THE EICOSANOID RESEARCH DIVISION

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OFERTA DE CONTRATO PREDOCTORAL ASOCIADO AL PROYECTO:

“Metabolismo y regulación de los plasmalógenos en inmunidad innata e inflamación. Papel de la lipina-2”

Ref: PID2022-140764OB-I00

Este documento consta de las siguientes secciones:

- Descripción extendida de la oferta de contrato predoctoral.
- Líneas de investigación, actividades y programas que se desarrollan en el grupo a los que se incorporaría la persona beneficiaria (en inglés).
- Historial científico-técnico del grupo: publicaciones de los últimos diez años.
- Historial científico-técnico del grupo: tesis doctorales defendidas en los últimos diez años.

DESCRIPCION EXTENDIDA DE LA OFERTA DE CONTRATO PREDOCTORAL

Se oferta un contrato predoctoral para trabajar en el grupo “The Eicosanoid Research Division” del Instituto de Biología y Genética Molecular (IBGM) del Consejo Superior de Investigaciones Científicas (CSIC) en Valladolid (http://www.balsinde.org). Nuestra aproximación científica para intentar descubrir nuevas formas de tratamiento de patologías humanas con un marcado carácter inflamatorio tales como la aterosclerosis, diabetes o cáncer es a través de estudiar defectos en la señalización celular mediada por lípidos en muestras de pacientes con enfermedad. Así, el trabajo a realizar por el/a candidato/a se centrará en la caracterización de los mecanismos de señalización intra- e intercelulares que ocurren durante la activación proinflamatoria de las células del sistema inmune innato en situaciones fisiopatológicas.

Dentro del amplia variedad de rutas de señalización que conectan la recepción de un estímulo con la ejecución de respuestas específicas, nuestro grupo se centra en aquellas que son mediadas por lípidos bioactivos. Los lípidos son fundamentales para la regulación celular y, por tanto, participan decisivamente en el mantenimiento de nuestros procesos homeostáticos. Los desequilibrios en el metabolismo de los lípidos son causa directa de estados patológicos como la diabetes o enfermedades cardiovasculares. Para poder tratar estas enfermedades con éxito, es importante saber qué lípidos están involucrados y qué hacen. Nuestro objetivo es entender cómo se regula el metabolismo de los lípidos en un contexto celular de activación inflamatoria.

La presente oferta de contrato predoctoral se enmarca dentro del proyecto de investigación titulado “Metabolismo y regulación de los plasmalógenos en inmunidad innata e inflamación”, financiado por el Ministerio de Ciencia e Innovación (PID2022-140764OB-I00). La lipina-2 es una fosfatasa de ácido fosfatídico dependiente de Mg^{2+} que participa en la ruta de biosíntesis de novo de los fosfolípidos. Esta enzima está ocupando en los últimos tiempos un lugar central en investigación inflamatoria debido a su participación en la regulación del ensamblaje del inflamasoma NLRP3, es decir, la plataforma multiproteica que media el procesamiento de la interleuquina-1β (IL-1β) en respuesta a agentes infecciosos y factores de estrés celular.

Trabajos previos del grupo han demostrado que los niveles de una clase de fosfolípidos relativamente menor, los plasmalógenos de etanolamina, están elevados en las mitocondrias de las células carentes de lipina-2 en comparación con las células normales. Estos aumentos son específicos de las mitocondrias, ya que no se observan cuando se utilizan homogeneizados de células enteras para los análisis lipidómicos. Por lo tanto, parece claro que existe algo único en los plasmalógenos de etanolamina de las mitocondrias que lo vincula directamente con las funciones reguladoras de la lipina-2. Desentrañar este algo, es decir, los mecanismos y acciones moleculares que involucran a los plasmalógenos de etanolamina y su relación con las respuestas mediadas por la lipina-2, constituye el objetivo principal de nuestro proyecto. Los plasmalógenos han recibido en general poca atención en comparación con muchas otras clases de lípidos a lo largo de los años. Sin embargo, esto está cambiando

recientemente debido a la posible asociación del metabolismo de los plasmalógenos con varios trastornos metabólicos y degenerativos, así como con el envejecimiento. Nuestro proyecto se articula en torno a tres objetivos específicos, todos ellos explorando territorios completamente desconocidos, que proporcionarán información clave para comprender cómo la lipina-2, al modular el metabolismo de los plasmalógenos, actúa como un freno que reduce los efectos nocivos de los factores de estrés que activan el inflamasoma. Dichos objetivos se formulan de la siguiente manera: (i) establecer los principios reguladores de la biosíntesis y degradación de plasmalógenos en macrófagos; (ii) definir el impacto del metabolismo de los plasmalógenos en la activación proinflamatoria de los macrófagos; y (iii) evaluar el papel de los plasmalógenos en modelos animales de enfermedades donde la activación del inflamasoma es clave.

