Editorial

Lipid phosphate phosphatase 3 LPP3 and its role in mitochondrial function

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Mini Chandra,[1] Jonathan Fox,[1] Sumitra Miriyala,[1] Manikandan Panchatcharam[1]
Department of Cell biology and Anatomy, Louisiana State University Health Sciences Center, USA

Correspondence: Manikandan Panchatcharam, Department of Cell biology and Anatomy, Louisiana State University Health Sciences Center, Shreveport, USA, Email mpanch@lsuhsc.edu

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Lipid phosphate phosphatases (LPPs) are integral membrane proteins which are Mg^{2+} - independent and N-ethylmaleimide insensitive enzymes responsible for the dephosphorylation of lipid phosphates such as phosphatidic acid (PA), lysophosphatidic acid (LPA), sphingosine 1-phosphate (S1P) and diacylglycerol pyrophosphatase.[1] The mitochondrion is an active organelle which requires a constant source of phospholipids for homeostasis. The mitochondrial phospholipids such as phosphatidyl glycerol (PG) and phosphatidylethanolamine (PE) are synthesized in the mitochondrial membranes by Phosphatidic acid (PA) and lysophosphatidic acid (LPA) which are their precursors.[2] They are critical in controlling mitochondrial homeostasis Osman C[3] by influencing mitochondrial fusion,[4] fission[5] and mitochondrial membrane proteins.[6] Organelles within a cell have contact sites to exchange metabolites and information in order to ensure cell survival.[7] Since the endoplasmic reticulum (ER) is a major source of lipid production in a cell, the ER and mitochondria communicate via contact sites known as the mitochondria-ER associated membranes (MAMs).[8] This interface plays many roles in regulating the mitochondrial functioning Michel AH[9] by the exchange of phospholipids between these two organelles,[10] among which are the regulation of mitochondrial fusion,[11] fission and lipid metabolism.[12] Thus mitochondria is dependent on the ER to provide phospholipids such as LPA and PA.[13] One of the main roles of lipid phosphates such as LPA, PA and Diacylglycerol (DAG) in the organelles is to maintain the cell membrane. The proper formation of cell membrane is essential for generating transport carriers involved in the transport of lipids and proteins from the Golgi apparatus to other sub cellular locations. The Golgi apparatus also houses the signaling and metabolic proteins. These transport carriers such as vesicles and tubules are generated in tightly regulated stages and the membrane deformation is prevented by many molecules which are proteins[14,15] and lipids controlling protein functions and altering the properties of the bilayer membrane.[16,17] Transport carriers are generated via the action of Phosphatidic acid phosphatases (PAPs) which dephosphorylates PA to produce DAG.[18] LPP is an isoform of Phosphatidic acid phosphatase (PAP) and plays an important role in the production of lipid signaling metabolites due to their function of dephosphorylation of lipid phosphates.[19] Among the mammalian isoforms of LPPs, the enzyme lipid phosphate phosphatase 3 (LPP3) is encoded in the gene PPAP2B in humans.[20] The importance of LPP3 is demonstrated in mice models where embryos with deficiency of LPP3 by inactivating Ppap2b result in embryonic lethality due to failure to develop an extra embryonic vasculature.[21] It is expressed mainly in the heart, lung and cerebellum.[22] In the organelle they are located in the plasma membrane[23] and end membrane namely the endoplasmic reticulum (ER), Golgi complex and endosomes.[18] In plasma membrane, their active catalytic site is located on the outside enabling them to interact with extracellular lipid phosphates. On the endomembrane it is located on the luminal side.[24] In addition to the above mentioned locations of LPP3, recently the presence of LPP3 in the ER-Golgi intermediate compartment (ERGIC), ER export sites (ERES) and Golgi complex has been demonstrated.[25] The results imply that LPP3 resides in the ER-Golgi intermediate compartment and constantly transports from the endoplasmic reticulum to the Golgi and vice versa. They determined the role of LPP3 in the functioning of the ERGIC by using propranolol which is an inhibitor of PAP[26] and suppressing LPP3 expression in HeLa cells. Propranolol treated cells showed less number of tubules and less motility in the ERGIC53-GFP expressing HeLa cells and the suppression of LPP3 exhibited decrease in LPP3 proteins. These results are an indication that LPP3 plays a role in the functioning and maintenance of ERGIC membrane. LPP3 is among the many enzymes which regulate membrane lipids in the secretory pathway.[25,27–29] It is responsible for the production of DAG by the dephosphorylation of PA both newly produced and the PA generated from the hydrolysis of Phosphatidylcholine (PC).[18] LPP3 depletion is associated with the low levels of DAG. The same group also established the role of LPP3 in the formation of transport carriers in the Golgi.[25] They examined the Rab6-GFP transport tubules and vesicles, and the effect of both propranolol and LPP3 knockdown in Rab6-GFP expressing HeLa cells on their generation. The propranolol treated cells showed decreased rate of formation of Rab6-GFP transport carriers and the LPP3 depleted cells showed fewer tubules though they were longer than those found in control cells which may be due to the role of LPP3 in the fission of these tubules. The transport of proteins from Golgi back to the ER is dependent on the coatomer protein I (COPI) which is said to regulate the formation of retrograde transport carriers.[30] Rab6 is also known to play a role in the retrograde transport from Golgi to ER.[31] Therefore, The involvement of LPP3 in these transport mechanisms was studied[25] and the results indicated that LPP3 has a role in COPI dependent pathway as well as in the Rab6 dependent pathway. In addition to having a role in the transport mechanisms, LPP3 is also involved in the formation of transport carriers at the ERGIC and Golgi, in both these pathways. In conclusion, LPP3 takes part in the maintenance of the physical and functional component of mitochondria by playing a role in the transport of phospholipids from the ER to the mitochondria via both formations of transport carriers as well as mechanism of lipid exchange between the organelles.

