Scavenger Receptor-mediated Uptake and Metabolism of Lipid Vesicles Containing Acidic Phospholipids by Mouse Peritoneal Macrophages*

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We studied the mechanism of uptake and metabolism of exogenous phospholipids in mouse peritoneal macrophages using vesicles composed of various phospholipids and cholesterol. Macrophages in culture were found to actively incorporate and metabolize phosphatidylycholine/cholesterol vesicles containing small amounts of acidic phospholipids such as phosphatidylycholine, phosphatidylinositol, or phosphatic acid and to store the fatty acyl chains and cholesterol in triacylglycerol and cholesteryl ester form in their cytosol. These cells exhibited massive amounts of oil red O-positive lipid droplets, a typical feature of foam cells. The metabolism of exogenous phospholipid vesicles was completely inhibited by chloroquine and cytochalasin B, suggesting that vesicle uptake occurs by endocytosis. A similar type of metabolism was observed in guinea pig peritoneal macrophages, macrophage cell line J774.1, but not in Swiss 3T3 fibroblasts.

Competition studies using various ligands for the scavenger receptor showed that acetylated low density lipoprotein (acetyl-LDL), dextran sulfate, or fucoidan was able to compete for up to 60% of the binding of phosphatidylyserine-containing vesicles, and that copper-oxidized LDL (oxidized LDL) competed for more than 90% of the vesicle binding. On the other hand, phosphatidylyserine-containing vesicles was able to compete for more than 90% of the binding of acetyl-LDL. These results indicate that acidic phospholipids are recognized by the scavenger receptors on the surface of macrophages and that more than one scavenger receptor exists on mouse peritoneal macrophages, i.e. one capable of recognizing acetyl-LDL, oxidized LDL, and an array of acidic phospholipids on membranes, and the other recognizing both acidic phospholipids and oxidized LDL but not acetyl-LDL.

Phospholipids in the plasma membrane of mammalian cells are not homogeneously distributed between both halves of the membrane bilayer (1–3). In intact cells, the outer surface of the membrane is characterized by the presence of neutral phospholipids, particularly phosphatidylycholine and sphingomyelin. The negatively charged phospholipids, such as phosphatidylyserine and phosphatidylinositol, are almost exclusively located in the inner leaflet of the bilayer. It has been demonstrated that phosphatidylyserine plays a crucial role in the recognition and clearance of damaged cells by resident macrophages such as Kupffer cells (4, 5), although little is still known about the mechanism of this recognition.

There is increasing evidence that macrophages play an important role in the development of early atherosclerotic lesions (6–9). The neutral lipid-laden foam cells that are typically found in atherosclerotic lesions of the arterial wall are known to be derived, at least in part, from macrophages that have become engorged with cholesteryl ester-rich lipoproteins. One of the critical questions that arises here is what the ligand in nature is responsible for the development of foam cells. Native low density lipoprotein (LDL)1 taken up through the apo-B/E receptor is not an effective cholesterol donor for foam cell formation. It has been shown that LDL acquires the capacity to induce foam cell formation by various modifications including acetylation (10), acetoacetylation (11), conjugation with malondialdehyde (12), and oxidation induced by either endothelial cells or copper ions (13–17). The uptake of these modified forms of LDL is mediated by so-called scavenger receptors on the surface of macrophages. Scavenger receptors have also been found on the surface of endothelial cells of rat liver sinusoids and bovine aorta (18, 19).

Recently, Skarlatos et al. (20) reported that activated platelets or particles released from them caused foam cell formation by cultured macrophages, although the mechanism of this process was not fully characterized. It is also well known that the transverse distribution of phospholipids in the plasma membrane is changed in such a way that a substantial amount of negatively charged phospholipids become exposed on the membrane outer surface upon stimulation (21).

These observations prompted us to study the mechanism of macrophage recognition and metabolism of membranes with exposed acidic phospholipids. For this we utilized artificial phospholipid vesicles as a model membrane by exploiting their ability to incorporate phospholipids of defined composition and also radioactive substrates. It was found that phospholipid vesicles containing acidic phospholipids such as phosphatidylyserine, phosphatidic acid, or phosphatidylinositol were effectively metabolized via the scavenger receptors of macrophages, inducing foam cell formation. The results suggest that more than one type of scavenger receptor in mouse peritoneal macrophages is involved in the uptake of membrane-exposed acidic phospholipids.

