British Journal of Pharmaceutical and Medical Research Vol.02, Issue 01, Pg.374-379, January-February 2017

Available Online at http://www.bjpmr.org

BRITISH JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

DOI: In-Process Volume 02, Issue 01, January-February 2017

Review Article

Nanomedicine: Possible Risks for Human Health

Pramod Singh Khatri and Satyender Mathur*

Head, Department of Clinical Research, Amity Medical School, Amity University, Gurgaon
*MSc Clinical Research, Amity Medical School, Amity University, Gurgaon.

ARTICLE INFO

Article History:
Received on 24th November, 2016
Peer Reviewed on 29th December 2016
Revised on 17th January, 2017
Published on 02nd February, 2017

Keywords:
Nanotechnology, Nano Sized, Drug Delivery Systems, Nanoparticles, Medical Imaging, Gene Therapy, Nanofibers, Macrophage, Endothelium, Intracellular Delivery, Extravasation, Toxicity

ABSTRACT

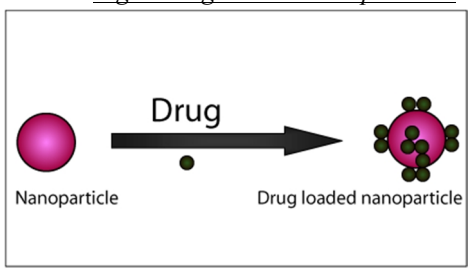
The use of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems has of recent times been referred to as "nano-medicine" by the National Institutes of Health. Research into the rational delivery and targeting of pharmaceutical, therapeutic and diagnostic agents is at the forefront of projects in nanomedicine. These involve the identification of precise targets (cells and receptors) related to specific clinical conditions and choice of the appropriate nanocarriers to achieve the required responses while minimizing the side effects. Mononuclear phagocytes, dendritic cells, endothelial cells, and cancers (tumor cells, as well as tumor neo-vasculature) are key targets. Today, nanotechnology and nanoscience approaches to particle design and formulation are beginning to expand the market for many drugs and are forming the basis for a highly profitable niche within the industry, but some predicted benefits are exaggerated. Nanomaterials can be beneficial for both in vivo and in vitro biomedical research and applications. The integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug-delivery vehicles.

INTRODUCTION:

Nanomedicine is the process of diagnosing, treating, preventing disease and traumatic injury, alleviating pain, preserving and improving human health, using molecular tools and molecular knowledge of the human body. In the nearest future, nanomedicine can address many important medical problems by using nanoscale-structured materials and simple nanodevices that can be produced today, including the interaction of nanostructured materials with biological systems[1]. In the mid-term, biotechnology will make possible even more noteworthy advances in molecular medicine and bio robotics, including microbiological biorobots or engineered organisms. In the longer term, perhaps 10–20 years from today, the earliest molecular machine systems and nanorobots may join the medical armamentaria, finally giving physicians the most powerful and effective tools imaginable to conquer human disease, ill-health, and aging.

Nanomedicine is the preservation and advancement of human health using molecular tools and molecular knowledge of the human body[2]. Nanomedicine will have extraordinary and far-reaching implications for the medical profession, for the definition of disease, diagnosis and treatment of medical conditions including aging, and ultimately for the advancement and extension of natural human biological structure and function. As the science and technology of nanomedicine speed ahead, ethics, policy and the law are struggling to keep up. It is important to proactively address the ethical, social and regulatory aspects of nanomedicine in order to reduce its adverse impacts on the environment and public health and also to avoid a public backlash. At present, the most significant concerns involve risk assessment, risk management of engineered nanomaterials and risk communication[3]. Future applications of nanomedicine will be based on the ability to build nanorobots. These nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes. Human health has always been determined on the nanometer scale; this is where the structure and properties of the machines of life work in every one of the cells in every living thing[4]. Nanoparticles do not behave similarly; their behavior within the biological microenvironment, stability, extracellular and cellular distribution varies with their chemical makeup, morphology and size. These aspects are discussed with respect to intravenous and subcutaneous routes of injection.

Fig:1 Drug Loaded nanoparticles



Macrophage as a target

The propensity of macrophages of the reticuloendothelial system for rapid recognition and clearance of particulate matter has provided a rational approach to macrophage-specific targeting with nanocarriers. The macrophage is a specialized host defense cell whose impact to pathogenesis is well known. Alterations in macrophage clearance and immune effector functions contribute to common disorders such as atherosclerosis, autoimmunity, and major infections[5]. The macrophage, therefore, is a valid pharmaceutical target and there are numerous opportunities for a focused macrophage-targeted approach (23–26). For example, although most microorganisms are killed by macrophages, many pathogenic organisms have developed means for resisting macrophage destruction following phagocytosis. Macrophages and dendritic cells play critical roles in determining immunogenicity and the generation of appropriate immune responses. Systems, such as numerous polymeric and ceramic nanospheres, nanoemulsions, liposomes, protein cage architectures and viral-derived nanoparticles act as powerful adjuvants if they are physically or covalently associated with protein antigens.