El personal predoctoral seleccionado se integrará en principio en todos los objetivos a realizar con el fin de proporcionarle una preparación y visión lo más amplia posible de un campo tan competitivo como es el de la señalización inmune mediada por lípidos. Además, el personal predoctoral seleccionado realizará un plan de formacióm en el marco de dicho proyecto que incluirá las siguientes tareas: asistencia al ciclo de seminarios semanales de investigación organizados por el instituto; asistencia a cursos de formación ofrecidos por la Escuela de Doctorado de la Universidad de Valladolid (idiomas, cómo hablar en público, utilización de medios audiovisuales, etc); cotutela de trabajos de fin de grado y participación como ayudantes de prácticas en cursos de máster; asistencia a congresos y cursos avanzados nacionales e internacionales relacionados con la temática de su investigación; defensa pública del trabajo realizado con una periodicidad no inferior a tres meses; asistencia y participación activa en los “group meetings” organizados por el laboratorio.

Nuestro grupo de investigación es desde hace ya años un referente mundial en el estudio de las reacciones inflamatorias mediante aproximaciones lipidómicas basadas en espectrometría de masas. La lipidómica es la ciencia ómica que se encarga de estudiar el devenir de los lípidos durante el desarrollo de distintos procesos celulares. Esta metodología está basada en el uso de espectrómetros de masas, que pueden definir de forma muy rigurosa la estructura y concentración de muy diversas moléculas.

El/la contratado/a predoctoral seleccionado/a formará parte de un equipo multidisciplinar centrado en el estudio de patologías de base inmunoinflamatoria y podrá aprender muy diversas técnicas, tales como cultivo celular, citometría de flujo, PCR cuantitativa, estudio de lípidos por cromatografía de capa fina y espectrometría de masas, immunoblot, microscopía confocal, etc. Prueba de la buena formación recibida, nuestro personal ha encontrado fácilmente empleo inmediatamente después de graduarse en centros de investigación tanto públicos como privados, así como en empresas de base biotecnológica.

LINEAS DE INVESTIGACION, ACTIVIDADES Y PROGRAMAS QUE SE DESARROLLAN EN EL GRUPO A LOS QUE SE INCORPORARIA LA PERSONA BENEFICIARIA

Our group has been conducting research on bioactive lipid signaling in Spain for more than 20 years now. The achievements obtained have been many along these years, as reflected by our publication records in discriminating journals, and continuous funding. Many of our contributions have received wide attention as manifested by the high number of citations received, which attests to their relevance and scientific impact. The group is well recognized at an international level by its long-standing contributions to understand the importance of cellular compartmentalization in the regulation of phospholipid hydrolysis and arachidonate signaling. Recent highlights of our research include the discovery of (i) a key enzyme mediating the removal of oxidized or otherwise damaged residues from membranes, i.e. the group VIA phospholipase A_2, (ii) the mechanisms through which lipin-2 regulates the inflammasome; (ii) the anti-inflammatory properties and mechanism of action of the uncommon fatty acid hypogeic acid (cis-7-hexadecenoic acid); (iv) the key role that lipin-1 plays in inflammation-driven colon carcinogenesis; (v) the differential involvement of plasmalogens in innate immune reactions, among others. Importantly, the team has pioneered in Spain the use of mass spectrometry-based lipidomic approaches to study lipid signaling in health and disease. Our group enjoys leadership status in this area that is reflected by the high number of requests to carry out lipidomic analyses from both Spain and abroad.

