Realizing the Clinical Potential of Cancer Nanotechnology by Minimizing Toxicologic and Targeted Delivery Concerns

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Abstract

Nanotechnology has the potential to make smart drugs that would be capable of targeting cancer but not normal cells and to load combinations of cooperating agents into a single nanosized particle to more effectively treat this disease. However, to realize the full potential of this technology, the negative aspects associated with these nanoparticles need to be overcome. This review discusses concerns in the field limiting realization of the full clinical potential of this technology, which are toxicity and targeted delivery. Strategies to overcome these hurdles are also reviewed, which could lead to attainment of the full clinical potential of this exciting technology. Cancer Res; 72(22); 5663–8. ©2012 AACR.

Introduction

Cancer is the second leading cause of death in the United States. In 2012, more than 577,190 Americans are expected to die from cancer. Despite the advances and progress made in understanding cancer biology and designing new drugs to fight this complex disease, these efforts are generally not effectively translated into the clinic. Traditional cancer treatments such as chemotherapy, radiation, and surgery are frequently limited. Limitations in cancer therapies and failure of either U.S. Food and Drug Administration (FDA) approved or newly developed anticancer agent occurs, in part, because of undesirable drug-associated side effects, low drug concentrations at the tumor site, and/or development of resistance (1, 2).

Novel targeted therapeutic approaches with improved efficacy having negligible toxicity are needed to more effectively translate basic science drug discoveries into clinical applications. Use of nanotechnology is one approach, which offers possible solutions to these impediments. Nanoparticle-based drugs have unique properties such as small size (1–100 nm), large surface-to-volume ratios (3), self-assembly, stability, specificity, drug encapsulation, and biocompatibility (4), which could be used to address many of the issues limiting the use of traditional drugs. Examples of cancer-related nanotechnologies include drug-delivery carriers such as nanoliposomes that are gaining in popularity for cancer therapy, nanosized-imaging agents such as C-dots, and theragnostics that could be used for both diagnostic purposes and for treating cancer.

Resistance is a major obstacle faced by traditional cancer drugs that might be overcome by using nanotechnology-based agents. Resistance to initially effective agents can occur because of overexpression of drug efflux pumps, increased drug metabolism, enhanced self-repairing ability, altered drug targets, or through bypassing the targeted proteins in a particular signaling pathway (5). Nanotechnology could be used to resolve some of these issues by developing agents that simultaneously target multiple processes or signaling pathways to more effectively prevent resistance. A recent example is vemurafenib, which is an agent targeting V600E-B-Raf in melanomas. In patients harboring V600E-B-Raf protein, tumor regression occurs in up to 80% of patients during the first 2-month treatment cycle using vemurafenib. However, the majority of patients initially responsive to the drug eventually developed drug-resistant tumors, mediated by alternate pathways of mitogen-activated protein kinase reactivation, or activation of compensating alternative survival pathways. Creating a single multidrug nanoparticle to target cancer cells and enabling drug accumulation in tumor cells could decrease resistance development (6, 7). A single nanoparticle with hydrophobic and hydrophilic zones for loading different types of drugs could be created and conjugated to cancer cell targeting moieties. A nanoparticle of this type could be loaded with traditional hydrophobic drugs such as vemurafenib and perhaps charged particles such as siRNAs to create optimal drugs combinations to prevent resistance development (8). Thus, nanoparticles might be the drugs of the future for overcoming the limitations encountered by traditional anticancer agents.

Although nanotechnology offers great promise for cancer treatment, the same properties that make nanoparticles unique can also limit efficacy. This review examines some concerns with regard to nanotechnology and discusses approaches to overcome these issues. Thus, this review is broadly divided into 2 parts, first discussing and detailing alternate pathways to more effectively prevent resistance. A recent example is vemurafenib, which is an agent targeting V600E-B-Raf in melanomas. In patients harboring V600E-B-Raf protein, tumor regression occurs in up to 80% of patients during the first 2-month treatment cycle using vemurafenib. However, the majority of patients initially responsive to the drug eventually developed drug-resistant tumors, mediated by alternate pathways of mitogen-activated protein kinase reactivation, or activation of compensating alternative survival pathways. Creating a single multidrug nanoparticle to target cancer cells and enabling drug accumulation in tumor cells could decrease resistance development (6, 7). A single nanoparticle with hydrophobic and hydrophilic zones for loading different types of drugs could be created and conjugated to cancer cell targeting moieties. A nanoparticle of this type could be loaded with traditional hydrophobic drugs such as vemurafenib and perhaps charged particles such as siRNAs to create optimal drugs combinations to prevent resistance development (8). Thus, nanoparticles might be the drugs of the future for overcoming the limitations encountered by traditional anticancer agents.

