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Publication Date

2018-08-08

Recent Advances in Nanoparticle-Based Cancer Drug Delivery

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Abstract

Cancer is among the leading causes of death worldwide, with the number of new cancer cases expected to rise to 22 million in the next two decades. Most chemotherapy drugs in the market are difficult to administer directly and many are toxic to healthy tissues and produce undesirable side effects. To overcome these limitations, recent advances in nanoparticle-based cancer drug delivery present a promising strategy to achieve high therapeutic efficiency of anticancer agents by providing protection during circulation and enhancing their bioavailability. This review describes strategies using nanoparticles to deliver anticancer agents and designs for stimuli-responsive drug release. The scope of this study is limited to only magnetic field, ultrasound, and pH stimuli-response methods. Potential adverse effects of nanoparticle accumulation in the body were also evaluated. Peer-reviewed studies that included “nanoparticle drug delivery” in the title and were published after 2014 were searched using the PubMed database. Articles published most recently were given priority. Despite the positive implication of nanoparticle cancer drug delivery to produce a greater therapeutic effect in comparison to current cancer treatments, further research regarding adverse effects is necessary. The unprecedented behavior of materials used for nanoparticle formulations, such as nonspecific toxicity and controlling penetration of biological barriers, are major hurdles to FDA approval. Long-term side effects of nanoparticles in the body and proper standards should be established for the examination of safety and efficacy issues before expanding the newly developed nanoparticle carriers into preclinical and clinical testing.

Introduction

Cancer is the second most common cause of disease-related death in the United States. An estimated 1.7 million new cancer cases diagnosed and 0.6 million cancer-related deaths are predicted for the year 2018 (1). Most chemotherapy drugs in the market are difficult to administer directly and many are toxic to healthy tissues and produce undesirable side effects (2). Gene therapy alone or in combination with chemotherapy are currently lacking in stability and tumor selectivity, affecting safe and effective delivery to the tumor site.

To overcome these limitations, recent advances in nanoparticle-based cancer drug delivery present a promising strategy to achieve high therapeutic efficiency of anticancer agents by providing protection during circulation and enhancing their bioavailability (3). Nanoparticles are attractive vehicles for anticancer agents, because of their controlled drug release and tumor-selective properties. This review describes strategies using nanoparticles to deliver anticancer agents and designs for stimuli-responsive drug release. Despite the positive implication of nanoparticle cancer drug delivery, research regarding adverse effects is necessary. Major hurdles such as nonspecific toxicity and controlling penetration of biological barriers still need to be

overcome before nanoparticle carriers can be FDA approved and used in clinical cancer treatment.

Stimuli-Responsive Drug Release

Recent progress in material science and drug delivery allows controlled mechanisms to be introduced in nanoparticle drug delivery systems. Such modifications to nanoparticles can be achieved by using stimuli-responsive materials. The stimuli-response delivery systems address the issues of controlled dose release of drug in response to various stimuli signals specifically produced in the tumor microenvironment (4). Therefore, in theory, almost no amount of drug is released until stimuli are applied. The following subsections focus on recent developments in the design of nanoparticle-based stimuli-responsive systems. This review will evaluate control drug release in response to external magnetic fields, ultrasound, and internal pH stimuli. Although temperature, light, electric pulses, enzyme concentration, or redox gradients are also being researched, those responsive systems are beyond the scope of this review.

Magnetic Field Stimuli

Cancer cells have a different membrane potential compared to normal cells, therefore, the electric field interaction between different cells are distinct. Magnetoelectric nanoparticles (MENs) can detect cancer cells from normal cells through the membrane's electric properties (5). The main advantages of superparamagnetic nanoparticles are that they can be visualized in magnetic resonance imaging (MRI) due to their paramagnetic properties. These magnetic properties allow them to be remotely navigated to the target site location or heated in the presence of an externally applied AC magnetic field. The heat produced by magnetic field then triggers the drug release (6). Because the drug is not significantly bioactive while it is attached to the nanoparticles, recent studies have shown that it is safe to move the drug-loaded MENs through the circulatory system towards the target site while reducing toxicity (7-9). These studies used mouse models tested with dendritic and gold MENs respectively, and found that biocompatible MNPs can be effectively employed as efficient drug-targeting systems. Due to their magnetic properties, these MNPs are potential drug delivery systems to deliver therapeutics at the specific site in vivo by application of an external magnetic field.

However, these studies require more research on toxicity impacts. The surface modification of the nanocarriers used in these studies is required for in vivo therapeutic delivery and for increasing their biocompatibility in clinical applications (5, 9). Even though metallic nanoparticles are biocompatible and immobile carriers, a significant fraction of metal particles can be retained and accumulated in the body after drug administration.

