Unique roles of nanotechnology in medicine and cancer

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Abstract
Here we review the scope of nanotechnology in Medicine and human cancer. The imaging and therapy agents can be co-delivered by same nanoparticle for integrated molecular diagnosis, therapy, and follow-up of cancer or ‘cancer theranostics’ is implying multimodal use of nanoparticles in cancer care. Nanoparticles are used for passive targeting and in conjugation with ligands for active targeting, to have optimum concentrations of imaging and therapeutic agents in the tumor cells specifically, sparing normal tissue from unwanted side effects. Potential utility of nanoparticles in the nano biosensors, nano fluorescent tag imaging, nano tumor mapping, nano gene profiling, nano molecular delivery, nano chemo-radio therapy, nano thermotherapy, nano photodynamic therapy, etc., is tending to revolutionize medicine particularly personalized cancer care and laboratory. Nanoparticle induced oxidative stress based inflammation reported by few studies; in lung, liver and brain required further investigations.

Key Words: Cancer, diagnosis, nanotechnology, treatment

Introduction
Nanotechnology having ability to engineer materials at the scale of nanometer (nm), has been facilitating research and technological developments relating to the use of nanoparticles (NPs) in the range of 1 to 100 nm for applications in the field of medicine. For their size NPs have unique operating ability in the complex bio-environment to interact at the level of biomolecules, and facilitated by nm size of the organic and inorganic molecules and atoms in the body (DNA 2.5 nm, Na atom 0.2 nm). For unique size, optical, electrical, magnetic, chemical, and ligands carrying properties nanoparticles can be targeted to the cancer cells with specificity and monitored efficiently with extreme precision in real-time. The present review explores scope of the nanoparticles in bioscience and applications in human cancer management.

Nanoparticle circulation is selectively facilitated by biological membranes. The blood vessel endothelial gaps facilitate extravasations and circulation of NPs of <5 nm size. Glomerular membrane allows clearance of NPs <6 nm size. Liver cells do uptake the NPs >8 nm size. The NPs with specific surface properties such as charge and hydrophobicity are phagocytosed by the Kupffer cells and cleared into the biliary system. Surface modification of NPs may prevent opsonization by the reticulo-endothelial system (RES), and facilitates their retention in blood circulation. For these reasons the nanoparticles have enhanced permeability and retention (EPR) and longer circulation time in the body.

The nanoparticle-EPR in a tumor is increased due to relative lack of lymphatic drainage, and over expression of vascular endothelial growth factor (VEGF) by tumor-cells promoting disorganized angiogenesis producing more permeable/leaky blood vessels. It leads to retention and accumulation of the nanoparticles in the tumor, and gives advantages of using nano-particulate contrast agents for tumor diagnostic MRI, optical imaging, photo acoustic imaging, as well as NP delivered therapy.

Nanoparticles may carry multiple chemotherapeutic, anti-angiogenic, and gene therapy agents simultaneously to the tumor site for synergistic therapeutic effect. Also the imaging and therapy agents can be co-delivered for integrated molecular/cellular diagnosis, therapy, and follow-up, referred as cancer theranostics. The multimodal utility of nanoparticle for therapy and diagnosis may be further enhanced by constructs capable of combining multiple functionalities into a single nano scale entity. A nanoparticle-tagged reporter, such as an apoptotic marker, may help signals about the payload delivery of the drug and reaching of the desired therapeutic effect in a patient. Nano biotechnology, thus, may facilitate the means for “personalized medicine” as per the diagnostic and cure requirements of the individual patients.

Targeting Strategies for Nanoparticles
Nano theranostics may use neutrally charged particles of average diameter of 10-100 nm and molecular weight around 30 kDa, it is referred as ‘Passive targeting’, which may be limited in utility for its low tumor specificity, thereby, lower than required concentration at the tumor target. Desired specificity and concentration hence, may require ‘Active targeting’ of the nano-vehicle with moieties such as small ligands, antibodies, and biomarkers capable of specific binding to tumor expressed molecular receptors, facilitating efficient tumor uptake, internalization and receptor-mediated endocytosis resulting in elevated concentrations in tumor cells.

Monoclonal antibodies (mAbs) in their engineered chimeric humanized and clinically non antigenic forms are being presently widely applied for the Active targeting. Several mAbs based nanotherapies like trastuzumab, cetuximab, rituximab, and bevacizumab had been already under trials. RNA aptamers to the vascular endothelial growth factor (VEGF) isoform with 2'-O-methylpurine and 2'-F pyrimidines are known to show anti-angiogenic properties, and the aptamers called Pegaptanib had been FDA approved for the treatment of neovascular macular degeneration. Another promising aptamers options for active nano targeting are, the oligonucleic acids with high specificity, small size, and reduced immunogenicity, albeit at high production costs. Besides, many tissue biomarkers also have been identified as possible targets of nano targeted drugs, including the transferrin receptor, epidermal growth factor receptor, folate receptor, and human epidermal receptor 2 (HER-2).