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Modulating toxicity to realize the full clinical potential of nanotechnology-based therapeutics

Nanotechnology has significant potential for delivering diverse cancer therapeutics into tumors in a fast, accurate, and cost-effective manner (9). However, potential toxicity associated with the nanoparticle itself can be a limitation. Toxicity mediated by the nanoparticle should be considered when selecting a particular type to carry out a required function and strategies designed to overcome this issue. Toxicity of nanoparticles can occur because of size, shape, charge, compositions, constituent leaching, and triggering of immune reactions.
Nanoparticles size and shape can cause toxicity because the body is designed to recognize and entrap foreign particles (10). Reports have shown that particles smaller than 80 nm are nontoxic; however, smaller particles (<10 nm) can cause significant toxicity, leading to malfunction of the body’s biochemical processes and even crossing biologic barriers (11, 12). Too large or too small nanoparticles can get entrapped in the reticuloendothelial portion of the immune system or other interstitial spaces in the body for prolonged periods of time (13). Decreasing particle size can also lead to an exponential increase in surface area to volume ratio, which can make the nanomaterial surface more reactive and prone to aggregation, either by self-reacting or by interacting with components in the biologic environment. This could then lead to irreversible deposition in tissues, interfering with critical biochemical or enzymatic functions. For example, intravenous injection of nanoparticles transports the agents into vital organs such as lungs, spleen, liver, and kidneys in addition to tumors. Particles smaller than 100 nm can be rapidly cleared, but nanoparticles larger than 100 nm tend to accumulate in the spleen (14), with a specific example showing that 40% to 50% of 400 nm nanoparticles were retained in this organ. Because the pore size of liver fenestrae is approximately 100 nm, particles smaller than this size tend to accumulate in the liver. Nanoparticles of 5.5 nm or smaller size, such as quantum dots, are rapidly excreted through renal pores, whereas larger particles tend to be retained in the circulation. Nanoparticle accumulation in tumors can also be regulated by particle size. It has been shown that 100 to 200 nm sized particles found accumulated 4-fold more effectively than those of 300 nm or smaller than 50 nm (15). Therefore, we suggest that the ideal nanoparticle should have a dimension of approximately 100 nm, which would be small enough not to cause toxicity because of deposition in tissues or organs but big enough to enter into the tumor cells to deliver the anticancer agents. To further minimize toxicity, reports have shown that coating nanoparticles with polyethylene glycol (PEG), chitosan, or other biomolecules can improve biocompatibility (16). Surface coating would minimize interaction of nanocarriers with external biologic fluids of body; thus size would be of lesser concern.

Shapes of nanoparticles play an essential role in cellular uptake and can thus modulate toxicity. Spherical gold nanoparticles are better taken into cells than rod shaped ones (17). Aspect ratio refers to the ratio of width to length and cells have been found to better endocytose lower aspect (1:3) ratio gold nanorods, than those with a higher (1:5) aspect ratio (17). Although gold nanorods are poorly taken-up by cells, they tend to be more toxic than spherical particles, suggesting that toxicity can be shape dependent. Shape-mediated toxicity can be modulated by addition of a capping agent. For example, a positive charge on nanoliposomes or CTAB-coated gold nanorods can lead to toxicity in animals (18), which can be decreased by replacing the capping with polyelectrolytes (19).

