APPLICATION OF NANOPARTICLES FOR USE IN CANCER THERAPY

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ABSTRACT

Nanoparticles have great potential for use in conjunction with both cancer treatment and diagnosis. The potential of nanotechnology in the treatment of cancer is so great because of the way we can manipulate the nanoparticles in order to carry out a precise function. In this paper we aim to explore the current and possible future developments of medical uses of nanoparticles in the treatment and detection of malignant tumours, first in general and then looking at specific projects in more detail. In conclusion this paper hopes to investigate and present the future and development of cancer therapy.

INTRODUCTION

A nanoparticle is defined as a small object or molecule with a diameter of less than 100 nanometres. They can be adapted for a variety of uses including drug targeting and as a way of reducing volatile organic compounds in air. It is the wide variety of possibilities for nanoparticles in biomedical, optic and electronic fields that give them such scientific interest. Nanoparticles can be manipulated to form nanoclusters, nanotubes or nanopowders and these in turn can be adapted for a specific purpose. Metal nanoclusters, for example, can be used as heterogeneous catalysts in reactions to reduce the activation enthalpy of the reaction and therefore increase the rate of reaction. Carbon nanotubes are folded sheets of carbon atoms. The carbon atoms are joined together with three other carbon atoms with sp^2 bonds; this is similar to the structure of graphite and due to this structure, carbon nanotubes are extremely strong: around 100 times stronger than steel. This strength allows for a variety of functions, for example as scaffolding for bone growth in tissue engineering, and they are also used to target cancer cells with radio waves in the method of Kanzius cancer therapy.

Although nanoparticles have a history of usage in pottery that extends back to the 9^{th} century, they are generally considered a modern science. Nanoparticles are usually formed in one of two main ways; attrition and pyrolysis. Attrition is where a ball mill is used to crush macro or micro particles. The intense crushing of these particles means that smaller 'nano' particles are formed. The second method, pyrolysis, is where liquid or gas vapour is driven through an orifice at high pressure and temperature, usually above 430 °C. A solid is formed and this is used in the recovery of oxide particles from by-products. This process usually forms nanoclusters rather than single nanoparticles.

Nanoparticles are considered so important because of the size-dependent properties that are found as a material nears the nano-scale. This is the result of the large surface area to volume ratio of the material. It is these different properties which have made them so important in medicine, as there is such a great variety of different treatments and therapies that could be developed.

Nanoparticle research in medicine has received a large amount of funding in the past five years, and the US National Institute of Health planned to set up four nanomedicine centres. Principally, research is taking place in the fields of drug delivery, imaging systems using Quantum dots and in surgery where nanoshells and lasers could be used to weld tissue back together. This could be vital in improving the way arteries are repaired and reducing risk of blood leaks after a kidney or heart transplant, or after the removal of a cancerous tumour.

Nanoparticles are also being used to develop drug delivery systems which can be combined with imaging techniques, so that it is possible visually to locate cancer cells during treatment. Drugs will be able to target specific cells using biosensors such as antigens or RNA. The nanoparticles will then be designed to enter the cell or attach to its surface where it can deliver the drug. The large surface area to volume ratio of nanoparticles means that many functional groups can be attached to them and this therefore enables drug delivery to occur. This will enable the treatment of cancers even once they have become very developed and also allow for more effective and safer treatment of difficult placed tumours which are hard to reach. Certain drugs have also been found to last longer when protected inside a nanoparticle, as they are less able to diffuse away. All these techniques can be used to help cure cancer or, failing that, to delay the growth of the cells.

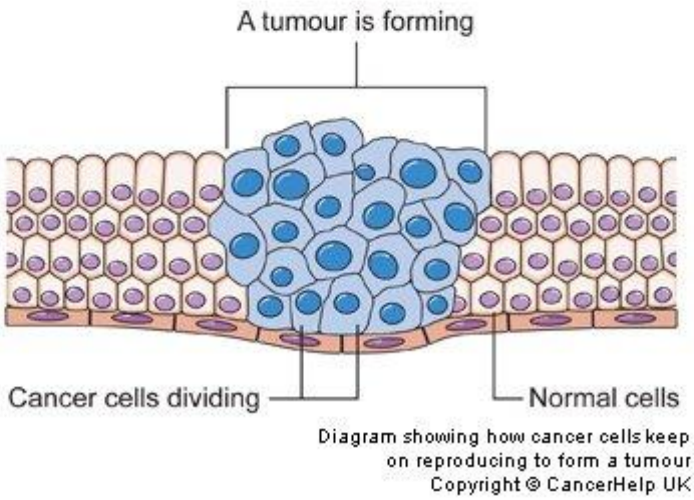

Figure 1. Diagram of a cancerous tumour developing.