**MATERIALS AND METHODS**

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1 The abbreviations used are: LDL, low density lipoprotein; HBSS, Hank's-buffered salt solution.

MATERIALS AND METHODS

Chemicals—Dulbecco's modified Eagle medium, RPMI-1640, penicillin (10,000 units/ml), streptomycin (10,000 units/ml), and new-
born calf serum were obtained from Flow Laboratories Inc. Glutamine (200 mM) solution and fetal bovine serum were obtained from GIBCO. Hank's buffer salt solution (HBSS) was obtained from Nissui Pharmaceutical Co., Ltd., Japan. GIT medium, a serum-free medium for cell culture containing basal medium (a mixture consisting of an equal volume of Ham's F-12 medium and Iscove's medium), partially purified and desiccated from bovine serum, ferrin, ethanolamine, and sodium selenite, was purchased from Nippon Seiyaku Co., Ltd., Osaka, Japan. ID[1-14C]Palmitoyl-glycercophosphocholine (100-120 mCi/mmol) was purchased from Amer sham, United Kingdom. Cholesterol, dietylphosphate, sphingomyelin, cytochalasin B, chloroquine, and fucoidan were purchased from Sigma Chemical Co., St. Louis, MO. Phosphatidylethanolamine and phosphatidylcholine were prepared from egg yolk phosphatidylcholine by transphosphatidylation catalyzed by phospholipase D from Actino madura sp. (22). Phosphatidylserine (22) and phosphatidylinositol (24) were purified from bovine brain and baker's yeast by column chromatography, respectively.

Cells—Female ICR mice (25-30 g) were obtained from Shizukou Animal Center, Hamamatsu, Japan. Mouse peritoneal macrophages were prepared as follows. Peritoneal cells were harvested from unstimulated mice using HBSS. The peritoneal exudate from 9 to 11 mice (5-10 x 10⁶ cells/mouse) was pooled, and the cells were collected by centrifugation (400 x g, 5 min, 4 °C) and washed once with 10 ml of HBSS. The cells were resuspended at 2 x 10⁶ cells/ml in GIT medium. Aliquots (1 ml) were dispensed into a 12-well plastic microplate and incubated at 37 °C for 2 h. Each plate was washed three times with HBSS, and the dried lipids were usually dispersed with a vortex mixer and incubated in a humidified CO2 (5%) atmosphere at 37 °C. After 2 h, each plate was washed once with HBSS, and the dried lipids were immediately replaced with 1 ml of Dulbecco's modified Eagle's medium containing 6% lipoprotein-deficient serum, penicillin (100 units/ml), and streptomycin (100 µg/ml) (hereafter referred to as medium A). Lipoprotein-deficient serum was prepared from fetal bovine serum according to the standard procedure (25). Guinea pig peritoneal macrophages were isolated from bovine peritoneal lavage according to the standard procedure and maintained in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum, penicillin (100 units/ml), and streptomycin (100 µg/ml) (26). Porcine aortic endothelial cells were prepared by the method of Nechi et al. (27). Porcine aortic endothelial cells and Swiss 3T3 fibroblasts were maintained in the same medium as that used for culture of guinea pig peritoneal macrophages. Monolayer cultures of 3774.1 cells were grown and maintained in RPMI-1640 containing 10% calf serum, penicillin (100 units/ml), and streptomycin (100 µg/ml).

