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Review

Cellular phospholipid uptake: Flexible paths to coregulate the functions of intracellular lipids

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ABSTRACT

Mammalian and arthropod cells acquire phospholipids by protein-mediated pathways that comprise selective and whole particle uptake routes. Phospholipid uptake critically supports cellular incorporation of nutrition-derived polyunsaturated fatty acids. It can occur jointly with cholesterol uptake, but intracellular processing of phospholipids is distinctively different from sterol processing. The newly imported phospholipids are utilized for production of bioactive lipids, such as thromboxane A_2 and lyso phosphatidic acid, and for synthesis of triacylglycerol. Class B scavenger receptor BI (SR-BI) represents a major mediator of the uptake of various phospholipids. The related scavenger receptor CD36, as shown here, also facilitates cellular phospholipid uptake. CD36 supports import of the choline phospholipids phosphatidylcholine (PC) and sphingomyelin (SM), but not of phosphatidylethanolamine (PE). Other transferases trigger cellular uptake of selective phospholipids, such as phosphatidic acid (PA) phosphatases that facilitate PA import and thereby modify cell survival and synaptic transmission. Phospholipid uptake depends on the activation status of cells. Activation of blood platelets indeed increases PE uptake. This is mediated by the serpin protein C inhibitor (PCI) and enhances thrombin formation. Exchange of phospholipids between blood cells and lipoproteins partially adjusts the lipid distribution pattern of blood cells to the one of lipoprotein particles. This in turn modifies the activities of cell membrane sodium transporters and could thereby contribute to sodium flux alterations in the metabolic syndrome. The in vivo relevance of phospholipid uptake in humans is indicated by comparable and reversible changes in the same phospholipid species in both lipoproteins and cells after rapid removal of low-density lipoproteins. Finally, cells also incorporate oxidized (pathogenic) phospholipids using partially overlapping entry pathways as native phospholipids which might support the ability of oxidized lipids to promote atherothrombosis.

1. Introduction

Phospholipids are essential building blocks of cellular membranes. Almost all cell functions accomplished at the level of the plasma membrane and of intracellular membranes are directly or indirectly regulated by changes in the localization and structure of phospholipids. Correspondingly, phospholipids are rapidly metabolized in response to interactions of extracellular signal mediators such as growth factors with their plasma membrane receptors. This is mediated by phospholipid-degrading enzymes, including, for example, phospholipases A_2 (PLA_2) that release polyunsaturated fatty acids from cell membrane phospholipids. These in turn can be metabolized to bioactive intra- or extracellular messenger molecules such as eicosanoids. Also, changes in cell activation and morphology are paralleled by a remodelling of the lateral and transverse organization of membrane phospholipids. This shapes such diverse processes as T cell receptor activation and pathogen internalization (via local accumulation of SM) contributing to plasma membrane domain formation [1], as well as apoptosis and blood coagulation (by inducing cell surface exposure of phosphatidylserine (PS) [2]). To ensure the precise functioning of these processes, a tight regulation of the intracellular localization and metabolism of phospholipids is required. This could be eminently supported by the uptake of extracellular phospholipids. Phospholipid uptake can in principle occur by two different mechanisms, whole donor particle uptake or selective uptake routes. Work performed in the last decade or so shows that cells acquire phospholipids to a substantial degree by selective uptake pathways (Fig. 1A). Thereby, phospholipids are transferred

Abbreviations: PC, phosphatidylcholine; PE, phosphatidylethanolamine; PA, phosphatidic acid; PI, phosphatidylinositol; SM, sphingomyelin; PS, phosphatidylserine; PL, phospholipid; DAG, diaclyglycerol; AA, arachidonic acid; PEMT, PE-*N*-methyltransferase; DGAT2, diacylglycerol: acyl-CoA acyltransferase; PAP, PA phosphatases; PLC, phospholipase C; PLA_2, phospholipase A2; SR-BI, class B scavenger receptor BI; PCI, protein C inhibitor; CTAP-III, connective tissue-activating peptide III; TXA_2, thromboxane A_2; COX-1, cyclooxygenase-1; HDL, LDL, VLDL, high, low and very low-density lipoproteins; PGPC, 1-palmitoyl-2-glutaroyl-PC; POVPC, 1-palmitoyl-2-(5-oxovaleroyl)-PC

