

Papel de las lipinas en inmunidad innata e inflamación

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Las lipinas son enzimas fosfatasa de ácido fosfatídico y su función celular en la regulación del metabolismo lipídico se ha descrito hace largo tiempo, particularmente en tejidos metabólicamente activos como el tejido adiposo o el hígado. En los últimos años se está acumulando evidencia el papel regulador clave de estas enzimas en células del sistema inmune innato. Las lipinas regulan eventos de señalización que ocurren a través de receptores inmunes tales como los toll y son parte integral de la maquinaria celular implicada en el almacenamiento de lípidos en estas células. Las mutaciones en los genes que codifican para los miembros de esta familia producen enfermedades hereditarias autoinflamatorias o enfermedades con un componente inflamatorio importante en seres humanos. En esta revisión se resumen los hallazgos recientes sobre el papel de las lipinas en las células del sistema inmune innato y en el inicio y el desarrollo de los procesos inflamatorios.

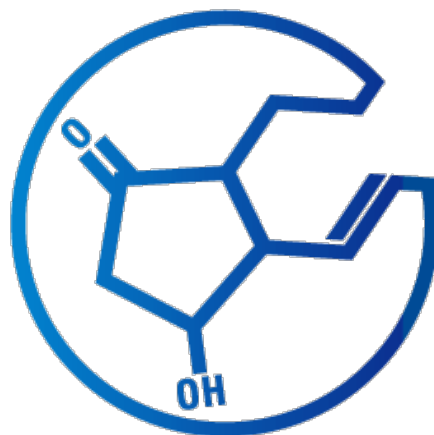
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REFERENCES

1. Guijas, C., J. P. Rodríguez, J. M. Rubio, M. A. Balboa, and J. Balsinde. 2014. Phospholipase A₂ regulation of lipid droplet formation. *Biochim. Biophys. Acta* 1841: 1661–1671.
2. Valdearcos, M., E. Esquinas, C. Meana, L. Peña, L. Gil-de-Gómez, J. Balsinde, and M. A. Balboa. 2012. Lipin-2 reduces proinflammatory signaling induced by saturated fatty acids in macrophages. *J. Biol. Chem.* 287: 10894–10904.
3. Meana, C., L. Peña, G. Lordén, E. Esquinas, C. Guijas, M. Valdearcos, J. Balsinde, and M. A. Balboa. 2014. Lipin-1 integrates lipid synthesis with proinflammatory responses during TLR activation in macrophages. *J. Immunol.* 193: 4614–4622.
4. Rubio, J. M., J. P. Rodríguez, L. Gil-de-Gómez, C. Guijas, M. A. Balboa, and J. Balsinde. 2015. Group V secreted phospholipase A₂ is up-regulated by interleukin-4 in human macrophages and mediates phagocytosis via hydrolysis of ethanolamine phospholipids. *J. Immunol.* 194: 3327–3339.
5. Balboa, M. A., J. Balsinde, and E. A. Dennis. 1998. Involvement of phosphatidate phosphohydrolase in arachidonic acid mobilization in human amnionic WISH cells. *J. Biol. Chem.* 273: 7684–7690.
6. Johnson, C. A., M. A. Balboa, J. Balsinde, and E. A. Dennis. 1999. Regulation of cyclooxygenase-2 expression by phosphatidate phosphohydrolase in human amnionic WISH cells. *J. Biol. Chem.* 274: 27689–27693.

