NANO TECHNOLOGY IN CANCER DIAGNOSIS AND TREATMENT: AN OVERVIEW

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Abstract

Nanotechnology provide innovative tools that shed greater light on life cycle of normal cells and the point at which molecular processes and changes within cells become correlated with development of cancer. It should be possible to obtain large amount of information from a small source. They aid in analysis of parameters such as cellular mechanics, morphology and cytoskeleton which has been hard to achieve using conventional technology.

Nano devices can detect cancer cells, identify cancer signatures and provide targeted delivery of anti cancer therapeutics and contrast agents to tumour cells. The obstacle to early detection of cancer lies in the liability of existing tools to detect molecular level changes during early phases in the development of cancer. Nano Technology is potential tool that could help detect the molecular changes and assist in focusing on preventive efforts.

Key words: Nanotechnology, Cancer, nanodevices, diagnosis, treatment.

Introduction

Nanotechnology is an area of science devoted to the manipulation of atoms and molecules leading to the construction of structures in the nanometer scale size range (often 100nm or smaller) which retain unique properties. NT deals with structures that range from 1 to l00nm- about the size of a virus – and derives its name from Greek word for "dwarf"[5]. "NT allows us to make materials that are thousands of times smaller than the smallest cell in the body "said James R Baker Jr, MD, Professor of biologic NT at University of Michigan in Ann Arbor. Because these materials are so small, they can easily get inside cells and change how they work[5].

NT is considered as an emerging technology that can have enormous positive impact on human health. Relevant Process of living organisms occur basically at nanometer scale, elementary biological units like DNA, Proteins or cell membranes are of this dimenision[4]. Nanoscale devices smaller than 50nm can easily enter most cells and those smaller than 20nm can move out of blood vessels as they Circulate through the body. Early detection of disease is often critical to how successful treatment can be. Therefore the development of new methods of diagnosis is a hot research field, where every small step is of great importance. The potential applications are predominantly in detection, diagnostics (disease diagnosis and imaging), monitoring and therapeutics.

Discussion

Products based on NT in medicine and medical technology are reaching the market with an anticipated enormous Positive impact on human health, in coming years.

NT can have an impact on the key challenges in cancer diagnosis and therapy. Nanotechnology's greatest advantage over conventional therapies may be the ability to combine more than one function. There is a lot of research going on to design novel nano devices capable of detecting cancer at its earliest stages, pinpointing its location with in the human body and delivering chemotherapeutic drugs against malignant cells.

The major area in which nanomedicine is being developed in cancer involves.

a) Early detection of tumours (analysis of cancer associated markers and designing contrast agents that improve the resolution of tumour area comparing with the nearby normal tissues)

b) Cancer treatment (Creating nanodevices that can release chemotherapeutic agents)

Tumour diagnostics and prevention

Prevention is the best cure for Cancer. Early detection will greatly increase survival rates an in situ tumour will be easier to eradicate than one that has metastasized[4].

Different kinds of nanoparticles suitable for drug and gene delivery, probing DNA structures etc. include

1. Liposomes
2. Polymeric Nanoparticles (Nano spheres and Nano capsules)
3. Solid lipid particles
4. Nano crystals
5. Polymer Therapeutics such as dendrimers, fullerenes.
6. Inorganic Nanoparticles (eg. Gold & Magnetic Nano particles)

Dendritic polymeric nano devices can detect cancer cells, identify cancer signatures and provide targeted delivery of anti cancer therapeutics. (i.e. Cis-platin, Methotrexate and Taxol) and contrast agents to tumour cells. The polymers show uniform uptake in cells and survive for more than two weeks inside the cells and do seem to be affected by body's multidrug resistance processes. The size of polymers is under filtration threshold of kidney and cannot cross blood brain barrier. Since there is nothing for host's cells to bind to, there is no immune reactivity.

Carbon nanotubes scan down DNA and look for single nucleotide polymorphism which make possible to detect whether an individual has a high-risk or low-risk configuration for developing the processes that lead to cancer. This technique can serve as an alternative to PCR and identify multiple nucleotide polymorphic sites in large strands on non amplified DNA at relatively high through put and low cost.