Numerous signal transduction processes involve lipids as signaling molecules. Many of these molecules are generated by phospholipases such as phospholipase A_2, which releases fatty acids like arachidonic acid, and lysophospholipids. Each of these products is implicated in signal transduction processes, but also serves as a precursor for platelet activating factor or the eicosanoids. The eicosanoids are a large family of bioactive mediators that derive from the enzymatic oxygenation of arachidonic acid. Prostaglandins, leukotrienes, thromboxane, lipoxins, are all members of the eicosanoid family. Circulating monocytes and tissue macrophages are major sources of these compounds. The eicosanoids are biomedically important because they mediate all four signs of inflammation, namely heat, redness, swelling and pain. Controlling the formation of eicosanoids has been found to be of great benefit for the treatment of acute and chronic inflammatory diseases.

Lipid signaling is also key to the development of cardiovascular disease, one of the most prevalent inflammatory disorders. Atherosclerosis is the primary cause for cardiovascular disease, and diabetes increases the risk several-fold by enhancing the formation and/or progression of atherosclerotic lesions, a process in which abnormally-activated monocytes and macrophages appear to play a major role. In diabetes, these cells appear to be in a proinflammatory state, releasing elevated amounts of cytokines and

eicosanoids that perpetuate the inflammatory condition. Monocytes/macrophages from diabetic patients have been found to exhibit enhanced expression of Toll-like receptors 2 and 4. These receptors sense bacterial pathogens but also endogenous danger molecules such as saturated free fatty acids, typically present at elevated amounts in obese individuals.

Our current research focuses primarily on the lipid signaling enzymes phospholipase A_2 and phosphatidate phosphatase, also called **lipin**. The latter is a key enzyme in the de novo pathway for glycerolipid biosynthesis, providing an excellent example that enzymes involved in this pathway may also act to initiate intracellular signaling. General events that we are interested in include (i) the spatiotemporal regulation of these phospholipases in a cellular context, which we study utilizing advanced microscopy techniques, (ii) pharmacological manipulation of enzymatic activity both in intact cells and in vitro, (iii) analysis of lipid metabolite production by state-of-the-art mass spectrometry (lipidomics & metabolipidomics), and (iv) the physiological functioning of these phospholipases in animal models.

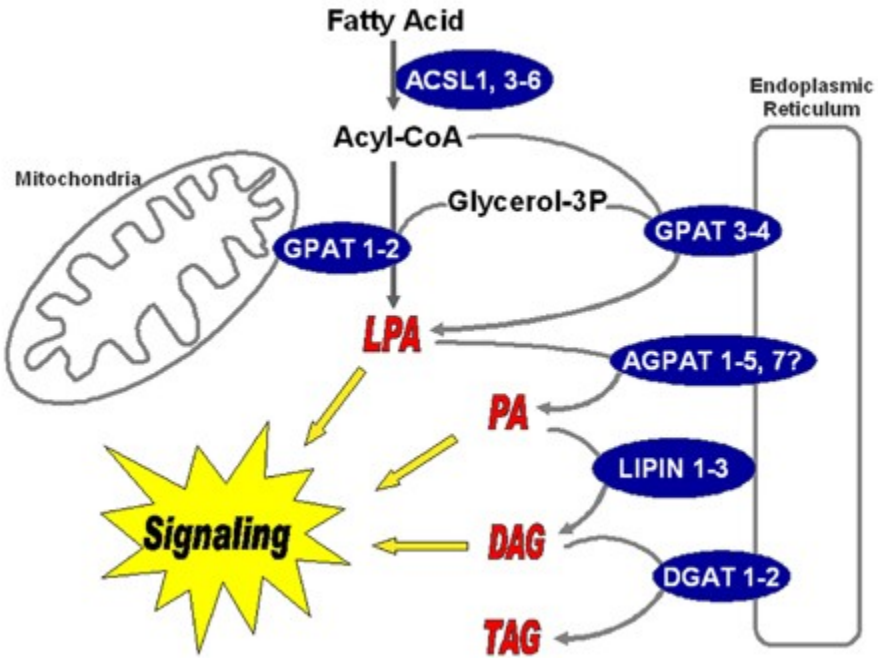

Figure 1. Intermediary metabolites of the de novo pathway of lipid biosynthesis also participate in signaling.