Preparation of Phospholipid Vesicles—Multilamellar phospholipid vesicles were prepared as described previously (28). A mixture of the desired lipids in chloroform was placed in a test tube. The solvent was removed in a rotary evaporator at about 40 °C under reduced pressure. The dried lipids were usually dispersed with a vortex mixer in 0.3 M glucose solution at 40-50 °C. The vesicles for the competition study were prepared as follows. Multilamellar vesicles prepared as above were washed three times with HBSS, and the dried lipids were dispersed in a solution of 0.1 M sodium dodecyl sulfate. An aliquot was taken for the determination of neutral lipids (triacylglycerol, cholesteryl ester) the plate was developed with hexane/ethyl ether/acetic acid (70:30:1 by volume). Each spot was located by staining with iodine vapor and scraped into a liquid scintillation vial in order to count the radioactivity. For determination of the amount of triacylglycerol and cholesteryl ester, the spots on the plate were scraped off and the lipid was extracted again by the method of Bligh and Dyer (29). Lipoproteins—LDL (density 1.019-1.050 g/ml) from fresh human plasma was isolated by preparative ultracentrifugation (30). Acetyl-LDL was prepared by incubating LDL with acetic anhydride as described by Basu and co-workers (30). Oxidized LDL was prepared by incubating LDL with 100 µM CuSO4 in phosphate-buffered saline at 37 °C for 24 h (31). 14C-Labeled LDL and acetyl-LDL were prepared by the iodine monochloride method (32).

Cellular Neutral Lipid Staining—Macrophages were cultured in a tissue culture chamber (8 chambers, Miles Scientific) with exogenous phospholipid vesicles or acetyl-LDL as described above. After 36 h, the cells were washed three times with phosphate-buffered saline and then fixed by soaking the cells in 3-4% formalin. Nuclei and intracellular neutral lipid droplets were stained with hematoxylin and oil red O, respectively. The stained cells were examined by light microscopy at x 400 magnification.

Other Analytical Methods—Protein concentration was determined using BCA protein assay reagent from Pierce Chemical Co. Cholesterol (33) and triacylglycerol content was measured as nmol of fatty acyl chains by the method of Nakagawa et al. (34) after alkaline hydrolysis.

RESULTS

Effect of Phospholipid Composition on the Cellular Uptake and Metabolism of Exogenous Phospholipid Vesicles—The association of vesicles with the cells was found to be dependent on vesicle composition (Fig. 1A). Vesicles containing phosphatidylcholine, phosphatidylethanolamine, or sphingomyelin did not show appreciable binding to the macrophages. In contrast, efficient association was observed for vesicles containing phosphatidylserine, phosphatidylinositol, or phoshocephosphocholine (200 mCi/mmol). After 3 h of incubation, phosphatidylinositol and triacylglycerol content was expressed as nmol of 14C-palmitate/mg cellular protein. Each value is the average of duplicate incubations. The abbreviations used in the figure are: PS, phosphatidylserine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PA, phosphatic acid; PC, phosphatidylcholine; SM, sphingomyelin.
A novel study investigated the uptake and metabolism of exogenous vesicles by macrophages. Macrophages were further examined using phosphatidylserine-containing vesicles. The association of the vesicles became almost maximal at 5-10% of phosphatidylserine in phospholipid vesicles. The accumulation of neutral lipids in the cells was time-dependent (Fig. 3). After 32 h, the amounts of cellular triacylglycerol and cholesteryl ester were increased approximately 7-fold (from 26 to 188 nmol fatty acyl chains/mg protein) and 20-fold (from 2 to 40 nmol/mg protein), respectively. When these macrophages were stained with oil red O, massive amounts of neutral lipid droplets were found in their cytosol, in contrast to the macrophages incubated with vesicles composed exclusively of phosphatidylcholine (Fig. 4). This morphological feature was very similar to that of macrophages incubated with acetyl-LDL, which is known to induce formation of foam cells. These results suggest that vesicles containing phosphatidylserine are able to induce foam cell formation from cultured macrophages. The requirement for acidic phospholipid such as phosphatidylserine in cellular association and the metabolism of exogenous phospholipid vesicles indicates the presence of a mechanism for the recognition of such phospholipids in macrophages.

Effects of Cytochalasin B and Chloroquine on the Metabolism of Phospholipid Vesicles by Macrophages—To study the pathway for the metabolism of exogenous phospholipid vesicles containing acidic phospholipid, the effects of cytochalasin B, a known inhibitor of endocytosis (35), and chloroquine, a known inhibitor of lysosomal degradative process (36, 37), were examined. Although the association of the phosphatidylserine-containing vesicles was not significantly affected by either of these drugs, the formation of neutral lipid was almost completely suppressed (Fig. 5).

