Nanotechnology in Cancer Detection and Treatment

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Abstract: ***Nanotechnology has taken great strides in the field of medicine with improved drug delivery systems. The application of nanoparticles in cancer detection and treatment has been prominent in recent years wherein unique properties can be utilized for detection of site specific tumors. The main objective of this review is to give an update on the available techniques and briefly describe the nano-medicines developed so far for an effective treatment. Conventional techniques face the problem of toxicity resulting from the administered drug. In addition to this, most of the techniques available detect cancer only after metastasis which hampers the effectiveness of the anti-cancer drug. Through the application of nanotechnology techniques, active cancer cells can be differentiated and treated without harming the healthy cells. This review discusses the use of nanoparticles like quantum dots and fullerenes for detection of cancer cells by acting as imaging agents. These are crucial for identifying the affected cells and tissues for effective measurement. Liposomes and dendrimers are used in treatment through development of advanced drug delivery systems. Some other nanoparticles like carbon nanotubes and magnetic nanoparticles have extended application in both imaging and treatment. Due to its wide ranging properties and diverse applications, the nanoparticles developed so far and nanotechnology as a whole has a huge potential in cancer treatment.***

Keywords:Cancer, Nanotechnology, Nano medicine, Nanoparticle.

1. Introduction

Cancer is caused due to the uncontrolled division of abnormal cells. One of the most common features is the potential to spread to other parts of the body. It has the capacity to destroy healthy cells and tissues which has proved to be fatal over the years. Normal cells are transformed into tumor cells when genetic factors of a person interact with some external agents like physical, chemical and biological carcinogens which are a multistage process [1]. In fact, it remains as one of the most common cause of death. Almost 90-95% cases on cancer are induced by environmental factors, for example, excessive exposure to UV radiation in case of skin cancer. The remaining 5-10% is due to inherited genetics [2]. There are about 100 different cancer types out of which the common ones are lung, stomach, liver, esophagus, colorectal, breast, melanoma and cervical cancer. According to the GLOBOCAN and WHO statistics, in 2012, there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within five years of diagnosis). Worldwide around 57% of new cancer cases, 65% of cancer deaths and 48% people are living with cancer in the span of five years [3]. The burden of cancer will increase to 23.6 million new cases each year by 2030. This represents an increase of 68% compared with 2012 [4]. The conventional methods which are still in practice include surgery, chemotherapy, radio therapy and targeted therapy. Surgery and radio therapy allows the removal of cancer cells only to that specific targeted area and chemotherapy that allows the drug to flow through the bloodstream or can be delivered directly to the specific area. Targeted therapy is a newer technique that allows the removal of cancer cells more precisely and thus leading to less damage to normal cells. The effectiveness of treatment can be judged on the basis of drug’s ability to target and kill cancer cells while leaving healthy cells intact. In fact, in designing anti-cancer agents, the most important feature should be differentiation of healthy and affected cells. Another factor to be taken into consideration is the bio-compatibility of the drug such that the side effects are reduced. The current available techniques are lacking behind when it comes the aforementioned factors. Newer techniques like nanotechnology are currently in research since it provides a promising approach when it comes to cancer cell selectivity and reduced side effects.

Nanotechnology is a science which deals with processes that occur at molecular end; supra molecular level resulting in nanoparticles of unique properties such as increased solubility and bio compatibility. It has wide ranging applications suchas bio-sensors. Due to increased surface modification properties, it can be used in targeted delivery in case of cancer detection. Nano-systems have an edge over conventional methods when it comes to drug delivery and toxicity. Some of the nanoparticles used for cancer detection and treatment include liposomes, dendrimers, fullerene, quantum dots, magnetic nanoparticles, gold nanoparticles, nano-wires, nano-shells and carbon-nanotubes. Nanotechnology in conjunction with medicine provides an important platform where nano-carriers can be manipulated as well as used for multifunctional properties. It is one of the most promising approaches in detection and treatment of cancer.

