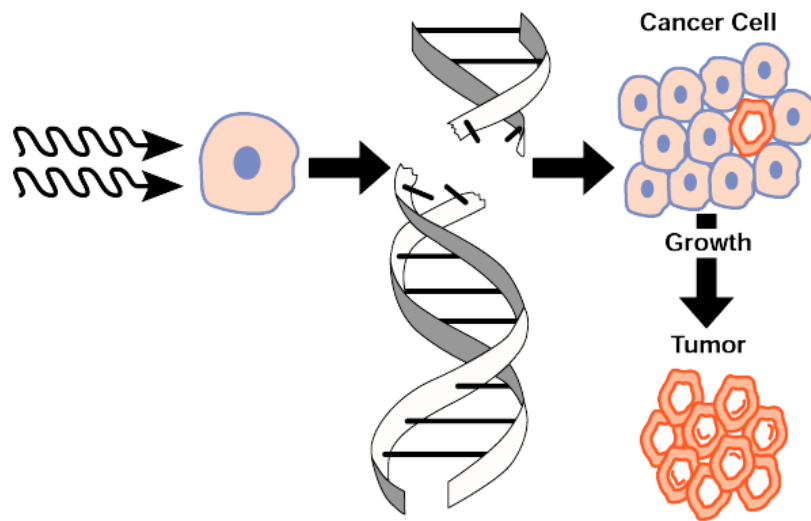


NANOTECHNOLOGY IN CANCER DIAGNOSIS AND TREATMENT

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ABSTRACT

The study of nanotechnology enables us to perform tasks that involve atomic precision, manipulation, accurate co-ordination and accessibility to minuscule details. Cancer causes 13 % of all deaths and medicine now needs a device that can handle and operate within the human body, has great selectivity, is fast, more precise, more reliable, more accurate, less labour-intensive, cheaper, relatively easier to use and minimizes any (permanent) damages to the body. Nanotechnology promises earlier and better diagnosis and also direct and more selective treatment.

INTRODUCTION

All matter is made up from atoms which are very tiny parts that bind together and determine the properties of the object. These atoms are the smallest unit of an element and also contain even smaller units, called protons and neutrons which are situated in the nucleus of an atom (nucleons) and electrons in shells that orbit the nucleus. The Scanning Tunnelling Microscope (1982) and the Atomic Force Microscope (1986) made it possible to create an image of a surface at atomic scale. They have also allowed us to replace and manipulate individual atoms.

As nanotechnology is the engineering of systems at an atomic scale, it allows us to conclude that nanotechnology also refers to the ability to manufacture from the smallest possible parts up to whole objects.

Nanotechnology has been around for a very long time and since then nanoparticles have been made by scientists and craftsmen. However, nanotechnology has now become interdisciplinary and requires biologists, chemists, physicists as well as material engineers to be involved. The development of nanotechnology progresses rapidly.

Nanotechnology can be applicable in many areas such as in commercial products (e.g. sun crème, tennis rackets, bicycles), medicine, agriculture, communications, energy, military purposes (e.g. smart dust) etc. However, it can also serve us the side effects of death and threats once it gets into the wrong hands or even when security and control over it is lost.

Nanotechnology will produce nanorobots which will function similarly to the huge manufacturing machines in factories but then on a much smaller scale. Nanorobots can be programmed to put together sequences of atoms and so build from the very bottom up to whole objects, monitor, record and analyse cellular and even atomic data, send messages to computers, detect atomic anomalies etc. As these nanorobots will have been built using nanotechnology too, they will have an excellent sensory ability.

Chips, nanorobots, nano-cages etc. are made up from buckyballs and carbon nanotubes. Buckminsterfullerene has a hollow shape that is made up from 60 carbon atoms.

Buckyballs have the prestigious characteristic of having a small mass and being very stiff. Carbon nanotubes however, are single walled and have a cylindrical structure with a very small length to diameter ratio, making them very light but much stronger and conductive than other materials.

