Lipid transfer proteins

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Lipid transfer proteins were discovered in our laboratory as a result of studies that began with the question: How are lipid components of plasma lipoproteins taken up by the liver cell? It soon became apparent that these cells contained a cytosolic factor (1), which transferred PC from one membrane to another. Upon demonstrating that the factor was nondialyzable, heat-labile, and sensitive to trypsin, the factor was assumed to be a protein. In as much as the factor accelerated the transfer of PC between microsomes and mitochondria to approximately equal extents, the protein was named phospholipid exchange protein (2). Similar observations soon followed from other laboratories. In addition, the systematic efforts to purify the exchange protein uncovered the presence of a variety of proteins that could accelerate the transfer of different phospholipid classes and the less polar lipids as well. Moreover, under the proper conditions, the proteins were shown to mediate net transfer reactions as well as equimolar lipid exchanges. Hence, by agreement between the major groups working in this area, the designation of these proteins was changed to "lipid transfer proteins" for generic usage. The more specific designations, for example, would then be "PC-specific transfer protein", abbreviated as PC-TP and "nonspecific transfer protein", abbreviated ns-TP.

Most of the transfer proteins discovered thus far have been identified as cytosolic proteins in various tissues of animals and plants. One cannot exclude the possibility, however, that the proteins were originally membrane-associated, but were released by the homogenization procedure. Such an occurrence has been observed for a lipid transfer protein, which appears to be associated largely with the microsomal fraction, but that can be released by the treatment of microsomes with low ionic strength buffers (3). Even during the homogenization of liver with 250 mM sucrose, 50 mM Tris, 1 mM EDTA, some of this transfer activity is found in cytosol, but was probably microsomal in origin.

One other class of lipid transfer proteins is found in blood plasma of some animal species (4, 5), including human plasma (6–14). These proteins may be rather nonspecific (15) or may accelerate the transfer of phospholipid preferentially (16, 17).

In subsequent sections I intend to review the distribution of lipid transfer proteins, how these proteins have been utilized to study lipid asymmetry in biological and in artificial membranes, and the effect of membrane lipid modification on enzyme activities. Some of these aspects of lipid transfer protein biochemistry have also been reviewed recently (18). Methodologies of assays, as well as other topics, have been discussed by Zilversmit and Hughes (19), Wirtz (20), Wetterau and Zilversmit (21), Akeroyd and Wirtz (22), Kader (23, 24), Bloj and Zilversmit (25, 26), Bergelson and Barsukov (27), and Rothman and Lenard (28). From these reviews it is evident that many varieties of lipid transfer proteins have been discovered in animal and plant cells and a more limited number in unicellular organisms.

NOMENCLATURE

Although knowledge about substrate specificity of these proteins, their mechanism of action, and kinetic properties has increased greatly, there is as yet no documented view as to their physiological role. Several authors have speculated, however, that one or more of the intracellular lipid transfer proteins might be involved in membrane biogenesis and, more specifically, in the transport of newly synthesized lipids to their functional sites. In order to accomplish this role, a lipid transfer protein must be able to promote net lipid transfer and/or "hetero-exchange." Net transfer of PC between multilamellar phospholipid vesicles and high density lipoprotein has been demonstrated for the ns-TP from beef liver (29), and to a lesser extent for the transfer of PC between phospholipid vesicles in the presence of PC-

Abbreviations: PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PG, phosphatidylglycerol; PC-TP, phosphatidylcholine-specific transfer protein; similarly PI/PC-TP, phosphatidylinositol/phosphatidylcholine-specific transfer protein (also known as PI-TP); ns-TP, nonspecific phospholipid transfer protein (also known as ns-PL-TP).

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TP (30). Hetero-exchange, i.e., the catalyzed unidirectional transfer of one lipid, which is coupled to, or associated with, the transfer of a different lipid in the opposite direction, has been observed for the ns-TPs in liver (31), the PI/PC specific lipid transfer proteins in brain and heart muscle (32, 33), and for the plasma lipid transfer protein (9).

TISSUE DISTRIBUTION OF LIPID TRANSFER PROTEINS

Liver

A PC-specific transfer protein has been purified (34, 35) from liver. The extensive literature on the purification and characterization of this transfer protein has been reviewed by Wirtz (20, 36). The primary structure has been reported (37) and the lipid-binding site has been identified (38). A radioimmunoassay has been developed (39) and subcellular and tissue distributions were determined (40). Most of the transfer protein in liver was present in cytosol (60%). The highest levels of this transfer protein were exhibited in rat liver and intestinal mucosa, with lower levels in kidney, spleen and lung, and hardly any in heart and brain.