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Conflict of interest

Author declares that there is no conflict of interest.

References

1. Brindley DN, Waggoner DW. Mammalian lipid phosphate phosphohydrolases. *J Biol Chem*. 1998;273(38):24281–24284.
2. Horvath SE, Daum G. Lipids of mitochondria. *Prog Lipid Res*. 2013;52(4):590-614.
3. Osman C, Voelker DR, Langer T. Making heads or tails of phospholipids in mitochondria. *J Cell Biol*. 2011;192(1):7–16.
4. Choi SY, Huang P, Jenkins GM, et al. A common lipid links Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. *Nat Cell Biol*. 2006;8(11):1255–1262.
5. Steenbergen R, Nanowski TS, Beigneux A, et al. Disruption of the phosphatidylserine decarboxylase gene in mice causes embryonic lethality and mitochondrial defects. *J Biol Chem*. 2005;280(48):40032–40040.
6. Chu CT, Ji J, Dagda RK, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. *Nat Cell Biol*. 2013;15(10):1197–1205.
7. Elbaz Y, Schuldiner M. Staying in touch: the molecular era of organelle contact sites. *Trends Biochem Sci*. 2011;36(11):616–623.
8. Raturi A, Simmen T. Where the endoplasmic reticulum and the mitochondrion tie the knot: the mitochondria-associated membrane (MAM). *Biochim Biophys Acta*. 2013;1833(1):213–224.
9. Michel AH, Kornmann B. The ERMES complex and ER-mitochondria connections. *Biochem Soc Trans*. 2012;40(2):445–450.
10. Flis VV, Daum G. Lipid Transport between the Endoplasmic Reticulum and Mitochondria. *Cold Spring Harb Perspect Biol*. 2013:5(6).
11. Marchi S, Patergnani S, Pinton P. The endoplasmic reticulum-mitochondria connection: one touch, multiple functions. *Biochim Biophys Acta*. 2014;1837(4):461–469.
12. Vance JE. MAM (mitochondria-associated membranes) in mammalian cells: lipids and beyond. *Biochim Biophys Acta*. 2014;1841(4):595–609.
13. Fagone P, Jackowski S. Membrane phospholipid synthesis and endoplasmic reticulum function. *J Lipid Res*. 2009;50(Suppl):S311–S316.
14. Roux A, Cuvelier D, Nassoy P, et al. Role of curvature and phase transition in lipid sorting and fission of membrane tubules. *EMBO J*. 2005;24(8):1537–1545.
15. Callan-Jones A, Sorre B, Bassereau P. Curvature-Driven Lipid Sorting in Biomembranes. *Cold Spring Harb Perspect Biol*. 2011:3(2).
16. Huijbregts RP, Topalof L, Bankaitis VA. Lipid metabolism and regulation of membrane trafficking. *Traffic*. 2000;1(3):195–202.
17. Lippincott-Schwartz J, Phair RD. Lipids and cholesterol as regulators of traffic in the endomembrane system. *Annu Rev Biophys*. 2010;39:559–578.
