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Editorial

Controlled Anticancer Drug Delivery

Wenge Liu*

Department of Biomedical Engineering, Duke University, USA

***Corresponding author:** Wenge Liu, Department of Biomedical Engineering, Duke University, USA, Tel: 9196605378; Fax: 9196605409; E-mail: wengeliu@duke.edu

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Introduction

One century after Paul Ehrlich first pioneered the concept that "we have to learn how to aim chemically" to treat disease, a concerted medical revolution has dedicated itself developing an ideal system for selectively delivering the high amounts of drugs to the site of the (tumor) while simultaneously sparing health tissue. In cancer research, however, most of the time and effort has been consumed in understanding the biological, molecular, and genetic underpinnings of tumors and the various defenses they manifest against treatment. The vast majority of these defenses exist as delivery barriers as drugs undertake the complicated process of selective vascular extravasation, migration through the tumor interstitium, penetration of the cellular membrane, intracellular trafficking, and localization to their final chemical target. Fortunately, this research has yielded important design criteria for the development of an idealized delivery system. Since most free drugs are inherently small in size (< 1kDa), they are less selective in only targeting diseased tissue and cause dose-limiting side effects. As such, most therapeutic drugs require modification to a larger 'carrier' molecule that endows them with targeted delivery abilities. Development of an idealized delivery system thus relies on the selection and thorough characterization of the carrier, which can be achieved following a three phase design scheme: 1) carrier design and selection, 2) assessment and optimization of *in vivo* transport from the administration to the site of treatment, and 3) the effective release and targeting of the drug at the site of action. With the proper design and investigation, a controllable system can be developed to create a therapy that is both highly efficient and sufficient to treat the targeted disease.

Design and Selection of the Drug Carrier for Optimal Pharmacokinetic Properties

With the advances made in tumor biology research, we now understand the impact a carrier's physicochemical properties can have on the systemic transport and intracellular trafficking processes that ensure effective drug delivery. The relative size, shape, charge, composition, and stimulus-sensitivity of a carrier molecule all can affect its pharmacokinetics, biodistribution, intra tumoral penetration, tumor bioavailability, and adverse side effects. Size and shape are particularly important as they influence whether a drug will interact with non-targeted organs and tissues. For example, small molecule drugs that are < 5nm often filtered out of circulation by the kidneys and induce the side effect of acute renal toxicity. Thus, one design parameter requires that drug-and-carrier conjugates have a cut-off size greater than 5.5 nm in order to prevent renal filtration. A second lower limit is imposed by liver filtration, as vascular fenestrations in the liver are 50–100 nm and particles smaller than 50 nm will interact with hepatocytes. The upper limit of particle size is influenced by two factors: tumor permeability and splenic filtration. Vascular fenestrations vary from 400 to 600 nm to microns among tumors. Prolonged drug circulation utilizing these parameters have enabled several strategies to leverage the enhanced permeability and retention (EPR) effect for tumor-specific targeting [1]. This has provided many chances to investigate the potential of polymer–drug conjugates to improve upon existing chemotherapy. Improved circulation half-life also results in improved dose efficiency as more drugs can reach the tumor.

Interstitial penetration of a delivered drug is often impeded by high cellular density, the external cellular matrix (ECM), and the interstitial fluid pressure (IFP) that drives molecule outward from the tumor center. Within the tumor interstitium, diffusion of the drug-carrier is diffusion dependent. Smaller sized carriers, regardless of *i.v.* administration or direct injection, help avoid steric hindrance and capture in this environment and can penetrate farther into the tumor to deliver their payloads. A net neutral charge on the carrier also allows it to penetrate up to three times farther than charge bearing counterparts. A neutral charge also improves the distribution homogeneity within the tumor tissue [2]. Tumor specific conditions, such as low pH, body temperature and externally focused stimuli can be utilized to design environmentally sensitive carriers for stimulus-responsive delivery behaviors. For example, thermally responsive peptides (elastin-like polypeptides, ELPs) and polymer constructs (TSLs) provide an interesting class of materials that can be triggered to accumulate at the tumor site by the extrinsic application of heat. The drug carrier design is the easy-controlled step, the control of tumor coverage and retention and drug release are more complication and need more efforts to realize the design idea input in this section.

Further research has also shown that different types of cancer exhibit unique tissue conditions. Development of drug carriers must then be based on the distinctive traits of the cancer, carefully designed, and selected. After initial carrier design, a more complicated analysis exploring its effective tumor penetration, coverage, retention, and drug release must be characterized both in vitro and in vivo.