Ongoing studies in our labs focus on the localization and stimulus-driven translocation of different members of the phospholipase A_2 and lipin families. Phospholipase A_2s cleave the fatty acid at the sn-2 position of phospholipids and thus constitute the earliest regulatory point of the eicosanoid biosynthetic cascade. Lipins dephosphorylate phosphatidic acid to form diacylglycerol, which can be used for the biosynthesis of glycerophospholipids and triacylglycerol, and may function as intracellular signalers as well. Current studies are carried out by transfecting chimeric constructs of green fluorescent protein (GFP) (or any of

its colored varieties) with the appropriate phospholipase. GFP is placed at either the N- or C-termini. of the enzymes. These constructs provide a very useful tool to visualize the intracellular movements of the enzymes in response to the different stimuli.

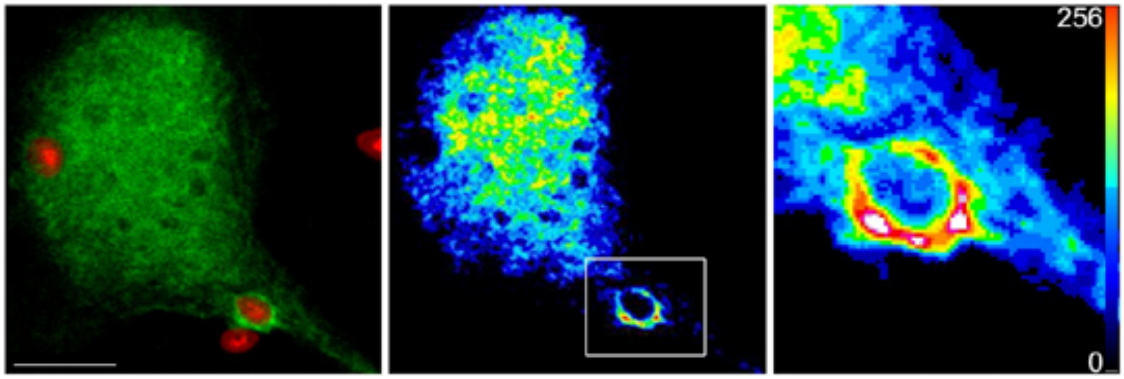

Figure 2. cPLA$_2$α translocates to the phagocytic cup in human macrophages, as demonstrated using GFP constructs.

Another of our goals is to apply a **lipidomics approach** to the study of the mechanisms governing the availability and oxidative metabolism of free arachidonic acid during activation of macrophages by stimuli of the innate immune response. Availability of free arachidonate is a limiting step for the synthesis of eicosanoids. While the pathways of fatty acid uptake, incorporation and remodeling in glycerolipids are well documented, the individual lipid species in which arachidonate is stored and released from have been very difficult to identify. This is so because of the impossibility of traditional methods for lipid separation (i.e. thin-layer chromatography, liquid chromatography) to differentiate among individual lipids within various classes and subclasses. This is now possible with the advent of electrospray mass spectrometry (ESI-MS). Application of this technology to the field of lipid biochemistry has been a major breakthrough in profiling the lipidomes of cells and tissues in physiological and pathophysiological conditions. We are conducting lipidomic analyses of all the lipid molecular species involved in arachidonic acid homeostasis, from those that act as acceptors of the fatty acid to those from which the fatty acid is liberated for subsequent eicosanoid synthesis, and including as well a full survey of arachidonate-derived oxygenated metabolites. These studies are also extended to other fatty acid and glycerophospholipid families such as e.g. the **plasmalogens**.

