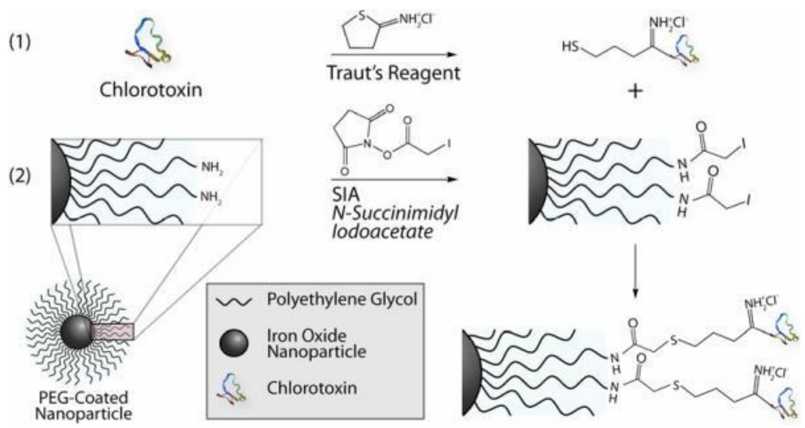

Figure 6-the structure of a superparamagnetic iron oxide nanoparticle

Common treatments of brain tumours

Primary brain tumours are usually removed surgically, in a very invasive procedure. The patient is placed under a general anaesthetic for the duration of the whole surgery. A craniotomy is performed where a section of the skull is cut out to reveal the brain and the tumour underneath. The tumour is then resected, fully or partially, with the aim being to remove as many of the tumour cells as possible. A biopsy may be performed in order to see what type of brain tumour the patient has. Chemotherapy is where drugs are given to the patient in order to kill the cancer, and radiotherapy uses ionizing radiation to kill cancer, A combination of these is sometimes used, if the entire tumour has not been successfully removed with surgery. The issue with radiotherapy is that the radiation also affects nearby healthy tissues and damages their genetic material. The issue with chemotherapy is that it uses cytotoxic drugs which kill all rapidly dividing cells, so therefore does not act in a way which specifically targets cancer cells. Normal body cells such as hair follicles and bone marrow cells divide rapidly, and can be killed as well, leading to side effects such as immunosupression and hair loss. The drugs work well on rapidly dividing tumours such as aggressive lymphomas, but not as well on slower dividing tumours like indolent lymphomas.

What nanotechnology involving treatments are there for brain cancer?

Nanotechnology Drug Targeting Glioma Brain Tumours

Scientists at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute made a discovery regarding the molecular structure of the most aggressive type of brain tumours, the glioblastoma multiforme (gliomas). Gliomas are malignant cancerous tumours and are very difficult to treat. They tend to spread rapidly by metastasis to healthy brain tissue and have been found to reappear in locations which make their surgical removal a very difficult task. In 80% of patients with gliomas, they cause seizures as they release toxic chemicals to kill healthy nerve cells, and can cause paralysis. They are resistant to chemotherapy and radiotherapy and the brain itself is protected by a blood-brain barrier and the immune system has mechanisms which thwarts most therapies. To make matters worse, they are the most common form of brain cancer with a high mortality rate and median survival rate of about 14 months.

The scientists discovered that there is a type of protein called laminin-411 that plays a major part in the tumour's tendency to create new blood vessels to aid its growth and development and metastasis. The ability of technology to block this protein could lead to an advance in glioma treatment. Using nanotechnology, a nanobioconjugate drug was created by the scientists that could be given to a patient intravenously and could then be carried in the blood to the glioma. It is comprised of nanoparticles of 20 to 30 nm in size, is based on a highly purified form of polymalic acid derived from the single cell organism Physarum polycephalum. It was created with the specific property of being able to permeate the tumour cells, and enter the endosomes. As endosomes mature, they become acidic and the chemical constituent of the drug is able to act at this point and break the endosomes' membranes. The tumour cells' production of laminin-411 is able to be blocked, preventing the protein from being formed and production of new tumour vessels. A bonus is that the drug is not toxic to healthy brain cells, so therefore do not share the disadvantages of chemotherapy. Studies in mice showed that large amounts of the drug could accumulate in the tumours and drastically reduce the growth of the tumour. Tumours affected by the drug became 90% smaller than without the drug. The drug is able to enter the brain and target the cancer specifically. Due to its strong chemical bonds, the components of the drug are able to avoid damage or separation in tissues or blood plasma during their transport through the human system. The anti tumour component is able to activate directly inside tumour cells, which is different from other nanomedicine drugs that activate at the site of tumour, not in the tumour cells themselves. The nanobioconjugate drug has been specifically designed to be able to produce a chain of biochemical events such as releasing the anti tumour drugs at the right place and time, homing in on the tumour cells directly, permeating the walls of blood vessels and dismantling processes which help the blood supplying vessels to the tumour grow. When the nanobioconjugate has accomplished its tasks, the body digests it completely, leaving no harmful residue. It is changed into carbon dioxide and water which is not toxic to healthy cells. Another advantage is that doesn't stimulate the immune system to produce reactions such as coughs or rashes or any other systems. Therefore, it is predicated that human trials of the drug may begin soon.