7. Astudillo, A. M., M. A. Balboa, and J. Balsinde. 2019. Selectivity of phospholipid hydrolysis by phospholipase A₂ enzymes in activated cells leading to polyunsaturated fatty acid mobilization. *Biochim. Biophys. Acta* 1864: 772–783.
8. Pérez-Chacón, G., A. M. Astudillo, D. Balgoma, M. A. Balboa, and J. Balsinde. 2009. Control of free arachidonic acid levels by phospholipases A₂ and lysophospholipid acyltransferases. *Biochim. Biophys. Acta* 1791: 1103–1113.
9. Astudillo, A. M., D. Balgoma, M. A. Balboa, and J. Balsinde. 2012. Dynamics of arachidonic acid mobilization by inflammatory cells. *Biochim. Biophys. Acta* 1821: 249–256.
10. Balsinde, J., M. V. Winstead, and E. A. Dennis. 2002. Phospholipase A₂ regulation of arachidonic acid mobilization. *FEBS Lett.* 531: 2–6.
11. Casas, J., M.A. Gijón, A.G. Vigo, M.S. Crespo, J. Balsinde, and M.A. Balboa. 2006. Phosphatidylinositol 4,5-bisphosphate anchors cytosolic group IVA phospholipase A₂ to perinuclear membranes and decreases its calcium requirement for translocation in live cells. *Mol. Biol. Cell* 17: 155-162.
12. Pindado, J., J. Balsinde, and M. A. Balboa. 2007. TLR3-dependent induction of nitric oxide synthase in RAW 264.7 macrophage-like cells via a cytosolic phospholipase 2/cyclooxygenase-2 pathway. *J. Immunol.* 179: 4821–4828.
13. Casas, J., C. Meana, E. Esquinas, M. Valdearcos, J. Pindado, J. Balsinde, and M. A. Balboa. 2009. Requirement of JNK-mediated phosphorylation for translocation of group IVA phospholipase A₂ to phagosomes in human macrophages. *J. Immunol.* 183: 2767–2774.
14. Casas, J., M. Valdearcos, J. Pindado, J. Balsinde, and M. A. Balboa. 2010. The cationic cluster of group IVA phospholipase A₂ (Lys488/Lys541/Lys543/Lys544) is involved in translocation of the enzyme to phagosomes in human macrophages. *J. Lipid Res.* 51: 388–399.
15. Ruipérez, V., A. M. Astudillo, M. A. Balboa, and J. Balsinde. 2009. Coordinate regulation of TLR-mediated arachidonic acid mobilization in macrophages by group IVA and group V phospholipase A₂s. *J. Immunol.* 182: 3877–3883.
16. Ruipérez, V., J. Casas, M. A. Balboa, and J. Balsinde. 2007. Group V phospholipase A₂-derived lysophosphatidylcholine mediates cyclooxygenase-2 induction in lipopolysaccharide-stimulated macrophages. *J. Immunol.* 179: 631–638.
17. Valdearcos, M., E. Esquinas, C. Meana, L. Gil-de-Gómez, C. Guijas, J. Balsinde, and M. A. Balboa. 2011. Subcellular localization and role of lipin-1 in human macrophages. *J. Immunol.* 186: 6004–6013.
18. Gubern, A., J. Casas, M. Barceló, D. Barneda, X. de la Rosa, R. Masgrau, F. Picatoste, J. Balsinde, M. A. Balboa, and E. Claro. 2008. Group IVA phospholipase A₂ is necessary for the biogenesis of lipid droplets. *J. Biol. Chem.* 283: 27369–27382.
19. Gubern, A., M. Barceló, J. Casas, D. Barneda, R. Masgrau, F. Picatoste, J. Balsinde, M. A. Balboa, and E. Claro. 2009. Lipid droplet biogenesis induced by stress involves triacylglycerol synthesis that depends on group VIA phospholipase A₂. *J. Biol. Chem.* 284: 5697–5708.
20. Gubern, A., M. Barceló, D. Barneda, J. M. López, R. Masgrau, F. Picatoste, C. E. Chalfant, J. Balsinde, M. A. Balboa, and E. Claro. 2009. JNK and ceramide kinase govern the biogenesis of lipid droplets through activation of group IVA phospholipase A₂. *J. Biol. Chem.* 284: 32359–32369.
21. Guijas, C., G. Pérez-Chacón, A. M. Astudillo, J. M. Rubio, L. Gil-de-Gómez, M. A. Balboa, and J. Balsinde. 2012. Simultaneous activation of p38 and JNK by arachidonic acid stimulates the cytosolic phospholipase A₂-dependent synthesis of lipid droplets in human monocytes. *J. Lipid Res.* 53: 2343–2354.
22. Meana, C., G. G. Rostán, L. Peña, L., G. Lordén, A. Cubero, A. Orduña, B. Györfy, J. Balsinde, and M. A. Balboa. 2018. The phosphatidic acid phosphatase lipin-1 facilitates inflammation-driven colon carcinogenesis. *JCI Insight* 3: e97506.
23. Lordén, G., I. Sanjuán-García, N. de Pablo, C. Meana, I. Alvarez-Miguel, M. T. Pérez-García, P. Pelegrín, J. Balsinde, and M. A. Balboa. 2017. Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation. *J. Exp. Med.* 214: 511-528.

24. Balboa, M. A., J. Balsinde, E. A. Dennis, and P. A. Insel. 1995. A phospholipase D-mediated pathway for generating diacylglycerol in nuclei from Madin-Darby canine kidney cells. *J. Biol. Chem.* 270: 11738–11740.
25. Balboa, M. A., J. Balsinde, and E. A. Dennis. 2000. Phosphorylation of cytosolic group IV phospholipase A₂ is necessary but not sufficient for arachidonic acid release in P388D₁ macrophages. *Biochem. Biophys. Res. Commun.* 267: 145–148.
26. Balboa, M. A., J. Balsinde, D. A. Dillon, G. M. Carman, and E. A. Dennis. 1999. Proinflammatory macrophage-activating properties of the novel phospholipid diacylglycerol pyrophosphate. *J. Biol. Chem.* 274: 522–526.
27. Balboa, M. A., J. Balsinde, C. A. Johnson, and E. A. Dennis. 1999. Regulation of arachidonic acid mobilization in lipopolysaccharide-activated P388D₁ macrophages by adenosine triphosphate. *J. Biol. Chem.* 274: 36764–36768.
28. Guijas, C., A. M. Astudillo, L. Gil-de-Gómez, J. M. Rubio, M. A. Balboa, and J. Balsinde. 2012. Phospholipid sources for adrenic acid mobilization in RAW 264.7 macrophages: comparison with arachidonic acid. *Biochim. Biophys. Acta* 1821: 1386–1393.
29. Guijas, C., C. Meana, A. M. Astudillo, M. A. Balboa, and J. Balsinde. 2016. Foamy monocytes are enriched in cis-7-hexadecenoic fatty acid (16:1n-9), a possible biomarker for early detection of cardiovascular disease. *Cell Chem. Biol.* 23: 689–699.
30. Balgoma, D., O. Montero, M. A. Balboa, and J. Balsinde. 2010. Lipidomic approaches to the study of phospholipase A₂-regulated phospholipid fatty acid incorporation and remodeling. *Biochimie* 92: 645–650.



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