Cancer

Cancer is caused by mutation which is a change in the base sequence of DNA. The triplet code, three nucleotides, codes for a specific amino acid, hence DNA codes for proteins. A mutation will cause none or the wrong proteins to be coded for, often with severe consequences. Every cell has DNA which also has oncogenes. These control the development and growth of the cell. If a mutation occurs, the oncogenes will produce an excessive amount of chemical signals that will result in the uncontrolled growth and cell division.

Cancer can be caused by genetic inheritance, DNA replication, high exposure to radiation, diet, radon, obesity, carcinogens, such as tobacco etc.

Cancer is a disease that displays loss of the ability to replicate with the right DNA in cells, uncontrolled growth of a group of cells by mitosis, invasion and destroying of nearby cells and tissues by releasing chemicals when the cancer cell wall gets ruptured, tumour cells metastasizing (spreading) to other parts of the body via the lymph or the blood, cells not dying as planned, losing orientation with other cells, losing the ability to communicate with the defence system and its protective cells and dominating the cell cycle.

DISCUSSION

Issues in Cancer diagnosis

After palpation, further diagnosis can be made using X-rays, Magnetic Resonance Imaging (MRI) devices, Computed Tomography scans (CT) and Ultrasound without having to cut open the patient's body.

MRI devices are very useful and can produce images with many different shades which help to distinguish between and examine different tissues and the powerful superconductive magnets that are in a vacuum are able to create an image of the body part to be examined in any plane: coronal, transverse and sagittal. However, this method requires patience and the ability to keep in the same position for a very long time. Beside that, MRI devices are also not developed enough to facilitate obese and claustrophobic patients. Functional Magnetic Resonance Imaging scan can create brain maps of nerve cell activity and Magnetic Resonance Angiography can create images of the circulatory system in any part of the body, but unfortunately these two types are yet to be developed.

Ultrasound devices (sonograms) use high frequency sound waves. The transducer emits sound waves that travel through the skin and reflect off the internal tissues. Depending on the characteristics of the internal tissues and boundaries, the waves are reflected in different ways. The computer processes the reflected waves and produces an image that shows the locations and types of the structures in that area. Ultrasound is very useful as no radiation is used, it's painless, quick, relatively easy to use and can help to identify lesions which cannot be detected on a mammogram. Sonograms however, are unreliable since there are many different cancers they cannot detect and also cannot distinguish between benign (non-cancerous) and malignant (cancerous) tumours, sometimes resulting in (risky) further procedures such as biopsies being done.

CT scans can only create images on the axial plane, thus not allowing proper 3D examination of tumours, and X-rays cannot create images of soft tissues. We can conclude that these are quite limited methods.

Nanotechnology in Cancer diagnosis

According to a research from John Hopkins University, very small crystals of semi-conductive materials called Quantum dots, attract DNA strands that are linked to cancer cells. Using pre-made biotin and fluorescent dyes which function as markers and directing some light on the Quantum dot, the location and amount of DNA methylation could be identified using an external spectrometer. Cancer cells and healthy cells could be distinguished from each other, simply by observing the colour on the spectrometer.

Chemist Shouheng Sun from Brown University and a team of researchers have created an iron oxide magnetic nanoparticle that has a very thin peptide coat with molecules that bind to cancer cells and then the nanoparticle transmits radio impulses which aid the MRI device to create clearer and better images of the area to be examined. Once the metal oxide nanoparticles bind to the cancer cells, they can be enlightened to improve the quality of the scans and help with detecting the severity of the tumour, e.g. benign/malignant/metastasizing.

Lab-on-a-Chip in Cancer diagnosis

Lab-on-chip means that you have one or a whole collection of machines, a lab, on one single chip. The lab-on-a-chip has modules; electrodes that are supplied with an electric current; reservoirs that hold liquids and particles and a microchannel through which fluids flow. Using hydrodynamic dielectrophoresis, the chip is able to analyse, manipulate, sort, transport and selectively filter cells continuously. Lab-on-a-chip is a microfluidic chip as it deals with the accurate control, behaviour and manipulation of fluids at a very small scale.