The targeted delivery of brain cancer drugs using nanoparticles across the blood-brain barrier

A challenge which presents itself in the treatment of brain cancer with drugs is the difficulty in delivering the drugs to the specific target region of the brain that is desired. In order to reach some cancerous tumours such as glioblastomas, it is necessary to transport the drugs across the blood-brain barrier (BBB), which can prove difficult. The BBB has a high vascular density and is full of multidrug resistant pathways that control and limit the transportation of molecules to the brain. If drugs do manage to cross the BBB, they tend to distribute rapidly to the whole brain instead of targeting the tumour. The aim is to produce therapeutic drugs which can be specifically targeted to cancerous tissue in the brain that can improve patient survival and have limited side effects on normal cells. The therapeutic resistance of glioblastomas are caused by the poor drug delivery due to the BBB which has high interstitial pressure and poor blood perfusion which are drug resistant mechanisms. Biological targeting can enable this to happen, where the drug is able to recognize certain markers present only in cancer cells and therefore move towards the cancer cells.

Nanospheres are able to target specific areas of the body and release drugs which can be contained within their unreactive shell. Due to the fact that they are able to target the brain cancer specifically, the side effects of the drug due to contact with healthy brain cells can be decreased, which is an advantage. They can be designed to release the drugs at the correct moment, when responding to certain stimuli. The small size of the nanoparticles gives them a large surface area to volume ratio which means that most of the drug in their shells would be located close to or at the surface of the particle, causing rapid drug release. Larger particles have larger volumes so more of the drug is trapped within the centre and hence diffuses out slower. The small size of the nanoparticles also means that they are able to cross the BBB more easily than previous particles as they have a higher intracellular uptake. In order to increase the circulation time of the nanoparticles in the brain, they are coated with a hydrophilic surface reactant which decreases the chances of them being opsonised (cleared from the circulation by the body's phagocytes). PEG is an example coating.

Conclusion

With regards to brain tumours, there have been some significant scientifical developments in the field of nanotechnology which contribute a great deal of future potential in the diagnostic and treatment techniques of cancerous brain tumours, specifically the common gliomas, for which research looks very promising in improving the quality of medical care for patients, which has been discussed in this paper. The development of new diagnostic techniques such as quantum dots and iron oxide nanoparticles have the potential to give patients a more comfortable and less invasive diagnosis, acting as a possible future substitute for the commonly practiced biopsy. Another key point is that the role of nanotechnology in the improvement of the quality of diagnostic imaging techniques proves effective in allowing early detection and diagnosis of tumours, which may not have been picked up using traditional imaging techniques with poorer image quality. The ability of nanoparticles to be able to specifically target cancerous brain tumours gives a promising possibility of minimising damage to healthy body cells, which is a disadvantage of some current treatment methods such as chemotherapy resulting in a great physical and emotional impact on the patient receiving treatment. This paper shows that there are already many exciting possibilities which are being developed to improve the quality of life of humans. At the moment, much of the testing has been done on mice and rats to check safety before being applied to the human anatomy, but the future looks very promising and with more research and development, hopefully some of the techniques involving nanoparticles discussed in this paper and other techniques in progress can be used effectively on humans and revolutionize the way in which medicine is practiced. In the future, these new nanotechnology procedures may take over and have the ability to fill out the flaws of the tradition procedures.

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