

# VI Reunión Red Glial Española

24 y 25 de Septiembre, 2013

Universidad de Oviedo

Facultad de Psicología

Sala de Grados (1º Planta)

Plaza Feijo s/n

33033 Oviedo

Comité Organizador:

**Red Glial Española**

Alfonso Araque, Anna Planas, Luis Miguel Segura,

Diego Gómez Nicola, Ismael Galve Roperh,

Jose Luis Marin Teva, Victoria Moreno,

Amanda Sierra, Marta Mendez y Jorge Arias



**RedGlialEspañola**



## **PROGRAMA DE LA VI REUNION RED GLIAL ESPAÑOLA**

**24 de Septiembre de 2013: Facultad de Psicología. Plaza Feijoo s/nº 33003 Oviedo. Sala de Grados (Primera Planta)**

**15:00** Presentación/Aertura Alfonso Araque

**15:45** Presentaciones orales:

Josep Saura. *Conditional C/EBP $\beta$ -deficient microglia show attenuated proinflammatory gene expression*

Diego Gomez-Nicola. *Regulation of microglial proliferation in chronic neurodegeneration*

Carme Sola. *Mecanismos implicados en el control de la expresion del receptor inmune inhibitorio microglial CD200R1 en presencia de neuroinflamacion*

Raul Estevez. *Analysis of a MLC1 KO mouse model provide new insights in the pathophysiology of the leukodystrophy MLC: Chloride channels are not working properly*

**17:15** Descanso

**17:45** Conferencia plenaria Jean Pierre Mothet (Titulo por confirmar)

**18:30** Presentaciones orales

Daniel Garcia-Ovejero. *Adult spinal cord stem cell niche: an insight into the actual human situation*

Javier Diaz-Alonso. *Expansion of Tbr2 intermediate progenitors in the developing mouse cortex via CB1 cannabinoid receptor/mTORC1 signaling*

Antonio J Jimenez. *Role of a particular astrocyte reaction in the repairment of the cerebral cortex*

Rosa De Hoz. *Efectos de un gen p53 supernumerario en la astrogliá de la retina del ratón*

**20:00** Clausura

**25 de Septiembre de 2013: Hotel Reconquista, sede del XV Congreso de la SENC**

**10:00** Presentación del II Premio Laia Acarin. Covadonga Room

**10:30** Asamblea general de la Red Glial Española. Covadonga Room

**11:00** Sesión de posters de la Red Glial Española. Patio de la Reina

## SEDES Y LOCALIZACIÓN

Los actos programados para el día 24 de Septiembre tendrán lugar en:

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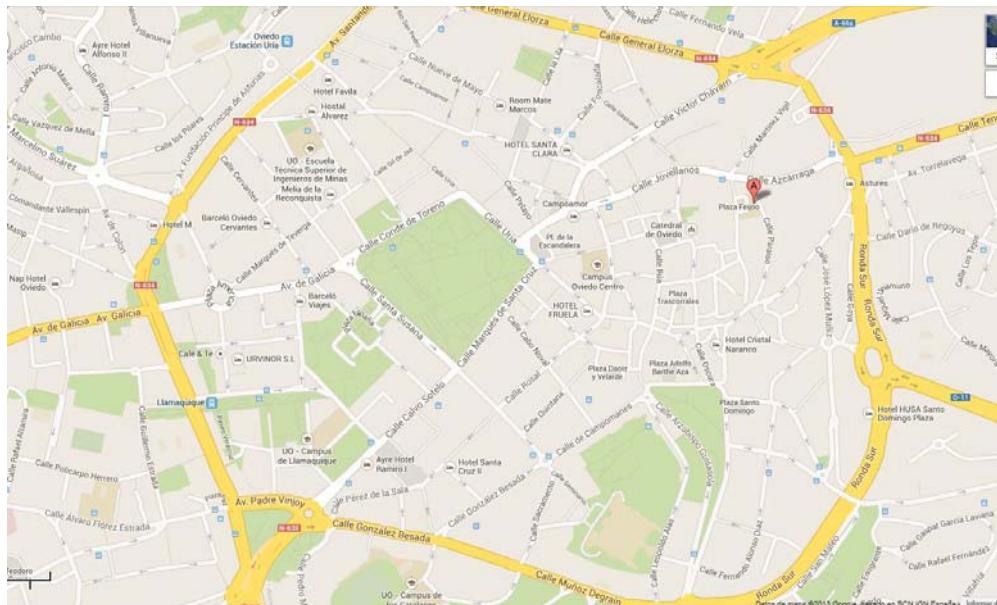
Facultad de Psicología  
Plaza Feijoo s/nº  
33003 Oviedo  
Sala de Grados (Primera Planta)

*\*La Facultad está situada justo detrás de la Catedral gótica de Oviedo*

### **Información complementaria:**

Hay una cafetería en la planta baja y servicios en la misma primera planta a 20 metros de la sala.

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Los actos programados para el día 25 de Septiembre tendrán lugar en:

MELIÁ HOTEL DE LA RECONQUISTA  
Gil de Jaz 16 - 33004, Oviedo. Tel: (34) 985 24 11 00  
Fax: (34) 94 985 24 60 11 -  
[www.hoteldelareconquista.com](http://www.hoteldelareconquista.com)

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Gomez-Nicola D, Fransen NL, Suzzi S and Perry VH

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Guido Dentesano, Joan Serratosa, Josep M. Tusell, Josep Saura y Carme Solà.