Liver contains other lipid transfer proteins as well. One of these is a ns-TP (26, 31, 41–45) that has been demonstrated to transfer all tested phospholipids (except cardiolipin) (46), glycosphingolipids, gangliosides (47), and cholesterol (31, 41, 48). This protein is probably identical to the sterol carrier protein (SCP-2), (48, 49). An additional glycolipid transfer protein was isolated from bovine spleen (50, 51) and may be present in rat liver cytosol as well (52). Pig liver probably contains several lipid transfer proteins, capable of accelerating the transfer of PC and PI (53, 54). Chicken liver has been found to contain PC-specific, and nonspecific- and sphingomyelin-specific lipid transfer proteins (55).

Brain and heart

A PI/PC-TP was purified from cytosol of beef brain (56, 57) and beef heart (33). From molecular weights, isoelectric points, and substrate specificities, the two organs appear to contain the same protein, which may also be present in the squid giant axon (58). The kinetics and phospholipid binding have been studied (59). Brain also contains a cytosolic protein that accelerates the transfer of glycolipids but not phospholipids (60, 61).

Tumors

The first lipid transfer protein purified from rat hepatoma 27 cells was named "universal lipid exchange protein" (62), but was characterized by a relatively high transfer activity for sphingomyelin. It differed in physical characteristics from the ns-TP from rat liver (41). Antibody to the transfer protein, found in hepatoma 27 cells, reacted with cytosol of various experimental tumors and of fetal rat liver, but only slightly with normal liver cytosol (63, 64). Morris hepatoma cells appear to contain little or no nonspecific-lipid transfer protein (65, 66). An increase in PC transfer activity may (65) or may not (39, 66) be present.

Lung

Several laboratories have studied lipid transfer proteins in lung, in part because of the presence of lung surfactant at the air/water interface of alveoli. The principal surfactant lipids are PC and PG. Thus it is of interest that lung transfer proteins for both lipid species have been described for rats (67–71), sheep (72), and rabbit (73).

Lipid transfer proteins in plant cells and bacteria

The presence of lipid transfer proteins in plant cells has been known since 1970 when Abdelkader and Mazliak (74) detected transfer activity in cauliflower florets and potato tubers. Recent advances in the isolation and characterization of lipid transfer proteins in plant materials have been reviewed by Kader, Douady and Mazliak (23). Active transfer was observed in castor bean endosperm for PC (75) and PE (76). The transfer protein from maize seedlings was purified to homogeneity (77). It has a molecular weight of 20,000, a pI of 8.8, and transfers PC, PI, and PE. Several lipid transfer proteins were also purified from spinach leaves (23, 78). Yeast cytosol contains transfer activities for PI and PC (79), and *Rhodopseudomonas sphaeroides* for PC, PE, and PG (80).

EXCHANGE VERSUS NET TRANSFER

As indicated earlier, the ns-TP is capable of redistributing the mass of total and of individual phospholipids between membranes. The distinction between transfer proteins was clearly evident when multilamellar vesicles, composed of PC and cardiolipin (9/1, mol/mol), were incubated with human plasma high density lipoproteins. The addition of PC-specific or the PI/PC-TP resulted in the transfer of PC from multilamellar vesicles to lipoproteins which equalled that in the reverse direction, i.e., an apparent exchange reaction. However, the addition of ns-TP resulted in the transfer of three times as much PC into the lipoproteins as was returned to the vesicle fraction. This net transfer was not the result of fusion of donor and acceptor particles as indicated by nonexchangeable markers.

The preponderant transfer of PC in one direction in the presence of ns-TP, under the same conditions in

which the more specific transfer proteins carry out a strict exchange reaction, appears to show that the mechanisms whereby lipid transfer is accelerated by different proteins are not the same. From studies on lipid/protein interaction one may conclude that the PC-TP and the PI/PC-TPs bind phospholipids (20). These results suggest that the efficiency of lipid transport in one direction depends on the availability and type of lipid transported in the reverse direction. A similar "coupled" transport of lipids between lipoproteins, in the presence of the plasma lipid transfer protein, has been observed (for a detailed discussion and additional references cf. 9). On the other hand, the occurrence of net phospholipid transfer in the presence of the ns-TP suggests that the mechanism whereby this protein accelerates lipid transfer differs from that of the more specific lipid transfer proteins.

