Review Article

NANOTECHNOLOGY: EMERGING CONCERNS

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Abstract

Nanoparticles are currently the subject of intense pharmacologic research because of their capacity to carry and deliver drugs to specific targets. The rapid expansion of nanotechnology has resulted in a vast array of nanoparticles that vary in size, shape, charge, chemistry, coating and solubility. This intrinsic property raises important questions regarding the potential for nanoparticles to carry toxic chemicals that may be present in the environment. The release of hazardous substances is a matter of concern for technology. In nanomedicine, optimizing the balance between persistence and excretion and preventing the release of toxic degradation products may reduce hazard. Thus, progress of nanotechonolgy should be compared to the toxicology of newly engineered nanoparticles.

Key Words : Nanotechnology, hazards

Nanotechnology and nanoengineering have produced significant scientific and technological advances in diverse fields including medicine and physiology. Nanotechnology is the engineering of molecular precise structures - typically 0.1µm or smaller- and ultimately, molecular machines. The prefix "nano" means to one-billionth. In the metric scale of linear measurements, a nanometer is one-billionth of a meter. Primarily in the materials science standard, the term "nanotechnology" is now commonly used to refer to the fabrication of new materials with nanoscale dimensions between 1 and 100 nm (1). The application of this nanotechnology to medicine comprises nanomedicine. It is the usage of molecular tools and molecular knowledge of the human body for the preservation and improvement of human health. For applications to medicine and physiology, the materials and devices in nanotechnology can be designed to interact with the cells and tissues at a molecular level with a high degree of functional specificity, thus allowing integration between technology and biological systems not previously attainable. Target-specific drug/gene delivery and early diagnosis in cancer treatment is one of the priority research areas in which nanomedicine will play a vital role.

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Recent advances in tissue engineering include the microelectromechanical systems and biocompatible electronic devices that have a significant rapid potential and sensitive detection of diseases related molecules, thus enabling changes at the molecular level in a small percentage of cells. Nanoparticles are considered to have the potential as novel intravascular or cellular probes for both diagnostic (imaging) and therapeutic purposes (drug/gene delivery), which is expected to generate innovations and play a critical role in medicine. Though at present applied nanotechnology to medicine and physiology is in its infancy, the breadth and pace of current research is impressive. One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Nanoscale devices are already proving that they can deliver therapeutic agents to target cells, or even within specific organelles (2). Applications include novel drug delivery systems like quantum dots (Qdots), nanoparticles (3,4), dendrimers, micelles molecular conjugates, liposomes, and ultrasound microbubbles, highly porous self-assembling bilayer tubule systems, protein based molecular computers, biomimetic self assembling molecular motors or the mechanical forces produced by RNA polymerase during protein transcription (5-9). Nanoparticles can be in the form of nanospheres (matrix systems in which drugs are dispersed throughout the particle) and nanocapsules (drug is confined in an aqueous or oily cavity surrounded by a single polymeric membrane. Poly(isobutylcyanoacrylate) has been used to make nanocapsules with an oily core for hydrophobic drugs. Some nanospheres are made of poly(isohexylcyanoacrylate), poly(methylcyanoacrylate) and biodegradable poly(ethylcyanoacrylate) (10). Further improvements to these nanospheres are by coating the nanoparticles with hydrophilic polymers like poly(ethylene glycol), poloxamines, poloxamers and polysaccharides to provide a "cloud" of hydrophilic and neutral chains at the particle surface. Molecules like poly(ethylene glycol) reduces nonspecific attachment or uptake (11). This allows longer circulation without being taken up by the body's macrophages, so as to direct more specific targeting (11). Nanoparticles can be used as tumor biomarkers. They help the detection process by concentrating and protecting a marker from degradation so that the analysis is more sensitive. Streptavidin-coated fluorescent polystyrene nanospheres used in flow cytometry to detect biological molecules have shown greater sensitivity as compared to conventional dyes (10). Presently, there are several types of nanoparticle used in molecular imaging in cancer diagnosis, such as liposomes, dye-molecule-doped silica nanoparticles, Qdots, gold nanoparticles (12), immunotargeted nanoshells, perfluorocarbon nanoparticles, nanoshells, and magnetic nanocrystals (13-15). Nanoparticle contrast agents are being developed for tumor detection purposes. Labeled nanoparticles and non-labeled particles are being tested as imaging agents in diagnosis procedures such as computed tomography and nuclear magnetic resonance imaging (10,17). Poly(D,L-lactide-co-glycolide) PLGA nanoparticles, are biocompatible and degradable with no toxicity. Cegnar et al. have investigated the use of PLGA nanoparticles containing cystatin, a potential anticancer drug inhibiting the tumor-associated activity of intracellular cysteine proteases cathepsins (16), as a carrier system to regress tumor growth, and showed that PLGA nanoparticles are useful for a rapid delivery of protein inhibitors into tumor cells, enabling an effective inhibition of the intracellular proteolysis (18,19).

Nanowires are laid down across a microfluidic channel allowing cells or particles to flow through it. The wires can detect the presence of genes and relay the information via electrical connections. This technology can help pinpoint the changes in the genetics of cancer. Nanowires can be coated with a probe such as an antibody that binds to a target protein. Proteins that bind to the antibody will change the nanowire's electrical conductance and this can be measured by a detector (20).