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S. Sirisi<sup>1,2</sup>, I. Ferrer<sup>1,2</sup>, C. Vilchez<sup>2</sup>, M. López de Heredia<sup>2,3</sup>, V. Nunes<sup>1,2,3</sup>, R. Estévez<sup>1,3</sup>

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D. Garcia-Ovejero<sup>1</sup>, Angel Arevalo-Martin<sup>1</sup>, Beatriz Paniagua-Torija<sup>1</sup>, José Florensa-Vila<sup>1</sup>, Isidro Ferrer<sup>2</sup>, Eduardo Molina-Holgado

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Javier Díaz-Alonso<sup>1,2</sup>, Tania Aguado<sup>1,2</sup>, Adán de Salas-Quiroga<sup>1,2</sup>, Zaira Ortega<sup>1,2</sup>, Inmaculada de Prada<sup>3</sup>, María Ángeles Pérez-Jiménez<sup>3</sup>, Eleonora Aronica<sup>4</sup>, Manuel Guzmán<sup>1,2</sup>, Ismael Galve-Roperh<sup>1,2,\*</sup>; [javierdiaz@bbm1.ucm.es](mailto:javierdiaz@bbm1.ucm.es)

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A.J. Jiménez<sup>1</sup>, R. Roales-Buján<sup>1</sup>, L. M. Rodríguez-Pérez<sup>1</sup>, M. D. Domínguez-Pinos<sup>1</sup>, A. Ho-Plagaro<sup>1</sup>, M. García-Bonilla<sup>1</sup>, M. C. Roquero-Mañueco<sup>1</sup>, M. I. Martínez-León<sup>2</sup>, S. Jiménez<sup>3,4</sup>, J. Vitorica<sup>3,4</sup>, A. Gutiérrez<sup>1,4</sup>, J. M. Pérez-Figares<sup>1</sup>

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## **C8. EFECTOS DE UN GEN P53 SUPERNUMERARIO EN LA ASTROGLÍA DE LA RETINA DEL RATÓN**

Rosa de Hoz<sup>1,a</sup>, Blanca Rojas<sup>1,b</sup> Juan J. Salazar<sup>1,a</sup>, Ana I. Ramírez<sup>1,a</sup>, Beatriz I Gallego<sup>2,b</sup>, Roberto Gallego-Pinazo<sup>3,c</sup>, María D. Pinazo-Durán<sup>4,d</sup>, , Manuel Serrano<sup>5,e</sup>, José M. Ramírez<sup>6,b</sup>

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## **POSTERS:**

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M. Benito Muñoz, C. Matute, F. Cavalieri

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M. Canedo-Antelo, C. Matute, M.V. Sánchez-Gómez

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Gallego Collado BI<sup>1,3</sup>, Ramírez Sebastián AI<sup>2,3</sup>, Salazar Corral JJ<sup>2,3</sup>, Rojas López B<sup>2</sup>, de Hoz Montañana, R<sup>2,3</sup> García Martín ES<sup>1,3</sup>, Triviño Casado A<sup>2</sup>, Ramírez Sebastián JM<sup>2</sup>.

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N. García-Mateo<sup>1</sup>, M.D. Ganfornina<sup>1</sup>, C. Lillo<sup>2</sup>, O. Montero<sup>3</sup>, M.A. Gijón<sup>4</sup>, R. Murphy<sup>4</sup>, D. Sánchez<sup>1</sup>

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Ana Belen Lopez-Rodriguez (1,2), Estefania Acaz-Fonseca (2), Maria-Paz Viveros (1), Luis M. Garcia-Segura (2).

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S. Martín-Suárez<sup>1,2</sup>, R. Valcárcel-Martín<sup>1,2</sup>, J. Pascual-Brazo<sup>3</sup>, A. Brewster<sup>4</sup>, AE. Anderson<sup>4</sup>, V. Baekelandt<sup>3</sup> and JM Encinas<sup>1,2,5</sup>.

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EM Medina-Rodríguez<sup>1</sup>, J Pastor<sup>2</sup>, R García de Sola<sup>3</sup>, C Gil<sup>4</sup>, A Martínez<sup>4</sup>, A Bribián<sup>1\*</sup> and F de Castro<sup>1\*</sup>.

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Maximina Monzón-Mayor<sup>1</sup>, María del Mar Romero-Alemán<sup>1</sup>, Elena Santos<sup>2</sup> and Carmen M. Yanes<sup>2</sup>.

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R. Valcárcel-Martín<sup>1, 2</sup>, S. Martín-Suárez<sup>1, 2</sup>, A. Sierra<sup>1, 2, 4</sup>, M. Maletic-Savatic<sup>3</sup> and J. M. Encinas<sup>1, 2, 4</sup>.

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A Wyssenbach, F Llavero, JL Zugaza, C Matute and E Alberdi

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C. Yanes<sup>1</sup>, E. Santos<sup>1</sup>, MM. Romero-Alemán<sup>2</sup>, N. Armas<sup>1</sup> & M. Monzón-Mayor<sup>2</sup>.

