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Editorial

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New Directions for Drug Delivery in Cancer Therapy

Drug delivery for cancer therapy has been extensively investigated since 1940s. The goals of drug delivery in cancer therapy have been to maximize the efficacy of the therapeutics and minimize their toxic side effects by increasing drug concentration in tumors, while lowering its concentration in normal tissues. Various drug delivery strategies have been explored, resulting in numerous clinical trials and a few approved delivery systems for clinical uses. Unfortunately, the drug delivery systems approved for clinical practice have not met the high expectation in cancer therapy, cure of the disease. There have been ongoing discussions in the community of cancer drug delivery about challenges and new directions of the field. This special issue intends to explore some new avenues of drug delivery to address the challenges in cancer therapy.

Published clinical data of eight major classes of drug delivery systems are reviewed by Lu and Qiao. The inability of these delivery systems to reach all cancer cells in solid tumors and the dynamic and heterogeneous nature of aggressive cancer remain to be the road blocks for achieving curative outcomes for various tested drug delivery systems. It is suggested that future research activities on cancer drug delivery should focus on addressing these challenges. Future perspectives for cancer drug delivery, including exploring the technologies for detecting and treating aggressive cancer at the earliest stage, overcoming the physical barriers, targeting multiple biological pathways, and developing precision medicine, are proposed to address the challenges in order to achieve a curative outcome in cancer therapy.

Homogeneous drug delivery in solid tumors has been one of the prime challenges in cancer therapy and is a critical step to achieve a curative therapeutic outcome. Kobayashi et al. have reported a strategy of using dual homogeneous illuminations with near-infrared light to improve the efficacy of photoimmunotherapy with IR700-conjugated panitumumab, a humanized monoclonal antibody against the epidermal growth factor receptor (EGFR), in treating solid tumors. The first light exposure facilitates and enhances homogeneous tumor uptake of the conjugate due to the initial effect of photoimmunotherapy. The second combined external and interstitial light illumination is applied to induce photoimmunotherapeutic effects throughout the solid tumors for achieving significantly improved efficacy.

Modification of the tumor microenvironment with drug delivery is a promising approach to improve the efficacy of cancer therapy. Wang et al. have developed cationic polymeric siRNA nanoparticles to modify the tumor microenvironment by targeting CCR2, a chemokine receptor, in monocytes for treating aggressive breast cancer. The siRNA nanoparticles result in blockage of monocyte recruitment and reduction of tumor-associated microphages in tumors. The treatment of a metastatic breast cancer model with the nanoparticles significantly delays tumor growth and prevents tumor metastasis. The combination treatment of the siRNA nanoparticles with doxorubicin-loading nanoparticles results in enhanced therapeutic efficacy in treating aggressive 4T1 breast cancer in a mouse model.

Nanosized drug delivery systems, including liposome and polymer based drug delivery vehicles, have received much attention in cancer nanotechnology. There is a need for the next-generation vehicles with improved in vivo properties. Good stability in the blood circulation of nanosized delivery systems is a crucial parameter for achieving optimal biodistribution, tumor targeting, and therapeutic efficacy. Etrych et al. have used tailor-made chemistry to fine-tune the structures and the bloodstream stability of biodegradable micelle-forming amphiphilic polymer-drug conjugates. It is observed that the bloodstream stability of the nanosized delivery system is critical for their efficient solid tumor accumulation and high in vivo antitumor activity.

Active targeting of the markers expressed on cancer cells with nanotechnology has the potential to specially target cancer cells and to enhance drug delivery to cancer cells. Zhong et al. reports the preclinical tests of an EGFR-targeted polymerosomal doxorubicin in a mouse model of ovarian cancer. The addition of the EGFR-targeting ligand GE11 increased tumor accumulation of the drug-loaded nanoparticles, resulting in remarkable potency marked by significantly prolonged survival rates.

The delivery of multiple therapeutics has a potential to overcome acquired resistance to a single therapy and to improve therapeutic efficacy via synergetic effects. Allen et al. demonstrate the effect of the loading ratio of paclitaxel and everolimus in a nanoparticle formulation on cytotoxicity and have identified an optimal synergetic drug ratio for treating breast cancer cells. The optimized nanosized system for the combination therapy has a potential to improve therapeutic efficacy with reduced toxic side effects. In a different approach, Lovell et al. highlight the potential of a combination of chemotherapy and photodynamic therapy, or chemophototherapy, with liposomes for cancer therapy. The combination therapy is highly efficacious in a mouse model of pancreatic cancer. The improved efficacy could be explained by photodynamic therapy-induced vascular permeabilization that led to a significant increase in drug influx into the tumor, resulting in improved treatment outcomes.

Targeting different biological pathways with drug delivery is another promising approach to achieve improved therapeutic efficacy. David et al. report a CD44-targeted polymer-paclitaxel conjugate for treating metastatic disease. Potent efficacy of this approach is shown in mouse models of triple negative breast cancer and melanoma. The specific binding of the targeted polymer drug conjugate with a peptide ligand to CD44v3 and CD44v6 on cancer cells fulfills two functions, targeted delivery of a chemotherapeutic agent and inhibition of cancer cell migration and invasion. The targeted polymer drug conjugate

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significantly suppresses the growth of the primary tumor and reduces metastasis in the lung.

