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Review

Lipid compartmentalization in the endosome system

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ABSTRACT

Lipids play an essential role in the structure of the endosomal membranes as well as in their dynamic rearrangement during the transport of internalized cargoes along the endocytic pathway. In this review, we discuss the function of endosomal lipids mainly in mammalian cells, focusing on two well-known components of the lipid rafts, sphingomyelin and cholesterol, as well as on three anionic phospholipids, phosphatidylserine, polyphosphoinositides and the atypical phospholipid, bis(monoacylglycero)phosphate/lysobisphosphatidic acid. We detail the structure, metabolism, distribution and role of these lipids in the endosome system as well as their importance in pathological conditions where modification of the endosomal membrane flow can lead to various diseases such as lipid-storage diseases, myopathies and neuropathies.

Contents

Abbreviations: AP-AB, anti-phospholipid antibody(ies); APS, anti-phospholipid syndrome; BMP/LBPA, bis(monoacylglycero)phosphate/lysobisphosphatidic acid; CAD, cationic amphiphilic drug(s); Chol, cholesterol; CL, cardiolipin; ECV/MVB, endosomal carrier vesicle(s)/multivesicular body(ies); EE, early endosome(s); ER, endoplasmic reticulum; GPI, glycosylphosphatidylinositol; GPL, glycerophospholipid(s); LE, late endosome(s); LD, lipid droplet(s); LDL, low-density lipoprotein(s); LSD, lysosomal storage disorder(s); MAM, mitochondrial-associated membrane(s); NCL, neuronal ceroid lipofuscinosis; PH, pleckstrin homology; PL, phospholipid(s); PM, plasma membrane; PtdChol, phosphatidylcholine; PtdGly, phosphatidylglycerol; PtdEth, phosphatidylethanolamine; PtdIns, phosphatidylinositol; PtdInsP, phosphoinositide(s); PtdIns(3)P, phosphatidylinositol 3-phosphate; PtdIns(3,5)P_2, phosphatidylinositol 3,5-bisphosphate; PtdIns(4,5)P_2, phosphatidylinositol 4,5-bisphosphate; PtdSer, phosphatidylserine; PUFA, polyunsaturated fatty acid(s); RE/ERC, recycling endosome(s)/endocytic recycling compartment(s); SL, sphingolipid(s); SM, sphingomyelin; TGN, trans-Golgi network.

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1. Introduction

Intracellular budding from the plasma membrane (PM) is the starting point of endocytosis (Fig. 1) requiring cooperation between proteins and lipids in order to induce membrane deformation, scission and fusion. While considerable progress has been made in understanding the role and characterizing proteins along the endocytic routes, less is known about the mechanism of internalization and the role of PM lipids in the endocytic pathway. Additionally, it is considered that the relative abundance of specific lipids vary along the endocytic pathway [1,2]. Recent studies have pointed out the essential role of PM lipid domains in the assembly of signaling platforms and their subsequent internalization [3,4]. PM lipids are constantly endocytosed and recycled back to the PM.

In this review, we focus mainly on the mammalian endosome system and describe the structure, the metabolism and the role of specific lipids found in the endosome system. Unraveling the function of endosomal lipids is crucial to understand their role during physiological events and diseases leading to the discovery of novel lipid-targeting therapeutic agents.

2. Lipid distribution

Lipids are not distributed equally among the subcellular organelles. In addition, lipids form specific domains in organelle and plasma membrane, displaying transversal asymmetry (between the two membrane leaflets) and/or lateral differences that are important in the dynamics of endocytosis. The PM has the highest, the Golgi an intermediate and the endoplasmic reticulum (ER) has the lowest concentration of sphingolipids (SL) and cholesterol (Chol) (relative to glycerophospholipids (GPL)) [5] (see Fig. 1 for the gradient distribution of the endosomal lipids and Fig. 2 for the lipid structure). In fact, specific lipids and lipid territories play a crucial role during the routing of cargo through the endosomal

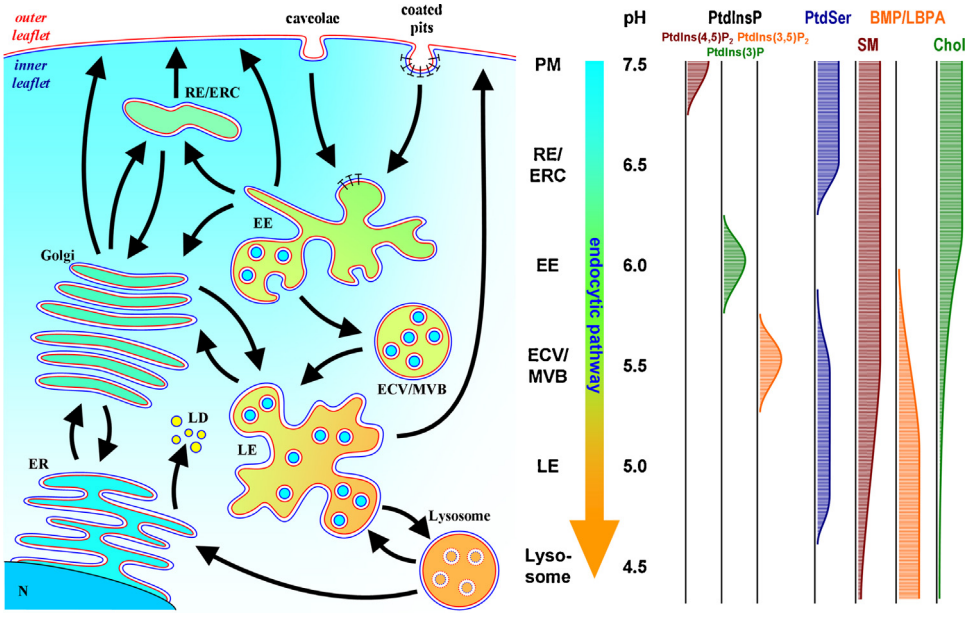

Fig. 1. The different lipids along the endocytic compartments. Independent of the endocytic route, internalized cargo first reaches the early endosome (EE) that serves as the primary hub through which cargo is further distributed to other endosomal compartments. Cargo collected into tubular domains of the EE undergoes recycling to the plasma membrane (PM) directly or indirectly through recycling endosome (RE)/endocytic recycling compartment (ERC). Alternatively, cargo destined for degradation will be collected in the vesicular regions of EE. Active membrane invagination processes are responsible for this multivesicular appearance, leading to free endosomal carrier vesicles (ECV)/multivesicular bodies (MVB) transporting the cargo to late endosomes (LE). Intraluminal components of the LE can be degraded in lysosomes, enter the retrograde pathway toward the trans-Golgi network (TNG) or be released into the cytosol after back-fusion with the limiting membrane of the LE, a process used by some toxins and virus. On the left side: the compartment color indicates internal pH. Membrane color indicates the relationship of each leaflet to the inner (blue) and outer (red) PM leaflet. Arrows indicate the transfer of membrane lipids and/or molecular cargo between the respective compartments. ER: endoplasmic reticulum; LD: lipid droplet; N: nucleus. On the right side: symbolic depiction of the gradient of lipids along the endocytic pathway: phosphoinositides (PtdInsP), sphingomyelin (SM), cholesterol (Chol), phosphatidylserine (PtdSer) and bis(monoacylglycero)phosphate/lysobisphosphatidic acid (BMP/LBPA).

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