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 compounds. 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 the EPR 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 (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).

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 easily be 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 the synergistic effects of drug combinations. 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 the EPR 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 (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).
Liposomal Delivery and Anticancer Drug Synergism

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