The chip has two parallel plate electrodes and a dielectric medium. As an electric current is applied to the electrodes, an electric field is formed that crosses the electrode gap. Dielectrophoresis focuses on particles at the centre of the microchannel, which is in the planer electrode gap. The Lab-on-a-chip gets implanted into the bloodstream and as blood that flows through the microchannel is non-uniform it will create a potential difference of the electric field, and thus the dielectrophoretic force.

Blood that flows through the microchannel acts as an electrolyte and different cells will, depending on their properties such as density and velocity, exhibit different dielectrophoresis and get attracted to different electric field intensities. If they exhibit positive dielectrophoresis they will be attracted to the electric field intensity and be moved away from the blood. If they exhibit negative dielectrophoresis they will be repelled into the space between the nanoparts over which the blood flows. These can then be easily flushed out due to the hydrodynamic force which is larger in the medium between the nanoparts. Different amounts of electrical energy should be applied to the electrodes in order to find the optimal differentiating dielectrophoretic force of specific subpopulations of cells.

The chip will be used as a cytometer and thus has many different modules, each with a different and specific task and many microchannels through which fluids and particles flow. The first module of the chip has many tiny magnetic nanoparts that are used to bind to/capture and isolate the tumour cells. The magnetic nanoparts are guided over a magnetic sensor with a single cell sensitivity that will count the number of circulating tumour cells present in the blood. Then, the tumour cells are separated and destroyed so that the genetic material can be extracted and amplified in order to study the metastasis. The genetic material is detected using an array of electrochemical sensors. This method could test the severity and development of the cancer cells particularly in leukaemia and help doctors decide what cure will cater for that particular cancer.

As the lab-on-a-chip will allow us to detect cancer before it starts metastasizing, Dr. Jonathan Uhr M.D. from the University of Texas South-western Medical Centre in Dallas informed that the lab-on-a chip 'would allow routine monitoring of blood tumour cells as part of medical examination, and could result in early detection and treatment.'

Issues in Cancer treatment

Sometimes cancer can re-occur after treatment; this is known as a relapse. According to Professor Wei Duan, 'cancer cells are particularly difficult to kill as they contain so-called cancer stem cells, the root or seed cancer cells that are resistant to drugs.' Malignant tumours are made up from cancer cells as well as a small number of cancer stem cells which are undifferentiated. Chemotherapy appears to only affect the cancer cells and not the undifferentiated cells. That's why using chemotherapy will kill the

enormous tumour but the stem cells will still be present and develop into new malignant cancer cells. Due to this and the dependence on the circulatory system for drug delivery, a large quantity of toxins is used in chemotherapy which results in severe pain and other side effects.

Cancer is a chronic illness and can be dealt with by different therapies such as surgery, chemotherapy, radiotherapy and also immunotherapy, monoclonal antibody therapy, vaccine therapy, palliative care (pain relieve treatment rather than cure e.g. local anaesthetic) and hormone replacements. Some of these methods, for example chemotherapy, affect the cancer cells the most due to their rapid growth and division but also damage healthy tissues and result in hair loss, organ damage, vomiting etc. Some of these methods will cure the patient depending on the length of time the cancer cells have developed for, which stage the tumour has reached, where the tumour is located in the body and what type of cancer it is.

Currently, a lot of medication is needed as a lot of medication is deactivated by the stomach acid and the treatment is very dependant on the timing and management of the patient as well as the patient's circulatory system. Besides, relapse cancers are also very hard to treat. The same treatment that's used before cannot be used a second time since the cancer cells will have mutated to become resistant to those drug molecules. In addition, it's very hard for the immune system to recognize and distinguish between normal healthy cells and cancer cells as there is very little difference between them. Blood vessels will form around the tumour in order to supply the tumour with oxygen to keep it alive and stimulate its growth and development. Although immunotherapy can help the immune system to recognise the antigens on the cancer cells and treat the cancer cells as foreign bodies, the immune response that's triggered may not be strong enough to destroy the cancer cells and the cancer cells may release substances that could affect the immune system.