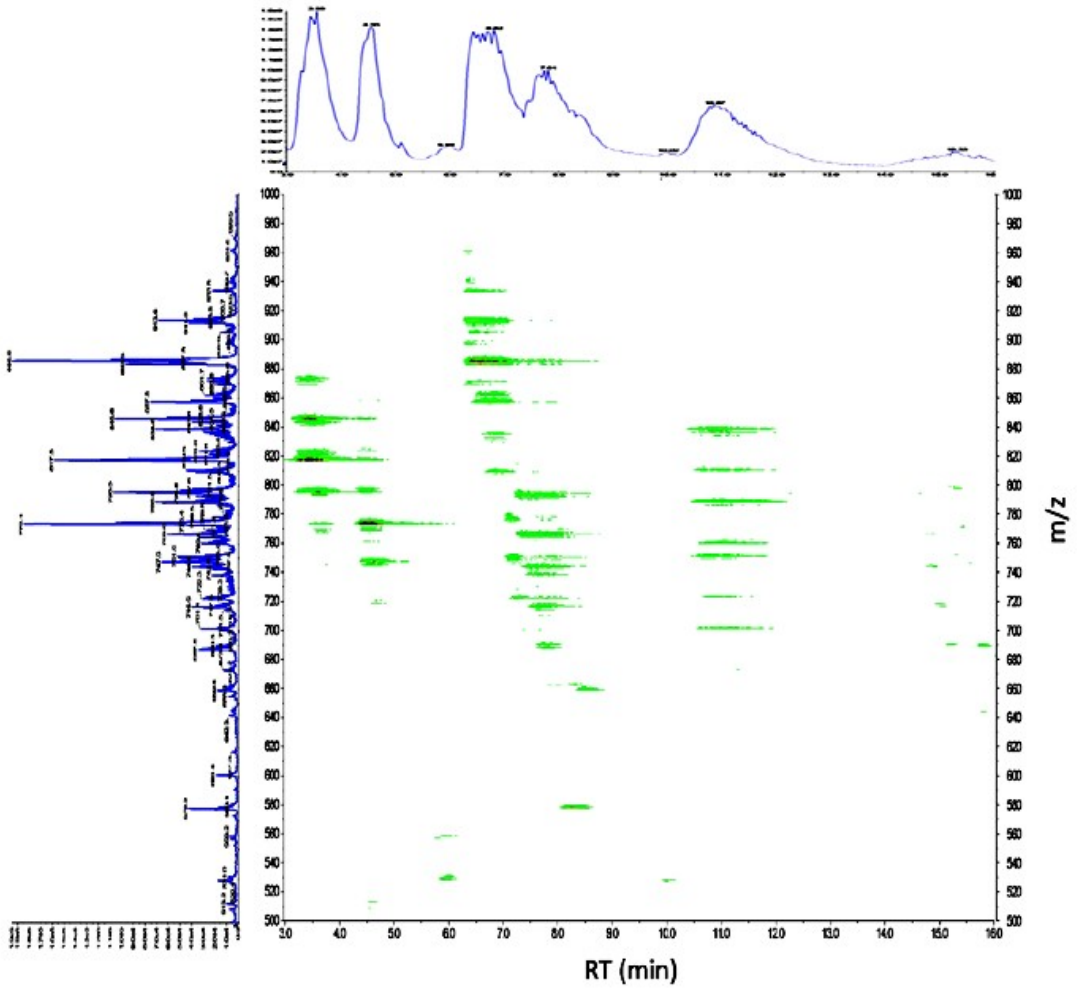

Figure 3. Analysis of cellular phospholipids by advanced mass spectrometry techniques.

We also conduct studies aimed to define the regulation of **lipid droplet formation** in cells involved in inflammation. Lipid droplets are cytosolic inclusions present in most eukaryotic cells that contain a core rich in neutral lipids such as triacylglycerol and cholesteryl esters and are surrounded by a phospholipid monolayer decorated with a variety of proteins. Initially regarded as inert neutral lipid-storage compartments, the interest for lipid droplets has increased recently because of their association with diabetes and atherosclerosis. Our results have defined group IVA phospholipase A_2 as a key regulator of lipid droplet formation. Also, subcellular localization studies have shown that lipin-1 localizes permanently on the surface of these organelles, thus suggesting a metabolic or regulatory role for this enzyme. Lipidomic analyses of the composition of lipid droplets formed under various conditions, have uncovered the presence of unusual fatty acids in these organelles, such as hpogeic acid (cis-7-hexadecenoic acid) Some of these fatty acids might play a role in regulating specific cellular responses.