Association of Phosphatidylserine-containing Vesicles with Various Types of Cells and Their Metabolism—Binding of phosphatidylserine-containing vesicles and neutral lipid production were observed not only with mouse peritoneal macrophages but also with guinea pig macrophages and macrophage cell line J774.1 (Table I). In contrast, neither association of phosphatidylserine-containing vesicles nor formation of neutral lipids was observed with Swiss 3T3 fibroblasts. Porcine aortic endothelial cells bound the vesicles but did not metabolize them appreciably, as evident from the poor formation of neutral lipids during culture. Macrophages from the peritoneal cavity of mouse or guinea pig as well as J774.1 cells are known to possess scavenger receptors and to metabolize acetyl-LDL. Endothelial cells, which also possess scavenger receptors and bind acetyl-LDL, do not, however, accumulate neutral lipids (19). The present findings suggest that scavenger receptors on either macrophages or J774.1 cells are involved in the process leading to metabolism of phosphatidylserine-containing phospholipid vesicles.

Competition by LDLs for the Binding of Phosphatidylserine-containing Vesicles to Macrophages—It was next examined whether the binding of phosphatidylserine-containing vesicles to macrophages was inhibited by chemically modified LDL and other ligands which compete for binding to the scavenger receptor. In this experiment, we used VETS of reasonably homogeneous diameter centered around 100 nm (see “Materials and Methods”), since multilamellar vesicles have a broad size distribution and most of them are sedimented to the bottom of the well during incubation with cells. VETS containing acidic phospholipids were able to induce neutral lipid accumulation by the cells, as in the case of multilamellar vesicles (data not shown). Unlabeled acetyl-LDL, oxidized LDLs, and native LDL were tested for their ability to compete for the cell binding of the radiolabeled phosphatidylserine-containing vesicles (Fig. 6). Oxidized LDL effectively inhibited the binding of phosphatidylserine-containing vesicles, whereas native LDL, which is not a ligand for the scavenger receptor, was unable to inhibit the binding. Acetyl LDL inhibited the binding at a maximum of 60% even at the highest...
Uptake and Metabolism of Lipid Vesicles by Macrophages

Fig. 4. Light microscopic appearance of macrophages incubated with phospholipid/cholesterol vesicles or acetyl-LDL. 5 x 10^6 peritoneal cells were dispensed into tissue culture chambers, incubated for 2 h at 37 °C, and washed three times with HBSS. Macrophage monolayers thus obtained were incubated in 0.2 ml of medium A containing phospholipid/cholesterol vesicles (A and B) (37 nmol lipids/well) or acetyl-LDL (C) (20 μg of protein/well) for 36 h. The vesicles were composed of phosphatidylcholine, phosphatidylserine, cholesterol, and dicetylphosphate at a molar ratio of 50:50:75:10 (A), or 100:0:75:10 (B). After incubation, the cells were washed three times with cold phosphate-buffered saline. Fixation and staining with oil red O and hematoxylin were performed as described under “Materials and Methods.” Magnification, × 400.

Fig. 5. Effect of cytochalasin B and chloroquine on the metabolism of phosphatidylserine-containing vesicles. Macrophage monolayers obtained from 2 x 10^6 cells were incubated in 1 ml of medium A with radiolabeled phospholipid/cholesterol vesicles composed of phosphatidylcholine, phosphatidylserine, cholesterol, dicetylphosphate, and 1,2-di[l-14C]palmitoyl-glycerophosphocholine at a molar ratio of 50:50:75:10:0.5 in the absence or presence of indicated amounts of either cytochalasin B (A) or chloroquine (B). After 10 h of incubation, formation of [14C]triacylglycerol (C) and [14C]cholesteryl ester (D) was determined as described under “Materials and Methods.” Each value is the average of duplicate incubation and is expressed as a percentage of that obtained in the absence of the drugs. The 100% values for the formation of triacylglycerol and cholesteryl ester were 0.07 nmol of [14C]-palmitate/mg cell protein and 0.04 nmol of [14C]-palmitate/mg cell protein, respectively.