Nanotechnology in Cancer treatment

Buckminsterfullerene can be used to contain the drug molecules in order to transport and deliver the drugs to tumours without destroying or damaging healthy tissues and also without being destroyed itself by the immune system. The buckminsterfullerene could be coated with hairs (liposome) on its surface in order to prevent proteins to bind to its surface and the immune system to recognise it as a foreign body and destroy it. Once the buckyball has reached the tumour, it could be opened to release the drug molecules. This could happen automatically due to the higher temperature of the tumour cells compared to healthy cells and also by light that could be directed to the tumour cells.

BioDelivery Sciences International have developed particles called nanocochleate (made from liposomes) within which drug molecules are contained in order to prevent the drug from getting destroyed by stomach acid. When the nanocochleate gets into the circulatory system it can then passively target and fuse with tumour cells in order to deliver the drug.

Researchers at Harvard Medical School have demonstrated that nanoparticles with specific molecules on the surface are attracted to cells with specific receptors. If the right molecules are used, the nanoparticles will actively target the cancer cells and when centred in the tumour, impulses can be sent to the core of the nanoparticle either in order to destroy and kill the cancer cells or in order to break the bonds between the chemicals within the cancer cells. 'Researchers at Deakin University, Melbourne, are in co-operation with Indian scientists to develop a Smart Bomb drug delivery system that could target and kill cancer cells without damaging the healthy cells.' They have discovered that cancer antibodies can specifically bind to cancer cells and therefore with a technique called 'RNA interference they will be able to develop a treatment with a similar effect.'

Some nanoparticles (nanoshells) with a shiny surface can be warmed up using an infrared laser. These nanoparticles should be directed to the tumour cells as close as possible using external magnetic devices. When these nanoparticles absorb the light, heat is created that could burn the tumour cells. This is very effective and less damaging to the human body as the nanoparticles are focussed and directed to specific cells. This method will also allow access to very small areas. For this method, nanotubes are used as they can come in different lengths and therefore absorb different frequencies of infrared light waves. This is important as efficient absorbance of the waves will result in efficient burning of the cancer cells, but in areas with many or closely situated blood vessels it is better to use low heat energy so that the circulatory system won't get damaged. Besides, if the tumour is near a blood vessel, the continuous flow of blood through it will cause the tumour to cool down and result in an ineffective treatment.

Medical device firm AngioDynamics in Queensbury, in New York came up with an electroporation device that can emit long and high Voltage pulses in order to create an electric field through and around the tumour. This could open the pores in cell membranes which could be kept open due to the long pulses and lead to apoptosis of the cells. Though, some research has proven that this method doesn't affect the structure of the vessels but does damage the cells that line the walls of the blood vessels. Using thin electrodes and low-wattage in thermal treatment such as nanoshells, is according to Francesco Garbagnati, the director of radiology at the National Cancer Institute of Milan, also effective and will leave the vessels intact.

Alternatively, the nanorobot could emit fine-tuned microwaves or ultrasonic signals to break the bonds between the dangerous chemicals the cancer cells contain without having to break the cell membrane of the cancer cells because that will result in the chemicals being released and affecting the adjacent healthy somatic cells. Otherwise, as much microwaves or ultrasonic signals as required should be emitted by the nanorobot in order to completely destroy the cancer cells if that's desired.

There is another method in which nanoparticles attached to T-lymphocytes carry a drug called interleukins. When the T-lymphocytes reach a tumour, the nanoparticle is activated and releases the drug that should cause the T-cells to reproduce very fast. If the number of T-cells in the tumour is high enough, then all cancer cells could be destroyed. Dr Irvin who led the team of MIT Engineers, said that this immune-cell therapy would 'cure rather than slow down the progression of the disease,' and could also be used in speeding up the process of blood cells mitosis after leukaemia patients have had their bone marrow transplant since all their own bone marrow will have been destroyed by radiation or chemotherapy before transplantation. This method will shorten the period of immune-suppression (vulnerability to infections due to lack of immune cells).

By Transmission Electron Microscopy Analysis, it has been proven that nbtrx3 nanoparticles can be absorbed by cancer cells. Nbtxr3 nanoparticles could be injected into the body which will attach themselves to tumour cells and then produce electrons that would destruct the tumour cells when activated with X-rays. This method has been tested on mice and has proven to be a lot more efficient and healthier than standard radiotherapy. However, further research has also indicated that some humans may be intolerant to nbtrx3 or multiple injections of it.

