

Commentary

Liposomal delivery as a mechanism to enhance synergism between anticancer drugs

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Liposomes, or phospholipid vesicles, have been recognized as a potential drug delivery vehicle for three decades (1). Depending on the drug of interest, liposomes can serve as a controlled release carrier or simply as a biocompatible solubilizing vehicle for poorly soluble agents. Because of their size, which typically ranges in mean diameter from 50 to 250 nm for the systemically administered vesicles, liposomes display some unique pharmacokinetic characteristics. These include clearance via the reticuloendothelial system, which results in a relatively long systemic circulation time, and hepatic and splenic distribution. Furthermore, liposomes exhibit preferential extravasation and accumulation at the site of solid tumors due to increased endothelial permeability and reduced lymphatic drainage in these tissues, which has been defined as enhanced permeability and retention effect (2). Liposomal delivery is therefore a means to modify the pharmacokinetic and pharmacodynamic properties of therapeutic agents. Such modifications can, in some settings, improve the therapeutic efficacy of anticancer drugs and reduce or modulate their toxicity profile. For example, long circulating polyethylene glycol-coated liposomal formulation of doxorubicin has been shown to exhibit increased solid tumor accumulation due to the enhanced permeability and retention effect and decreased dose-limiting cardiac toxicity relative to the free drug (3). Development of liposomes as a drug carrier has been marked by a number of key innovations. These include the development of remote drug loading methodologies based on pH or ionic gradient (4), polyethylene glycol-coated long circulating liposomes (3), cationic liposomes for nucleic acid delivery (5), pH-sensitive liposomes for cytosolic drug delivery (6), temperature-sensitive liposomes for burst release in response to hyperthermia (7), and targeted liposomes for selective delivery to tumor cells or endothelium (8).

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Mayer et al. (9) have investigated the application of liposomes as a delivery vehicle for drug combinations. The use of drug combinations is a widely adopted strategy in clinical cancer therapy. Although drug interaction at different drug ratios can be systematically studied *in vitro*, these ratios cannot be easily translated *in vivo* due to differential pharmacokinetic characteristics of different drugs. Coencapsulation of two drugs into liposomes can “synchronize” the distribution of the drugs if the drugs can be stably entrapped inside these liposomes. This theoretically would allow for a more direct translation of *in vitro* results to *in vivo*. This is very valuable because current drug combinations are evaluated empirically in the context of clinical trials. Liposomes carrying drug combinations exhibit pharmacokinetic properties of the carrier, such as long circulation, reticuloendothelial pathway of clearance, and enhanced permeability and retention-mediated tumor accumulation, which may enhance therapeutic efficacy and reduce toxicity of these drugs. Drugs stably entrapped inside a liposome are not biologically active and must be released to gain access to their intracellular target. A potential confounding factor in the liposomal codelivery of drug combinations, therefore, is that drug release from the liposomes may follow a different mechanism *in vitro* and *in vivo*. In solid tumors, following extravasation, liposomes have been shown to be predominantly taken up by tumor-infiltrating macrophages (10), which may in turn “activate” liposomal drug by breaking down the liposomes. Given the inherent differences between drugs, coencapsulated drug may be released from liposomes at different rates, making it more difficult to predict effective free drug concentrations inside the tumor microenvironment. Nevertheless, stable coencapsulation synchronizes drug distribution at least to the point of extravasation from the vasculature, provides delivery of combinations of drugs at a specific ratio, and may provide unique therapeutic advantages through therapeutic synergism. This concept has been elegantly shown by Mayer et al. (9) in studying combinations of irinotecan/fluorouridine, daunorubicin/cytarabine, and cisplatin/daunorubicin. In other studies, coencapsulated doxorubicin and verapamil was shown to be highly effective against cells that are multidrug resistant (11). It is conceivable such studies will yield many promising drug combinations with clinical potential. The ability of liposomal drug carrier to determine drug pharmacokinetics *in vivo* greatly enhanced the translational potential of drug combinations identified *in vitro* and thus provides a valuable tool for preclinical screening of drug combinations for clinical development.

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