Table I

Ability of various cells to bind and metabolize phosphatidylserine-containing vesicles

Cells were grown in the appropriate medium as described under “Materials and Methods.” Each cell type was incubated for 24 h at 37 °C in 1.0 ml of medium A with radiolabeled phospholipid/cholesterol vesicles (186 nmol lipids/well) composed of phosphatidylcholine, phosphatidylserine (PS), cholesterol, dicetylphosphate, and 1,2-di[l-14C]palmitoyl-glycerophosphocholine with a molar ratio of 50:50:75:10:0.5. The association of vesicles and the formation of neutral lipids (triacylglycerol plus cholesteryl ester) were expressed as nmol of [1-14C]palmitate/mg cellular protein.

<table>
<thead>
<tr>
<th>Cells</th>
<th>Association of PS-liposome</th>
<th>Formation of neutral lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse peritoneal macrophages</td>
<td>0.85</td>
<td>0.35</td>
</tr>
<tr>
<td>Guinea pig macrophages</td>
<td>1.03</td>
<td>0.16</td>
</tr>
<tr>
<td>J774.1 cells</td>
<td>1.25</td>
<td>0.29</td>
</tr>
<tr>
<td>Forcine aortic endothelial cells</td>
<td>0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>Swiss 3T3 cells</td>
<td>0.03</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Fig. 6. Ligand concentration. Dextran sulfate and fucoidan, which are known to inhibit completely the binding of [125I]-acetyl-LDL to cells (10), inhibited the binding of phosphatidylserine-containing vesicles at a maximum of approximately 60% (data not shown). The binding of [125I]-acetyl-LDL was almost completely inhibited by phosphatidylserine-containing vesicles (Fig. 7). In addition, oxidized LDL was able to block the rest of the binding of the vesicles which was not inhibited by acetyl-LDL (Table II). The binding of phosphatidylinositol- or phosphatidic acid-containing vesicles to macrophages was inhibited by both oxidized and acetyl-LDL in a similar manner to phosphatidylserine-containing vesicles (Fig. 8).

Discussion

We have studied the mechanism of uptake and metabolism of exogenous liposomal lipids such as phospholipid and cholesterol by cultured mouse peritoneal macrophages. Macrophages did not incorporate or metabolize exogenous phospholipid vesicles to any significant extent, unless the vesicles...
obtained from 1 X 10^6 peritoneal cells were incubated at 37 °C in 0.5 ml of medium A containing 25 μM chloroquine with radiola beled phospholipid/cholesterol vesicles (93 nmol lipids/well) and the indicated amounts of competing compounds. The composition of the vesicles was the same as described under Fig. 5. After 4 h of incubation, the cells were washed, and the radioactivity associated with them was measured. Each value is the average of duplicate incubations and is expressed as a percentage of that obtained in the absence of competing compounds. The 100% value for binding was 9.84 nmol of ^14C-palmitate/mg cell protein.

Macrophage monolayers obtained from 1 X 10^6 peritoneal cells were incubated at 37 °C in 0.5 ml of medium A containing 25 μM chloroquine with the radiola beled phospholipid/cholesterol vesicles (93 nmol lipids/well) and the indicated amounts of competing compounds. The composition of the vesicles was the same as described under Fig. 5. After 4 h of incubation, the cells were washed, and the radioactivity associated with them was measured. Each value is the average of duplicate incubations and is expressed as a percentage of that obtained in the absence of competing compounds. The 100% value for binding was 1.08 nmol of ^14C-palmitate/mg cell protein.

