Liposomes and Immunobiology

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LIPOSOMES AND IMMUNOBIOLOGY

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LIPOSOMES AND IMMUNOBIOLOGY

PREFACE

This Symposium derived from the organizers' interests in both immunology and in the new exciting field of "liposomology." Since the first observation and description of lipid vesicles by Alec Bangham and his colleagues in 1965, these vesicles have been employed in virtually every aspect of biology. For example, they have been used as model membranes, as fusogenic agents in cell hybridizations, as carriers of proteins and drugs, and as immunologic adjuvants. From a clinical point of view, the liposome has been perceived as an ideal carrier of biologically active materials, especially since liposomes can be prepared from common lipid constituents of cell membranes. The early excitement centered on its use as a vehicle for anti-cancer drugs. However, these hopes have not been fully realized due to the lack of predictable targeting of liposomes for selected tissue delivery. Nevertheless, one area of clinically-relevant research seems to have emerged--that of the liposome's applications in immunobiology.

The intent of this Symposium was to focus on the ramifications of liposome interactions on the immunobiology of the host. The scope of this volume includes presentations of liposome use in immune systems, and the optimization of liposome manufacture for such applications. The juxtaposition of two seemingly unrelated areas, that of macrophage function and/or antigen processing and immune responsiveness with that of liposome biology, has been deliberate. The common denominator of this coupling resides in the observations that macrophage-processed antigens or chemically-altered antigens that favor cell-mediated immune responses are more lipoidal and hydrophobic than native antigens that elicit humoral immunity. The possibility that through appropriate presentation of antigens by liposomes one may be able to selectively generate either cellular or humoral immune responses is very attractive. Thus, the Symposium was organized so that participants addressing the selective generation of cellular responses through modified antigens were integrated with those describing liposome systems for delivery of various immunogens.

Clinically, liposomes will probably have their first impact as adjuvants. Liposomes are capable of generating immune responses with antigens that are poorly immunogenic; this includes soluble proteins, as well as viral and parasitic particles. Because of the liposome's generally non-toxic nature, its employment as an adjuvant is very promising when one compares the alternative forms of adjuvants for clinical use, such as the Freund's adjuvants or precipitated aluminum hydroxide. Several papers in this volume focus on the effect of liposomes on various immunologically important membrane molecules, e.g., histocompatibility antigens, surface immunoglobulins, and lectin receptors. Whether the reported alterations in receptor mobilities induced by in vitro

liposome treatment is detrimental in vivo (or even occurs) or is, indeed, the reason for the liposome's efficacy in eliciting enhanced immune responses remains to be determined. Success in employing the liposome as a target for cell-mediated and antibody-dependent cellular cytotoxic assays has been elusive. Unlike the early studies utilizing liposomes for targets of antibody-mediated, complement-dependent lysis, specific cellular lysis has not been conclusively demonstrated. It is suggested that additional molecules (e.g., histocompatibility antigens) may be required to accompany the antigen for insertion into liposomes in order to provide a proper target complex for specifically cytotoxic lymphocytes.

Several papers focus on liposome applications in cancer therapy. A potentially exciting use of liposomes may be in the bypassing of membrane receptors to activate cells. An example of this application is presented in the use of liposomes bearing "macrophage activation factors" to stimulate macrophages in an animal with metastatic cancer. This approach exploits the ability of macrophages to distinguish between abnormal (or tumor) cells and their normal cell counterparts. Additionally, the use of local heating of cancerous tissue to release drugs from thermolabile liposomes is presented.

This record of the speakers' presentations is a tribute to their creativity and insight into liposome applications. The organizers hope that a synthesis of the contents from this volume will thus provide additional approaches for the generation of liposomes in selective stimulation of host functions.

Houston, Texas
April 9, 1980

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LIPOSOMES AND IMMUNOBIOLOGY

Tom/Six, eds. Liposomes and Immunobiology

AN OVERVIEW: LIPOSOMES AND IMMUNOBIOLOGY--MACROPHAGES, LIPOSOMES, AND TAILORED IMMUNITY

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INTRODUCTION

Given:	Lipoidal Antigen	⟶	Cell-mediated immunity
	Liposome	=	Lipid vesicle
To Prove:	Liposome + Antigen	⟶	Cell-mediated immunity