2. Background on Targeted Drug Delivery

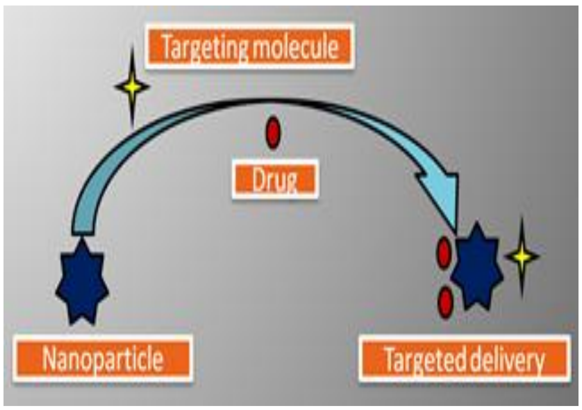

Figure 1: Targeted drug delivery

Targeted drug delivery is a process in which the required drug is encapsulated by a nanoparticle. The specific receptors on cell surface react with the drug encapsulated by the nano-carriers or nanoparticles. The effective drug delivery systems must meet certain criteria. The nanoparticles must have high loading capacity for selected drug, high response to stimuli, high bioavailability and stability. In addition to this, specific targeting, long circulation and intracellular delivery are some of the features. The nano-systems can identify biomarkers and detect tumor cells [5, 6]. In this regard, nanotechnology protects drug from degradation before they reach their target and enhances absorption of drugs into tumors [7]. Another conclusion we can draw is that using nanoparticles, the drug release rates can be precisely controlled while reducing the side-effects [6]. The nanoparticles which are used as drug delivery vehicles are generally <100nm in size and they consist of different bio-degradable materials such as natural or synthetic polymers, metals or lipids [8] along with their applications. Two of the nano-formulated drugs available in the market today are Abraxine and Doxil. Abraxine is a human albumin based nano-formulated drug with a size of around 100nm. It is also known as ABI-007 or nanoparticle albumin bound [nab]-Paclitaxel [PTX]. To reduce side effects, albumin has been used to conjugate PTX with Cremophor. Doxil is the formulation of doxorubicin in nano-liposome and has shown significant improvements over free doxorubicin[10, 11]. In some other clinical trials, various combinations of drugs have been implemented. In [9], doxorubicin and docetaxel has been reported to be used in-vitro for detection and treatment of prostate cancer and various other types. Similarly, for treatment of lung carcinoma and melanoma, a combination of combretastatin and doxorubicin has been used in-vivo.

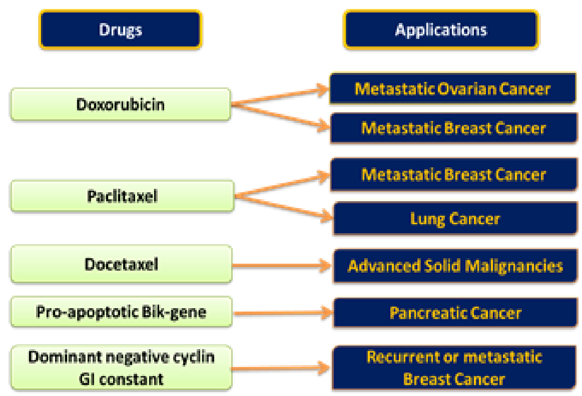

Figure 2: Nano formulated dugs and their applications [9, 10, 11]

3. Nanotechnology in Cancer Detection

The detection of cancer at an early stage is one of the factors to be considered for effective cancer treatment. With advancements in technologies, newer techniques like optical based imaging have been used for cancer detection. The use of nanoparticles for image contrast and enhancement has enabled improvements in cancer imaging. Some of the nanoparticles listed below have proven to be useful tools in cancer detection.

3.1 Quantum Dots

Quantum dots are nano-crystals ranging from 2-10nm which have extensively attracted great interest in the field of biology and medicine because of its unique optical and electrical properties. Quantum dots have a distinct advantage over conventional biomarkers because of their high photo stability and size tunable excitation [14]. The use of quantum dots hasbeenextended in the NIR wavelength range as an imaging probe. The main advantage of the technique is that it increases the depth of tissue penetration which will lead to more accurate detection in-vivo [10, 15]. Some of the materials best suited in building up quantum dots are cadmium sulphide and

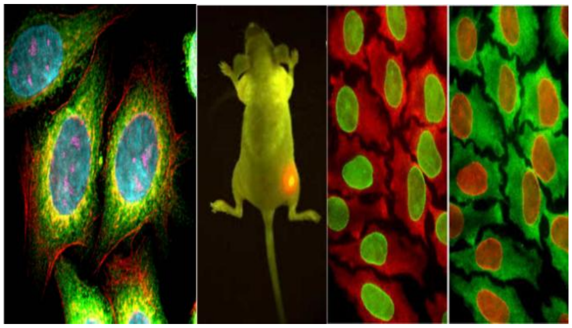

Figure 3: Bio-imaging using Quantum-dots

cadmium selenide. However, based on factors like toxicity and bio-compatibility, Zinc Sulfide is preferred [16]. Applications of quantum dots include in-vivo and in-vitro imaging, live cell imaging and single molecule tracking. It is used for the detection of lung cancer, breast cancer, prostate cancer and pancreatic cancer, detection of primary tumor in vitro, prostate cancer, targeting and imaging melanoma and also detection of thyroid carcinoma antigen [15, 16, 17]. Some of the applications shown in figure 3 include protein detection in cancer cells and tumour detection in mice.