TABLE II

<table>
<thead>
<tr>
<th>Competing compounds</th>
<th>Binding of ^14C-vesicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg protein/ml</td>
<td>% of control</td>
</tr>
<tr>
<td>Acetyl-LDL (0)</td>
<td>100.0</td>
</tr>
<tr>
<td>Acetyl-LDL (0.4)</td>
<td>46.8</td>
</tr>
<tr>
<td>Acetyl-LDL (0.4)</td>
<td>+ Acetyl-LDL (0.1) 50.0</td>
</tr>
<tr>
<td>+ Acetyl-LDL (0.9)  42.2</td>
<td></td>
</tr>
<tr>
<td>Oxidized LDL (0.4)  15.3</td>
<td></td>
</tr>
<tr>
<td>+ Oxidized LDL (0.9) 9.8</td>
<td></td>
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It was suggested from the following observations that phospholipid vesicles bearing exposed acidic phospholipids such as phosphatidylserine, phosphatidyllysino- sitol, or phosphatidic acid, efficient association with macrophages was observed. Incubation under the present conditions caused massive intracellular accumulation of neutral lipids, and the cells showed the typical features of foam cells. These results suggest that not only modified plasma lipoproteins but also membrane fragments bearing exposed acidic phospholipids could be taken up by macrophages, inducing foam cell formation. By using phospholipids radiolabeled at their fatty acyl portions, which were incorporated into vesicles, we found that macrophages in culture actively incorporate and metabolize phosphatidylserine-containing vesicles, and that fatty acyl chains derived from the phospholipids are reutilized for the synthesis of cellular triacylglycerol and cholesteryl esters, both of which are eventually stored in the cytosol. The metabolism of the vesicles was almost completely inhibited by either cytochalasin B or chloroquine. The results suggest that endocytosis and lysosomal hydrolysis are involved in the process. Phospholipids in vesicles taken up by the macrophages would be hydrolyzed by lysosomal phospholipases, and free fatty acids produced in the lysosomes might be predominantly reutilized for the synthesis of both triacylglycerols and cholesteryl esters.

It was suggested from the following observations that phospholipid vesicles bearing exposed acidic phospholipids such as phosphatidylserine on their surface might be recognized by the scavenger receptors on macrophages. 1) Cells expressing scavenger receptors were able to effectively metabolize phospholipids of vesicles containing acidic phospholipid. 2) Ligands for scavenger receptors such as acetyl-LDL, oxidized LDL, dextran sulfate, and fucoidan competed for the binding
of the vesicles to the macrophages. It should be stressed here, however, that acetyl-LDL, dextran sulfate, or fucoidan competed only partially for the vesicle binding, whereas the competition shown by oxidized LDL was almost 100%. Quite recently, it was proposed that mouse peritoneal macrophages may compete at least two classes of scavenger receptor: one is a receptor recognizing both acetyl-LDL and oxidized LDL, and the other is a receptor recognizing oxidized LDL but not acetyl-LDL.(38) Phosphatidylserine-containing vesicles shared a common feature with oxidized LDL; both competed almost completely for binding to each other.

It is widely accepted that scavenger receptors may recognize the anionic surface of a ligand. Acetylation or oxidation of LDL causes an increase of net anionic charge by blocking the amino groups of apoprotein B. Acquisition of a net negative charge is not, however, the only factor involved in recognition by the receptor, since polyanionic substances such as heparin, polyadenylic acid, and polycytidylic acid are not good receptor ligands (39). Net negatively charged residues located at a certain distance may be recognized by the receptor. Phospholipid vesicles bearing exposed acidic phospholipid on their surface may provide a proper environment for recognition by the scavenger receptor. Recognition of phosphatidylserine by macrophages has been reported by several groups. For example, Raz et al. (40) reported that multilamellar vesicles consisting of phosphatidylserine, phosphatidylcholine, and lyso-phosphatidylinositol as well as phosphatidylserine are also recognized by macrophages via scavenger receptors. These results support the idea that the molecular structure of phosphatidylserine may not be recognized by the receptor, whereas the array of acidic phospholipids on the membrane may be recognized.

The density of acidic phospholipids in membranes is important, and 5% of the acidic phospholipid in the vesicles is enough for recognition. Phosphatidylserine is known to be located in the inner leaflet of the plasma membrane, and its content in the plasma membrane is 10–20% depending on cell type. It has been shown previously that activation of platelets by physiologic stimuli results in exposure of a substantial amount of phosphatidylserine on the membrane outer surface (21). Recently Skarlatos et al. (20) have reported that activated platelets and the vesicles released from them induced foam cell formation by cultured macrophages or aortic smooth muscle cells. In addition, platelets from patients with hypercholesterolemia possess a high intracellular level of cholesterol ester (41). Deteriorated cells, which are accumulated in damaged peripheral vessels, as well as activated cells including platelets, may bear phosphatidylserine exposed on their surface and thus could be taken up by macrophages via the scavenger receptor pathway. This process may contribute at least partially to the induction of foam cell formation.

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Scavenger receptor-mediated uptake and metabolism of lipid vesicles containing acidic phospholipids by mouse peritoneal macrophages.
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