Drug delivery with nanotechnology also offers a unique opportunity for cancer immunotherapy. Steinmetz et al. have investigated the efficacy of different plant virus-like particles for cancer immunotherapy in a mouse model of melanoma. Although the groups previously reported the remarkable efficacy of in situ vaccination with cowpea mosaic virus (CPMV)-based nanoparticle formulations, they demonstrate that while in situ treatment with a different viral formulation of tobacco mosaic virus (TMV) slows down tumor progression, it—no matter of size and shape—does not reach the efficacy as shown for CPMV. Differential potency of CPMV vs TMV is explained with differences in immune activation leading to distinct remodeling of the immune profile within the tumor microenvironment. These data indicate that some plant viral platforms are more suitable for application as in situ vaccines than others. Understanding the intricate differences and underlying mechanism of immune activation may set the stage for the clinical development of these technologies. Taking steps toward translation, Steinmetz, Fiering, and Hoopes et al. have assessed the efficacy of in situ vaccination technology in companion dogs with spontaneous melanoma. Two nanotechnology platforms, the plant viral nanoparticle technology derived from cowpea mosaic virus and magnetic iron oxide nanoparticles inducing hyperthermia, are combined with radiation therapy. The combination of immunotherapy and radiation therapy is particularly powerful due to the synergetic effects of the abscopal effect or radiation therapy-associated immune activation and immunotherapy. Treatment studies in canine patients suggest that the combination of an in situ nanoparticle vaccine with hypofractionated radiation potentiates immune cell infiltration in the tumor, extends the tumor control interval, and has systemic therapeutic potential.

Another approach to biology-inspired immunotherapy is described by Zhang et al., who have developed biomimetic nanoparticles displaying cognate antigens to target red blood cell-specific B cells. Efficacy of this approach is demonstrated in mouse models of alloimmunity and autoimmunity. The nanoparticles functionalized with endogenous red blood cell membranes are used to tag and identify subpopulations of autoimmune B cells. While this approach has implications for the detection and treatment of various immune hypersensitivities, the ability to specifically eliminate autoimmune cell subsets may also help to prevent immune cell malignancies.

Drug delivery technologies can be used in the development of precision medicine for cancer therapy. Morita et al. reports immunoliposomes conjugated with TRA-8, an antibody against death receptor 5 (DR5), to target an apoptosis mechanism for cancer therapy. Multiple copies of TRA-8 antibodies or Fab' fragments are incorporated on the liposome surface to facilitate trimerization of DR5, which then induces apoptosis of cancer cells. Precision targeting to DR5 positive cancer cells with the immunoliposomes results in high cytotoxicity to the cancer cells and low toxicity to normal cells. Other apoptosis inducing antibodies are similarly incorporated on immunoliposomes, resulting in enhanced efficacy. The apoptosis inducing immunoliposomes are a promising new therapy for precision cancer treatment.

Cancer gene therapy constitutes another approach for precision cancer therapy. Specific delivery of therapeutic nucleic acids into cancer cells is a critical step to achieve effective cancer gene therapy. Cervia and Yuan summarize the recent progress on electrotransfection of plasmid DNA for cancer gene therapy. As compared to carrier-based gene delivery, electrotransfection has the advantage of low immune response, multiple administrations, and less off-target effect. The mechanisms of electrotransfection for intracellular gene delivery are discussed in detail. The authors have also proposed approaches to improve electrotransfection for intracellular gene delivery.

Exosomes play a pivotal role in cellular communications and are considered as a promising new class of drug delivery systems for precision cancer therapy. Liu et al. have summarized the unique advantages of exosomes for drug delivery, including good biocompatibility, high stability, preferred tumor homing and adjustable targeting efficiency, and the characteristics of exosomes for drug delivery. The review presents a thorough discussion on the sources, purification and characterization, modification, drug loading, cellular targeting, biodistribution and tumor targeting of exosomes for drug delivery to cancer, and their potential and challenges for clinical application as drug delivery systems.

In summary, the articles included in this special issue represent several exploring aspects of new avenues of cancer drug delivery. While some strategies focus on designer-made nanoparticles for improved delivery, others turned toward nanoparticle−biointerfacing strategies to reprogram tumor immunity. Efficient delivery of cancer therapeutics into cancer cells in solid tumors or the targeting of immune cell populations within the tumor microenvironment is a complicated and challenging process. Although safe and efficient delivery of cancer therapeutics throughout solid tumors is still a daunting task, the complex biology and dynamic evolution of aggressive cancer cells often render cancer therapies ineffective and diminish clinical treatment outcome. In order to achieve a curative outcome with drug delivery, new concepts and strategies need to be explored to address the challenges that impede safe and efficient drug delivery into solid tumors. Novel drug delivery technologies should be developed along with new discoveries of cancer biology and applied with emerging therapies to achieve desirable therapeutic outcomes in the healthcare of cancer patients.

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