

Targeting nanomaterials: future drugs for cancer chemotherapy

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Concerning the recent articles published in your journal on multifunctional nanosystem for cancer chemotherapy.¹ It should be an admirable approach to kill cancer cells, with the least side effects on normal tissues and cells. During the past few decades, various chemotherapeutic agents, such as cyclophosphamide, fluorouracil, platinum-based compounds, anthracycline, hydroxycamptothecin and paclitaxel, have been designed and proved to be effective toward cancer cells. However, regrettably, these drugs are non-targeted to cancer, and thus serious side effects to normal cells or tissues are unavoidable.² Therefore, new drugs with selective cytotoxicity become an important research focus in cancer chemotherapy. Another obstacle for chemotherapy is the multidrug resistance. Actually, several targeted drugs such as RTK inhibitors, FTase inhibitors, tumor angiogenesis inhibitors, campath, avastin and erbitux, have been commercialized and widely used clinically.³ However, drug resistance seriously limited their anticancer efficacy. Nanotechnology-based approaches are anticipated to provide a new breakthrough for targeting cancer cells and bypassing their multidrug resistance.⁴

Zhang et al¹ have developed two biodegradable novel drug delivery systems: poly(ethylene glycol)-modified docetaxel-lipid-based-nanosuspensions (pLNS), to increase the cycle time of the drugs within the body and enhance the accumulation of the drugs at the tumor sites, and targeted docetaxel-lipid-based-nanosuspensions (tLNS) using folate as the targeting ligand, which could target cancer cells overexpressing folate receptor (FR). In vitro cytotoxicity was employed to evaluate the effects on human hepatocellular liver carcinoma HepG2 (FR-) and B16 (FR+) cells and the results showed that the cytotoxicity of tLNS against B16 cell lines was superior to pLNS, while no significant difference was observed for HepG2 cells. Moreover, in vivo anticancer efficacy evaluation showed that tLNS exhibited higher efficacy in reducing the tumor volume compared with pLNS. These results reveal the application potential of tLNS to enhance the accumulation of the drugs in cancerous tissues and cells.

Similarly, Du et al⁵ entrapped RGD peptide with poly(ethylene glycol)-modified stearic acid-grafted chitosan (PEG-CS-SA) nanomicelles via chemical reaction in the presence of N,N'-disuccinimidyl carbonate. Moreover, doxorubicin (DOX) was chosen as a model anticancer drug to investigate the drug entrapment efficiency, in vitro drug-release profile and anticancer activities of drug-loaded RGD-PEG-CS-SA micelles in cells overexpressing integrins and integrin-deficient cells. Their results indicated that RGD-modified micelles could significantly increase the

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intracellular DOX concentration and induce apoptosis in integrin-overexpressing BEL-7402 human hepatocellular carcinoma cells, but not in Hela human epithelial carcinoma cells. These results indicate that surface modification of PEG-CS-SA nanomicelles with RGD could be effective in selectively killing integrin-overexpressing tumor cells and minimizing the side effects on normal cells.

Nanosystem functionalized with carbohydrate, such as polysaccharides, a class of biopolymers naturally originated from plants or animals,⁶ could specifically interact with lectins that have been found overexpressed in the surface of cancer cells and malignant tissues.⁷ Therefore, we explored a simple method for functionalization of selenium nanoparticles (SeNPs) to enhance the cellular uptake and selective anticancer activity by surface decoration of *Spirulina* polysaccharides (SPS).⁸ The underlying molecular mechanisms were also investigated and the results revealed that SPS effectively increased the apoptosis-inducing activity of SeNPs. Moreover, we also demonstrated another strategy for preparation SeNPs through direct nanolization of gray Se by dissolving in PEG. The PEG-functionalized SeNPs exhibited higher potency toward doxorubicin-resistant hepatocellular carcinoma cells.⁹ Our results suggest that the strategy to use PEG200 as a surface decorator could be a highly efficient way to enhance the anticancer efficacy of nanomaterials.