Control of Tumor Coverage and Retention

The exploitation of stimulus-sensitive systems to trigger aggregation and morphological changes has been widely investigated. A new concept of controlling the tumor coverage and retention (C&R) has gained importance in drug delivery as a consequence of the growing evidence [3]. The balance of C&R ensures cancerous cells are appropriately exposed to the chemotherapy agents and is vital to complete tumor regression. The aforementioned tumor obstacles of tumor blood vessels wall, high interstitium fluid pressure (IFP),

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heterogeneous tumor perfusion, vascular permeability, and cell density are critical factors that impact a new delivery system's ability to control the C&R[4]. The primary design criteria is for a drug to penetrate the tumor interstitium so that it will cover the tumor, yet stop at the tumor border before leaking out. The most effective anticancer drug delivery design would freely penetrate and distribute through entirety of the tumor interstitium and be retained within the tumor environment for a long duration in order to effect proper the necessary therapy. As penetration and retention are both driven by diffusion, an inherently size-dependent process, this presents a design dilemma: maximal interstitial distribution (coverage) or longer tumor specific retention. Smaller molecules achieve wider coverage in tumor interstitium but are cleared faster due to the IFP. Larger drug carriers have improved tumor retention in the tumor interstitium as they resist the IFP through steric interactions with the ECM and high cell density, but likewise are incapable of diffusing to ensure homogenous coverage. Fortunately, recent developments in 'smart' – stimulus-responsive – peptides, polymers and lipid drug carriers have made it possible to control temporal-spatial dynamics of drug diffusion (liquid phase) and aggregation (solid phase) to achieve both coverage and retention within a tumor. These systems use external stimuli to trigger a physiological phase transitions in the carrier, including thermo sensitive polymers using applied hyperthermia, pH-responsive polymer in acidic tumor tissue or lysosomes, bi-zwitterions compounds under electrostatic force fields, and magnetic particles in a magnetic field. For example, external hyperthermia was applied in combination with a systemically administered, thermo sensitive polymer that was conjugated to drug. The soluble polymer conjugate was driven to preferentially assemble *in situ* at the site of the tumor due to the localized heating and resulted in the high accumulation of payload within the tumor.

Finally, the method of delivery can impact which design criteria is of higher importance. Systemic (*i.v.*) administration prioritizes penetration as carriers extravasate at the edges of tumors. Direct intratumoral (*i.t.*) delivery prioritizes retention to ensure the injected dose is locally maintained in the tumor. It is worth noting that modern *i.t.* drug delivery techniques are proving attractive alternatives to systemic drug delivery for the therapy of solid tumors. These technologies circumvent many of the problems inherent in systemic drug delivery – poor extravasation, low tumor penetration, rapid drug clearance and exposure of healthy tissues– while retaining their anti-cancer therapeutics within the tumor for extended periods of time. *I.t.* drug administration may have the potential to achieve better tumor penetration and concentration by controlling initial convection (infusion force), leveraging the intratumoral pressure to assist with drug distribution, and a concentration gradient driving therapeutics to the all of tumor margins. In addition, modern advances in quantitative *in vivo* imaging have been critical for monitoring tumor coverage and retention of drug delivery systems. Current imaging methods include MRI, CT scans, fluorescent microscopy, and SPECT and are requisite for assessing effective C&R characteristics in both the developmental and clinical settings.

Controlled Drug Release at the Site of Action

Even with optimal pharmacokinetics and sufficient tumor coverage and retention, all the drugs (the sole exception being radionuclide isotopes) cannot exert the maximal efficacy without first being released from the carrier in its free, activated form. Furthermore, macromolecular and nanoparticle drug carriers must release their low-MW cargo at their target to improve drug diffusion and homogenously distribute throughout the tumor tissue. After aggregation, controlled drug release at the target site can be fine-tuned based on designing the carrier's response to a number of possible stimuli. Most stimulus-responsive release strategies are divided into two categories of stimuli: tumor specific environment features(up-regulated enzymes, low extracellular pH, etc.) and extrinsically triggered (heat, ultrasound, light, etc.). For example, MMP-cleavable linkers provide an enzymatic stimulus specific to tumors that allow for localized release of chemotherapeutics. Studies have found that conjugation of doxorubicin to albumin, via an MMP-sensitive linker, has led to greater cytotoxicity against renal carcinoma cells when compared with an MMP-insensitive control. Local hyperthermia, exemplifying physically controllable stimuli, can potentially play a key role in achieving targeted drug release. For example, localized hyperthermia is required for triggering drug release from temperature-sensitive liposome's (TSLs). The liposome acts as a protective carrier, allowing increased drug to flow through the bloodstream by minimizing clearance and non-specific uptake. On reaching micro vessels within the tumor, hyperthermia is applied and the drug is quickly released and penetrates within the solid tumor. In this situation, localized hyperthermia can be induced by a variety of methods including radiofrequency, electric current, microwaves, laser, and high intensity focused ultrasound (HIFU). Of these heating methods, HIFU is superior for precision and control for noninvasively heating targeted tumor tissues. Physical stimuli can also offer the dual benefit of conferring a secondary cancer killing therapy, as is commonly seen with hyperthermia.

Conclusion

Effective chemotherapy regimens recognize the critical importance of drug delivery in treating cancer. The design of drug carriers that are capable of penetrating throughout the tumor interstitium to reach neoplastic cells distant from the tumor vasculature is critical to achieving positive clinical outcomes. Herein, a variety of modern strategies and techniques were discussed that can improve penetration, distribution, and retention for surmounting the traditional barriers of tumor treatments. These strategies are of great interest, both experimentally and in the clinic, as they seek to further the targeted treatments originally envisioned by Paul Ehrlich. As the field progresses, advances in intracellular targeting will come in to focus as delivery systems will seek to selectively seek and damage specific organelles and DNA structures to halt tumorigenic proliferation. Meanwhile, therapies that leverage molecular targeting as well as extrinsically controlled stimuli will become staples in clinical regimens.

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