Carbon nanotubes are also being used to make DNA biosensors. This uses self-assembled carbon nanotubes and probe DNA oligonucleotides immobilized by covalent binding to the nanotubes. When hybridization between the probe and the target DNA sequence occurs, the change is noted in the voltammetirc peak of an indicator (21). The DNA biosensors being developed are more efficient and more selective than current detection methods.

Nanoscale cantilevers are built using semiconductor lithographic techniques. These can be coated with molecules (like antibodies) capable of binding to specific molecules that only cancer cells secrete. When the target molecule binds to the antibody on the cantilever, a physical property of the cantilever changes and the change can be detected.

Nanoshells help in the destruction of solid tumors using high thermal therapies i.e laser light, focused ultrasound and microwaves(22). Nanoshells have a core of silica coated with an ultra-thin metallic layer, normally gold (23) By adjusting the core and shell thickness, nanoshells can be designed to absorb and scatter light at a desired wavelength.

Nanoscale devices have the potential to radically change cancer therapy by increasing the number of highly effective therapeutic agents. Nanoparticles can serve as customizable, targeted drug delivery vehicles capable of ferrying chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. Though nanotechnology has the power to radically change the way cancer is diagnosed, imaged and treated fears about the potential toxicity of nanoparticles and nanoshells to the human body cannot be overruled. While the small size of nanoparticles is what makes them so useful in medicine, it is also the factor that might make them potentially dangerous to human health. The biodistribution and movement of nanoparticles through tissues, and the phagocytosis, opsonization, and endocytosis of nanoparticles are all likely to affect on the potential toxicity of nanoparticles. Recently, the new term of "nanotoxicology" has been often used by nanobiologists and pharmacologists. For several nanoparticles, oxidative stress-related inflammatory reactions have been observed (24). Presently, to better understand the potentially harmful side effects of nanomaterials, many nanobiologists call for an extensive investigation of nanotoxicological issues (25,26). Nanoparticles cause some toxicities in the liver, spleen, kidneys, lymph nodes, heart, lungs, and bone marrow. Some nanoparticles are readily transported throughout the body. They are deposited in these organs, penetrate cell membranes, lodge in mitochondria, and may trigger injurious responses.

Nanoparticles have almost unrestricted access to the human body. The actual hazards of nanoparticles are variable, depending on characteristics of the specific nanoparticle. The various hazards of nanoparticles may be during nanoparticle production and processing (27,28), products with inherent dispersive nanoparticles (29,30) or when nanoparticles are fixed in products (31,32).

The ultrafine particulate matter acts as a carrier of toxic chemical such as polycyclic aromatic hydrocarbons as the drugs are delivered directly to the target tissue. Nano-sized particles are able to evade the detection by the body's immune system as well as have the ability to pass through the blood brain barrier. Normally, exogenous particles or foreign substances that enter the bloodstream are absorbed by specialized phagocytes that are responsible for protecting the body from "foreign substances". However, anything smaller than 200nm is no longer absorbed by phagocytes thus nanoparticles can travel though the blood and move randomly throughout the entire body. Nanoparticles have increased surface area to volume ratios that dramatically increase their reactivity. The surface reactivity of nanoparticles can, depending on the type of coating, cause chemical damage to surrounding tissues. Nanoparticles are not detected by the macrophages in the lungs and may negatively affect lungs leading to pulmonary inflammation (30) and consequently translocate through alveolar cell membranes into the general circulation. Pulmonary inflammation may trigger systemic inflammation, which, in turn, may lead to cardiovascular disease (33). Furthermore, nanoparticles may be translocated from the nasal region of the respiratory tract to the brain via the olfactory bulb (34) and the blood (35). Ingestion of some inorganic nanoparticles may negatively affect the intestines due to immune reactions and possible translocation from the intestines to other organs, carrying an inflammation hazard (36). Dermal exposure to nanoparticles may be hazardous when such particles are photocatalytically active and can penetrate into the living part of the skin (34).

The exact distribution of nanoparticles in the body depends on the coating. Biodegradable substances are normally decomposed and their waste products excreted by the kidneys and intestines. However, non-biodegradable nanoparticles have been studied and it seems that they accumulate in certain organs, especially the liver. It is not known how long the deposits stay, the potential harm they may trigger, or the dosage that causes harm (37,38). Thus, this is a huge area of concern. Nanoparticles can agglomerate at high concentrations. When agglomerated the particles no longer remain in the nano scale size range. They either retain the toxic properties or de-agglomerate remains an unanswered question. Depending on the excretion and disposal of nanomedicines, these nanoparticles can be released into the water or the air. Artificially manufactured nanoparticles will be new to the environment in type and quantity. They constitute a new class of non-biodegradable pollutants.

Nanomedicine for cancer has the ability to improve health care by leaps and bounds. However, there is a possibility that the application of nanotechnology will be too expensive such that we further segregate the rich and the poor. Moreever, with such technology, nanomedicine has the potential to increase the life span of human beings. It will create populations with a large proportion of elderly people - an aging society. The elderly are going to require more health attention and consequently more health expenditures.

Hence, progress of nanotechnology should be compared to the toxicology of newly engineered nanoparticles. Achieving these goals will promote in a safe and profitable nanotechnology.

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