Leaching of the constituents of nanoparticles is another cause of toxicity. Nanocarriers, composed of metals or semiconductors can be oxidized to corresponding ions when exposed to body fluids (20). Gold nanorods or nanocages can be used as cancer therapeutics because of infrared light-absorbing property, which leads to generation of heat and cancer cell killing by photothermal ablation therapy (21, 22). Although gold is a biocompatible material, oxidized ions can lead to complex formation with biologic components, hindering key enzymatic function or induction of toxicity because of free radical production (23). Chemical composition and surface chemistry of nanomaterials used for drug delivery applications will largely dictate the type of chemical interaction that might occur between the nanomaterials surface and body’s cells, tissues, or organs (24). In our opinion, surface functionalization should be used to reduce the toxicity of metal-based nanomaterials by forming a thick surface coating to reduce oxidation into ions (25).

Similarly, oxides and quantum dots are made of heavy metals that could release ions causing toxicity. Iron oxides can be used for drug delivery and imaging but may oxidize to Fe^{3+} ions, which can lead to production of hydroxyl radicals by Fenton Chemistry (26). Quantum dots are 1 to 10 nm small nanoparticles that have unique optical and electronic properties, with size-tunable light emission and better photostability than conventional dyes for cancer imaging (27). However, quantum dots contain heavy metals such as cadmium, and concerns about possible leaching limits use in humans. Quantum dots with different emission spectra can be used to simultaneously track multiple tumor markers (28). Use of cadmium-free quantum dots (CFQD) are being explored in response to the heavy metal leaching concern. CFQD conjugated with tumor-targeting ligands or antibodies can be synthesized using rare earth metal-doped oxide in phosphor, which contains phosphorescent materials and fluorescent materials, having excitation wavelength in the UV spectrum and emission wavelength controlled by the type of rare earth doping. These particles have a large stokes shift, which is the difference between the band maxima of the absorption and emission spectra of the same electronic transition and emission that is narrower than CdSe quantum dots. A recent example are C-dots (Cornell-dots), which are silica-based fluorescent nanoparticles recently granted Investigational New Drug status for cancer imaging by the FDA for clinical evaluation in human phase 1 trials (29). These silica nanoparticles contain a dye glowing 3 times brighter than free dyes when excited and might replace quantum dots without toxicity-related concerns.

Regardless of chemical composition, the physiologic characteristics of nanoparticles are prone to change when in contact with blood, which can cause toxicity (9). Blood proteins interact with nanoparticles, which eventually modulate half-life and biodistribution (13). Formation of a protein corona over the surface of nanoparticles is well described and believed to be a dynamic event, affecting the hydrodynamic radius of nanoparticles to modulate stability and overall surface functionality (13). Therefore, the physical state, stability, and types of biomolecules on the nanoparticle surface under in vivo conditions can regulate pharmacokinetic or pharmacodynamic properties (13). In our opinion, complete characterization of any new nanoparticle under physiologic conditions is important.
Recognition of nanoparticles by immune cells may activate or suppress the immune system or be recognized as foreign material and rapidly cleared from the body. These effects may promote autoimmune or inflammatory disorders or make the host prone to infections or cancer. Recognition of nanoparticles as foreign objects by immune cells could cause a multilevel immune response, which might lead to toxicity, lack of therapeutic efficacy, rapid clearance, or lethality (30). To reduce this concern, the surface of nanoparticles can be coated with nonopsonic proteins (31). Another possibility is to coat nanoparticles with a nonspecific antibody through its Fc domain or with blood proteins. PEGylation is also frequently used to avoid immune system recognition.

Lipid- and polymer-based nanoparticles are being widely used for drug delivery applications, with some already approved for clinical use (32). Positively charged liposomes are toxic to cells compared with negatively charged or neutral ones (33). However, because of electrostatic interaction with negatively charged molecules such as nucleic acids (plasmids or siRNA), cationic liposomes are useful for delivering these genetic therapeutic agents into tumors. To minimize toxicity mediated by the positive charge, incorporation of neutral or negatively charged lipids can decrease the charge, thus reducing toxicity. Constituent lipids in nanoliposomes can also alter normal immune function, causing toxic responses. Most nanoliposomal formulations are made up of phospholipids and cholesterol, which are known to be biocompatible, but anti-phospholipid and anti-cholesterol antibodies can cause immune complement system activation (34). Thus, patients having high titers of these antibodies may recognize these nanoparticles and eliminate them from the body. Use of natural lipids (such as occurring in archaeosomes) can reduce this concern. Archaeosomes, made up of naturally occurring archaeal membrane lipids, have been used for drug and vaccine delivery (35).