Nanowires having the unique properties of selectivity and specifity can be designed to sense molecular markers of malignant cells. They are laid down across a micro fluidic channel and they allow cells or particles to flow through it. Nanowires can be coated with a probe such as an antibody or oligonucleotide, a short stretch of DNA that can be used to recognize. Proteins that bind to the antibody will change the nanowires electrical conductance and this can be measured by a detector. As a result, proteins produced by cancer cells can be detected and earlier diagnosis of tumour can be achieved.

Nanoparticle Contrast agents are being developed for tumour detection purposes. Labelled and nonlabelled nanoparticles are already being tested as imaging agents in diagnostic procedures such as nuclear magnetic resonance imaging. Such nanoparticles are paramagnetic ones, consisting of an inorganic core of iron oxide coated or not with polymers like dextran. There are two main groups of nanoparticles

1) Super paramagnetic iron oxides whose diameter size is greater than 50nm
2) Ultra small super magnetic iron oxides whose nanoparticles are smaller than 50nm

Quantum dots being the nanoscale crystals of a semiconductor material such as cadmium selenide, can be used to measure levels of cancer markers such as breast cancer marker Her-2, actin, micro fibril proteins and nuclear antigens.[4]

Gold nanoparticles used as optical probes for early detection of oral cancer. They can be conjugated to antibodies or peptides through electrostatic interaction or coordinate bonding to probe for specific cellular biomarkers (EGFR) with high specificity and affinity. Gold nanoparticles provide useful optical signals for molecular specific information.

Nano-Bio-Chip sensor technique found to be promising new diagnostic tool for early detection of oral cancer. Further trials need to establish their effectiveness.

Tumour treatment

Frequent challenges encountered by current cancer therapies include nonspecific distribution of antitumour agent, inadequate drug concentrations reaching the tumour, and

limited ability to monitor therapeutic responses. Poor drug delivering to the target site leads to significant complication, such as multidrug resistance.[1] Current NT promises solutions to several of the current obstacles facing cancer therapies. Nanoparticles have size of 5nm to 200nm, allowing their unique interaction with biological systems at the molecular level. As a result of their materials composition, nanoparticles are capable of self assembly and maintaining stability and specificity which are crucial to drug encapsulation and biocompatibility.

Nanoparticlaes used as drug delivery vehicles are generally <100nm in at least one dimension and consist of different biodegradable materials such as natural or synthetic polymers, lipids or metals. For therapeutic applications drugs can either be integrated in the matrix of the particle or attached to the particle surface[2]

An effective approach for achieving efficient drug delivery would be to rationally develop nanosystems based on the understanding of their interaction with the biological environment, target cell population, target cell surface receptors, changes in cell receptors that occur with progression of disease, mechanism and site of drug action, drug retention, multiple drug administration, molecular mechanism and patho biology of the disease under consideration[2].

Nanoparticles can consist of a number of materials, including polymers, metals and ceramics. Many types of nanoparticles are under various stages of development as drug delivery systems, including liposomes and lipid based carriers (such as lipid emulsions and lipid –drug conjugates, polymer microspheres, micelles and various ligand – targeted products (such as immunoconjugates).[5]

Liposomes and other lipid based nanoparticles liposomes are self assembling, spherical, closed colloidal structures composed of lipid bilayers that surround a central aqueous space. Liposomes are most studied formulation of nanoparticle for drug delivery. Liposomal formulation has shown an ability to improve the pharmakinetics and pharmodynamics of associated drugs. One strategy to achieve tumour-specific targeting is to conjugate a targeting moiety on the outer surface of the lipid bilayer of the liposome that selectively delivers drug to the desired site of action[1].

Polymeric Nano Particles

Nano particles can be coated with hydrophilic polymers. Coating can efficiently protect nanoparticles from capture by macrophages. The increased hydration also helps nanoparticles to be more water soluble and less sensitive to enzymatic degradation, there fore enhancing biocompatibility.