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Ester Bonfill-Teixidor, Angélica Salas, Isabel Pérez-de Puig, Anna M. Planas

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M. Martín-Estebeñá, JL. Marín-Teva, MA. Cuadros, A. Sierra, MC. Carrasco, RM. Ferrer-Martín, D. Martín-Oliva, R. Calvente, J. Navascués.

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**P19. DESACOPLAMIENTO APOPTOSIS-FAGOCITOSIS DURANTE LA EXCITOTOXICIDAD ASOCIADA A LA EPILEPSIA.**

O. Abiega<sup>1,2</sup>, S. Beccari<sup>1,2</sup>, J. M. Encinas<sup>1,2,3</sup>, A. L. Brewster<sup>4</sup>, A.E. Anderson<sup>4</sup>, M. Maletic-Savatic<sup>4</sup>, C. Matute<sup>1,2</sup>, A. Sierra<sup>1,2,3</sup>

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**LISTA DE PARTICIPANTES**

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**CONDITIONAL C/EBPB-DEFICIENT MICROGLIA SHOW ATTENUATED PROINFLAMMATORY GENE EXPRESSION**

Pulido-Salgado M (1), Valente T (1,2), Vidal-Taboada J (1), Straccia M (1,2), Tusell JM (2), Solà C (2), Saura J (1)

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**Introduction:** We have recently shown that the transcription factor CCAAT/enhancer binding protein  $\beta$  (C/EBP $\beta$ ) regulates proinflammatory gene expression in activated microglia. Microglial C/EBP $\beta$  is therefore a potential target to attenuate the neurotoxic effects of neuroinflammation. Mice with specific C/EBP $\beta$  deletion in microglia are required to test this hypothesis *in vivo*, since C/EBP $\beta$  knockout mice show multiple phenotypic alterations as a result of the widespread expression of C/EBP $\beta$ . There is not a gold standard promoter for microglial Cre expression. Among other promoters CD11b, CX3CR1 and Lysozyme M (LysM) have been used to this end.

**Objective:** We have generated LysM-Cre/C/EBP $\beta$ fl/fl mice with two main aims: 1) To validate the use of LysM as a suitable promoter for microglial gene deletion by Cre-Lox recombination. 2) To analyze the effects of the absence of microglial C/EBP $\beta$  *in vitro* and *in vivo*

**Methods and Results:** LysM-Cre/C/EBP $\beta$ fl/fl mice were fertile and viable and did not show female infertility and high perinatal mortality described in C/EBP $\beta$  knockout mice. Western blot and immunocytochemistry experiments revealed the presence of C/EBP $\beta$  in wild-type but not in LysM-Cre/C/EBP $\beta$ fl/fl microglial cultures. In wild-type primary mixed glial cultures C/EBP $\beta$  immunoreactivity was observed both in astrocytes and microglia, whereas in LysM-Cre/C/EBP $\beta$ fl/fl mixed glial cultures it was detected in astrocytes, but never in microglia, thus demonstrating the microglial specificity of LysM-Cre recombination. To assess the functional outcome of microglial C/EBP $\beta$  deficiency, we analyzed LPS+IFN $\gamma$ -induced NO production and we observed a marked decrease in LysM-Cre/C/EBP $\beta$ fl/fl microglial cultures. Finally, we have analyzed the effect of genotype (wild type vs C/EBP $\beta$ -deficient) and treatment (control vs LPS+IFN $\gamma$ ) on global RNA expression by using RNAseq in primary microglial cultures. Preliminary results show a marked attenuation of LPS+IFN $\gamma$ -induced changes in proinflammatory gene expression profile in C/EBP $\beta$ -deficient microglia.

**Conclusion:** These findings show that LysM-Cre promoter causes recombination in virtually all microglial cells in primary culture and it is therefore suitable for microglial-specific gene deletion *in vitro*. They also show that microglial C/EBP $\beta$  absence results in a marked attenuation of the proinflammatory gene expression profile. Experiments are in progress to determine the degree and specificity of microglial C/EBP $\beta$  deletion *in vivo* in these mice. Supported by grants PI10/378 and PI12/709 from Instituto de Salud Carlos III, Spain.

**Keywords:** Microglia, Astrocytes, C/EBP $\beta$ , Transcription factors, NOS2, LPS, IFN $\gamma$ , Transgenic mice,

## REGULATION OF MICROGLIAL PROLIFERATION IN CHRONIC NEURODEGENERATION

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An important aspect of chronic neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's and prion disease, is the generation of an innate inflammatory response within the central nervous system (CNS). Microglial and astroglial cells play a key role in the development and maintenance of this inflammatory response, showing enhanced proliferation and morphological activation. Using a laboratory model of chronic neurodegeneration (ME7 murine model of prion disease), we studied the time-course and regulation of microglial proliferation. Our results show that resident microglial cells have an increased proliferation rate during the development of the disease, leading to a significant increase in the population, without a contribution from circulating cells. Microglial proliferation is differentially regulated in diverse regions of the CNS, pointing to a heterogeneous development of the pathology. We have identified novel molecular regulators of the proliferative response, and addressed the significance of the contribution of microglial cells to the pathological course of the disease by modifying their proliferation. We also found a correlation of our results with the scenario present in chronic human neurodegenerative conditions variant Creutzfeldt-Jakob Disease (vCJD) and Alzheimer's disease.

