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Editorial Open Access

Nanomedicine in Cancer Treatment: Drug Targeting and the Safety of the used Materials for Drug Nanoencapsulation

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Editorial

Cancer is still one of the major health problems of modern societies since it is the second cause of death (23.2%) after cardiovascular diseases (25.4%) [1]. Although, a lot of progress has been done in recent years by developing new drugs for treating cancer, major disadvantages still remain. The conventional chemotherapy, administration of drugs with the usual formulations, is characterized by significant problems. The drug, after systemic administration overwhelms the body acting generally non-selectively in both diseased and the healthy cells (toxicity side effects). Furthermore, relatively high doses at regular intervals must be administered in order to achieve the desired therapeutic levels in target cells. The development of medications that may provide the selective action of anticancer drugs only the affected tissue may dramatically improve the quality of life of patients and their families by eliminating the side effects of conventional chemotherapy.

In recent years there is a huge research effort to develop more effective forms of administration of anticancer drugs, called controlled and targeting systems, into cancer cells [2]. Several drug-delivery technologies have emerged and a fascinating part of this field is the development of nanoscale drug delivery devices. Nanoparticles (NPs) have shown many implications for the development and success of new therapeutic strategies for anticancer drug delivery, peptide and protein delivery and gene therapy. Furthermore, NPs and other colloidal drug-delivery systems modify the kinetics, body distribution and drug release of an associated drug [3]. Nanoparticle-based drug-delivery systems have made a remarkable difference in site-specific release of chemotherapeutic agents, owing to their physical and chemical characteristics and biological attributes [4,5].

The most important categories of nanocarriers showing the highest clinical and commercial interest for anticancer drugs are: a) liposomes (small spherical lipid vesicles with size typically 25-200 nm), b) the polymeric micelles (spherical colloidal particles with a size typically 20-100 nm) c) dendrimers (branched polymeric macromolecules with size 10-100 nm), d) quantum dots (semiconductor nanocrystals with a diameter of 2-10 nm) e) biodegradable polymeric nanoparticles (solid spherical nanoparticles of biocompatible polymers with sizes < 1000 nm), f) the water-soluble polymer-drug conjugates (macromolecular drugs) and g) hybrid inorganic/organic nanoparticles [6].

Although nanoparticles have tremendous potential for a host of applications, their adverse effects on living cells have raised serious concerns recently for their use in the healthcare and consumer sectors [7]. The behavior of nanoparticles is relatively different from larger particles of the identical material. Nanoparticles have shown biological functions such as killing pathogenic bacteria and viruses (e.g. flu), but research has also shown that nanoparticles may produce adverse effects (dose related) in human cells on contact. There is a correlation between a decrease in particle size and an increase in toxicity, because of larger surface area. The high surface area and high local charge densities generate a large area which can interact with surrounding biological molecules. *In vitro* cytotoxicity studies of nanoparticles using different cell lines, incubation times, and colorimetric assays are increasingly being published [8]. With each of these nanoparticles, different data have been published about their cytotoxicity due to varying experimental conditions as well as differing nanoparticle physiochemical properties.

The safe use of inorganic nanoparticles in biomedical applications remains an unresolved issue. To date, the question remains whether inorganic NPs are safe to be used for biomedical purposes. More and more data are becoming available regarding NP toxicity, but a lot of effort is still required in order to truly advance our knowledge in this field [9].

Synthetic amorphous silica (SAS), in the form of pyrogenic (fumed), precipitated, gel or colloidal SAS, has been used in a wide variety of industrial and consumer applications including food, cosmetics and pharmaceutical products for many decades. Based on extensive physico-chemical, ecotoxicology, toxicology, safety and epidemiology data, no environmental or health risks have been associated with these materials if produced and used under current hygiene standards and use recommendations [10]. It was believed that none of the SAS forms, including colloidal nano-sized particles, were shown to bio-accumulate and all disappear within a short time from living organisms by physiological excretion mechanisms with some indications that the smaller the particle size, the faster the clearance is. However, in recent articles it was demonstrated that SAS can induce cytotoxic effects [11]. Silica nanoparticles (25–200 μg/ml) induced cytotoxicity and oxidative stress in human liver (HepG2) cells in a dose-dependent manner [12]. The cytotoxic activity of amorphous silica nanoparticles is mainly influenced by surface area and not by aggregation [13].

Super paramagnetic iron oxide nanoparticles (SPIONs) have been widely utilized for the diagnosis and therapy of specific diseases, as magnetic resonance imaging contrast agents and drug-delivery carriers, due to their easy transportation to targeted areas by an external magnetic field [14]. From the toxicological observations it was suggested that the functional groups and sizes of SPIONs are critical determinants of cellular responses, degrees of cytotoxicity and genotoxicity, and potential mechanisms of toxicity. Nanoparticles with various surface modifications and of different sizes induced slight, but

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possibly meaningful, changes in cell cytotoxicity and genotoxicity, which would be significantly valuable in further studies of bio-conjugation and cell interaction for drug delivery, cell culture, and cancer-targeting applications.