3.2 Carbon Nanotubes

CNT belong to the family of fullerenes and are formed of coaxial graphite sheets (<100 nm) rolled up into cylinders. Structurally there are two types: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). It possesses properties such as high aspect ratio, ultra-light weight, tremendous strength and high thermal conductivity. However, in the field of cancer, diagnostic and therapeutic, three main properties have been exploited i.e., small size, high surface area to volume ratio and their ability to contain chemicals [18, 19, 20]. The surface of carbon nanotubes can be modified with proteins for cellular uptake which are then heated up upon absorbing near-IR light wave. When exposed to near-IR light, carbon nanotubes quickly release excess energy as heat (~70ºC) which can kill cancerous cells[21]. Due to their unique properties, they have wide ranging applications in cancer diagnosis and therapy. Some of the notable applications in cancer diagnosis are molecular imaging with single-walled carbon nanotubes and cancer biomarker detection. It is also used for drug delivery and thermal therapy. CNTs have proposed as a promising tool for detecting cancer at early stages with high sensitivity, selectivity and low detection limit [18]. Figure 4 shows the Schematics of a functionalised single-walled carbon nanotube with Cyanine Dye #3Labelled DNA (Cy3-DNA).

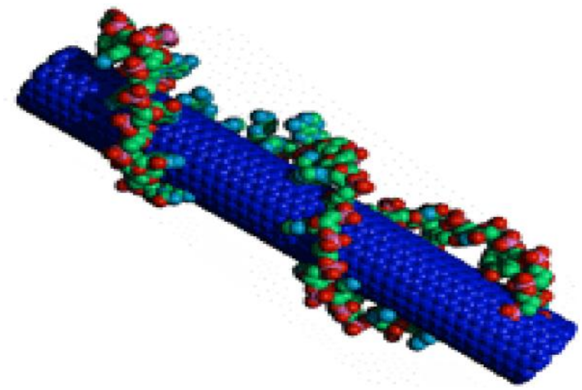

Figure 4: Targeted single-walled carbon nanotubes[12]

3.3 Metalic nanoparticles

Metallic nanoparticles have attractive properties like high surface Plasmon resonance, optical properties which can be tuned from visible to infra-red range. They possess large surface energy and have the ability to adsorb small molecules. Gold, silver and platinum are some of the metallic nanoparticles that have been used for cancer diagnosis and therapy. Gold nanoparticles have already been used as a vehicle for the delivery of anti-cancer drugs such as paclitaxel. The properties of gold nanoparticles including small size, bio-compatibility, high atomic number and ability to bind targeting agents gives an advantage over other nanoparticles to be used as contrast agents. The formation of bubble around the overheated gold nanoparticles in liquid environment followed by generation of acoustic and shock waves protein inactivation has become a profound area of research. Gold has also been used together with magnetic materials to improve the photo thermal effect to accelerate the death of cancer cells [21, 22, 23, 24]. Platinum nanoparticles act as prominent radiation sensitizers in radiotherapy cancer treatment showed improvements in biological efficiency of radiations, leading to amplified damage in DNS from tumor cells when compared to metal atoms [22]. Silver nanoparticles can be used for both active and passive targeting of drugs. It has been emerged as an attractive candidate for delivery of various small drug molecules or large biomolecules like proteins, DNA or RNA. An attempt to use silver nanoparticles as an anti-cancer agent has been proven to be successful. Limitations like toxicity and larger nanoparticles involves in targeting of silver nanoparticles to cancer cells [25]. Figure 5 shows the gold nanoparticles used for detecting cancer cells.