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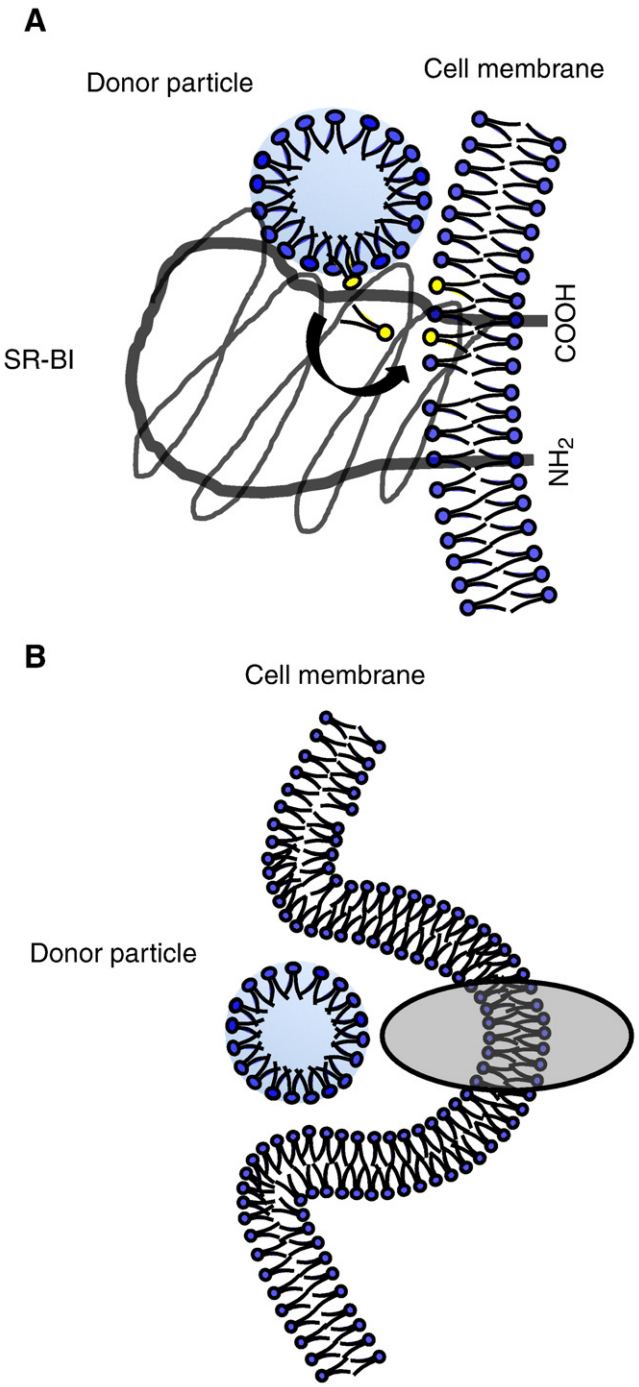

Fig. 1. Selective uptake and whole particle-entry of phospholipids into cells. A, By means of selective phospholipid transfer, specific phospholipids are extracted from extracellular donor particles and subsequently inserted into the cell membrane. Among the mediators of selective uptake are class B scavenger receptors such as SR-BI which consist of a large extracellular domain that performs the lipid transfer, two transmembrane domains and cytoplasmic N- and C-terminal portions. Donor particles can be plasma lipoproteins in which phospholipids form the surrounding monolayer. The scheme illustrates the principle of selective uptake, but is not meant to indicate its exact mechanism. B, In contrast to selective transfer, whole particle uptake results in the internalization of all particle-embedded lipid species into cells. This internalization which is in particular mediated by transmembrane proteins (as indicated) occurs in general via endocytic pathways.