Nanorobots in Cancer treatments

We already have a working nanotechnology of cell biology. Nanorobots will probably be wet and have a soft, squishy structure as they, unlike hard metal surfaces, won't be covered in bioprotein and therefore won't be expelled from the body. Using cell biology and "wet chemistry" we will be able to produce nanorobots that can function, process information and also move inside the body. They would probably have been made with lipid macromolecules and could be powered with chemicals such as ATP and carry genetic information that is specific to the body environment for it to work properly.

Nanorobots get implanted into the bloodstream, search for, detect and attack circulating cancer cells. They can also be used in chemotherapy for drug delivery in order to maintain the full effectiveness and efficiency of the medication. This way, only

small doses of medication, in the medicine cavity, is required as nanorobots can be directed using signals.

Nanorobots could also be powered using two electrodes on it which again use the blood as an electrolyte to create an electric current between the electrodes (like a battery). Capacitors which store electrical energy and unlike a battery have a reasonable power supply to weight ratio could also be used.

Nanorobots could also hold a small amount of chemicals (ATP) which could function as a fuel source that could be converted into energy when combined with the blood. Some blood could be burnt by a chemical reaction in order to obtain energy.

The nanorobot could also be attached to an external electrical power supply with a wire or instead, an optical power supply that uses light through fibre optics and upon arrival on board of the nanorobot, the light could be converted into electrical energy.

A nanorobot with a piezoelectric membrane (crystals that vibrate and give off ultrasonic signals as a result of an electric charge being applied on them) could receive ultrasonic signals and convert them into electricity (sonoporation).

A nanorobot could also emit ultrasonic signals which could be detected using external ultrasonic sensors. MRI scans will allow doctors to detect the magnetic field of the nanorobot, using X-rays (but further development is needed to make it suitable for nano scale) and with a lot more development, nanorobots may be equipped with a camera so that the internal of the body can be observed externally. Scientists in Israel created a microrobot and a magnetic field which caused the microrobot's arms to vibrate and move the robot forward. Capacitors in the nanorobot would also create a magnetic field and pull conductive fluid in one side and force it out on the other side so that the nanorobot could be pushed forward. However, we don't know to what extent the capacitors and nanorobots' arms will be able to go in the future because blood is quite viscous.

Finally, a radioactive dye, such as fluorescent could be injected into the patient's body. A fluoroscope and a MRI scan are then used to detect the nanorobot. Otherwise, the nanorobot could also emit some dye as it goes along leaving a marked path behind that could be used to analyse where it is in the body.

Nanotechnology will produce Smart Implants which would use systems that could detect and evaluate what therapy is required and automatically give the right therapy and right amount of medication. Insulin pumps are an example of this method but then on a much bigger scale.

CONCLUSION

There are many ways of improving cancer diagnosis, examination and treatment using nanotechnology. Each method has its own advantages, disadvantages and area/tasks it focuses on. Making an improvement in cancer diagnosis (time and examination) will be revolutionary as that's when main decisions will be made.

Nanotechnology requires a lot of research and experiments since trying it out on a real human body without it being almost 100% secure, could result in permanent or severe damage to that person's body. Scientists attempt to develop methods in order prevent the nanoparticles from attacking the healthy somatic cells and destroying the immune system.

There are great hopes for nanoparticles, however, the fact that we may allow them into our body in order to "repair" us does not mean that we should be treated like robots, hence the ethical issues. However, as it does less/no damage to the human body and besides also cures the disease, it is important to bare in mind that it might decrease suffering, increase life expectancy and the quality of life as it only acts on the disease whilst leaving the rest of the body untouched.

Some people fear the self-assembling grey goo, in which case nanorobots will practically eat our environment whilst building on themselves. On the other hand, many people also find it quite difficult to visualize this. If you weigh out the advantages over the risks, we can clearly notice that we could hugely benefit from nanomedicine.

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