**Targeting nanoparticles to tumor cells to improve the clinical potential of nanotechnology**

Nanotechnology has potential for selectively delivering anticancer agents into tumor cells without affecting normal healthy tissues. Many successful drug delivery strategies have incorporated targeting capabilities of nanoparticles. However, this area needs development and further implementation for clinical applications. Nanoparticle-based drug and gene delivery or expression approaches occur through passive or active targeting of tumor tissues.

**Passive targeting.** Passive targeting is mediated by the inherent characteristics of the tumor itself to retain drug-carrying nanoparticles. Most passive targeting occurs because of the enhanced permeability and retention (EPR) effect mediated by leaky vessels (36). Tumor blood vessels, unlike those occurring in normal tissues, have 600 to 800 nm wide gaps between adjacent endothelial cells, leading to a defective vascular system with poor lymphatic drainage (36). This enables nanoparticles to extravasate into the extravascular space and accumulate in tumor tissues (36). A 10-fold increase in drug retention is caused by the EPR effect when using nanoparticles as delivery vehicles compared with free drug alone (37). However, as the environment inside the tumor is not homogeneous, drug retention tends not to be uniform. Therefore, in our opinion, characteristics of tumor vasculature anomalies should be exploited for better nanocarriers retention at the tumor site mediated by the EPR effect. For example, use of angiotensin-II (AT-II), known to cause blood vessel hypertension (38) can be used along with the drug carrying nanoparticles. Hypertension induced by AT-II in normal tissues causes constriction of the vessel smooth muscle layer resulting in higher blood pressure and flow rates, while blood flow volume remains constant. Conversely, in tumor tissues, because of absence of a smooth muscle layer in vessels, blood flow volume cannot be regulated; therefore, this hypertensive state would boost the EPR effect and could be used to drive nanoparticle accumulation in tumors, especially as vessel density is higher in tumors than in normal tissues.

The tumor microenvironment can also modulate the passive accumulation of nanoparticles. Tumor tissues have acidic microenvironments ranging from a pH of 4 to 5, partly caused by high rates of glycolysis and glucose consumption, metabolizing lactate even under aerobic conditions (39). Therefore, use of pH-responsive nanoparticles can enhance passive drug delivery in acidic tumor tissues. Protease-sensitive polymers such as PEGDA peptide macromer containing MMP (matrix metalloproteinases) substrate, polypeptides with a high degradable (HD-MMP) and a low-degradability (LD-MMP) sequence have already shown success in drug delivery in vivo (40). MMPs are overexpressed in tumor tissues and degrade extracellular matrix (41). Therefore, incorporation of MMPs in nanoparticles could assist drug release into tumor tissues. Synthesis of a polymeric nanoparticle containing a MMP protease sensitive substrate polypeptide with a HD-MMP and LD-MMP sequence and/or encapsulating pH or temperature-sensitive molecules can be used for passive accumulation and destruction of tumors. Similarly, thermolabile nanoparticles accumulating passively in tumors can be used to cause a local hyperthermic effect to destroy tumors (42).

**Active targeting.** Active targeting requires nanoparticle conjugation to antibodies, aptamers, cytokines, peptides, or other relevant targeting ligands that can recognize markers on the surface of cancer cells. Antibody-mediated targeted delivery of drug by gold, iron oxide, silica, liposomes, or polymeric nanostructures can be used to deliver these agents to the surface or into cancer cells (43). Monoclonal antibodies or antibody fragments (such as antigen-binding fragments or single-chain variable fragments) are being used as ligand-targeted therapies. Antibody fragments can be more useful than antibodies because they tend to be less immunogenic, are associated with decreased clearance rate, and increased circulation half-lives, which enables drug carrying nanoparticles to have sufficient time to be distributed and effectively bind to targeted cancer cells in the body (44). Aptamers are DNA or RNA 3-dimensional structures recognizing and binding to specific target moieties and having similar selectivity as antibodies. Aptamers can be better targeting agents than antibodies because antibodies can have problems with conjugation, bad site specificity, and high immunogenicity, which cause concerns for clinical applications. Recently, aptamer-
mediated cancer cell–specific cisplatin delivery has been found effective for targeting multiple cancer cell lines (45). Aptamers are generally thought not to be immunogenic and can be cleared from the body after degradation by nuclease and are thus associated with negligible toxicity.