Our results demonstrate that microglial proliferation is an important feature of the evolution of chronic neurodegenerative disease, with direct implications for understanding the contribution of the CNS innate immune response to disease progression.

*Palabras clave: microglia, neurodegeneración, proliferacion, neuroinflamacion*

## MECANISMOS IMPLICADOS EN EL CONTROL DE LA EXPRESIÓN DEL RECEPTOR INMUNE INHIBITORIO MICROGLIAL CD200R1 EN PRESENCIA DE NEUROINFLAMACIÓN

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Las células de la microglía son los principales componentes del sistema inmune intrínseco del sistema nervioso central. En presencia de estímulos nocivos, desarrollan fenotipos reactivos destinados a re establecer la homeostasis cerebral y minimizar el daño neuronal. Sin embargo, la microglía reactiva produce una serie de factores, típicos de una respuesta inflamatoria, con un efecto neurotóxico potencial. Por lo tanto, el progreso y la resolución de la activación microglial deben estar estrictamente controlados para evitar posibles efectos secundarios nocivos. Señales neuronales juegan un papel importante en el control del estado de activación microglial. Entre ellas, mecanismos inhibitorios, como la interacción ligando-receptor CD200 (neuronal)-CD200R1 (microglial), mantienen la respuesta proinflamatoria microglial reprimida en condiciones fisiológicas. Se han descrito alteraciones en la expresión de CD200 y CD200R1 en el cerebro de individuos con enfermedades neurodegenerativas. Creemos que la modulación de la señalización CD200-CD200R1 podría ser una diana interesante para combatir la neuroinflamación como estrategia terapéutica adicional en enfermedades neurodegenerativas.

Se conocen poco los mecanismos moleculares implicados en la regulación de la expresión de CD200 y CD200R1. Utilizando aproximaciones experimentales *in vitro*, hemos estudiado la regulación de la expresión de CD200R1 en microglía por factores de transcripción implicados en la respuesta inflamatoria. Nos hemos centrado en C/EBP $\beta$ , que induce la expresión de genes proinflamatorios, y PPAR- $\gamma$ , involucrado en la inhibición de la respuesta proinflamatoria. Hemos observado que C/EBP $\beta$  contribuye a la inhibición de la expresión de CD200R1 que se detecta en respuesta a un estímulo proinflamatorio. A su vez, agonistas PPAR- $\gamma$  impiden dicha inhibición e inhiben la respuesta inflamatoria microglial. Además, la señalización vía CD200R1 está implicada en el efecto neuroprotector de dichos agonistas frente a la muerte neuronal inducida por microglia reactiva.

*Financiación: Fundación La Marató de TV3, proyectos PI10/378 y PI12/00709 del Instituto de Salud Carlos III. GD tiene un contrato predoctoral del IDIBAPS.*

*Palabras clave que identifican la línea de trabajo: enfermedades neurodegenerativas, neuroinflamación, microglía, respuesta inmune, CD200R1*

**ANALYSIS OF A MLC1 KO MOUSE MODELS PROVIDE NEW INSIGHTS IN THE PATHOPHYSIOLOGY OF THE LEUKODYSTROPHY MLC: CHLORIDE CHANNELS ARE NOT WORKING PROPERLY**

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Cell volume regulation is pivotal to ensure normal brain function. Its alteration can represent a serious challenge for neuronal survival due to space constrictions within the skull. Thus, brain edema is a major problem in neurology, leading to death in most cases, and it is caused by many defects such as stroke or brain cancer, among others. Our research approaches the study of cell volume regulation in the context of the human genetic disease Megalencephalic Leukoencephalopathy with subcortical Cysts (MLC), as a working model to study brain ionic transport pathophysiology.

MLC brains are affected by chronic white matter oedema suggesting a disruption in water and ion homeostasis in astrocytes, which in turn may alter their cell volume regulation abilities. MLC pathology was shown to be primarily caused by a defect in a highly conserved oligomeric plasma membrane protein named MLC1. MLC1 is mostly expressed in astroglial processes and presents low homology to ion channels.

However, both the pathophysiological mechanism of MLC disease as well as MLC1 function remained unknown until today, although MLC1 has been related with the activation of volume-regulated chloride channels. Recently, we have identified the second gene responsible for MLC pathology (i.e., GLIALCAM) (1) and described its biochemical role as a MLC1 beta subunit (2). Moreover, we have shown that GlialCAM protein functions as an accessory subunit of the chloride channel ClC-2 (Jeworutzki *et al.*, *Neuron* (2012)). In this meeting, we will provide new studies with a KO model of MLC1, indicating that dysfunction of chloride channels is a common physiopathological mechanism in MLC disease.

*Palabras clave:* *Leucodistrofia, glia, canales cloruro, volumen celular, sifoneo potasio*

## **ADULT SPINAL CORD STEM CELL NICHE: AN INSIGHT INTO THE ACTUAL HUMAN SITUATION**

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During the last few years, several groups have described the existence of neural stem/precursor cells around the central canal of the adult rodent spinal cord. This has uncovered an endogenous potential to replace damaged cells after injury, but it is unknown if it is also present in humans. Indeed, there are reports claiming that human central canal collapses in the adult life and may be different from that found in rodents.