18. Sciorra VA, Morris AJ. Sequential actions of phospholipase D and phosphatidic acid phosphohydrolase 2b generate diglyceride in mammalian cells. *Mol Biol Cell*. 1999;10(11):3863–3876.
19. Brindley DN, Pilquil C. Lipid phosphate phosphatases and signaling. *J Lipid Res*. 2009;50(Suppl):S225–S230.
20. Roberts R, Sciorra VA, Morris AJ. Human type 2 phosphatidic acid phosphohydrolases. Substrate specificity of the type 2a, 2b, and 2c enzymes and cell surface activity of the 2a isoform. *J Biol Chem*. 1998;273(34):22059–22067.
21. Escalante-Alcalde D, Hernandez L, Le Stunff H, et al. The lipid phosphatase LPP3 regulates extra-embryonic vasculogenesis and axis patterning. *Development*. 2003;130(19):4623–4637.
22. Ren H, Panchatcharam M, Mueller P, et al. Lipid phosphate phosphatase (LPP3) and vascular development. *Biochim Biophys Acta*. 2013;1831(1):126–132.
23. Alderton F, Darroch P, Sambi B, et al. G-protein-coupled receptor stimulation of the p42/p44 mitogen-activated protein kinase pathway is attenuated by lipid phosphate phosphatases 1, 1a, and 2 in human embryonic kidney 293 cells. *J Biol Chem*. 2001;276(16):13452–13460.
24. Long JS, Pyne NJ, Pyne S. Lipid phosphate phosphatases form homo- and hetero-oligomers: catalytic competency, subcellular distribution and function. *Biochem J*. 2008;411(2):371–377.
25. Gutiérrez-Martínez E1, Fernández-Ulibarri I, Lázaro-Diéguez F, et al. Lipid phosphate phosphatase 3 participates in transport carrier formation and protein trafficking in the early secretory pathway. *J Cell Sci*. 2013;126(Pt 12):2641–2655.
26. Pappu AS, Hauser G. Propranolol-induced inhibition of rat brain cytoplasmic phosphatidate phosphohydrolase. *Neurochem Res*. 1983;8(12):1565–1575.
27. Morikawa RK, Aoki J, Kano F, et al. Intracellular Phospholipase A(1)γ (iPLA(1)γ) Is a Novel Factor Involved in Coat Protein Complex I- and Rab6-independent Retrograde Transport between the Endoplasmic Reticulum and the Golgi Complex. *J Biol Chem*. 2009;284(39):26620–26630.
28. Schmidt JA, Brown WJ. Lysophosphatidic acid acyltransferase 3 regulates Golgi complex structure and function. *J Cell Biol*. 2009;186(2):211–218.
29. Bechler ME, Doody AM, Racoosin E, et al. The phospholipase complex PAFAH Ib regulates the functional organization of the Golgi complex. *J Cell Biol*. 2010;190(1):45–53.
30. Cosson P, Letourneur F. Coatomer (COPI)-coated vesicles: role in intracellular transport and protein sorting. *Curr Opin Cell Biol*. 1997;9(4):484–487.
31. White J, Johannes L, Mallard F, et al. Rab6 coordinates a novel Golgi to ER retrograde transport pathway in live cells. *J Cell Biol*. 1999;147(4):743–760.

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