Ligand receptor–based drug delivery approaches need significant improvement for clinical translation (46). For successful ligand receptor–mediated drug delivery, internalization of the targeted nanoparticle is essential (46). If antibodies or other targeting ligands cannot mediate internalization, drug released by the nanoparticles can be taken by cancer cells through simple diffusion or by other similar transport mechanisms. Drug released outside the cells can disperse into the surrounding tissues, causing unwanted side effects and toxicity. Therefore, our opinion is that targeted nanoparticles should always be designed to initiate internalization into the cancer cell, which can be achieved through selection of appropriate targeting receptor or ligands. Molecules, such as antibodies, growth factors, or cytokines, can facilitate nanoparticle uptake into targeted cells by endocytosis (47). Bioactive peptides (<50 amino acids) can also be used for this purpose. Tumor vasculature also expresses angiogenic markers on the surface of blood vessels that are absent or almost undetectable in normal blood vessels, which are easily accessible and can be targeted (48).

Nanoparticle systems containing distinct targeting moieties have been approved, and some are currently being evaluated in clinical trials. For example, a recent phase I clinical trial in humans used a transferrin-targeted nanoparticle designed by self-assembly of siRNA, a cyclodextran-based polymer, adamantane–PEG, and adamantane–PEG–transferrin for uptake into cancer cells (49). Another recent system involves approximately 7 nm C-dots for melanoma tumor imaging that were conjugated to α,β targeting moieties to mitigate issues related to size and promote tumor imaging for evaluation in phase I trials (50). The biggest concern is the cost that the targeting moiety adds to the final drug product; however, we feel the benefit outweighs this concern.

Masking of targeted or nontargeted nanoparticles can be used to enhance uptake in tumor tissue. Macrophages and phagocytes can recognize nanoparticles circulating in the blood, so strategies are needed to make the nanoparticles "invisible" to the immune cells to facilitate uptake. "Stealthy" nanoparticles have been made by PEylation of the surface, which makes them less detectable by phagocytes (51). Similarly, use of hydrophilic polymers (such as poloxamine, poloxamers, and polysaccharides) to cap conventional nanoparticles can decrease uptake by the mononuclear phagocytes system (MPS; ref. 52). The coating provides a dynamic "cloud" of hydrophilic and neutral functional groups on the surface, repelling plasma proteins and makes the nanoparticle MPS invisible (53). This increases the circulation time and promotes the potential for better drug retention and thus efficacy. As described above, nanoparticles are prone to be coated by proteins from body fluids to form a "corona," which might lead to the opsonization and phagocytosis by the reticuloendothelial system (13). PEG coating can provide steric hindrance to nanoparticles to decrease aggregation during circulation, thereby preventing opsonization and increasing the circulatory half-life, which results in a greater EPR effect. However, PEG coating can have negative effects because the longer circulation time may delay the uptake of nanoparticles by tumor cells. Therefore, in our opinion, it is important to consider these issues and balance them to create nanoparticles that are stable in body fluids with optimal circulation half-lives for maximal delivery of the drug into tumor tissue.

Conclusion

Cancer nanotechnology is gaining importance as an approach to overcome obstacles faced by traditional cancer drugs. However, this technology faces hurdles that need to be surmounted to realize its full clinical potential. Nanoparticle toxicity and directed delivery to cancer cells are concerns, requiring better characterization of nanoparticles, understanding the behavior and type of interactions with human tissues and fluids. Immune system concerns also require careful consideration when using this technology. Despite these issues, nanotechnology remains a useful approach to develop drug vehicles for combining multiple cooperating anticancer agents. This approach can provide innovative strategies for solid tumor oncology research, but targeted delivery is needed to improve specificity and reduce unwanted side effects. To take advantage of the full potential of nanotechnology, the collaborative efforts of experts in nanotechnology, physics, chemistry, biology, and oncologists are needed to resolve issues associated with toxicity and targeted delivery.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Writing, review, and/or revision of the manuscript: S. Singh, A. Sharma, G.P. Robertson

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