LIPOSOME TARGETING TO MACROPHAGES: OPPORTUNITIES FOR TREATMENT OF INFECTIOUS DISEASES

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INTRODUCTION

The central role played by cells of the mononuclear phagocyte system (MPS) such as alveolar macrophages, hepatic Kupffer cells, splenic and lymph node macrophages, tissue histiocytes and circulating blood monocytes in the complex host reaction to neoplastic and infectious diseases has attracted increasing attention during the past 10 years. This interest stems from the experimental studies illustrating that macrophages when appropriately activated* play a major role in host defense against tumors and infectious microorganisms in vivo and also display enhanced tumoricidal and microbicidal activity in vitro1^-3. These observations, coupled with the disappointing results obtained in both clinical and experimental studies with immunologically-specific therapeutic modalities mediated by T and B lymphocytes in cancer immunotherapy has led to a renewed interest in the functions of macrophages and NK cells. Additionally, there is needed a reappraisal of the potential therapeutic benefit of augmenting non-specific host defense mechanisms mediated by mononuclear phagocytes for adjunct therapy of neoplastic and infectious diseases. For this reason, a significant effort is now being undertaken by many laboratories to identify and characterize compounds collectively referred to as biological response modifier agents (BRM) that can augment macrophage-mediated host defenses in vivo1^-4.

*The term "activated macrophage" used in this article refers only to those macrophages displaying enhanced microbicidal or tumoricidal activity.
The ability to selectively target drugs to specific cells within the body has been one of the most coveted goals in experimental and clinical therapeutics ever since Paul Ehrlich proposed the use of "bodies which possessed a particular affinity for a certain organ...as carriers by which to bring therapeutic agents to the certain organ." Since that time, a wide variety of macromolecular, particulate and cellular matrices have been proposed for use as drug carrier systems. These include: antibodies, dextrans, plasma proteins, polynucleotides, red blood cells, polymorphonuclear leukocytes, gelatin or albumin microspheres, synthetic polymeric nanoparticles, multiphase microemulsions and liposomes. Many of these systems have failed to fulfill their initial promise; however, interest in targetable drug delivery systems remains high.

The current information on the application of liposomes to drug delivery in vivo, with specific reference to the use of liposomes for the delivery of antibiotics and BRM to macrophages in vivo for augmenting non-specific host defenses against infectious diseases will be reviewed. Also discussed is the potential toxic liability of liposomal drug carriers and developmental hurdles that must be overcome to ensure the successful commercialization of a liposome-based drug delivery system.

LIPOSOMES

Liposomes are aqueous dispersions of phospholipids forming closed structures composed of either one (unilamellar) or several (multilamellar) lipid bilayers, each bilayer completely surrounding an internal aqueous space. Their potential value as drug carriers stems from their ability to encapsulate a wide variety of water soluble compounds in their internal aqueous space(s) and also incorporate a variety of lipophilic compounds within the lipid bilayer(s). Furthermore, specific recognition ligands such as monoclonal antibodies or integral membrane proteins can be covalently coupled to the surface of the liposomes to serve as targeting molecules to ensure the interaction of the liposomes with defined molecules on target cells.

Although many elegant methods have been devised for the preparation of liposomes, very few were designed for the specific purpose of using liposomes as a drug delivery system. For this reason, the majority of published work on liposome-mediated drug delivery in vivo focuses primarily on two classes of liposomes: small unilamellar liposomes (SUV) and large multilamellar liposomes (MLV). These classes of liposomes were developed largely as model membrane systems for analyzing the physicochemical properties of lipid bilayers and have been adopted largely without modification for use in drug deliver. As such,