A cancer cell is a cell which is part of a malignant tumour. Normal cells are able to divide by mitosis accurately, to stop dividing at the right time, to destroy themselves if they are damaged and develop into specialised cells. However, cancer cells differ from this description because they reproduce uncontrollably. This leads to the formation of a cancerous tumour, as in Figure 1, and cancer cells may not be able to self destruct when their dividing becomes uncontrolled.

This research paper is based on the ways in which nanoparticles can be manipulated to prevent further growth of tumours and even kill the cancerous cells. We looked at a variety of different techniques, some of which are in the process of being developed and some are already in use.

DISCUSSION

In recent years nanoparticle research has expanded and nowadays nanoparticles can be applied in tissue engineering and in the detection of certain molecules such as pathogens, proteins and cancerous tumours. These applications are of great benefit and lately nanoparticles have had increasing input into the destruction of cancerous tumours in the body.

Photodynamic therapy

Photodynamic cancer therapy has been adapted using nanoparticles in order to reduce the side effect caused by the unadapted therapy which makes the patient very sensitive to light. The original photodynamic treatment involves a drug called a photosensitizer combined with a special wavelength. The photosensitizer is injected into the bloodstream of the patient and this results in it being absorbed by the cells of the body. The agent resides in the cancer cells more than in the normal body cells which means that this is an effective way of treating cancer while causing limited harm to other body cells. The photosensitizer is left for 48-72 hours in order to allow most of the drug to leave the healthy body cells but remain in the cancerous ones. The tumour is then exposed to the specific light wavelength producing an active form of oxygen that destroys the nearby cells. However because the photosensitizer drug is injected into the patient's body and absorbed by normal body cells, the person who is undergoing the treatment can become sensitive to light for approximately 6 weeks after treatment which is an unnecessary side effect. However, using nanoparticles would limit this side effect and possibly remove it altogether because the drug could be enclosed in a nanoparticle and therefore be transported to the specific cancerous cells. This would limit the absorption of the drug into the unaffected body tissues as the drug cannot spread around the body as it did when it was injected into the bloodstream. This means that when the body cells are exposed to the light only the cancer cells are affected. Consequently the person does not become sensitive to light as the cancerous cells are the only cells which are exposed to the drugs.

Kanzius RF therapy

Kanzius RF therapy is a relatively new therapy that is being developed to cure cancer and clinical studies for this technique are expected to begin in 2012. The main idea is that carbon nanotubes would be inserted into or around cancerous cells. Radio waves would then be used to excite the nanoparticles which would create heat energy that could burn the cluster of cancerous cells. The radio waves would be produced by a generator with a mounted transmitting and receiving head which allows the field to be adjusted both vertically and horizontally. A field would be generated with a diameter of 30cm and peak intensity located within the radius. Kanzius aims to make its treatment non-invasive and it is hoped that further research will enable the nanoparticles to be targeted accurately. It is hoped that if the nanoparticles can be made to target cancer sites preferentially, cancerous cells could be killed whilst leaving healthy sites relatively unharmed. However, this technique is not fully developed at present.

Imaging and Detection

Nanoparticles can also be used in the process of detecting and then diagnosing tumours. Quantum dots are nanocrystals of semiconductor materials, for example cadmium selenide, linked to antibodies. They combine to form molecules which are able to detect many different substances at the same time. They can also detect molecules on the surface and present inside cancer cells which is very useful in diagnosing which cells are cancerous.