We have studied human central canal in healthy volunteers by Magnetic Resonance Imaging, (1) to test if central canal collapse is a normal event or a postmortem artifact, like some authors interpret, and (2) to establish the normal levels of canal patency in the whole non-lesioned spinal cord. We have also used histochemistry and immunohistochemistry on fixed postmortem human tissue (control individuals deceased without a specific spinal cord damage) to study the structure of the central canal at different stages of obliteration.

We report that the absence of a patent canal is a common feature in the general population older than 18 years (less than 20% of individuals show patency at any level of the cord). We also report that human spinal cord central canal is notably different than its equivalent in rats and mice both in structure and in cytological composition. This may require a reappraisal of human ependyma as a neurogenic niche and its role in reparative strategies after spinal cord pathologies.

*Funded by The Wings for Life Spinal Cord Research Foundation and Fundación Mutua Madrileña*

**Palabras clave:** *Spinal cord, Neurogenesis, human, ependyma*

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**EXPANSION OF TBR2 INTERMEDIATE PROGENITORS IN THE DEVELOPING MOUSE CORTEX VIA CB<sub>1</sub> CANNABINOID RECEPTOR/MTORC1 SIGNALING**

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The CB<sub>1</sub> cannabinoid receptor regulates different aspects of cortical development and neuronal differentiation. Here we demonstrate that this receptor drives the expansion of the intermediate cortical progenitor pool in the developing mouse brain by inducing the expression of Tbr2/Eomes via the mammalian target of rapamycin complex 1 (mTORC1) pathway. Pharmacological stimulation of CB<sub>1</sub> receptor signaling in cortical slices and progenitor cell cultures increased Tbr2-expressing progenitor generation and mTORC1 pathway activity, assessed as the phosphorylation of its substrate the ribosomal protein S6, while acute CB<sub>1</sub> receptor genetic ablation exerted the opposite effects. Luciferase reporter assays based on Pax6-responsive elements and the Tbr2 promoter, together with ChIP analysis, showed that the CB<sub>1</sub> receptor drives Tbr2 expression downstream of Pax6 induction in an mTORC1-dependent manner. Examination of CB<sub>1</sub> receptor-deficient mouse embryos revealed premature cell cycle exit of cortical progenitors, decreased number of Radial Glial (Pax6+) and Intermediate progenitor (Tbr2+) cells, and reduced mTORC1 activation in the ventricular and subventricular zone. Likewise, CB<sub>1</sub> receptor knockdown *in utero* reduced Tbr2-positive cell generation. Characterization of CB<sub>1</sub> receptor expression in samples from patients of type IIb focal cortical dysplasia and tuberous sclerosis, two diseases characterized by developmental focal cortical malformations associated to overactivation of the mTORC1 pathway, revealed an enrichment of CB<sub>1</sub> receptor expression in phospho-S6-positive cells.

Altogether, our results demonstrate that the CB<sub>1</sub> receptor exerts a crucial role in tuning dorsal telencephalic progenitor proliferation by inducing the Pax6/Tbr2 axis via the mTORC1 pathway.

*Keywords:* *Cortical development, Endocannabinoid signaling, Radial Glia, Pax6, Tbr2, mTOR signalling.*

**ROLE OF A PARTICULAR ASTROCYTE REACTION IN THE REPAIRMENT OF THE CEREBRAL CORTEX**

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In congenital hydrocephalus there is a defect in the development of the neuroepithelium/ependyma preceding ventriculomegaly and followed by a reaction of periventricular astrocytes. The role of such astrocytes that replaces the absence of ependyma was investigated using an animal model of the disease (hyh mouse) and in necropsies of human foetuses. Histopathological examination, in vitro and in vivo and experiments using intracerebroventricular injections of tracers, and quantifications by real time RT-PCR of neuroprotective and neuroinflammatory factors were performed. The astrocytes were found forming an integrated cell layer of cells coupled with gap junctions containing connexin 43, projecting microvilli towards the ventricle surface, expressing high levels of aquaporin 4, and presenting an endocytic activity. The astrocyte cell layer and the ependyma also revealed similar behaviours for transcellular and paracellular transport of molecules. The astrocytes were found as a primary source of TNF-alpha and they also expressed the TNF-alphaR1 receptor, suggesting an autocrine control of the proper reaction. The quantification by real time RT-PCR of TNF-alpha and the TNF-alphaR1 performed in hyh mice with two different progressions of the disease, severe and compensated, showed a tight correspondence of their levels with the morbidity. The study of the microglia has shown that these cells could be subtly activated or in an alert stage. The obtained evidence suggests that reactive astrocytes could represent an attempt to re-establish brain homoeostasis at both sides of the ventricle surface.

*Supported by the grants PS09/0376-PI12/0631 to AJJ; SERAM to MIML; PI12/01431 to AG; and PI12/01437 to JV.*

*Key words:* *astrocyte reaction, microglial reaction, ependyma, TNF-alpha, TGF-beta1, neurodegeneration, brain cortex*

## EFFECTOS DE UN GEN P53 SUPERNUMERARIO EN LA ASTROGLÍA DE LA RETINA DEL RATÓN

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**Propósito:** Estudiar la influencia de un gen supernumerario p53 en las características de los astrocitos de la retina de ratón.

