Title

Phosphatidic acid: a lipid regulator of the Hippo pathway

Journal

Molecular & Cellular Oncology, 6(1)

ISSN

2372-3548

Authors

Han, Han

Vargas, Rebecca

Seo, Gayoung

et al.

Publication Date

2019-01-02

DOI

10.1080/23723556.2018.1558683

Peer reviewed

MOLECULAR & CELLULAR ONCOLOGY
2019, VOL. 6, NO. 1, e1558683 (3 pages)
https://doi.org/10.1080/23723556.2018.1558683

Taylor & Francis
Taylor & Francis Group

AUTHOR'S VIEW

Phosphatidic acid: a lipid regulator of the Hippo pathway

Han Han, Rebecca Vargas, Gayoung Seo, and Wenqi Wang

Department of Developmental and Cell Biology, University of California, Irvine, CA, USA

ABSTRACT

The Hippo pathway, a signaling pathway highly conserved across species, plays a crucial role in organ size control and cancer suppression. Our recent study shows that phosphatidic acid can regulate the Hippo pathway through a physical lipid-protein interaction, providing additional insights into the Hippo-related tissue homeostasis and cancer development.

ARTICLE HISTORY
Received 12 November 2018
Revised 29 November 2018
Accepted 10 December 2018

KEYWORDS
Phospholipase D; Phosphatidic acid; Hippo pathway; mTOR

Main text

Multicellular organisms have an unknown mechanism for precisely controlling their organ size and tissue shape and the Hippo pathway has shed light on this mystery. The Hippo pathway was first identified in *Drosophila*, where the deletion of Hippo pathway components resulted in overgrowth of multiple tissues.[1] The mammalian Hippo pathway is composed of a kinase cascade, which includes serine/threonine kinases Mammalian sterile 20-like 1/2 (MST1/2) and Large tumor suppressor homolog 1/2 (LATS1/2), adaptor proteins Salvador (SAV1) and MOB kinase activator 1 (MOB1), and downstream effectors Yes-associated protein (YAP) and WW domain-containing transcription regulator protein 1 (WWTR1, also called TAZ). MST1/2 phosphorylate and activate LATS1/2, which then phosphorylate YAP/TAZ to allow the 14–3-3 proteins to bind. This binding sequesters YAP/TAZ in the cytoplasm and inhibits their transactivation properties in the nucleus. However, the physiological regulations of the Hippo pathway are largely unknown.

Phosphatidic acid (PA) can serve as a lipid second messenger to directly associate with cellular proteins and regulate their intracellular signaling pathways affecting cell adhesion, migration, membrane remodeling and cell polarization.[2] Since the concentration of PA in cellular membranes is less than 5% of the most abundant membrane phospholipid phosphatidylcholine (PC), the enzymes that control PA production play a key role in the PA-mediated signaling transduction.[3] One of such metabolic pathways to generate PA is the hydrolysis of PC as catalyzed by phospholipase D (PLD). In mammals, two isoforms of PLD, PLD1 and PLD2, who are ubiquitously expressed throughout different cell types and tissues, are known involved in this process. These two PLD enzymes have been implicated in numerous human diseases such as neurodegenerative diseases, blood disorders, and cancer. Elevated activity and expression of PLD1/2 have been found in various cancer types. In addition, PLD1/2 are downstream of protein kinase C, small GTPases and receptor tyrosine kinases.[4] Intriguingly, many of these known PLD-activators have also been identified as Hippo pathway regulators.[1]

Pieces of evidence have shown that PA supplement can decrease phosphorylation level of YAP;[5] however, there is no direct evidence linking PLD-PA lipid signaling to the Hippo pathway. In our recent work,[6] we uncovered an unexpected mechanism by which PA regulates the Hippo pathway. PA physically interacts with LATS and one Hippo upstream component Neurofibromin 2 (NF2, also called Merlin), respectively disrupting the formation of LATS-MOB1 complex and the NF2-mediated LATS membrane translocation and activation, eventually inhibiting the LATS activity. Moreover, cellular PA level was significantly decreased under Hippo-activating conditions, and inhibition of PA production by PLD inhibitors suppressed YAP's oncogenic functions. These findings are highly relevant to YAP activation in breast cancer, a cancer type with rare mutation rate in Hippo pathway components. The analyses of PLD1 and YAP via breast cancer sample tissue array and The Cancer Genome Atlas database revealed a significant positive correlation between PLD1 expression and YAP activation, suggesting the PLD1-PA-YAP axis as a therapeutic target in breast cancer treatment.[6]