ALTERATION OF MEMBRANE LIPID COMPOSITION

Cytosolic lipid transfer activity has been used to label cultured neuroblastoma cells with radioactive PC and sphingomyelin for the study of cellular lipid degradation (81, 82). Platelet phospholipids have been enriched in linoleyl-phospholipids by incubation with vesicles in the presence of phospholipid transfer protein (83). Transfer proteins have also been used to alter the composition and/or fluidity of membranes. In human erythrocyte ghosts, for example, cholesterol content could be decreased and PC increased by incubation of these membranes with PC vesicles in the presence of ns-TP from beef liver (84). In similar incubations, rat synaptic plasma membranes showed altered cholesterol/phospholipid ratios (85). In rat liver mitoplasts (inner mitochondrial membrane plus matrix), incubated with phospholipid vesicles and ns-TP, PC content increased and PE decreased markedly resulting in a 20–35% increase in total mitoplast phospholipids (29, 86).

DO MEMBRANE LIPIDS AFFECT ENZYME ACTIVITIES?

Rat liver microsomes, when incubated with sonicated phospholipid vesicles of different composition in the presence of ns-TP, will undergo marked changes in lipid content (86–88). Glucose-6-phosphatase activities did not appear to depend on microsomal cholesterol or phosphatidylinositol content. Enzymatic activities were inhibited slightly by increasing the fatty acid saturation of PC and were lowered more extensively by partial loss of microsomal PE. Others (89) have described a dependence of this microsomal enzyme on phosphatidylserine as well as PE in normal liver and hepatoma. In contrast, liver microsomal pyrophosphatase was not affected by these lipid substitutions (90). Lipid modifications of rat liver microsomes by means of the lipid transfer reaction led to a decreased cytochrome P-450 activity when lysoPC was introduced followed by a reactivation when PC was introduced subsequently (91, 92).

It is also possible to modify mitochondrial enzyme activities by lipid alterations. Mitochondria from hepatoma 27 show both an abnormally low PC content and a lower than normal activity of monoamine oxidase. The introduction of additional PC by the lipid transfer reaction resulted in increased enzyme activity (93).

A role for lipid transfer proteins in supplying membrane-bound enzymes with relatively insoluble substrates has also been observed. For example, SCP_2 (94) or the ns-TP, which were shown to be identical, increased the esterification of cholesterol by rat liver (95) and by hepatoma (96) microsomes. This protein also stimulated adrenal mitochondrial pregnenolone synthesis from cholesterol of adrenal lipid droplets (97). Alteration of phospholipid fatty acid composition by the lipid transfer reaction also altered microsomal cholesterol esterification (98). This could not be accounted for entirely by changes in membrane fluidity.

MEMBRANE STRUCTURE DETERMINATION WITH LIPID TRANSFER PROTEINS

Johnson, Hughes, and Zilversmit (99) used lipid transfer activity to measure PC asymmetry in small unilamellar vesicles. Two findings emerged from this study: *1*) due to curvature of the vesicles, about twice as much PC was present in the outer than in the inner leaflet of the bilayer, and *2*) little or no phospholipid translocation across the bilayer (flip-flop) took place. This observation was extended to phospholipid vesicles of different sizes (100, 101) and to vesicles containing labeled cholesterol (102) and other phospholipid species (31, 33, 103). This and similar work from other laboratories have been reviewed (18, 20, 25, 27, 28, 36, 104).

When similar techniques were applied to biological membranes, the results differed from those observed in lipid vesicles. For example, bilayer translocation of phospholipid in normal human red blood cells was very slow, but was accelerated in sickled cells (105). In rat erythrocytes the translocation $t_{1/2}$ spanned an interval of 2–7 hr (46, 106, 107), and in rat liver microsomes the translocation $t_{1/2}$ was less than 30 min (108–110) and was similarly rapid for rat sarcoplasmic reticulum (111). In part, the presence of transmembrane proteins might account for the more rapid translocation of lipid (112) as well as for lipid asymmetry. The presence of nearly

all of the PE on the cytosolic side of the erythrocyte, whereas both PC and sphingomyelin are present primarily in the outer portion of the membrane, probably exclude the type of mechanisms that depend upon the maintenance of asymmetry by active transport. Instead, it seems probable that the segments of protein protruding from the bilayer create a free energy gradient or a biphasic environment in which the lipids exhibit a dynamic equilibrium while maintaining unequal concentrations on the two sides of the membrane.

The work from our laboratory, described in this report, was supported in part by HL 10940 from the National Heart, Lung, and Blood Institute of the U.S. Public Health Service.

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