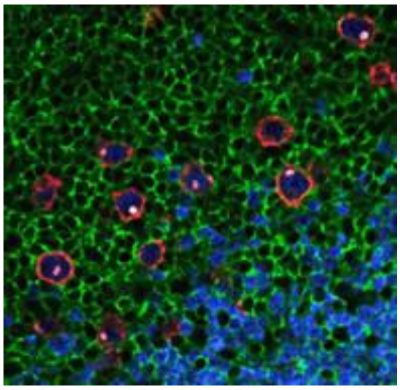

Figure 2. Cells from an individual with Hodgkins Lymphoma

For example, in figure 2, we can see Reed-Sternberg cells from an individual with Hodgkins Lymphoma, highlighted with a red outline and blue and white internal staining. They can be used to monitor levels of cancer markers, such as actin, microfibril proteins and the breast cancer marker Her-2. Quantum dots are extremely useful for bio labelling because of their properties: they are strong and also very stable. Typical fluorescent dyes generate a much less powerful fluorescent signal than quantum dots meaning that they are far less effective. As quantum dots can also be produced in multiple colours, different antibodies can be tagged with uniquely coloured quantum dots. A new optical spectroscopy and data analysis system has been developed which is able to ignore the background fluorescence emitted by the samples. This system is far more accurate and can also work out the specific amount of a given biomarker, so levels can be compared in different samples. The new system can work so accurately that it should be possible to detect very small changes in tumour development and distinguish between different types of tumour.

Drug Targeting

Scientists at Harvard Medical School and the Massachusetts Institute of Technology carried out research into embedding nanoparticles with the cancer drug Taxotere. The scientists then injected these nanoparticles directly into the cancerous tumours in mice which had been implanted with prostate cancer human tumours. The nanoparticles which enclosed the Taxotere drug were a mixture of hydrogen and carbon monomers. These monomers form a polymer containing bits of the drug incorporated in its fabric and attached to a substance that is attracted to cancer cells. The nanoparticle polymer, once at the tumour, gradually dissolves and this exposes the drug which was bound in the polymer. The dissolving of the nanoparticle releases the drug which then kills the tumour. The 100 mice used in the experiment were split into groups and the different groups were injected with different substances. The researchers found that mice injected with just the drug with no nanoparticle encasing died from the effect of the drug whereas those mice who had been administered the drug enclosed in the hydrogen and carbon polymer survived and furthermore their cancer tumour completely disappeared. The targeting of the drug to the tumour is still an aspect of this treatment which needs to be developed but those tumours that can be directly injected with the nanoparticles, as they are accessible and have not spread, can be treated with this type of action. The scientists also tested the effects of injecting the drug into the bloodstream and found that the drugs were ending up in the liver and spleen causing toxic levels of chemotherapy drugs to be released to healthy tissue when the nanoparticle encasing dissolved. This is a problem and means that the use of nanoparticles to treat cancer with tumours that are less accessible needs to be further developed. However, future research into the directing of these nanoparticles will, it is hoped, increase the successfulness of this technique.

If this technique can be developed completely it would mean that doctors could inject human patients with nanoparticles enclosing chemotherapy drugs such as Taxotere which could then travel in the bloodstream to the tumour and, once there, release the drugs to the cancerous cells leaving the normal body tissues unharmed.

RNA modification

A recent new study has shown that nanoparticles can also be adapted to carry a specific type of RNA interference component to solid tumours. The RNA interference reagent, more specifically siRNA, coats the nanoparticle which then transports it intravenously to the cancerous cells and once there, interferes with the production of the enzyme which is important in the growth of melanoma tumours. Researchers found that the nanoparticles accumulated within the cancer tumour and they also found that the levels of the enzyme they were attempting to interfere with, the M2 subunit of ribonucleotide reductuse, were lower in the tumours that the nanoparticles had targeted than those which nanoparticles had not been directed at. This was the first study which concluded there was specific interference to the gene expression in the tumour because of the siRNA reagent coating the nanoparticles. This technique has not been fully developed and therefore future research is necessary in order to develop this technique completely in order to destroy and kill melanoma tumours. Researchers also hope to extend the successfulness of this approach by evolving the technique to deal with other types of tumour and specifically with the interference of tumour cell growth.

Nanoparticles containing bee venom

Scientists have also developed the use of bee venom as a possible way of curing cancer. Successful research carried out at Washington University School of Medicine in St. Louis tested nanoparticles carrying a toxin found in bee venom, melittin, and their effect on tumour cells in mice. The researchers found that the nanoparticles killed the tumour cells and cured the mice. Melittin is an ideal cancer therapy as it is a powerful chemical which kills cells by destroying their cell membranes by ripping the cells apart. However, the chemical has the same effect on normal healthy cells. It is hoped that the use of nanotechnology to transport this drug will enable the drug to be directed to the specific cells and therefore kill the tumours. Nanoparticles called 'nanobees' can be programmed to ignore most cells while targeting those cells with the specific antigen on their surface. The nanoparticles containing melittin could be programmed to target the specific proteins which are found on the cell membrane of the cancer cells. The nanobee, after detecting the cancer protein, injects melittin into the cancer cell causing the cancer cell to be destroyed without the toxin having an effect on the surrounding cells in the body. This treatment was tested on mice with two different strains of cancer (melanoma and human breast cancer) and the scientists found that the drug which had been injected had slowed the growth of both types of cancer, but was more effective on the shrinking of the melanoma cancers. This is a promising treatment even though it is not fully developed and it could become a widespread solution to cancer treatment and to the problem of drug delivery.