In the recent relevant studies, Zhang et al^{10–12} explored the cell functions (including adhesion, proliferation, apoptosis and vascular endothelial growth factor (VEGF) secretion) decreasing activity of poly(lactic-co-glycolic acid) (PLGA) nanotopographies with different size and surface property to lung epithelial carcinoma cells and breast adenocarcinoma cells. The nanomaterials could be used to inhibit the growth, proliferation and angiogenesis of tumors, which open up new vistas for majorizing the surface and size of nanomedicine with antitumor properties.

As a novel idea of drug design in the future, nanomedicine shows great potential in cancer chemotherapy. For instance, liposomes, nanomicelles, PLGA nanoparticles and carbon nanotubes, are now used as drug delivery carriers

to improve the solubility, bioavailability and controlled release of anticancer drugs. Moreover, nanocarriers provide a potential to conjugate ligands that target to different kinds of cancer cells or tissues. As a developing interdisciplinary, there are still some problems to be solved in cancer nanotechnology, such as the toxicity and safety, which require special consideration in future works.

Disclosure

The authors report no conflicts of interest in this letter.

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Authors' response

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We are very grateful for allowing us the opportunity to respond. And we also appreciate the letter by Chen et al. In the letter, Dr Chen makes the important point that nanomedicine has the potential to increase the specificity of cancer treatment and bypassing their multidrug resistance.

Precisely so, nanotechnology, the new science of small, has a deep impact on solving many of the problems associated with conventional anticancer drugs based on their unique physical and biological properties.^{1,2} Two nanotechnology-based cancer drugs, Doxil and Abraxane, are now readily accessible for cancer patients, though their potential toxicity and lower specificity should not be dismissed. Nevertheless, nanotechnologies for medical applications have been maturing. Researchers are aiming to develop more specific and safer nanomaterials to diagnose, treat and, eventually, prevent this disease.³

Recently, an innovative lipid-based nanocarrier, DTX loaded lipid based-nanosuspensions (LNS) has been developed in our group.⁴ This lipid-based nanocarriers holds the common advantages of lipid-based nanocarriers, while avoiding their shortcomings. (1) LNS have no drug leakage problems; (2) carry adequate amounts of drug and without excessive loading of the organism with foreign material; (3) formulate compounds that are insoluble in both water and oil; (4) the drug loading of LNS is high and the administration volume is significantly reduced. More importantly, DTX-LNS was produced by high pressure homogenization which is the simplest method and has been successfully employed in large-scale production. Thus, DTX-LNS is a promising drug delivery system appropriate for large-scale production.

Nowadays, the idea behind cancer therapy that is being elucidated is that chemotherapy drugs can be specifically delivered to cancer cells by exploiting their same unique properties that made their detection, targeting and treatment

possible.⁵ An ideal, smart nanocarrier, would be attained by the more sophisticated design expected to be able to carry one or more drugs for therapy, specific moiety for targeting, imaging agent for detection, stimulus-sensitive element for controlled release of drugs, and a stabilizing polymer for biocompatibility.

Active targeting cancer therapy has the potential to change current cancer treatment scenarios.⁵ However, realizing targeting and large-scale production at the same time is always a big challenge for nanosuspensions. To solve this puzzle, in our group, targeted DTX-LNS was produced by the lipid incorporation method. Consequently, targeted DTX-LNS, both appropriated for large-scale production and with high specificity, was obtained.⁶

Chemotherapeutic loaded nanomaterials targeting the tumor site are not only expected to eliminate adverse side effects, but also to pave the way of eradicating cancer and many other complex diseases by bringing a more effective, specific, and personalized nanomedicine.⁷ However, as mentioned in Dr Chen's letter, we must also consider their current limitations and the important challenges for the future development of nanomaterials. Moreover, the design of these functional devices depends mainly on our understanding of the mechanisms involved in their cellular uptake and intracellular disposition.⁸ Unfortunately, little is known about the fate of nanoparticles in the human body. The limited understanding of its cellular uptake would be a roadblock to its effective application. Thus, understanding of the cellular uptake mechanism is much required to design more efficient nanocarriers and has become arguably the hot topic in the molecular pharmaceutical field in the last 5–10 years, which is also one focus of our research efforts. Researchers are confident in the prospect of nanomaterials and are making efforts in this direction looking forward to effective targeting nanomedicine on the market.

Disclosure

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