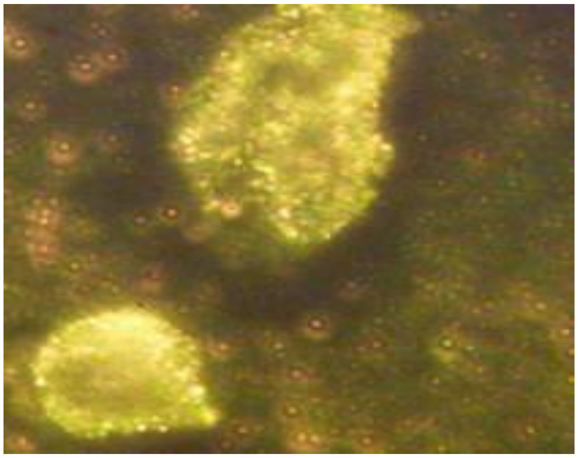

Figure 5: Gold nanoparticles detecting cancer cells [24]

4. Nanotechnology in cancer treatment

The use of nanotechnology in cancer treatment offers some exciting possibilities and newer platforms which includes minimal damage to healthy tissue and organs and elimination of cancer cells before they form tumor. Some of the nanoparticles used for cancer treatment are liposomes, dendrimers and magnetic nanoparticles.

4.1 Liposomes

Liposomes are small artificial vesicles which are incredibly biodegradable. The confinement and protection of the drug enclosed is done by the fatty layer on the liposomes. In this way, efficacy is improved keeping toxicity to healthy cells minimized. Their size ranges from 25nm to 10µm depending on the preparation method. Sizes which are less than 400nm can rapidly penetrate tumour

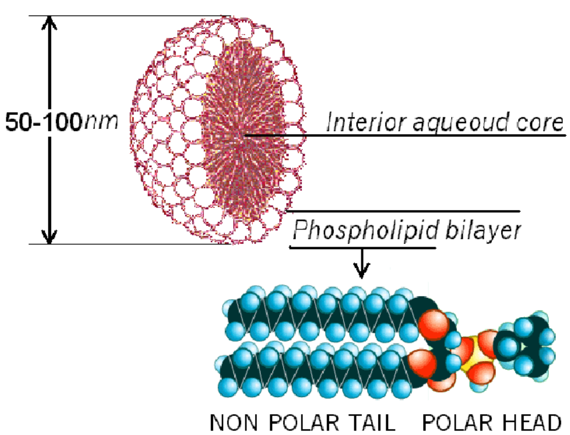

Figure 6: Liposomes for drug delivery [12]

sites from the blood stream by the endothelial wall in healthy tissue vasculature. Because of their unique structure, liposomes are considered as a versatile platform for combination drug delivery because they can simultaneously load hydrophilic drugs in their aqueous core and hydrophobic drugs in their lipid bi-layered membrane. Some of the liposomal products used currently for cancer treatment include Doxil, DaunoXome®, DepoCyt® and ONCO-TCS, which are liposomal formulations of doxorubicin, daunorubicin, cytarabineand vincristine, respectively [12, 21, 26]. Figure 6 shows the cross section of a liposome used for drug delivery.

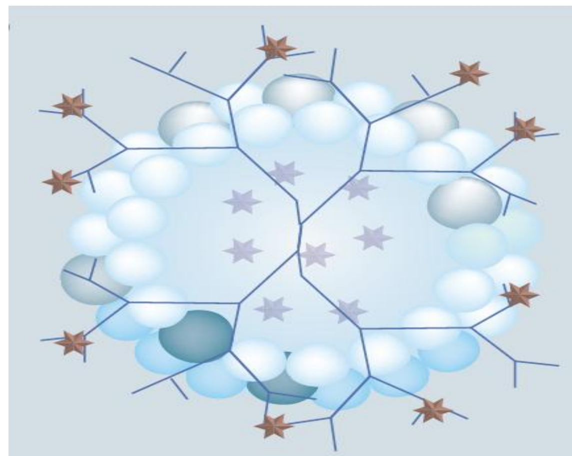

Figure 7: Dendrimers based formulation of drugs for treating cancer [9]

4.2 Dendrimers

Dendrimers generally possess multiple branches which is advantageous when it comes to multifunctional applications. In cancer, treatment and drug delivery systems can be used to carry multiple drugs at the same time to tumor site improving efficiency and reduces the time constraint. It has gained interest because of their cylindrical structures which often comes with unique properties. Sensitivity of imaging can be improved since they can be targeted to a single site and the unique architecture enables for multivalent attachment of imaging probes, as well as targeting moieties. In this way, it improves the therapeutic index of cytotoxic drugs by direct delivery to cancer cells and also offers drug resistance in tumor cells [9, 12, 26]. Figure 7 shows the dendrimers carrying multiple chemotherapy drugs for treating cancer.