**Métodos:** Ratones adultos (12 meses) C57BL/6 fueron distribuidos en dos grupos de estudio: 1) ratones con dos copias extras del gen p53 (“super p53”; n=6); 2) ratones control de edad (WT; n=6). Las retinas se procesaron como montajes planos y se tiñeron con técnicas de inmunohistoquímica, usando como anticuerpo primario anti-GFAP. Los astrocitos GFAP+ se contaron manualmente y se calculó el área media ocupada por un astrocito.

**Resultados:** En comparación con los controles, en los ratones “super p53”: i) no se observaron cambios en la distribución de los astrocitos; ii) los astrocitos mostraron cambios morfológicos; iii) el área media ocupada por un astrocito fue significativamente mayor ( $p<0.05$ ; Student's t-test); iv) el número de astrocitos fue significativamente mayor tanto si se consideraba la retina completa ( $p<0,01$  Student's t-test), como en las zonas intermedia y periférica cuando se estudiaba por áreas ( $p<0.05$ ; Student's t-test).

**Conclusiones:** El aumento del número de astrocitos observado en las retinas de los ratones “super p53” podría aumentar la capacidad antioxidante de la retina y en consecuencia, mejorar su resistencia al estrés oxidativo.

**Key words:** *Astrocito. Gen p53. Retina. Estrés oxidativo. Ratón. Modelo de ratón Super p53.*

## **ROLE OF NOTCH SIGNALING PATHWAY IN ASTROGLIOSIS.**

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Notch signaling pathway has been widely studied in the context of central nervous system development, due to its pivotal role in cell-fate decisions. In addition, it has been recently proposed that alterations in Notch signaling may contribute to neurodegeneration. Given that chronic inflammation is patent in most neurodegenerative diseases, the objective of the present study is to determine whether and how Notch signaling is altered in cortical derived astrocytes under inflammatory conditions *in vitro*. Primary cultured astrocytes were treated with bacterial lipopolysaccharide (LPS) to induce astrogliosis *in vitro*. Under these conditions we observed changes in cell shape (stellation phenomenon), an enhancement in the mRNA levels of proinflammatory cytokines and a downregulation of Notch signaling pathway. In order to determine the possible functional role of the LPS-induced Notch regulation, astrocytes were transfected with an overexpression plasmid for the Notch intracellular domain (NICD), which is the canonical activator of the pathway. Cells transfected with the NICD showed an increase in the expression of Hes5, indicating an enhanced activation of Notch. Despite keeping the Notch pathway constitutively active, LPS treatment was still able to induce its effects in morphology and gene expression. In addition, LPS treatment still decreased Notch activity when cells were cotreated with factors that are known to reduce the expression or proinflammatory cytokines, such as 17- $\beta$  estradiol or insulin-like growth factor. These findings indicate that Notch is downregulated in astrocytes under inflammatory conditions. However, our results suggest that this change in Notch signaling is independent of the action of LPS on the morphology and expression of proinflammatory cytokines in astrocytes. Further studies should determine the role of Notch on astrocytes under inflammatory conditions.

*Supported by Ministerio de Economía y Competitividad (grant number BFU2011-30217-C03-01).*

*PALABRAS CLAVE:* Notch, inflammation, LPS, cytokines.

## ADENOSINE RECEPTOR A1 INHIBITS NEURONAL DIFFERENTIATION FROM MULTIPOTENT STEM CELLS

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**Objectives.** The main objective of this work was to investigate the role of extracellular adenosine and its receptors in modulating neuronal differentiation of neural stem cells (NSC) from adult subventricular zone (SVZ).

**Material and methods.** Neuronal differentiation was evaluated on a single clonogenic neurosphere by immunofluorescence as a ratio between  $\beta$ III tubulin (early neuronal marker) vs total cells, or by cytofluorimetry. Functional genomic analysis of differentiation was performed using an array containing genes relevant to neurogenesis. Differential expression of adenosine receptors was analyzed by qRT-PCR. In vitro results were confirmed in vivo by intracerebroventricular (icv) infusion of adenosine analogues.

**Results.** We found that adenosine reduces neuronal differentiation of adult NSC. The effect was most evident on the transient amplifying cells (C cells) as demonstrated by citofluorimetry assay. Adenosine A1 receptor (Adora1) mRNA was the most upregulated in contrast to the majority of genes represented in the macroarray used for screening. Upregulation of Adora1 was confirmed by qRT-PCR and Western blot, while the involvement of these receptors in the negative modulation of neuronal differentiation was further assessed using the specific agonist CPA and antagonist PSB36. Neurons generated during differentiation in the presence of adenosine showed an inhibition of vesicular transport to the synaptic terminal, which could be one of the causes of neuronal differentiation reduction. This modulation was confirmed also in vivo after icv infusion of CPA. This agonist significantly reduced the number of DCX+ (neuroblast marker) /BrdU+ cells in the olfactory bulb (OB) whereas no significant changes were observed in the SVZ with GFAP+ (multipotent marker) /BrdU+ or nestin+ (C cells marker) /BrdU+, demonstrating that activation of Adora1 in animals reduces neuronal differentiation in the SVZ and further migration to the OB.

