Magnetic Resonance-Guided Drug Delivery

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KEYWORDS

• MR imaging • Drug delivery • Tumor targeting • Nanomedicine • Cancer
• Thermosensitive liposome • High-intensity focused ultrasound • Imaging guidance

KEY POINTS

- MR imaging can enable planning, monitoring, real-time control, and posttherapy assessment of tumor-targeted drug delivery.
- Use of MR imaging to guide the combination of hyperthermia and thermosensitive drug delivery systems constitutes an effective approach for enhancing drug delivery to tumors.
- MR-guided high intensity focused ultrasound (MR-HIFU) is a particularly promising technique for improving delivery of systemically administered therapies and potential modulation of the tumor microenvironment.

ADVANCED DRUG DELIVERY SYSTEMS

Targeted drug delivery, whereby therapeutic agents are transported from the site of administration specifically to diseased tissues, remains a "holy grail" of pharmaceutical research. This concept has significant potential in oncology, since side effects from chemotherapeutic drugs with narrow therapeutic windows (the range between effective and toxic doses) can limit the dose and compromise the efficacy of treatment. Recent progress in pharmaceutical nanotechnology has led to the development of a variety of advanced drug delivery systems (DDS) with the capacity to transport small-molecule drugs to tumors, resulting in reduced systemic toxicity and improved treatment outcomes.

In general, DDS-based drug formulations possess several advantages over their conventional counterparts, including (1) enhanced tumor targeting, (2) extended systemic circulation, and (3) controlled drug release. Careful design of DDS can exploit these characteristics to dramatically increase the safety margin of cytotoxic drugs with traditionally narrow therapeutic windows. Examples of DDS used for this purpose include polymeric micelles,[1] liposomes,[2] polymer-drug conjugates,[3] and antibody-targeted therapies (**Fig. 1**).[4] To date, liposomes have achieved significant success, with several formulations receiving clinical approval and many others, including temperature-sensitive liposomes (TSLs), are in clinical trials.[2]

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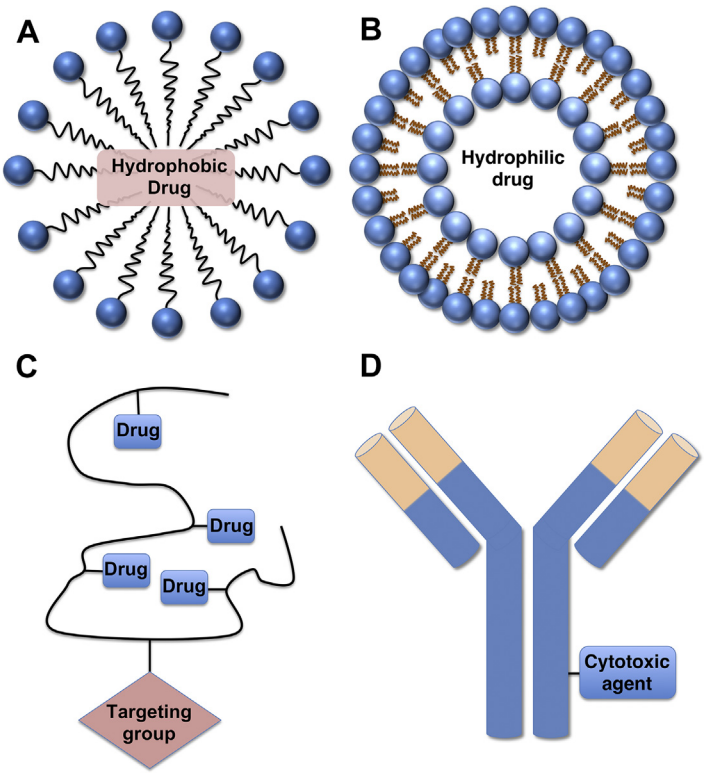

Fig. 1. Examples of drug delivery systems: micelles (*A*), liposomes (*B*), polymer-drug conjugates (*C*), and antibody conjugates (*D*).

DDS may be "passively" targeted by exploiting features of the tumor microenvironment to enhance drug accumulation, and/or "actively" targeted by binding of DDS to cancer cells or endothelium via specific chemical affinity. Tumor accumulation via passive targeting is achieved because of the characteristically hyperporous blood vessels of neoplasms (resulting in increased extravasation of macromolecules and nanoparticles) and dysfunctional lymphatic drainage, a phenomenon referred to as the enhanced permeability and retention (EPR) effect.[5] Active tumor targeting exploits the specific molecular affinity of bioactive ligands, such as peptides and antibodies, for cellular receptors preferentially expressed in malignant tissues to enhance tumor localization, retention, and cellular uptake.[6]

Barriers to Effective Drug Delivery

Following successful tumor targeting, stable DDS tend to be confined to perivascular tissues because of their limited penetration into the tumor interstitium.[7–9] If the drug remains bound to or encapsulated by the carrier, concentrations deep within the interstitium and in regions of low vascular density or high interstitial pressure will be limited. Recent efforts to improve drug delivery have focused on increasing both the amount and bioavailability of drugs delivered to a tumor by incorporating external release stimuli into the drug delivery paradigm. Drug release may be triggered by endogenous stimuli such as tissue pH[10] and redox reactions[11] associated with the microenvironment of tumors, or by application of exogenous triggers such as alternating magnetic fields,[12] heat,[13] and light.[14] Unlike endogenous stimuli, the spatiotemporal application of exogenous triggers can be controlled, providing a means for modulating drug release.

Insufficient dosing of tumors during chemotherapy resulting from poor intratumoral drug distribution and penetration is regarded as a major limitation of intravenous drug delivery. Many factors present barriers to drug delivery at the intratumoral level, including inefficient angiogenic vessels, the spatial heterogeneity of the tumor vasculature network, high cellular and stromal density, and elevated interstitial fluid pressure, among others.[1,15–17] Indeed, numerous studies have demonstrated the limited penetration of both conventional and DDS-based chemotherapy from tumor blood vessels into the interstitium.[8,9,18] These regions, deep within the interstitial space, are prone to transport-mediated and hypoxia-mediated drug resistance, and are a cause of