4.3 Magnetic nanoparticles

Magnetic nanoparticles have been used in bio-medical field including cancer treatment. One of the most widely used nanoparticle of this kind are the super magnetic iron oxide nanoparticles (SPIONs).

One of the distinguishing features of SPIONs for drug deliver is their applicability for both magnetic properties and anti-body attachment which will improve targeting capability. Magnetic iron oxide particles offer a huge advantage over the other particles since they are highly bio-compatible [6, 23]. Magnetic nanoparticles are currently in development as a promising new type of cancer treatment which selectively heat tumor cells to temperatures high enough to kill cancer cells without harming normal ones. This destroys tumors and leads to the activation of immune system to attack other cells throughout the body. In fact, the heat produced can kill the cancer cells and releases the drug from the nanoparticles directly inside the cancer cells [27]. Magnetic-radiated hyperthermia can be used for local tumor treatments. It also ramps up the immune system to find and destroy distant cells. This is because cancer cells produce more heat shock proteins (HSPs). When cancer cells are heated to high temperatures, they produce HSPs in high quantities which in turn binds to antigens (molecules or proteins that trigger and immune response). When some cells are destroyed by the heat, their HSPs and antigens are released into the body that attracts cells from the immune system which then interact with the HSP-antigen complex and used them to hunt down other cancer cells that were not damaged by the initial heating [28].

5. Limitations and Future Prospects

One of the most prominent challenges is that of clinical translation. There are only six FDA approved nano-medicines: Adcetris (Brentuximabvedotin) and Kadcyla (Trastuzumabemtansine) are antibody-drug conjugates, Doxil (liposomal doxorubicin), Abraxane (human serum albumin non-specifically bound to paclitaxel), Marqibo (liposomal vincristin), and DaunoXome (liposomal daunorubicin).One of the challenges with these medicines is the lack of complete elimination from the body. Currently available techniques have to undergo extensive research to check the accuracy and their relevancy to the real patients. Some other challenges can include limited knowledge about the cancer physiology and poor functionalization of the available nano-medicines [29]. The bio-safety of the nanoparticle is another roadblock because of the host's overwhelming response to the invading Nanoparticles [30].Although nano-medicines impose no threats immediately, long term side effects are yet to be tested. Another limitation is the cost of the nanomedicines. Despite all of these limitations, the use of nanotechnology in detection and in drug delivery systems has grown exponentially over the years. The combination of the conventional methods with the nano-medicines provides a promising way where nanotechnology can be employed in the treatment of Cancer. Multifunctional nanoparticles provide a new way of embedding various functions into one system to detect and kill cancer cells simultaneously. Better and stable systems for controlled release of drugs have to be designed. A better understanding of the properties of the carrier and mechanism of loading can provide a technological breakthrough. In future, the chemicals and materials used for making the nano-materials should be formulated for its activity and toxicity. Thus, the outcome for patients with metastatic cancer will greatly improve if nanoparticles are developed with the right therapies in the right direction.

6. Conclusion

Cancer being an uncontrolled disease leads a patient to death. Various methods and protocols such as chemotherapy, radiology and surgery have been used which has many side effects that make patients feel unbearable pain and deep anxiety. The emergence of nanotechnology has made a significant effect on cancer detection and treatment. Nanotechnology has the ability to serve as a tool which can change the foundation of cancer diagnostic treatment and prevention. The main advantage is the small size of nanoparticles which helps in reaching the roots of cancer cells. Advanced and effective drug delivery systems have been designed in the past few years. Some of the nanoparticles used in Cancer therapy have unique properties like bio-compatibility which becomes ideal when designing effective systems. Nano-systems can not only cure cancer but can also cure damage cells and regeneration of cells. The use of nanoparticles can improve the harmful side effects of conventional techniques like chemotherapy and radiotherapy. The selective heat deposition to tumor cells is another advantage of nanotechnology which provides a versatile platform to cure cancer. Different types of cancer cells have unique properties that can be exploited by nanoparticles to target the cancer cells. In future, nano-robots could repair disease cells, eliminate bacterial infection in a patient without using treatment with antibiotics, perform surgery at the cellular level, remove individual disease cell and even repair the defective portion of defective cell. Nanotechnology has greater potential to save lives than any other method that we use today. It has become a boon in medical field even by delivering drugs to specific cells using nanoparticles. Thus, nanotechnology can lead to a revolution where thebody organs will have the ability to protect itself from harm and can lead a healthy life. It is a technology capable of many more breakthroughs.

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