**Conclusions.** Here we demonstrated that adenosine negatively modulates neuronal differentiation of neural stem cells from adult subventricular zone through the activation of Adora1.

**Keywords:** multipotent stem cells, neurospheres, adenosine, neurogenesis, neuronal differentiation

**Acknowledgments.** This study was supported by MINECO, CIBERNED and Gobierno Vasco. MBM holds a fellowship from UPV/EHU.

## TARGETING THE BH3-ONLY PROTEINS AND p53 PATHWAY TO PROTECT OLIGODENDROCYTE PRECURSOR CELLS FROM AMPA-INDUCED DAMAGE

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Extracellular glutamate accumulation in the CNS and subsequent overstimulation of its ionotropic receptors is deleterious to oligodendrocytes and their precursors (OPCs), induces myelin damage and contributes to the pathophysiology of multiple sclerosis and diseases undergoing myelin destruction. Here we have investigated the role of BH3-only proteins BID and PUMA in OPC apoptosis after AMPA receptor activation. Cultured OPCs subjected to brief and moderate AMPA receptor stimulation increase the levels of active form of BID (tBID), which translocates into mitochondria leading to its disruption and releasing apoptogenic molecules. In turn, tBID inhibition with BI6C9 prevents the rise of tBID levels, abolishes mitochondrial dysfunction and protects from excitotoxic insults both OPCs and mature oligodendrocytes. Since BID is a specific substrate of caspase-8, we examined the role of its intrinsic inhibitor c-FLIP<sub>L/S</sub>, and we detected that AMPA induces an early and transient decrease in c-FLIP<sub>L/S</sub> levels, preceding caspase-8 activation and BID cleavage. This gives c-FLIP<sub>L/S</sub> an important role in the early regulation of AMPA-induced apoptosis and suggests that its modulation soon after the insult can rescue oligodendrocytes from dying.

Additionally, the induction of cell death by p53 occurs via both target gene activation, like PUMA, and transcription-independent mechanisms at the mitochondria level. Indeed, we observed that a moderate activation of AMPA receptors in cultured OPCs elevated the levels of p53 and PUMA proteins, and of phosphorylated-p53, a state that favors its mitochondrial insertion. Preincubation of OPCs with pifithrin- $\mu$ , inhibited p53-mitochondria association, reduced p53/PUMA overexpression and prevented AMPA-induced excitotoxicity. This beneficial effects were not observed using pifithrin- $\square$ , an inhibitor of p53 accumulation in the nucleus.

Together, these results show c-FLIP/tBID and p53/PUMA pathways as key regulators of AMPA-induced mitochondrial dysfunction and cell death in cultured OPCs and suggest that modulation of these death pathways may help in developing novel oligoprotective drugs with therapeutic potential.

*Supported by grants from MICINN (SAF2010-21547), CIBERNED and Gobierno Vasco. M.Canedo-Antelo holds a MICINN fellowship (BES-2011-047822).*

## LA MICROGLÍA EN BASTÓN NO APARECE ENTRE LOS CAMBIOS MICROGLIALES DE LA RETINA CONTRALATERAL EN UN MODELO DE GLAUCOMA

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**PROPOSITO:** Analizar los cambios cualitativos en la población microglial, tras dos semanas de hipertensión ocular (HTO) unilateral inducida por láser en los ojos con HTO y en los contralaterales no tratados.

**MÉTODOS:** Ratones Swiss albinos adultos se distribuyeron en dos grupos: control (n=6) e HTO (n= 6). Montajes planos de retina se marcaron con anticuerpos contra Iba-1, MHC-II, ED-1 y NF-200.

**RESULTADOS:** En ambos grupos se observaron células ramificadas Iba-1+ en la capa de fibras nerviosas que se relacionaban con los vasos sanguíneos. En los ojos con HTO y en los contralaterales, las células Iba-1+ presentaban signos morfológicos de activación y sobreexpresión de MHC-II y ED-1. Sin embargo, sólo en los ojos con HTO se observaron microglías en bastón paralelas al curso de los axones y que se relacionaban con células ganglionares (CGR) NF200+ (signo de degeneración). La microglía en bastón mostraba cambios morfológicos y de inmunotinción MHC-II y ED1 sugerentes de distintos niveles de activación.

**CONCLUSIONES:** Tras 15 días de HTO unilateral, la microglía de la retina de los ojos con HTO y de los contralaterales no tratados presenta signos de activación. Sin embargo, sólo se detecta microglía en bastón en los ojos HTO, los únicos que tienen GCR con signos de degeneración (NF-200+). La activación de la microglía en los ojos contralaterales podría estar ejerciendo una función neuroprotectora.

*Palabras Clave:* hipertensión ocular, láser, microglía, retina, inmunohistoquímica, MHC-II, ED-1.

## **ROLE OF APOLIPOPROTEIN D IN MACROPHAGE RECRUITMENT AND MYELIN PHAGOCYTOSIS**

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Apolipoprotein D (ApoD) is a Lipocalin expressed in the peripheral nervous system (PNS) by Schwann cells and fibroblasts and its expression is strongly induced upon injury. We are interested in the function of ApoD in the molecular events that take place after a PNS injury. We have studied *in vivo* the process of Wallerian degeneration following sciatic nerve crush and we have assayed *ex vivo* the phagocytosis of labelled myelin from wt and ApoD-KO mice by flow cytometry.