During past decade, the application of polymer based drug delivery systems in oncology exponentially with advent of biodegradable polymers. In these polymers, drugs are physically dissolved, entrapped, encapsulated or covalently attached to the polymer matrix. The resulting compounds may have different structures including micelles and dendrimers. Both natural (albumin, Chitosan, Heparin etc) and Synthetic (Poly-L- Lactide, Poly- [L-glutamate] Poly [D, L Lactide-Co-glycolide], [PEG, etc], biodegradable polymers are being exploited as drug delivery systems.

Targeted Delivery of Therapetic Nano Particles

Nanoparticle delivery of anticancer drugs to tumor tissues can be achieved by either passive or active targeting.

Passive targeting takes advantage of the inherent size of nanoparticles of tumour vasculature, such as the enhanced permeability and retention effect (EPR) and the tumour microenvironment. This approach can effectively enhance drug bioavailability and efficacy.

Angiogenesis is crucial to tumour progression. Blood vessels in tumour tissues have gaps as large as 600 to 800 nm between adjacent endothelial cells. This defective vascular architecture coupled with poor lymphatic drainage includes EPR effect which allows nanoparticles to extravasate through these gaps into extra vascular spaces and accumulate inside tumour tissues.

The accumulation of nano particles in tumours depend on factors including the size, surface characterstics and circulation half-life of the nano particles and the degree of angiogenesis of the tumour.

Hyper proliferative cancer cells have profound effects on their surrounding

microenvironment. Tumours must adapt to use glycolysis (hypoxic metabolism) to obtain extra energy, resulting in an acidic microenvironment. In addition cancer cells over express and release some enzymes that are crucial to tumor migration, invasion and metastasis, including matrix metalloproteinases (MMP). When certain PH-sensitive molecules are incorporated into liposomes, drugs can be specially relased from the complexes by change in PH. The PH-sensitive liposmes are stable at physiologic conditions (PH 7.2) but degraded in tumour-associated acidic area[1].

The polymeric nanoparticles that have been tested clinically so far have mostly lacked a targeting moiety and instead relay mainly on the EPR effect of tumours, the tumour microenvironment, and tumour angiogenesis to promote some tumour selective delivery of nanoparticles to tumour tissues. However, these drug delivery systems have intrinsic limitations to the degree of targeting specificity they can achieve. In the case of the EPR effect, while poor lymphatic drainage on the one hand helps extravasated drugs to be enriched in the tumour interstitium on the other hand, it induces drug outflow from the cells as a result of higher osmotic pressure in the interstitium, which eventually leads to drug redistribution in some portions of the cancer tissue[1].

To overcome these limitations a targeting ligand or an antibody is conjugated to nanoparticles. By incorporating a targeting molecule that specifically binds an antigen or receptor that is either uniquely expressed or over expressed on tumour cell surface, the ligand-targeted approach is expected to selectively deliver drugs to tumour tissues with greater efficiency. Such targeted nanoparticles may constitute the next generation of polymeric nanoparticle drug delivery system. Indeed, several targeted polymeric nanoparticle are currently undergoing preclinical studies.

Choice of Target Receptor

Selection of the appropriate receptor or antigen on cancer cells is crucial for the optional design of targeted nanoparticles. The ideal targets are those that are abundantly and uniquely expressed on tumour cells, but have negligible or low expression on normal cell. Whether the targeted nano-conjugate can be internalized after binding to the target cell is another important criterion in the selection of proper targeting ligands. The concentration of drug is much higher when the drug is released from nanoparticles in the cytoplasm after internalization[1]

Choice of targeting ligand

One of the greatest challenges to the design of nanoparticles than can selectively and successfully transport drug to cancerous tissues is the choice of targeting agents.

A variety of tumour targeting ligands, such as antibodies, growth factor, or cytokines, have been used to facilitate the uptake of carrier into target cells.