A wide application of carbon nanotubes (CNTs) is on the way, owing to their unique structural, optical, mechanical and electronic properties, high specific surface area, and facile functionalization. SWCNTs have potential application in new cancer therapies, particularly when the drug delivery capacity and their ability to absorb NIR radiation are considered [15]. The presence of the carboxylic groups enables the attachment of molecules such as antibodies, glycoproteins, lectins, and carbohydrates, allowing the SWCNTs to be used to specifically target cancer cells. Although many efforts have been made to carefully investigate the *in vitro* and *in vivo* toxicity of CNTs, researchers still fail to reach consensus on the toxicity of CNTs [16]. Cytotoxicity tests revealed a concentration- and time-dependent loss of V79 cell viability after exposure to all tested materials in the following sequence: asbestos>CNF>SWCNT [17]. Evidences for MWCNTs cytotoxicity were also recently reported in several cells [18].

Except these nanoparticles polymeric macromolecules were also used extensively for drug carriers. The use of biodegradable polymers for anticancer drug delivery has gained increasingly interest during the past 5–10 years. In recent years, polymer-based nanomedicine, a field that includes the use of polymer–DNA complexes (polyplexes), polymer–drug conjugates, and polymer micelles bearing hydrophobic drugs, has received increasing attention for its ability to improve the efficacy of cancer therapeutics. Owing to their small size and excellent biocompatibility, nanosized polymer therapeutic agents can circulate in the bloodstream for long periods of time, allowing them to reach the target site. In addition, chemical modification of polymer therapeutic agents with ligands capable of specifically binding receptors that are over-expressed in cancer cells can markedly augment therapeutic efficiency [19].

Dendritic scaffold has been found to be suitable carrier for a variety of drugs including anticancer, anti-viral, anti-bacterial, anti-tubercular etc., with capacity to improve solubility and bioavailability of poorly soluble drugs [20]. In spite of extensive applicability in pharmaceutical field, the use of dendrimers in biological system is constrained because of inherent toxicity associated with them. This toxicity is attributed to the interaction of surface cationic charge of dendrimers with negatively charged biological membranes *in vivo*. Interaction of dendrimers with biological membranes results in membrane disruption via nanohole formation, membrane thinning and erosion. Dendrimer toxicity in biological systems is generally characterized by hemolytic toxicity, cytotoxicity and hematological toxicity.

Until today, for the development of biodegradable nanoparticles aliphatic polyesters of PCL, PHB, PLA, PGA and copolymers of PLGA are used [21]. Last years, new biocompatible aliphatic polyesters were also synthesized and studied as appropriate drug nanocarriers [22-24]. Among the nanoparticulate carriers, PLGA NPs have tremendous potential in the applications combining targeting, imaging, diagnostics and therapy. Conjugation or encapsulation of drugs in PLGA nanocarriers reduces the undesirable shortcomings of these therapeutic agents, such as short circulation half-life and non-site-specific targeting, resulting in undesired systemic side effects. These drug-loaded PLGA conjugates not only prolong the *in vivo* circulation time of the therapeutics from several minutes to several hours but also reduce cellular uptake along the endocytic route [25]. The potential advantage of biodegradable carriers as compared to their non-degradable counterparts is their reduced toxicity and the avoidance of accumulation of the polymer in the cells after repeated administration [26]. Furthermore, these biocompatible polyesters can be hydrolyzed in the human body to non toxic byproducts such as diols and acids (lactic acid) [27]. Increasing experience in the field of preparation, characterization, and *in vivo* application of PLGA nanoparticles has provided the necessary momentum for promising future use of these agents in cancer treatment, with higher efficacy and fewer side effects [28]. An additional advantage of these nanoparticles is that can be also used for drug targeting. This possibility of drug targeting into tumor cells is based on binding to the surface of nanocarriers "guiding" molecules (antibodies or antibody fragment, peptides, small molecules) that recognize and bind to receptors which are expressed exclusively by tumor cells [29]. For active targeting of nanoparticles in cancer cells, folic acid will be used as a guide molecule. The folate receptor is over-expressed on the cell membrane of cancer cells in the brain, kidney, breast, ovarian and lung, whereas is absent from normal cells. This has led recently to the use of folic acid molecule as a guide for targeting tumor cells [30].

Drug conjugation to a biocompatible polymer is also an alternative procedure for anticancer drug administration [31]. Their advantages are that can enhance its aqueous solubility, but also changes drug pharmacokinetics at the whole organism and even sub-cellular level with the possibility to clearly enhance drug therapeutic value. At the beginning, development of polymer–drug conjugates was strongly focused towards cancer therapy. In fact, 15 out of the 16 conjugates currently in clinical trials were designed as anticancer agents.

According to the above mentioned the safe use of inorganic nanoparticles in biomedical applications remains an unresolved issue since the most of them causes cytotoxic effect. However, it seems that drug polymer conjugates and biocompatible polyesters can be safely used as anticancer drug nanocarriers without the risk of materials cytotoxicity.

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