The approach in which cell cultures or experimental animals are exposed to ultra-high nanoparticle concentrations to ensure cytotoxicity leads to unrealistic results (6). They cannot be extrapolated to the human scenario since diagnostic and therapeutic interventions usually only require the administration of minimal concentrations. Therefore, potentially scientifically

unreliable data and such practices can be dangerous to the public if these nanoparticles are developed without further research.

Ultrasound Stimuli

Ultrasound-sensitive drug delivery systems can improve targeted delivery of drugs into specified tissues, while reducing the systemic dose and toxicity. Sonoporation is an important mechanism for stimuli-enhanced delivery of therapeutics in this system through vasculature openings (10). It is induced by ultrasound-triggered oscillations and destruction of microbubbles. Ultrasound interaction with nanoparticles induces enhanced drug delivery and can also be used in image-guided delivery.

Research studies have concluded that these nanoparticle capsules work as diagnostic agents upon low-power (100mW/cm²) ultrasound irradiation and act as therapeutics upon high-power (>10W/cm²) ultrasound irradiation (11). The researchers observed that drug release was gradual at lower power and swift at higher power. In additional studies using copper oxide loaded PLGA, polyacrylic/calcium phosphate hybrid, and high-density lipoprotein nanoparticles respectively, cell growth inhibition was significantly increased in when researchers loaded the cancer drug into nanodroplets upon ultrasound exposure (12-14). The results from these studies indicate a that ultrasound irradiation produces a greater therapeutic effect in comparison to their control group. The in-vivo results of both studies also demonstrated efficient tumor suppression (13, 15).

These studies are restricted by their toxicity assessments. Chronicity of nanoparticle need more thorough long-term evaluation before therapeutic applications. These studies evaluated the gels for nanoparticle stability after 9 days and mice models for approximately 3 to 4 weeks (12, 14). It is possible that significantly more time is necessary to assess long-term effects. In addition, different studies apply different particle formulations, leading to conflicting and unreliable results. Because different materials are used, more emphasis should be placed on defining the dose of nanoparticles in relation to the route of administration. End-organ accumulation and distribution, as well as metabolism and excretion, are variable depending on the routes of administration.

pH Stimuli

Tumor tissues form acidic microenvironments through their abnormal metabolism and protein regulation. This pH abnormality (4-6.5) can be exploited in tumor-targeted delivery (4). Nanocarrier structures can be changed by chemical bond association or charge reversal for specific drug release. pH sensitive microspheres can be used because they are stable under normal physiological pH level of 7.4 but are degraded when exposed to low pH environments found in tumors.

Many studies have shown that by using conjugates of different materials such as mesoporous silica, fluoruous polymers, and hyaluronic acid conjugates, drug release rates were enhanced compared to the control group. Mimicking the tumor microenvironment, increased cell

uptake and reduced cytotoxicity was observed (16-18). These studies demonstrate the growing importance for these systems in drug delivery applications.

However, most of these pH stimuli induced systems are still in the early stages of development. Thorough optimization of the synthesis procedures is needed before these systems can transition into clinical settings. Many of the studies have produced promising in vitro results, but only a few have entered in vivo trials (18, 19). Simplified systems with strong stimuli-responsive characteristics may drastically influence the chances for clinical applications. Stimuli-responsive drug delivery systems have the potential to replace current drug delivery approaches, but these hurdles must be addressed beforehand.

Adverse Effects of Nanoparticles

As extreme care is taken towards the utilization of biodegradable, biocompatible, and nontoxic NPs in cancer therapy, the adverse effects of nanocarriers are expected to be significantly reduced compared to current drug methods. However, the adverse effects of nanoparticles themselves still warrant further research. Studies have shown that exposure of human endothelial cells to NPs can cross blood-brain barriers and lead to cytotoxicity genotoxicity, and impaired cell signaling (20). Exposure to test species have also resulted in accumulation of NPs in pulmonary, cardiac, brain, and neural systems (21, 22). While most NPs show slight toxicity when exposed to animals, certain NPs such as iron oxide and titanium dioxide NPs show the ability to induce oxidative stress and biological damages (21, 23). It is important to note that materials that are not harmful in their bulk form may be toxic on the nanoscale level.

Particle characteristics such as the size, surface area, shape, and charge of NPs could be related to their adverse effects during the delivery (24). The large specific surface area of NPs may result in the formation of hydrogen peroxide or superoxide due to the presence of electron acceptor and donor sites on their surfaces. Imbalance in redox state translate into production of damaging amounts of reactive oxygen species (25). The formation of reactive O₂ species has been reported as one of the main process by which these NPs exert their harmful effects. Literature shows that long term inflammation and oxidative stress present in a cell ultimately leads to DNA damage (26, 27). Nanogenotoxicity is a new term that has emerged in the field of nanotechnology used to highlight NP induced genotoxicity and carcinogenesis (28). Continuous production of reactive oxidative stress causes mutagenesis due to the oxidation, hydrolysis and deamination of nucleic acid bases, and carcinogenesis due to the gene deletion, and insertion. Therefore, size, surface area, and shape is an essential parameter to consider while assessing nanogenotoxicity and the harmful effects of nanomaterials.