Ligands targeting cell-surface receptors can be natural materials like folate and growth factors, which have the advantages of lower molecular weight and lower immunogenicity than antibodies. However, some ligands, such as folate that is supplied by food, show naturally high concentration in the human body and may compete with the nano-particle-conjugated ligand for binding to the receptor reducing intracellular concentration of delivered drug. Recent advances in molecular biology allow modified antibodies to be used as targeting moieties in an active-targeting approach. MAbs or antibody fragments are most frequently used ligands for targeted therapies. Whole MAbs have two binding domains showing high binding avidity. The Fc domain of MAb can induce complement mediated cytotoxicity leading to additional, cell- killing effect[1]

The use of antibody fragments as targeting moiety can reduce immunogenicity and improve pharmacokinetic profiles of nanoparticles.

Future directions

Recent advances in molecular, biological and genetic diagnostic techniques have begun to explore cancer-associated biomarkers and their implications for development and progression of cancer and to reveal that cancer is controlled by complex multi-factorial mechanism rather than single factor

Molecularly targeted therapy is a recent introduction with understanding of the cancer behaviours at the molecular level. Assays to accurately and quickly quantify several cancer–related biomarkers simultaneously on single tumour specimens will be enabled by virtue of

advances of nanotechnology for example : use of conjugated quantum Dots potentially allows five cancer – related proteins to be detected on same tissue section.

In addition to ex vivo analysis for the detection of early cancer and profiling of molecular biomarkers, in vivo imaging of cancer using several types of nanoparticles has also been investigated together with the progression of nanoscale drug delivery system. The development of multifunctional nanoparticles may contribute significantly to the realization of individualized therapy for cancer. Ideally, for constructing multifunctional nanoparticles, an appropriate combination of agents (Therapeutic agent and targeting moiety) will be chosen based on accurate biological information with the tumour with imaging materials attached on the nanoparticle surface. Nanoparticles may eventually be capable of detecting malignant cells, pinpointing and visualizing their location in the body, killing the cancer cells with minimal side effects by sparing normal cells and monitoring treatment effects in real time.

There are certain critical questions that need to be addressed in the rational design and applications of nanoparticles before further clinical development, such go how the association or conjugation of a therapeutic agent to ligand or carrier changes the pharmakinetics, biodistribution and side effects of nanotherapecitic drugs, how the safety profile of a nanoparticles changed after conjugation , such an coating with quantum Dots, how we can minimize the potentical toxicity of polymeric nanoparticles that is inherent from the accumulation of a nonbiodegradable polymer with size over renal threshold and how side effects resulting from the ability of nanoparticles to cross the BBB can be prevented or diminished. These questions are critically important and hitherto under studied

Attracted by the rapid and promising progress in nanotechnology, physicists, chemists, engineers, biologists and clinicians will continue to challenge themselves to develop novel and efficacious nanosystems for the diagnosis and treatment of cancer.

Possible Risk for human health and Ethical Questions

While products based on nanotechnology are actually reaching the market, sufficient knowledge on the associated toxicological risks in still lacking. The literature on toxicological risks of the application of NT in medical technology in scarce.

Reducing the size of structure to nano level results in distinctly different properties. As well as the chemical composition, which largely dictates the intrinsic toxic properties very small size appears to be a dominant indicator for drastic or toxic effects of particles. It is generally accepted that nanoparticles pose a separate problem with in the area of toxicology, designated an nanotoxicology.[4]

Therefore, chemicals and materials in nanoformulation need to be evaluated for their activity and toxicity as nanoparticles. Chemical composition, which dictates the intrinsic toxic properties of the chemical, is significant importance in determining the toxicity of particles.

It has been found that biodegradable substances are normally decomposed and their waste products excreted by the kidneys and intestines. However, nonbiodegradable nanoparticles have been studied and it seems that they accumulate in certain organs, especially to the liver. It is not clarified, the potential harm they may trigger, or at what dosage, but further investigation is need.

Ethical and moral concerns also need to be addressed in parallel with the new developments in some areas, for example, neuroethics need to be investigated before brain and neural system research.

Conclusion

Nanotechnology is fast expanding area of research anticipated to lead to development of novel, sophisticated applications which recognize cancer cells, deliver drugs to target tissue, reporting out come of therapy, monitor intracellular changes to help prevent precancerous cells from becoming malignant. The future remains exciting and wide open for ongoing efforts by scientists, researchers and medical personnel can sincerely ensure to do big things using the very small.

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