The Biology Behind

The Potential of Drug-carrying Immunoliposomes as Anticancer Agents


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The demand for increased specificity of anticancer agents to target tumors has resulted in numerous strategies, including oncogene-selective inhibitors, gene and antisense therapies, and mAbs, as well as combinations thereof. Although many of the regimens are already in use, the need for more effective targeted drug delivery methods requires further refinement of anticancer therapies. Improved delivery of drug-carrying immunoliposomes is one approach to this problem. In their recent report, Park et al. (1) present the feasibility of this system as a potential anticancer regimen.

Cytotoxic drug incorporation into liposomes has been reported since the mid-1970s. These early reports laid the groundwork for selecting therapeutic agents amenable to incorporation by liposomes, as well as determining optimal liposome size and net charge required for effective drug delivery (2). Early reports also noted the problems associated with liposome-mediated drug delivery; liposomes were removed from circulation by fixed macrophages in the RES, particularly in the liver and spleen. Thus, although first-generation liposome-incorporated drugs may be effective in macrophage-related diseases, particularly in the liver and spleen, many other tumors would require other drug-targeting mechanisms.

Later studies refined many of the considerations required for effective liposome-mediated drug delivery (3). Today, drugs of various chemical properties have been successfully packaged, including hydrophilic drugs such as N-(phosphonoacetyl)-L-aspartate, hydrophobic drugs such as paclitaxel, and amphipathic drugs such as doxorubicin.

Optimal liposome size depends on the tumor target. In tumor tissue, the vasculature is discontinuous, and pore sizes vary from 100 to 780 nm. By comparison, normal vascular endothelium is <2 nm in most tissues, 6 nm in postcapillary venules, 40–60 nm for the kidney glomerulus, and up to 150 nm for sinusoidal epithelium of the liver and spleen. Most liposomes are 65–125 nm (4). In general, for a given liposome composition, the larger the liposome, the faster the clearance by the RES (5–7).

Negatively charged liposomes were believed to be more rapidly removed from circulation than neutral or positively charged liposomes; later studies have indicated that the type of negatively charged lipid affects the rate of liposome uptake by the RES. For example, liposomes containing negatively charged lipids that are not sterically shielded (phosphatidylserine, phosphatidic acid, and phosphatidylglycerol) are cleared more rapidly than neutral liposomes of similar composition. However, liposomes containing sterically shielded lipids (ganglioside-GM1 and phosphatidylinositol) are cleared even more slowly than neutral liposomes (8).

Thus, one way to reduce liposomal uptake by the RES is by creating sterically stabilized liposomes. “Steric stabilization” refers to the colloidal stability resulting from addition of hydrophilic polymers or glycolipids into liposomes. The best-studied stabilizers are polyethylene glycol and ganglioside GM1. Sterically stabilized liposomes showed prolonged lifetimes in the circulation as compared with nonstabilized liposomes (9–13). Also, sterically stabilized liposomes are less reactive toward serum proteins and less susceptible to RES uptake than nonstabilized liposomes (9). The mechanism by which sterically stabilized liposomes are thought to decrease RES-mediated uptake is that the stabilizer occupies the space immediately adjacent to the liposomal surface, excluding other macromolecules from this space. Consequently, access to and binding of blood plasma opsonins to the liposome surface are hindered, preventing interactions with RES macrophages. However, although sterically stabilized liposomes prolong circulation time and decrease liposomal uptake by the RES, they do not actively target the liposome to the tumor.

One effective means of targeting tumors would be via conjugation of antitumor antibodies or portions of antibodies to liposomes (immunoliposomes). In this approach, it has become apparent that many factors must be taken into consideration, including proper choice of target antigen, antibody function, and antibody-liposome linkage (14). Thus, tumor antigens must be identified, and the biological response of a given antibody toward the tumor antigen determined.

Identification of tumor-specific antigens has proven difficult because most tumors do not express unique antigens. Rather, they can express the same antigens as normal tissue but in greater quantities compared with normal cells. Additionally, many tumors do not overexpress the antigens homogeneously throughout the primary tumor or may not express them in metastases. Some antigens may be shed or secreted, leading to potentially high levels of soluble antigen that could interfere with immunotherapies. Despite the potential difficulties, the successful use of mAbs such as herceptin in immunotherapy suggests that immunoliposomes may represent a viable approach.

Chimeric or humanized mAbs can reduce the host response...
against the therapeutic antibody (15). Removing the Fc portion of the IgG antibody can also reduce antigenicity. In addition, cellular internalization of antibodies increases efficacy of drug delivery, presumably by inducing tumor cells to endocytose immunoliposomes. This is the case with the HER2-targeted immunoliposomes, which distribute within solid tumors and not simply in the extracellular space surrounding the tumor blood vessels (14, 16).

Thus, effective targeted drug delivery using immunoliposomes requires considerations of liposome, Ab, and the chemotherapy agent, as well as their interactions with each other and the targeted cell. These considerations are summarized by Park et al. (14) and Table 1. In their current report, Park et al. (1) used sterically stabilized liposomes, a humanized or completely human anti-HER2 Fab' fragment, and doxorubicin. Doxorubicin, which has a relatively broad activity against a variety of tumors, can be efficiently loaded into and effectively delivered by the liposomal carrier. In this report, Park et al. (1) demonstrate that the doxorubicin-containing anti-HER2 immunoliposome is more effective than any portion of these components in reducing growth of HER2-overexpressing breast cancer cells that were s.c. implanted into nude mice. These results demonstrate that immunoliposomes can overcome the potential barriers for delivery into tumor tissues, suggesting that with proper construction of the Fab' fragment of a properly chosen mAb, proper liposome composition, and proper drug loading, immunoliposomes can be effective anticancer agents. However, several questions must be addressed. For example, are anti-HER2 immunoliposomes also effective in orthotopically, rather than s.c., implanted HER2-overexpressing breast tumors? Can immunoliposomes (anti-HER2 or others) effectively treat metastatic lesions, because small lesions (<1.2 mm) appear to be avascular (17–20)? Thus, micrometastases may not be particularly amenable to treatment with i.v.-administered liposomal drugs that require extravasation for activity.

As the use of immunoliposomes as anticancer agents approaches clinical trials, more questions arise. What are the immediate and long-term effects of immunoliposome administration in patients? Will immunoliposomes, similar to mAbs, also be able to overcome potential barriers such as tumor heterogeneity? Will immunoliposomes be effective in combination therapies? These and other questions await further studies.

References


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