If this technique can be developed completely it will mean that doctors will be able to inject human patients with nanoparticles enclosing chemotherapy drugs such as Taxotere which will then travel in the bloodstream to the tumour and once there release the drugs to the cancerous cells leaving the normal body tissues unharmed.

As discussed above, there are many different methods and ideas being developed, however in the future it is hoped that the new technologies can be used alongside each other to provide a far more successful treatment of cancer. Researchers and doctors will be able to work together to provide an earlier and more accurate diagnosis, more effective treatment and hopefully treatment that is less invasive and uncomfortable for the patient than treatment that sometimes occurs today.

Ethical Issues

Although there are undeniable benefits of nanoparticle research in medicine and in the way in which cancer is treated, it is always important to take ethical issues into account. Animal testing is a vital element of the research and testing process and it has enabled the development of many important drugs that have changed the way we live today. However, many believe that as animals are unable to consent to such tests, unlike humans, it is wrong to subject them to this. A major issue is that animal testing also often involves pain and discomfort. It is not always possible for pain-relieving medication to be used as this can interfere with the drug being tested. It is widely accepted that animals should be treated with care and respect in order to minimise their suffering even though the debate over testing on animals is ongoing.

There are also environmental concerns about nanotechnology. Nanoparticles can be released into the water or into the air which can adversely affect our surroundings. So, before nanoparticles can be released we need to carry out relevant investigations into the possible effects on the environment so that they do not cause harm. As nanoparticles are a relatively recent discovery, they form a new type of non-biodegradable pollutants; this means that it is difficult to predict their future effect on the environment.

Nanoparticles in the air could severely affect human health because they can remain airborne for long periods of time due to their small size. Their size means that they can pass through the body undetected by the immune system and are able to pass through the blood brain barrier which could be extremely dangerous. This means that they could be inhaled by humans and damage their respiratory systems. There are also concerns about the effect of nanoparticles on water and soil, polluting these and in turn damaging plants and the ecosystem. Due to the size of nanoparticles, it will be extremely difficult to remove nanoparticle pollution from the environment so it is very important to find alternative and safe methods of disposing of nanoparticles. As nanoparticles have a large surface area to volume ratio they are very reactive and having invaded the body, they can lead to chemical harm in tissues. Full experiments should be carried out before nanomedicine can be used in order to reduce the unintended side effects of injecting nanoparticles into the body. Another harmful effect on the human body is that the nanoparticles would accumulate in organs, especially the liver, as they are non-biodegradable and scientists need to be sure that they do not impair any of the functions carried out in the body. Before nanoparticles can be widely used to treat cancer, we must find out about how the nanomedicines will affect the body and how this can be counteracted.

CONCLUSION

Nanoparticle research is an increasingly important and viable method of expanding the way in which we can treat cancer tumours in patients. At this moment in time, although there have been many breakthroughs in the research, there is still a long way to go. Drug targeting could be used as a way of preventing damage to surrounding tissues as well as of destroying the cancerous cells. Methods of diagnosing and identifying cancerous cells, for example using Quantum dots, will also be very useful in the early detection and therefore prevention of tumour growth. At present it seems that the future of cancer treatment and diagnosis lies with nanoparticles as the greatest opportunity available in science.

However, there are problems with the use of nanoparticles in medicine which need to be resolved. Before the use of nanoparticles to target cancer cells can become widespread it is imperative that further research is undertaken to find ways for this to be done safely. Cancer is a disease that affects such a large percentage of the population that it is essential that not only do we improve treatment fast, but that any new treatment has been properly trialled and tested. If new developments were used too hastily there could be devastating effects so it is important that a balance is found. It is also important that we consider the implications of the use of nanoparticles on the environment, as this is an issue with ever increasing importance in society today.

In conclusion, although nanoparticles are not yet ready for extensive use in medicine, the research being carried out holds great potential for future developments. Nanoparticles could be the way forward for treating cancerous tumours and hindering the effects of cancers as a whole.

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