Plasma Lipoproteins with Bioregulatory Properties Including the Capacity to Regulate Lymphocyte Function and the Immune Response

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Abstract

Consideration of the effects of nutrition and of lipids on the immune competence and the characteristics of host resistance to neoplasia requires consideration of the plasma lipoproteins. A wide variety of regulatory effects of lipoproteins on the immune response, immune mediation pathways, cellular metabolism of the immune system, and antigen-nonspecific host resistance mediated by the lymphoid and reticuloendothelial systems has recently been recognized. Observations coupled with initial evidence for differences in lipoproteins in cancer patients suggest that lipids or lipid metabolism may be of significance in the biology of neoplasia.

Plasma lipoproteins possess well-recognized transport functions in vivo. Lipoproteins are complex, noncovalently organized particles composed of a variety of lipids and a variable array of apoprotein chains. To consider the effects of lipids on cells in vivo requires consideration of the concentration and composition of the various plasma lipoproteins, not only because they are the usual mode of transport of lipids to cells but also because lipoproteins are influenced profoundly by nutrition.

Certain classes as well as minor subsets of plasma lipoproteins can regulate selected metabolic functions of a variety of cell types; more than 10 forms of bioregulatory phenomena have been attributed to plasma lipoproteins. More than one-half of these described bioregulatory properties involve the regulation of lymphocyte function in vitro or the immune response in vivo and in vitro.

Among the bioregulatory properties of lipoproteins, the first and most extensively documented has been the general property of LDL to support cholesterol and regulate cholesterol biosynthesis (4). The receptor dependence of this function has been established by Brown and Goldstein (4) and has been extended to the lymphocyte by Ho et al. (17). The biological effect appears to be mediated by the sterol content and is operative via regulation of 2 enzymes in sterol biosynthesis (β-hydroxy-β-methylglutaryl-CoA reductase and acyl-CoA:cholesterol acyltransferase). HDL’s have also been observed to bind to cells (21) and to participate in the regulation of cholesterol content by facilitating cholesterol egress. VLDL’s have been demonstrated to specifically inhibit the initiation of prereplicative protein synthesis and subsequent DNA synthesis in fetal rat hepatocytes in the studies of Leffert and Weinstein (18). Lipoproteins which have yet to be well characterized have been demonstrated by Lint et al. (20) to inhibit attachment of the C567 complex of complement to cell surfaces, suggesting that selected lipoproteins exercise a potentially important modulating effect upon the mediation of immune attack mechanisms. Recently, Leong et al. (19) have demonstrated that a lipoprotein fraction of mouse serum specifically neutralizes infectivity of xenotropic murine leukemia virus.

The concept that plasma lipoproteins regulate lymphoid function in a biologically significant fashion, particularly in reference to host resistance to tumors, has evolved during the past 4 years and represents the first of the recognized immunoregulatory functions of lipoproteins. This evolved from identification by Chisari and Edgington (7) of lymphocyte-regulatory defects associated with hepatitis virus infections in humans and led to the identification and purification of a unique trace subset of LDL. This lipoprotein was shown to metabolically regulate erythrocyte rosette-forming function of a T-lymphocyte subset in vivo and in vitro and was mediated via a specific receptor for this lipoprotein (RIF) (8). RIF may suppress T-suppressor lymphocytes, and the persistence of RIF is associated with evolution to chronic active hepatitis following infection with hepatitis B virus (9), a candidate human oncogenic agent. Another lipoprotein with characteristics similar to those of RIF has been described in association with Hodgkin’s disease by Fuks et al. (16). This lipoprotein also appears to influence erythrocyte-rosette-forming function of T-lymphocytes and may account for defective lymphocyte responsiveness in vitro.

Waddell et al. (26) have described inhibition of lymphocyte proliferation in vitro in hereditary type IV and V hyperlipidemia and have attributed this to the chylomicrons and VLDL. Chisari (6) has further characterized this pathway, including in vivo effects. Recently, it has been observed by Benditt et al. (2) that HDL may contain serum amyloid Protein A and that this protein within the HDL complex is capable of suppressing lymphocyte function (3).

The existence of a normal lipoprotein that could regulate lymphocyte function was first suggested in 1975 (7) and was reported in detail by Curtiss and Edgington (12) in 1976. One of the more active lipoproteins was a minor subset of LDL, which was designated LDL-In. Subsequently, 5 additional laboratories have confirmed and extended the observations of the immunoregulatory properties of human plasma lipoproteins, including suppression by VLDL (24, 26), by the intermediate-density lipoprotein (22) which appears to be identical with LDL-In (12), and regulation of tumor-cytidal capacity of activated macrophages (5). Zimmerman and Kern (28) have described a selective antimitogenic constituent in normal serum which is...
capable of inhibiting the induction of immunoglobulin production. The similarity of properties to those of LDL-In (15) suggests that they may be the same.

Studies by Curtiss and Edgington (14) have demonstrated that lymphocytes possess a saturable surface receptor specific for LDL-In. LDL-In acts directly on the lymphocyte (13), and this lipoprotein can regulate the immune response in vivo (10, 11). There is a differential sensitivity of T-helper, T-suppressor, and B-lymphocytes to LDL-In (15), and recent studies (Chart 1) indicate that it can influence tumor survival and growth in experimental animals, apparently by virtue of its effects on the host immune response.

Non-plasma lipoproteins have also been implicated in immunoregulation. Yamazaki et al. (27) have demonstrated that VLDL and LDL but not HDL or the delipidated fractions of ascites fluid from MM46 tumor-bearing mice inhibit antibody-dependent, microphage-mediated tumor lysis in vitro.

While in some of these systems the existence of specific lymphocyte surface receptors for the regulatory lipoprotein has been demonstrated, the constituent of the lipoprotein that mediates the biological activity has not been determined, and a number of components are being considered currently, including cholesterol, oxygenated sterols, fatty acids, and glycolipids. Recent work in our laboratory has demonstrated that the biological effects of LDL-In do not result from oxygenated sterols or cholesterol but might be mediated by the polar lipids. It has recently been reported that the biologically active moiety of 2 previously described lymphokines produced by dividing human T-cells in culture, one an inhibitor of lymphocyte proliferation and immunoglobulin production and the other an enhancer of antibody production, are both polar lipids. Only a very limited number of reports are available regarding plasma lipoprotein levels in cancer patients. HDL was observed by Nydegger and Butler (24) to be significantly decreased in cancer patients, independent of the stage of cancer. A new proteolipid associated with cancer and with potential immunological properties has been extracted from HDL by Skipski et al. (25). Barclay et al. (1) observed that HDL concentrations were decreased in patients with cancer as well as in normal subjects with family histories of cancer. In a 5-year prospective study, 4 of 13 patients with family histories of cancer and low levels of HDL developed cancer, whereas none of the epidemiologically matched normal subjects with normal levels of HDL developed cancer.

Thus, a number of immune functions in vitro as expressed by both lymphocytes and macrophages may be significantly influenced by lipoproteins present in plasma or other extracellular fluids, and these lipoproteins and possibly their lipid constituents may play a biologically critical role in modulation of cellular function, including the immune response to tumors. In turn, the composition and concentration of lipoproteins are influenced by nutrition (23).

### References

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