Endothelium as a target

The concept of targeting to the blood vessels is an eye-catching one, particularly with the view that the endothelium plays a vital role in a number of pathological processes including cancer (dysregulated angiogenesis), inflammation, oxidative stress and thrombosis. Indeed, a number of studies have demonstrated a level of control of arrest and distribution of passively targeted nanoparticles by specific endothelial cells, and these were linked to the surface properties of the carrier[6]. For instance, early studies of polystyrene nanoparticles, designed to minimize Kupffer cell uptake, indicated exclusive arrest by the bone marrow sinus lining endothelial cells in rabbits. Arrest was followed by receptor-

mediated internalization. Another example is the localization of intravenously injected polysorbate 80-coated nanoparticles to murine and rat blood-brain endothelial cells. Recent studies have shown that cationic liposomes within 1hour of entering the circulation are internalized into endosomes and lysosomes of endothelial cells in a characteristic organ- and vessel-specific manner. These patterns seem to bear no relationship to the morphological characteristics of the endothelium associated with a particular site, but probably reflect vessel-specific expression of receptors for which such particles, or their surface-associated blood proteins, are ligands.

Extravasation: targeting of solid cancers

The development of "stealth" technologies has provided opportunities for passive accumulation of intravenously injected nanoparticles (20 –150 nm) in pathological sites expressing "leaky" vasculature by extravasation (24). Although, attempts have included delivery of drugs and imaging agents with different nanoscale technologies to the underlying parenchyma of injured arteries and rheumatoid arthritis, the majority of efforts are concentrated on solid tumors. As a result of perfusion heterogeneity, the spatial distribution of stealth nanoparticles in solid tumors is heterogeneous and unpredictable[7]. As has been elegantly demonstrated by Researchers, structural and functional defects of blood and lymphatic vessels within solid tumors impede efficient delivery of not only systemic nanoparticles, but macromolecules. Already compromised by abnormal hydrostatic pressure gradients, compressive mechanical forces generated by tumor cell proliferation cause intratumoral vessels to compress and collapse. Tumor-specific cytotoxic therapy, reducing tumor cell number, may result in more effective delivery, by decompressing these same vessels; however, this enhanced perfusion could provide a route for metastasis.

Nanoparticles for cytoplasmic drug delivery

Endosomal membrane breaching is particularly important for readying MHC class I-restricted cytotoxic T lymphocyte responses, for survival of genetic materials against nuclease degradation in the lysosomal compartment, or for those drugs that must reach cytoplasm in sufficient after endocytic delivery with nanoparticulate carriers. Here, there are advances in particle engineering too[8]. For instance, nanoparticles made from poly (DL-lactide-co-glycolide) can leak from the endo-lysosomal compartment within minutes of internalization in intact form and reach the cytoplasm. The mechanism of rapid leakage is by selective reversal of the surface charge of nanoparticles from the anionic to the cationic state in endo-lysosomes, thus resulting in a local particle-membrane interaction with subsequent cytoplasmic release. Another impressive approach for cytoplasmic delivery of nanoparticles is their surface manipulation with short peptides known as protein transduction domains such as HIV-1 TAT protein transduction domain (TAT PTD), which is a short basic region comprising residues, or heterologous recombinant TAT-fusion peptides.

Cell death and gene therapy

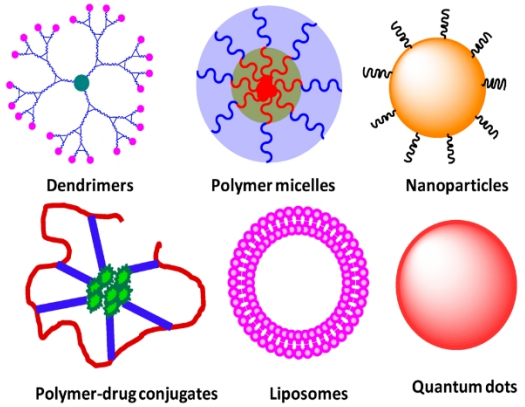
A very clear warning is evident from the poor success in human gene therapy with viruses. Although, viral vectors are extremely efficient delivery systems for nucleic acids, they can induce severe immunotoxicity as well as inadvertent gene expression changes after random integration into the host genome[9]. These issues have generated a surge in design and engineering of synthetic polycationic non-viral gene transfer systems. However, the polycationic nature of the gene- delivery vehicles can induce immediate or delayed cytotoxicity by mechanisms involving necrosis as well as apoptosis. Necrosis may occur as a result of membrane deterioration or pore formation after interaction between the cationic components of the delivery system with cell surface proteoglycans and negatively charged proteins in cytoskeleton, such as actin. In the case of Jurkat T cells the apoptotic mechanism appears to be due to polycation-mediated release of Bcl-2-sensitive proteins such as cytochrome c from the mitochondrial intermembrane space and altered mitochondrial functions[10]. However, different cationic materials depending on their molecular weights and polydispersity, may initiate apoptosis at different times and by different mechanisms or modes.