Potential Uses
Nanotechnology manifests itself in a wide range of materials that can be useful in the field of medicine. The
nanoparticles are designed with a chemically modifiable surface to attach a variety of ligands that can turn them into biosensors, molecular-scale fluorescent tags, imaging agents, targeted molecular delivery vehicles, and other useful biological tools. Diagnosis and treatment of cancer are the two most important fields that can be revolutionized with the help of nanotechnology. Nanotechnology’s applications in cancer diagnosis include tumor localization, tumor margin detection, identification of important adjacent structures, mapping of sentinel lymph nodes, and detection of residual tumor cells or micro metastases. From the point of view of treatment the nanoparticles target the delivery of drugs, radiotherapy, phototherapy, immunotherapy more precisely to the tumor cells.

**Application in cancer diagnostics**

Studies in gene and related protein expressions (genomics and proteomics) have made it possible to trace such changes in tissue for the purpose of early cell molecular diagnosis of the disease for the preventive and therapeutic purposes. Both the in vitro and in vivo molecular tests are being worked out. In vitro patients’ genetic material (DNA) samples are examined for gene expression in terms of RNA production, single nucleotide polymorphisms (SNPs), and corresponding protein expressions with single amino acid variations for genetic molecular diagnosis of the disorders and sensitivity to chemical substances for the purpose of theranostics.

DNA analysis chips devised for DNA analysis are currently available for the scientific biomedical research, awaiting clinical applications. DNA chip comprises of an inert support carrying microarrays of thousands of single strand DNA molecules with different base sequences. DNA from tissue sample is labeled with suitable radioactive or fluorescent material and can be identified on the basis of its binding spot on the DNA chip, an information which may help quick determination of the therapy. The diagnostic DNA chips are being developed for leukemia’s and the mouth and throat tumors, and using different sensitivity and specificity nanotechnological modalities, are very likely going to emerge as cost effective and convenient diagnostic procedure for personalized theranostics.

The bio-chip is micro-fluidic device, in fact a lab on chip and promising hope for future pocket size bio-chip laboratory, or at-clinic or at-home non-laboratory settings for diagnosis of diseases particularly cancer based on nano analytic procedures with advantages of minimized analytical procedures, applications, transport, micro measurements and instrumentations.

For cancer imaging, nanotechnology is applicable for protein and cancer cell sensing and nano-vector high-contrast imaging. Nanoparticle selective tagging had been successfully applicable to important targets, including microbes, biomarkers, and individual molecules such as proteins and DNA, to improve the yield of cancer cells captured. Nanoparticles also offer fluorescent nano platforms and it is possible to image a single cell or an entire organism in vivo. Dual-mode nanoparticles can be imaged with MR and optical imaging to increase accuracy by cross evaluation and detection of breast, lung, colon, prostate, and ovarian cancers’ hidden or overt metastatic colonies at the time of presentation. Advances in nanotechnology may lead to a nanoparticle-based MRI, positron emission tomography (PET), single photon emission tomography, and computed tomography (CT) enhancing sensitivity and specificity for tumor imaging.

**Application in cancer treatment**

With the advent of nanotechnology, ligands-targeted therapeutic strategies, using immunotoxins, radio immunoglobulins and drug immunoconjugates are being developed to overcome the problems of conventional chemotherapy in cancer. Two therapeutic nanocarriers; (a) nano-liposome and (b) nano-albumin have been approved...
by the US FDA for clinical practice. Liposomal doxorubicin and albumin bound paclitaxel (Abraxane®) are EPR-based nanovector applications for the breast cancer chemotherapy.[32] The nanomedicines have advantages over other cancer therapeutics since (i) nanosystems can themselves have therapeutic or diagnostic properties and can be designed to carry a large therapeutic ‘payload’; (ii) nanosystems can be attached to multivalent targeting ligands, which yield high affinity and specificity for target cells; (iii) nanosystems can be made to accommodate multiple drug molecules that simultaneously enable combinational cancer therapy and (iv) nanosystems can bypass traditional drug resistance mechanisms. By passive and active targeting, the nanocarriers can achieve increased intracellular concentration of drugs in cancer cells enhancing anticancer effect, and sparing the normal tissues from toxicity.[33]

Radionuclide targeted nanoparticle mediated internal radiotherapy is another emerging mode of cancer therapy. Applications of the high and low energy [between 0.1 MeV to 2.2 MeV (multiples of electron volt, 1 Mev = 1,000,000 eV)] β-emitter radioisotopes are ideal for the treatment of small to large clusters of tumor cells. The maximum tissue penetration range (1-10 mm) and “cross-fire effects” of β-particles [with energy range between 0.1-2.2 MeV] can kill tumor cells in close proximity to the neo-vasculature. Alpha-emitters [having high-linear energy transfer (LET 80 keV/μm) and short range energy depositions, with tissue penetration range of 50-100 μm] hold great therapeutic promises for tiny and micro-metastatic cancer foci. Monoclonal antibody conjugated α-emitters have shown high specific killing effects and minimal normal tissue damages in the animal model tumors.[34]