directly from extracellular donors into the cell membrane, most likely primarily into the extracellular leaflet of this membrane. The selective uptake pathway, which does not involve internalization of the entire particles, is supported by a distinct group of proteins. After their incorporation, the newly acquired phospholipids can induce fast and dynamic changes in the phospholipid architecture of the cell membrane and subsequently also in intracellular membranes. Importantly, by means of selective phospholipid uptake, the membrane distribution of phospholipids can be rapidly adapted to the demands of a distinct cell function. In addition to selective uptake pathways, cells can incorporate entire lipid particles (e.g. plasma lipoproteins) which are generally mediated by endocytosis/phagocytosis and results in an unspecific incorporation of all particle lipids, including phospholipids (Fig. 1B). The present review aims at summarizing the functions, consequences, pathological alterations and mechanisms of phospholipid uptake into cells.

2. Blood cells acquire polyunsaturated fatty acids via phospholipid uptake

Blood circulation has evolved during metazoan evolution to supply distantly located cells with cell survival factors (such as oxygen and glucose) and to remove degradation products of cell metabolism (such as CO_2). Any loss of blood from blood vessels threatens to impair the supply of nutrients to organs. To prevent this, blood platelets are rapidly recruited to blood vessel injuries and enable the build-up of a thrombus that provides a provisional closure of the wound. Within the blood stream, platelets are exposed to circulating lipoproteins (as all other blood cells). These lipoproteins are mainly represented by low-density lipoproteins (LDL) and high-density lipoproteins (HDL) in humans.

Lipoproteins mediate the exchange of lipids between different organs and are hence main extracellular carrier of phospholipids in blood, lymph and interstitium. Within the lipoprotein structure, phospholipids are localized together with free cholesterol in the monolayer surrounding these particles. Given the continuous interaction of platelets with lipoproteins in vivo, the nature of an earlier suspected exchange of phospholipids between plasma lipoproteins and platelets (summarized in [3]) was investigated. LDL and HDL particles were radioactively and fluorescently labeled in their phospholipid and apoprotein fractions and incubated with isolated blood platelets. Thereby, major phospholipids carried by LDL and HDL particles were found to be rapidly transferred into platelets, including PC, SM and PE [4]. The uptake was selective as it was not associated with endocytosis of the particles. Since pretreatment of platelets with elastase reduced the phospholipid uptake (without altering lipoprotein binding), it was inferred that the phospholipid uptake is protein-mediated [4]. Nonetheless, phospholipid uptake did not require integrin αIIbβ2, a potential LDL receptor of the platelet cell membrane [5]. The findings unambiguously demonstrated that cells can take up phospholipids via a selective endocytosis-independent and protein-facilitated entry pathway.

Subsequent work indicated that apart from HDL and LDL also very low-density lipoproteins (VLDL) supply platelets with phospholipids and that platelet phospholipid uptake required a calcium-dependent cytosolic phospholipase A_2 [6,7]. Of note, in platelets activated by their major physiological activator thrombin, phospholipid import of PC [6] and PE [8] was stimulated. This suggested a substantial, yet unknown role for the phospholipid uptake during platelet activation (see below). In line with this proposal, LDL particles were observed to supply platelets with phospholipid-bound polyunsaturated fatty acids such as arachidonic acid (AA; 20:4*n*-3/ω3) [9] (Fig. 2). In mammals, polyunsaturated fatty acids with ≥4 double bonds, such as AA and other members of the *n*-3 and *n*-6 family of unsaturated fatty acids, are acquired from the diet to a substantial extent. After their absorption in the small intestine, these fatty acids are incorporated into extracellular lipoproteins (chylomicrons), transported to the liver and hence incorporated into nascent VLDL particles. VLDL particles subsequently secreted by the liver are in part metabolized to LDL and HDL, whereby the dietary fatty acids are distributed to the different