Our recent studies dealing with the role of lipins in **innate immune signaling** and their involvement in pathophysiological states have yielded very interesting results. For

instance, we showed that, upon palmitate overload, lipin-2 controls the production of the proinflammatory cytokines TNF-α and IL-6, and the chemotactic factor MCP-1 in macrophages. We have extended these studies to the generation of IL-1β by classical activators of the NLRP3 inflammasome, i.e. bacterial lipopolysaccharide (LPS) plus ATP, and found a similar role for lipin-2; that is, the enzyme decreases NLRP3 activation, this occurring by a mechanism involving inhibition of the activation and sensitization of the purinergic receptor $P2X_7$, and K^+ efflux. Thus our work provided convincing evidence that the autoinflammatory disease known as Majeed syndrome, which develops in patients with a mutated *LPIN2* gene, –encoding lipin-2–, is an **NLRP3 inflammasomopathy**. Our studies support the emerging paradigm that lipin-2 acts as a **cellular brake** that reduces the deleterious effects of cellular stressors which activate pro-inflammatory pathways in macrophages including the NLRP3 inflammasome.

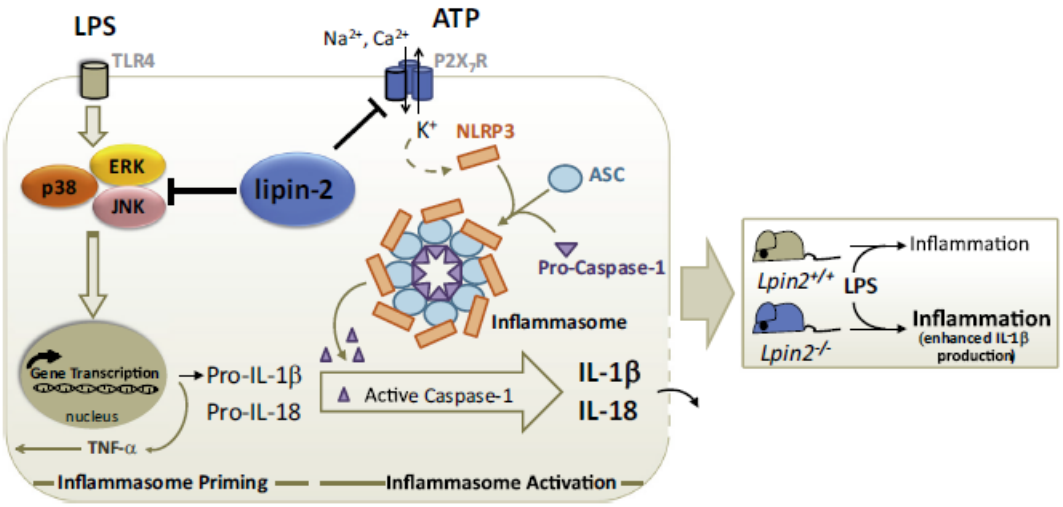

Figure 4. Lipin-2 controls inflammasome activation.

On the other hand, our studies with another member of the lipin family, **lipin-1**, have unveiled its role in the development of inflammatory diseases such as colitis and colitis-drivev carcinogenesis, and also in metabolic diseases with an inflammatory component like rhabdomyolisis or alcoholic liver disease.

To conclude, all of our lines of research rely heavily on biochemical and analytical methods to identify specific reactions and the mechanisms through which the products of said reactions are formed. With this information, we expect to delineate pathways responsible for disease. We combine a range of chemical, biochemical, pharmacological, and molecular cell biology techniques to study pathophysiologically-relevant problems involving alterations in lipid metabolism and signaling.

PUBLICACIONES RECIENTES DEL GRUPO RECEPTOR
(ULTIMOS 10 AÑOS)

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3. Bermúdez, M.A., Rubio, J.M., Balboa, M.A. & Balsinde, J. (2022) Differential mobilization of the phospholipid and triacylglycerol pools of arachidonic acid in murine macrophages. *Biomolecules* 12: 1851 **(Q1, Biochemistry & Molecular Biology – IF: 6.064)**

4. Albert, M.; Vázquez, J.; Falcón-Pérez, J.M.; Balboa, M.A., Liesa, M., Balsinde, J. & Guerra, S. (2022) ISG15 as a novel regulator of lipid metabolism and implications for its antiviral activity. Microbiol. Spectr. 10: e03893-22 **(Q1, Microbiology – IF: 9.043)**

5. Bermúdez, M.A., Pereira, L., Fraile, C., Valerio, L., Balboa, M.A. & Balsinde, J. (2022) Roles of palmitoleic acid and its positional isomers, hypogeic and sapienic acids, in inflammation, metabolic diseases and cancer. *Cells* 11: 2146 **(Q2, Cell Biology – IF: 7.666)**

