

Connecting Lipid Metabolism to Inflammation: Unexpected Fatty Acids in Lipid Droplets

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Activated human peripheral blood monocytes contain unusual amounts of an isomer of palmitoleic acid, cis-7-hexadecenoic acid, stored in cytoplasmic lipid droplets. This acid shows a strong anti-inflammatory character in vitro and in vivo and its levels appear to be regulated by the pro-inflammatory state of the cells. Detection of this fatty acid might constitute a useful as a biomarker of ‘foamy monocytes’ for the early detection of cardiovascular disease.

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Part A – Intro

Slide 1 – Title: “When Lipid Metabolism Meets Inflammation

Slide 2 – Fat-loaden macrophage (Martín’s)

Slide 3 – Lipid Droplets: Composition and Funtions

Slide 4 – Initiation of Atherosclerosis

Slide 5 – Initiation of Atherosclerosis (AA appearing)

Part A – Background Data

Slide 6 – AA Induces Neutral Lipid Droplet Formation (Microscopy)

Slide 7 – AA Induces Neutral Lipid Formation (Mass Analysis)

Slide 8 – Fatty Acid Content of TAG and CE (Mass Analysis)

Slide 9 – Lipid Inflammatory Signals Regulate Cellular Lipid Metabolism

Part B – The New Isomer!

Slide 10 – Two 16:1 Isomers in Monocytes (1 – Neutral Lipids)

Slide 11 – Two 16:1 Isomers in Monocytes (2 – Phospholipids)

Slide 12 – Two 16:1 Isomers in Monocytes (3 – Standards)

Slide 13 – The Second 16:1 Isomer Is 16:1n-9

Slide 14 – Metabolic Origin of 16:1n-9?

Slide 15 – Fatty Acid Methyl Ester (FAME) Fragmentation Spectra

Slide 16 – Fatty Acid Methyl Ester (FAME) Fragmentation Spectra (2)

Slide 17 – Effect of Etomoxir on 16:1n-9 Accumulation

Slide 18 – Lipid Inflammatory Signals Regulate Cellular Lipid Metabolism

Slide 19 – Distribution of 16:1 Isomers Between Lipid Classes (1)

Slide 20 – Distribution of 16:1 Isomers Between Lipid Classes (2)

Slide 21 – Distribution of 16:1 Isomers Between Lipid Classes

Slide 22 – Assessing the Biological Effects of 16:1n-9

Slide 23 – 16:1n-9 Possesses Anti-inflammatory Properties in vitro

Slide 24 – 16:1n-9 Possesses Anti-inflammatory Properties in vivo

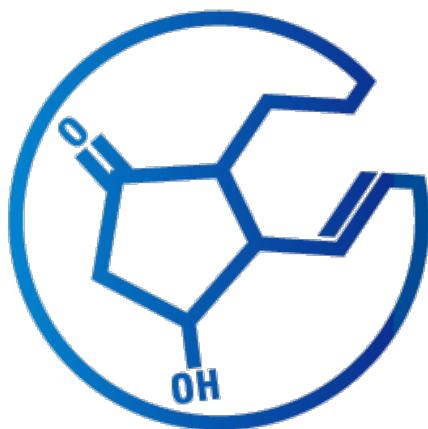
Slide 25 – 16:1n-9 as a novel anti-inflammatory fatty acid

Slide 26 – Acknowledgments. Fin de la cita.

REFERENCES

1. Valdearcos, M., E. Esquinas, C. Meana, L. Gil-de-Gómez, C. Guijas, J. Balsinde, and M. A. Balboa. 2011. Subcellular localization and cellular role of lipin-1 in human macrophages. *J. Immunol.* 186: 6004-6013.
2. 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.
3. 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.
4. 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.
5. 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.
6. Balsinde, J., and M.A. Balboa. 2005. Cellular regulation and proposed biological functions of group VIA calcium-independent phospholipase A₂ in activated cells. *Cell. Signal.* 17: 1052-1062.
7. Balsinde, J., and E. A. Dennis. 1996. The incorporation of arachidonic acid into triacylglycerol in P388D₁ macrophage-like cells. *Eur. J. Biochem.* 235: 480-485.
8. Astudillo, A. M., G. Perez-Chacón, D. Balgoma, L. Gil-de-Gómez, V. Ruipérez, C. Guijas, M. A. Balboa, and J. Balsinde. 2011. Influence of cellular arachidonic acid levels on phospholipid remodeling and CoA-independent transacylase activity in human monocytes and U937 cells. *Biochim. Biophys. Acta* 1811: 97-103.

9. Astudillo, A. M., G. Pérez-Chacón, C. Meana, D. Balgoma, A. Pol, M. A. del Pozo, M. A. Balboa, and J. Balsinde. 2011. Altered arachidonate distribution in macrophages from caveolin-1 null mice leading to reduced eicosanoid synthesis. *J. Biol. Chem.* 286: 35299–35307.
10. Gil-de-Gómez, L., A. M. Astudillo, C. Meana, J. M. Rubio, C. Guijas, M. A. Balboa, and J. Balsinde. 2013. A phosphatidylinositol species acutely generated by activated macrophages regulates innate immune responses. *J. Immunol.* 190: 5169–5177.
11. Gil-de-Gómez, L., A. M. Astudillo, C. Guijas, V. Magriotti, G. Kokotos, M. A. Balboa, and J. Balsinde. 2014. Cytosolic group IVA and calcium-independent group VIA phospholipase A₂s act on distinct phospholipid pools in zymosan-stimulated mouse peritoneal macrophages. *J. Immunol.* 192: 752–762.
12. Pérez-Chacón, G., A. M. Astudillo, V. Ruipérez, M. A. Balboa, and J. Balsinde. 2010. Signaling role for lysophosphatidylcholine acyltransferase 3 in receptor-regulated arachidonic acid reacylation reactions in human monocytes. *J. Immunol.* 184: 1071–1078.
13. Balgoma, D., A. M. Astudillo, G. Pérez-Chacón, O. Montero, M. A. Balboa, and J. Balsinde. 2010. Markers of monocyte activation revealed by lipidomic profiling of arachidonic acid-containing phospholipids. *J. Immunol.* 184: 3857–3865.
14. 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.
15. 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.
16. 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.
17. 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.



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