The toxicity of nanoparticles also depends on whether they are persistent or cleared from the different organs of entry and whether the host can raise an effective response to sequester or dispose of the particles (28). Nanoparticles that can undergo mechanisms such as apoptosis and genotoxicity which results in toxicity. Apoptosis is programmed cell death that occurs in multicellular organisms. This process involves various events such as chromosome condensation,

nuclear fragmentation, cell shrinkage, and DNA decay (29). Apoptosis can be initiated by an intrinsic pathway, meaning that the cell kills itself because it senses cell stress, as well as an extrinsic pathway, in which the cell kills itself because of signals from other cells. In case of NPs, they are interacting with macrophages which causes the activation extrinsic pathway of apoptosis (28).

Another common adverse effect is related to hypersensitivity reactions after intravenous injection (24). These can be controlled by patient premedication or by decreasing the infusion rate of the product. Stimuli-induced reactions that require hypersensitivity often fail to occur after repeat administration of the drug delivery system (30, 31). Based on these studies, there are many gaps regarding the reactions of oxide-based nanomaterials with various components of the immune system. This warrants further research and the adverse effects of the remaining material after drug delivery must then be considered. Therefore, biodegradable NPs with a constrained life expectancy no longer than medically required would be ideal for clinical practices.

Conclusion

Various nanoparticle formulations are currently being developed and explored as delivery vehicles for cancer therapeutics. Advanced delivery systems have also been designed to deliver drugs specifically to the tumor site, based on their stimuli-responsive properties. Targeted nanoparticles deliver therapeutic agents to specific receptors that are overexpressed in tumor cells, thereby enhancing their therapeutic efficiency.

The main advantages of using delivery vehicles for cancer therapeutic agents are their enhanced bioavailability, controlled release, ability to prevent degradation, and preferential delivery to the tumor site. Many research studies have demonstrated that therapeutic agents can be loaded onto nanoparticles for cancer treatment (3, 4). Each of these therapeutic agents differ in their physicochemical characteristics and their mechanisms of action, and require a specific dose to be released in the tumor site. Stimuli-responsive drug release methods include magnetic field, ultrasound, and pH stimuli. All three of the approaches reduced toxicity compared to their control groups (6, 9, 11, 12, 17, 19).

However, many biological obstacles must be overcome before drugs can reach the target cancer cells. Nanoparticles passing the blood-brain barrier, accumulating in organ systems, and creating oxidative stress is a major cause for concern (22, 23, 25). It is difficult to balance the promising results of the cancer eliminating research studies with the negative potential side-effects that accompany nanoparticle drug delivery.

Therefore, translating these nanoparticle systems to clinical settings is challenging. Animal models cannot always be extrapolated to the human scenario because of dosage concentration differences (6, 24). Because each study often uses different materials, more emphasis should be placed on defining the dose of nanoparticles in relation to the route of administration. The long-term effects of nanoparticle drugs in the body must also be evaluated. Carrying on the studies for longer periods of time may be necessary to observe the full effects of the nanoparticle accumulation. Many of the studies have produced promising in vitro results, but

only a few have entered in vivo trials (10, 18, 19). Obstacles, such as maintaining the stability of therapeutic agents, controlling their pharmacokinetics, reducing toxicity, and achieving targeted delivery, must be overcome when designing nanoparticles that utilize stimuli-responsive delivery strategies such as magnetic field, ultrasound, and pH stimuli.

It is crucial to compare toxicity results from different studies with caution, as current toxicity protocols lack uniformity with respect to nanoparticle formulations and application protocols (20, 22, 24). It has become apparent that a unifying protocol for the toxicological profiling of nanoparticles may be required in order to achieve reliable outcomes that have realistic implications for the human use of nanoparticles. Further research and a standard system to evaluate nanoparticle toxicity may be necessary for nanotechnology to be fully implemented in the clinical setting.

The unprecedented behavior of materials used for nanoparticle formulations, such as off-target effects or nonspecific toxicity, maintaining consistency in particle synthesis, and controlling penetration of biological barriers, are major hurdles to FDA approval (25, 27, 31). Therefore, many of the nanoparticle systems that appear promising in vitro may not be successful in vivo (30). Proper standards should be established for the examination of safety and efficacy issues before expanding the newly developed nanoparticle carriers into preclinical and clinical testing. Implementing proper regulatory measures, a deep understanding of tumor biology, and thoughtful use of technology advancements are necessary to speed the possible use of these nanoparticle systems in mainstream cancer treatment.

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