PA can be produced with different fatty acid chain number, length and saturation status, which result in numerous PA species and distinct cellular functions. In our unpublished study, we investigated the binding affinities of several PA species with LATS and NF2, where LATS and NF2 primarily interacted with saturated PA with C16:0 acyl chains (1,2-Dipalmitoyl-sn-glycero-3-phosphate, DPPA). Other PA species such as saturated PA with long acyl chain (1,2-Distearoyl-sn-glycero-3-phosphate, DSPA), unsaturated PA (1,2-dioleoyl-sn-glycero-3-phosphate, DOPA), saturated lysoPA (1-stearoyl-2-hydroxy-sn-glycero-3-phosphate, SLPA), and saturated PA with short acyl chains (1,2-dihexanoyl-sn-glycero-3-phosphate, DCPA) could reduce YAP phosphorylation, while DPPA showed the most dramatic effect, correlating with the binding affinities with LATS and NF2. Interestingly, we also found that unsaturated acyl chain PA species, but not DPPA, can activate the mammalian target of rapamycin (mTOR) pathway and result in an increase of

CONTACT Wenqi Wang wenqiw6@uci.edu Department of Developmental and Cell Biology, University of California, Irvine, CA 92697, USA

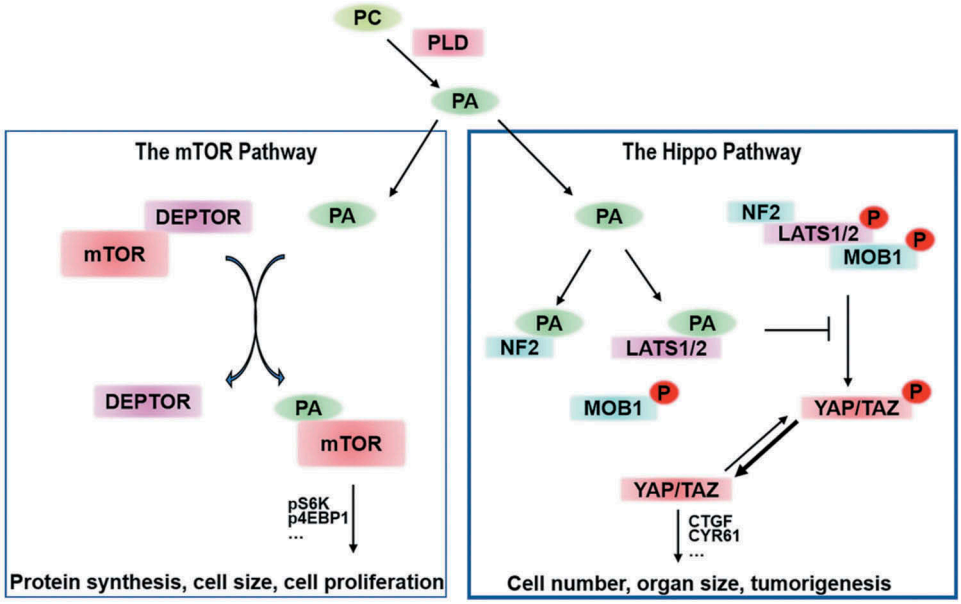

Figure 1. PLD-PA regulates Hippo and mTOR signaling.

The phospholipase D (PLD)-mediated phosphatidic acid (PA) production can regulate both the mammalian target of rapamycin (mTOR) and the Hippo pathway through the PA-mediated lipid-protein interactions. PA directly binds the FK506-binding protein (FKBP)-rapamycin-binding (FRB) domain of mTOR and displaces Dishevelled, Egl-10 and Pleckstrin (DEP) domain-containing mTOR-interacting protein (DEPTOR) to activate the mTOR (*left*). In the meantime, PA directly binds to the Hippo pathway components Neurofibromin 2 (NF2) and Large tumor suppressor homolog 1/2 (LATS1/2) to inhibit the NF2-mediated LATS membrane translocation and activation, and the association between LATS1/2 and their adaptor protein MOB kinase activator 1 (MOB1), which eventually targets LATS and activates Yes-associated protein (YAP) and WW domain-containing transcription regulator protein 1(WWTR1, also called TAZ) (*right*). PC, phosphatidylcholine.

ribosomal protein S6 kinase phosphorylation, which is consistent with a previous study.[7] These findings provide an opportunity to link the PA-related lipid signaling to organ size control through two well-established size-related pathways, mTOR and the Hippo, through generation of different PA species (Figure 1). Indeed, PLD-PA signaling is known to regulate the muscle size through activating mTOR and promoting mitogenesis and skeletal muscle growth;[8] loss of YAP prior to denervation leads to muscle atrophy, while overexpression of YAP in the mouse tibialis anterior results in hypertrophy.[9] These evidences suggest that the PLD-PA pathway can control skeletal muscle homeostasis by modulating these two pathways. The interplay between the Hippo pathway and mTOR signaling in controlling the size of other tissues/organs deserves further investigation.