Thermotherapy as stand alone or in combination with chemo, radio and immune therapies, in Medicine, utilizes tumor cell sensitivity to the rise of temperature comparative to normal tissue cells. It has applications for a) tumor heating [41 to 45°C] to induce cell damages, and b) thermal ablation [50°C to 70°C] for destruction of pathology affected cells. Successful thermotherapy should ensure tumor disappearance, diminution, or at least the growth arrest. Nanotechnology introduced in the thermo therapy use of ferromagnetic or super paramagnetic (SPM) particles in infusible fluid vehicles, to have optimal tumor concentration, then use of external electromagnetic field for heat generation to have nano-thermo-therapeutic effect. Gold nanoparticles and carbon nano-tubes are also being used in addition to magnetic nanoparticles for nano-thermo-therapy.[35]

Photodynamic therapy is another emerging treatment modality using light-sensitive molecules [photo sensitizers] targeting to the cancer cells then exposing them to near-infrared light. The irradiation excites transfer of electron-energy from photo sensitizer molecule by two types of photodynamic reactions [Figure 3]. 1) An electron from photosensitizer transfers to oxygen producing reactive oxygen species (ROS) or free radicals like superoxide (O₂⁻), hydrogen peroxide (H₂O₂), hydroxyl (OH⁻) and hydroperoxyl (HO₂⁻) radicals. 2) An electron spin exchange occurs between the photo sensitizer and triplet oxygen (¹O₂), resulting in the production of cytotoxic singlet oxygen (¹O₂). Singlet oxygen is the prime mediator of phototherapy causing oxidation and degradation of cellular membranes of the targeted cancer cells. Nanophototherapy is applicable for treating oncological, cardiovascular, dermatological, ophthalmic, and immunological disorders, reducing the burden of surgery and scarring. Since photo sensitizers are mostly hydrophobic and poorly water-soluble, it required advanced delivery systems for their cell targeting hence, different strategies have been investigated, using photosensitizer conjugation and encapsulation in colloidal carriers such as liposome, oil dispersion, and polymeric nanoparticles.[5]

**Nano-toxicity and therapy limitations**

The tissue cells readily take up nanoparticles via active and passive mechanisms and the same NPs in the cells may show different behavior due to variations in particle size, shape, surface coating and charge. This makes the categorization of nanoparticle behavior in the biological systems intricate and identification of nanoparticle hazards difficult. Unlike classical toxicology, nanoparticle dose metric is not straight-forward, the protocollization of bioassays involving nanomaterials is still under development and not yet internationally validated. Many more variables, like dispersion, agglomeration, aggregation, concentration, and matrix require further considerations while working with the nanomaterials in vitro and vivo. Although nanodrug entry routes [Figure 4]
A silent polymorphism in the MDR1 gene changes substrate. Several nanoparticles are able to cross the blood brain barrier through intravenous route and may cause neurotoxicity. There were already some reports of nanoparticles to detect and kill cancer cells simultaneously. Safe use of nanoparticles in biomedicine/cancer medicine required studies for detailed understanding of biocompatibility and toxicity of nanoparticles. Nanoparticles have been reported to cause oxidative distress and inflammation in lung, hepatic inflammation and decreased coagulation factor production in rat liver, and neurotoxicity

for major putative targets have been identified, detailed mechanisms and pathways are yet to be worked out. The interaction of nanoparticles with skin has recently received significant attention, in the view of nano-toxicity, because of the increasing use of nano particles in stain-resistant clothing, cosmetics, and sunscreens. The dermal route of exposure is also important because of the tendency of agglomerated airborne nanoparticles to settle on skin surface, and the difficulties in preventing contact with these particles and penetration. In vitro, flexing of skin has shown to increase dermal penetration of micron-sized dextran particles and derivatized fullerenes.

**Contraindications**

Free radical/oxidative activity of nanoparticles has been reported to cause oxidative stress and lung inflammation, and may likely cause genotoxicity.[38-40] The Kupffer cells in liver are portal of nanoparticle clearance, and like of the macrophages known to be affected by NPs oxidative stress to produce inflammatory mediators such as TNFα.[42] In rat liver, the nano drugs were reported to cause oxidative stress and cell injury, leading to inflammation, alterations in hepatic production of clotting factors, and systemic thrombosis.[43,44] Several nanoparticles are able to cross Blood brain barrier through intravenous route and may cause neurotoxicity. There were already some reports of nanoparticle neurotoxicity both in the vitro and in vivo, and are under further investigations.[45]

**Conclusion**

Nanotechnology is fast facilitating scope of nanoparticle in bioscience and cancer care. The evolving discipline of Nano theranostics coming up with promising potentials for convenient early diagnosis and therapy of the diseases, particularly cancer, tailored to individual's molecular profile for personalized oncology/medicine, and future possibilities of laboratory in pocket. Nanoparticles provide a new generation of cancer therapeutics. Development of multifunctional nanoparticles might eventually render nanoparticles to detect and kill cancer cells simultaneously. Safe use of nanoparticles in biomedicine/cancer medicine required studies for detailed understanding of biocompatibility and toxicity of nanoparticles. Nanoparticles have been reported to cause oxidative distress and inflammation in lung, hepatic inflammation and decreased coagulation factor production in rat liver, and neurotoxicity in vitro and vivo requiring further confirmations.

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