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10. Balboa, M.A. & Balsinde, J. (2021) Phospholipases: from structure to biological function. *Biomolecules* 11: 428 **(Q2, Biochemistry & Molecular Biology – IF: 4.879)**

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43. Gil-de-Gómez, L., Astudillo, A. M., Meana, C., Rubio, J. M., Guijas, C., Balboa, M. A. & Balsinde, J. (2013) A phosphatidylinositol species acutely generated by activated macrophages regulates innate immune responses. *J. Immunol.* 190: 5169–5177 **(Q1, Immunology – IF: 5.362)**

TESIS DOCTORALES REALIZADAS EN EL GRUPO RECEPTOR
(ULTIMOS 10 AÑOS)

PhD Theses Completed

1. **Patricia Monge Bartolomé** (predoctoral fellow from Junta de Castilla y León). Thesis title: "Análisis lipidómico de los cambios en el metabolismo lipídico que tienen lugar durante la activación de los macrófagos peritoneales de ratón por estímulos proinflamatorios." University of Valladolid. Date: December 7, 2022. Publications: *Biomolecules 10: 542, 2020*; *Biomedicines 8: 274, 2020*.

2. **Laura Pereira de Blas** (predoctoral fellow from Junta de Castilla y León) Thesis title: "Estudio lipidómico de la activación y maduración de células dendríticas. Efecto del ácido araquidónico y de los isómeros del ácido hexadecenoico." University of Valladolid. Date: July 14, 2022. Publications: *J. Lipid Res*. 59: 237–249, 2018; *J. Lipid Res*. 59: 2308–2320, 2018; *Cells* 8: 941, 2019; *Cells 11, 2146, 2022*; *Cell Death Differ. 29: 2362–2380, 2022*.

3. **Miguel Angel Bermúdez Arias** (FPI predoctoral fellow from "Convocatoria de contratos predoctorales del Subprograma Estatal de Formación", ref. BES-2017-079872, associated to grant SAF2016-80883-R). Thesis title: "Regulación de la respuesta inflamatoria de las células fagocíticas por lípidos. Papel del ácido araquidónico y de los isómeros del ácido palmitoleico." University of Valladolid. Date: May 28, 2021. Publications: *Cells* 8: 941, 2019; *Biomedicines 8: 480, 2020*; *Biomedicines 9: 1891, 2021*; *Cells 11, 2146, 2022*; *Biomolecules 12: 1851, 2022*.

4. **Patricia Lebrero Fernández** (predoctoral fellow from Universidad de Valladolid). Thesis title: "Phospholipid arachidonic acid remodeling in macrophages: Role of plasmalogen species." University of Valladolid. Date: November 22, 2019. Publications: *Front. Immunol*. 8: e1251, 2017; *J. Lipid Res*. 59: 237–249, 2018; *Cells* 8: e799, 2019.

5. **Nagore de Pablo Herranz** (FPU predoctoral fellow from Ministerio de Educación, Cultura y Deporte). Thesis Title: "Modulation of macrophage antiviral responses by lipin-2." University of Valladolid. Date: November 18, 2019. Publications: *J. Exp. Med*. 214: 511–528, 2017; *Biochim. Biophys. Acta* 1864: 1328–1337, 2019.

6. **Miren Itziar Sanjuán García** (FPI predoctoral fellow from "Convocatoria de contratos predoctorales del Subprograma Estatal de Formación", ref. BES-2014-069034, associated to grant SAF2013-48201-R). Thesis title: "Regulation of macrophage responses to palmitic acid." University of Valladolid. Date: November 15, 2019. Publications: *J. Exp. Med*. 214: 511–528, 2017.

7. **Gema Lordén Losada** (FPU predoctoral fellow from Ministerio de Educación, Cultura y Deporte). Thesis title: "Regulación de la activación del inflamasoma NLRP3 en macrófagos". University of Valladolid. Date: July 11, 2016. Publications: *J. Immunol*. 193: 4614–4622, 2014; *Biochim. Biophys Acta* 1861: 1083–1095, 2016; *J. Exp. Med*. 214: 511–528, 2017; *JCI Insight* 3: e97506, 2018.