The immune response. The immune response represents a complex physiological system that responds to chemical insults to the host's biological integrity and involves the *differentiation of host reactivities into two general categories* (Fig. 1): cellular and humoral. These insults can be in soluble form or attached to cells. These foreign materials (antigens) can be derived from exogenous (infectious microbes) or endogenous (abnormal, tumor cells) sources. Humoral responses are associated with a class of lymphocytes that arise in the bone marrow and repopulate into peripheral lymphoid tissues. These bone marrow-derived, B cells[1] (also termed bursal-equivalent or gut-associated cells), are the precursors of immunoglobulin (Ig) secreting plasma cells (P) that mediate humoral immunity (HI). On the other hand, cell-mediated immunities (CMI) including transplant rejection, delayed hypersensitivity, graft versus host reactivity, and tumor immunity are effected primarily by thymus-derived T lymphocytes. These effector T cells comprise another class of lymphocytes that have traversed the thymus to acquire their unique capacity to respond to antigens. Immunologic memory (or the capacity to respond in an accelerated fashion to a second exposure of an antigen) resides in long-lived

[1] Abbreviations: B cell, the precursor of the plasma cell (Bursal equivalent, Bone marrow-derived, or gut-associated cells); Ig, immunoglobulin, used synonomously with Ab, antibody, in this paper; P, plasma cell is the Ig secreting cell; IR, immune response; T cell, thymus-processed lymphocyte involved in CMI; CMI, cell-mediated immunity, cellular immunity; HI, humoral (antibody) immunity; Ag, antigen; Immunogen, an antigen capable of eliciting an immune response; C_8, C_{12}, or C_{18}, hydrocarbon chain of 8, 12, or 18 carbon units; PC, phosphatidylcholine; SPH, sphingomyelin; PS, phosphatidylserine; PE, phosphatidylethanolamine; MLV, multilamellar vesicle; SUV, small unilamellar vesicle; LUV, large unilamellar vesicle; REV, reverse phase evaporation vesicle; DDA, dimethyl-dioctadecylammonium bromide; TNP-BSA, trinitrophenylated-bovine serum albumin; SRBC, sheep red blood cells.

T and B cells. As a generalization, particulate antigens such as cells elicit cell-mediated immune responses while soluble antigens, formed in various combinations with proteins, carbohydrates, and lipids, activate the antibody-mediated immune system (Fig. 2).

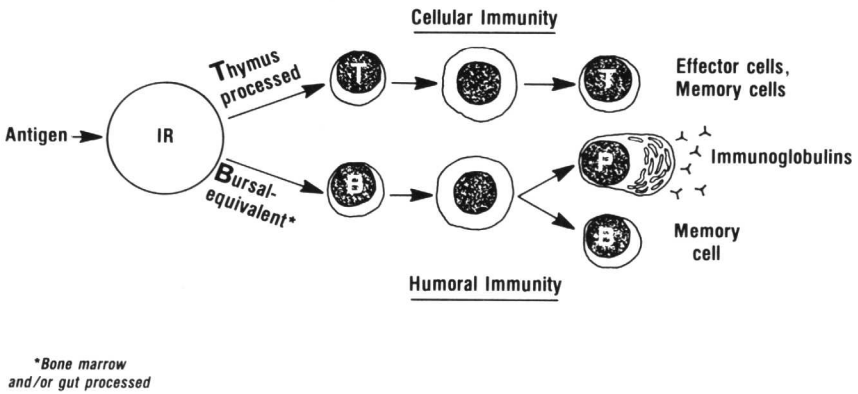

Fig. 1. Host immune response (IR) to antigen.

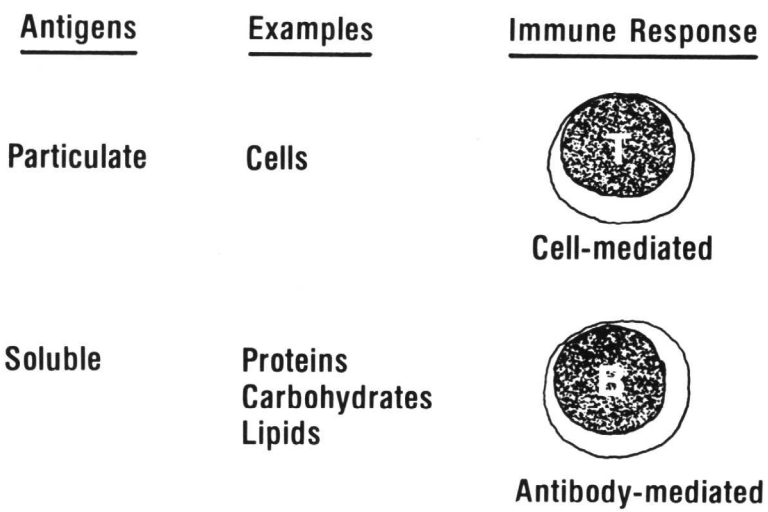

Fig. 2. Generalization of immune responses elicited by two classes of antigens.