The increasing studies show that the Hippo pathway effectors YAP/TAZ play an essential role in mechanotransduction. Interestingly, Meng *et al.* recently reports that under a soft matrix stiffness (1KPa), accumulation of membrane-associated phosphatidylinositol 4,5-bisphosphate (PtdIns[4,5]P2) can increase PLD activity to generate PA and activate Ras-related protein Rap-2 (RAP2) GTPase, which consequently activates LATS and inhibits YAP/TAZ.[10] Given the fact that most of our PA-related studies were performed in the cells that were cultured on plastic dishes, a relative stiff condition, these findings further highlighted a complex role of PLD-PA signaling in regulation of the Hippo pathway under different physiological conditions.

In summary, our study not only identified the PA-related lipid signaling as a key regulator of the Hippo pathway, but also proposed a potential therapeutic strategy for cancer treatment by targeting the PLD-PA-YAP axis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by an NIH grant (GM126048) and a Research Scholar grant from American Cancer Society (RSG-18-009-01-CCG)].

ORCID

Han Han http://orcid.org/0000-0003-2222-5270
Rebecca Vargas http://orcid.org/0000-0002-9850-7568
Wenqi Wang http://orcid.org/0000-0003-4053-5088

References

1. Yu FX, Zhao B, Guan KL. Hippo pathway in organ size control, tissue homeostasis, and cancer. Cell. 2015;163(4):811–828. doi:10.1016/j.cell.2015.10.044. PMID:PMC4638384.
2. Bruntz RC, Lindsley CW, Brown HA. Phospholipase D signaling pathways and phosphatidic acid as therapeutic targets in cancer. Pharmacol Rev. 2014;66(4):1033–1079. doi:10.1124/pr.114.009217. PMID:4180337.
3. Fang YM, Vilella-Bach M, Bachmann R, Flanigan A, Chen J. Phosphatidic acid-mediated mitogenic activation of mTOR signaling. Science. 2001;294(5548):1942–1945. doi:10.1126/science.1066015.
4. Frohman MA. The phospholipase D superfamily as therapeutic targets. Trends Pharmacol Sci. 2015;36(3):137–144. doi:10.1016/j.tips.2015.01.001.
5. Yu FX, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, Zhao J, Yuan H, Tumaneng K, Li H, et al. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling.

Cell. 2012;150(4):780–791. doi:10.1016/j.cell.2012.06.037. PMID: 3433174.
6. Han H, Qi R, Zhou JJ, Ta AP, Yang B, Nakaoka HJ, Seo G, Guan K-L, Luo R, Wang W. Regulation of the hippo pathway by phosphatidic acid-mediated lipid-protein interaction. Mol Cell. 2018;72(2):328–40.e8. doi:10.1016/j.molcel.2018.08.038.
7. Yoon M-S, Rosenberger Christina L, Wu C, Truong N, Sweedler Jonathan V, Chen J. Rapid mitogenic regulation of the mTORC1 Inhibitor, DEPTOR, by phosphatidic acid. Mol Cell. 2015;58 (3):549–556. doi:10.1016/j.molcel.2015.03.028.
8. Jaafar R, De Larichaudy J, Chanon S, Euthine V, Durand C, Naro F, Bertolino P, Vidal H, Lefai E, Nemoz G. 2013. Phospholipase D regulates the size of skeletal muscle cells through the activation of mTOR signaling. Cell Commun Signaling. 11:55. doi:10.1186/1478-811X-11-55.
9. Goodman CA, Dietz JM, Jacobs BL, McNally RM, You JS, Hornberger TA. Yes-associated protein is up-regulated by mechanical overload and is sufficient to induce skeletal muscle hypertrophy. FEBS Lett. 2015;589(13):1491–1497. doi:10.1016/j.febslet.2015.04.047.
10. Meng ZP, Qiu YJ, Lin KC, Kumar A, Placone JK, Fang C, Wang KC, Lu SC, Pan M, Hong AW, et al. RAP2 mediates mechanoresponses of the Hippo pathway. Nature. 2018;560 (7720):655. doi:10.1038/s41586-018-0444-0.