8. **Carlos Guijas Maté** (predoctoral fellow from Universidad de Valladolid). Thesis title: "Regulación de la formación de gotas lipídicas por ácido araquidónico en monocitos humanos". University of Valladolid. Date: March 18, 2016. Publications: *Biochim. Biophys. Acta* 1811: 97–103, 2011; *J. Immunol*. 186: 6004–6013, 2011; *Biochim. Biophys. Acta* 1821: 1386–1393, 2012; *J. Lipid Res*. 53: 2343–2354, 2012; *J. Immunol*. 190: 5169–5177, 2013; *J. Immunol*. 192: 752–762, 2014; *J. Immunol*. 193: 4614–4622, 2014; *Biochim. Biophys. Acta* 1841: 1661–1671, 2014; *J. Immunol*. 194: 3327–3339, 2015; *Cell Chem. Biol*. 23: 689–699, 2016; *J. Lipid Res*. 59: 237–249, 2018; *Cancers* 11: 524, 2019, *Cells* 8: 941, 2019; *Biomolecules 10: 891, 2020*; *Cells 10: 447, 2021*;

9. **Lucía Peña Moreno** (FPI predoctoral fellow from "Convocatoria de contratos predoctorales del Subprograma Estatal de Formación", ref. BES-2008-009356, associated to grant SAF2007-60055) Thesis title: "Papel de la fosfolipasa A_2 citosólica de grupo IVA en la diferenciación

adipocítica y en el desarrollo de obesidad inducida por dieta rica en grasa". University of Valladolid. Date: July 25, 2014. Publications: *J. Biol. Chem.* 287: 10894–10904, 2012; *J. Immunol.* 193: 4614–4622, 2014; *Biochim. Biophys Acta* 1861: 1083–1095, 2016; *JCI Insight* 3: e97506, 2018.

10. **Luis Gil de Gómez Sesma** (FPI predoctoral fellow from "Convocatoria de contratos predoctorales del Subprograma Estatal de Formación", ref. BES-2008-004681, associated to grant BFU2007-67154) Thesis title: "Estudio lipidómico de la liberación de ácido araquidónico asociada a la respuesta inmune innata". University of Valladolid. Date: January 25, 2013. Publications: *Biochim. Biophys. Acta* 1811: 97–103, 2011; *J. Immunol.* 186: 6004–6013, 2011; *J. Biol. Chem.* 287: 10894–10904, 2012; *Biochim. Biophys. Acta* 1821: 1386–1393, 2012; *J. Lipid Res.* 53: 2343–2354, 2012; *J. Immunol.* 190: 5169–5177, 2013; *J. Immunol.* 192: 752–762, 2014; *J. Immunol.* 194: 3327–3339, 2015; *Front. Immunol.* 8: 1251, 2017; *Biomedicines 8: 274, 2020*.

PhD Theses in Progress

1. **Alvaro Garrido Jiménez** (predoctoral fellow from Junta de Castilla y León) Provisional thesis title: "Lipidomic studies in cells deficient in lipins -1 and -2." University of Valladolid. Expected date of defense: October 2023. Publications: *Biomolecules 10: 542, 2020*.

2. **Javier Martínez García** (predoctoral fellow from Junta de Castilla y León) Provisional thesis title: "Regulation of lipin-2-mediated responses by interferons" University of Valladolid. Expected date of defense: 2024. Publications: none yet.

3. **Teresa Garrido García** (FPI predoctoral fellow from "Convocatoria de contratos predoctorales del Subprograma Estatal de Formación", ref. PRE2020-091973, associated to grant PID2019-105989RB-I00). Provisional thesis title: "Phospholipid signatures that define novel activation states of macrophages." University of Valladolid. Expected date of defense: 2025. Publications: none yet.

4. **Laura Valerio Núñez** (predoctoral fellow from Junta de Castilla y León) Provisional thesis title: "Anti-inflammatory responses of macrophages and their regulation by lipin-2." University of Valladolid. Expected date of defense: 2026. Publications: *Cells 11, 2146, 2022*.

5. **Cristina Fraile Sánchez** (predoctoral fellow from Junta de Castilla y León) Provisional thesis title: "Signal-specific reprogramming of the macrophage lipidome." University of Valladolid. Expected date of defense: 2026. Publications: *Cells 11, 2146, 2022*.