Dendrimers and Dendrimer-Based Devices

Dendrimers represent yet another nanostructured material that may soon find its way into medical therapeutics. Starburst dendrimers are tree-shaped synthetic molecules with a regular branching structure emanating outward from a core that form nanometer by nanometer, with the number of synthetic steps or "generations" dictating the exact size of the particles, typically a few nanometers in spheroidal diameter (Fig:2). The peripheral layer can be made to form a dense field of molecular

groups that serve as hooks for attaching other useful molecules, such as DNA, which can enter cells while avoiding triggering an immune response, unlike viral vectors commonly employed today for transfection. Upon encountering a living cell, dendrimers of a certain size trigger a process called endocytosis in which the cell's outermost membrane deforms into a tiny bubble or vesicle[11]. The vesicle encloses the dendrimer which is then admitted into the cell's interior.

Fig:2 types of nanocarriers for drug delivery applications



Microchips for drug delivery

These are microfabricated devices that incorporate micrometer-scale pumps, valves, and flow channels and allow controlled release of single or multiple drugs on demand. These devices are particularly useful for long-term treatment of conditions requiring pulsatile drug release after implantation in a patient. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering micro-reservoirs, which are filled with drugs[12]. Thus, controlled delivery systems can be designed to release pulses of different drugs by using different materials for the membrane. Recently, microchip devices of 1.2 cm in diameter and thickness of approximately 500um with 36 drug reservoirs were fabricated from poly (L-lactic acid). The drug reservoirs were covered with poly (D,L-lactic-co-glycolic acid) membranes of different molecular masses.

Medical Nanorobotics

The third major development pathway of nanomedicine—molecular nanotechnology (MNT) or nanorobotics—takes as its purview the engineering of complex nano- mechanical systems for medical applications. Just as biotechnology extends the range and efficacy of treatment options available from nanomaterials, the advent of molecular nanotechnology will again expand enormously the effectiveness, precision and speed of future medical treatments while at the same time significantly reducing their risk, cost, and invasiveness. MNT will allow doctors to perform direct in vivo surgery on individual human cells[13]. The ability to design, construct, and deploy large numbers of microscopic medical nanorobots will make this possible.

Carbon nanotubes

Carbon nanotubes belong to the family of fullerenes and consist of graphite sheets rolled up into a tubular form. These structures can be obtained either as single- (characterized by the presence of a single graphene sheet) or multi-walled (formed from several concentric graphene sheets) nanotubes. The diameter and the length of single-walled nanotubes may vary between 0.5–3.0 nm and 20 –1000 nm, respectively. The corresponding dimensions for multi-walled nanotubes are 1.5–100 nm and 1–50nm, respectively. Carbon nanotubes can be made water soluble by surface functionalization. Molecular and ionic migration through carbon nanotubes can happen, thus offering opportunities for fabrication of molecular sensors and electronic nucleic acid sequencing. Carbon nanotubes can apparently cross the cell membrane as 'nanoneedles' without upsetting the membrane and localize into cytosol and mitochondria. However, the mechanisms are poorly described.

Quantum Dots and Nanocrystals

Fluorescent tags are usual in medicine and biology, found in everything from HIV tests to experimentations that image the inner functions of cells[15]. But different dye molecules must be used for each color, color-matched lasers are needed to get each dye to fluoresce, and dye colors tend to blend together and fade quickly after one use. "Quantum dot" nanocrystals have none of these shortcomings. These dots are tiny particles measuring only a few nanometers across, about the same size as a protein molecule or a short sequence of DNA. They come in a nearly unlimited palette of sharply-defined colors which can be customized by changing particle size or composition. Particles can be excited to fluoresce with white light, linked to biomolecules to form long-lived sensitive probes to identify specific compounds up to a thousand times brighter than conventional dyes used in many biological tests and can track biological events by simultaneously tagging each biological component (e.g., different proteins or DNA sequences) with nanodots of a specific color[16].

Closing Remarks:

In the first half of the 21st century, nanomedicine is expected to eliminate practically all common diseases of the 20th century, and almost all medical pain and suffering as well. It is a bright future that lies ahead for nanomedicine, but we shall all have to work hard to make it a reality. The nanotechnology will aid to improve health by enhancing the efficacy and safety of nanosystems and nanodevices. Moreover, early diagnosis, implants with improved properties, cancer treatment and minimum invasive treatments for heart disease, diabetes and other diseases are anticipated. In the coming years, nanotechnology will play a key role in the medicine of tomorrow providing revolutionary opportunities for early disease detection, diagnostic and therapeutic procedures to improving health and enhancing human physical abilities, enabling precise and effective therapy that suits the patient. Nanomedicine is in its infancy, having the potential to change medical research dramatically in the 21st century. Nanomedical devices can be applied for analysis, imaging, detection, diagnostic and therapeutic purposes and procedures, such as targeting cancer, drug delivery, improving cell-material interactions, scaffolds for tissue engineering, and gene delivery systems; and provide innovative opportunities in the fight against incurable diseases. Many novel nanoparticles and nanodevices are expected to be used, with an enormous positive impact on human health. Over the next ten to twenty years nanotechnology may profoundly transform science, technology and society offering a noteworthy opportunity to enhance human health in novel ways, especially by enabling early disease detection and diagnosis, as well as specific and effective therapy tailored to the patient.

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