The analysis of cellular processes and protein or mRNA expression of a group of signalling molecules induced by injury shows that the lack of ApoD results in an exacerbated MCP-1 and TNFa-dependent macrophage recruitment. At the injury site, free AA increases in the wt. Lack of ApoD results in higher basal levels and a injury-triggered decrease of AA. Control by ApoD of the availability of AA to produce the lipid mediators involved in macrophage recruitment is therefore a key mechanism that conditions Wallerian degeneration and injury resolution later on.

On the other hand, the phagocytosis of ApoD-KO CNS myelin is less efficient than the phagocytosis of wt myelin, therefore there are also genotype-dependent differences in myelin composition and/or in the interaction between myelin and macrophages. An electron microscopy analysis of myelin preparations reveals that the CNS myelin from ApoD-KO mice has abnormal periodicity and shows defective myelin compaction. Lipid analysis of ApoD-KO myelin shows an altered phospholipid composition, particularly in phosphoinositid species. This is related to changes in the expression of myelin proteins such as Mbp or Mag. A study of the function of ApoD in the myelination process is currently underway.

Our results demonstrate that ApoD function is relevant for both, myelin membrane properties that influence myelin-macrophage interactions, and the control of the lipid-mediated signalling events controlling the extent of macrophage recruitment.

*Support:* MICINN(BFU2008-01170; BFU2011-23978), JCyL(VA180A11-2).

*Myelin, Schwann cells, Macrophages, peripheral nervous system injury, myelination.*

## SEXUAL DIMORPHISMS IN RECOVERY TIME AND SEQUELAE AFTER TRAUMATIC BRAIN INJURY IN MICE.

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Traumatic brain injury (TBI) constitutes the primary cause of death in young individuals and, together with its consequences, is a very significant public health problem. This type of lesion triggers intracellular signalling cascades that activate glial cells leading to the secondary damage of TBI. This includes neurotoxicity, neuroinflammation, blood-brain barrier (BBB) disruption, oxidative stress, brain oedema, axonal injury and functional impairment. Traditionally, animal and clinical studies have employed male subjects assuming that results from male studies in TBI models would apply to females too. However, emerging evidences demonstrate that there are sex differences in secondary damage after brain trauma and that hormonal fluctuations during the cycle play a very important role controlling the outcome after TBI. The goal of our study was to determine the possible existence of sexual dimorphisms in recovery time, lesion severity, behaviour alterations and molecular changes in several parameters after TBI.

Our results showed that TBI induces, in both sexes, a neurological impairment 24h and 48h after lesion that recovered 2 weeks after lesion. However, when we measured oedema formation in the contralateral hemisphere, we saw that TBI induced an increase in the percentage of water content in males at 24h and 48h after TBI that disappeared 2 weeks after lesion whereas in females, the levels of oedema did not differ from control at any time after lesion. To further clarify these results, we will analyze different proteins present in glial cells (astroglia and/or microglia) that are involved in neuroinflammation (IL-1 $\beta$ ), structure and function of the BBB (AQP-4 and MMP-9), steroidogenesis (Aromatase, ER- $\alpha$  and ER- $\beta$ ) and the activation of endocannabinoid system (CB1 and CB2 receptors, MAGL and NAPE-PLD).

*Acknowledgements:* GRUPOS UCM-BSCH: 951579, Red de trastornos adictivos RD12/0028/0021.

*Keywords:* Traumatic brain injury, sexual dimorphisms, murine model, neuroinflammation, behaviour.

## ACTIVATION OF NFAT TRANSCRIPTION FACTORS IN NEURAL PRECURSOR CELLS INDUCES ASTROCYTE DIFFERENTIATION

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The nuclear factor of activated T cells (NFAT) was initially described as a family of transcription factors with key functions for lymphocyte maturation and activation, so that NFAT is implicated in the progression of inflammation. However, NFAT factors are also expressed in other tissues including the nervous system, where they control mechanisms related to cell survival, proliferation, differentiation, migration, adhesion and activation. Our previous work described the presence of the NFAT system in astrocytes, and found a link between NFAT activation and metalloproteinase expression as well as glial reactivity during ischemia, and traumatic and excitotoxic brain injury. In addition, we have recently detected NFAT expression in neural precursor cells (NPCs) leading us to investigate NFAT roles in NPCs. The present work analyzes possible NFAT connections with proliferation and differentiation of NPCs cultured as neurospheres from neonatal mouse subventricular zone (SVZ). Adenoviral infection to overexpress a constitutively-active form of isoform NFATc3 induced a phenotypic change in NPCs, so that adhesion and migration was stimulated while cell cycle was arrested. Meanwhile, cells extended thin and branched processes, and GFAP was upregulated. All together, our observations indicate that NFAT promotes astrocitic differentiation in NPCs. Funded by SAF2009-12869 (P. Tranque) and PI09/0218, PI12/0238 (E. Cano).

**Key words:** NFAT, neural precursor cells (NPCs), astrocytes, cell differentiation, adhesion, migration

## REDES FUNCIONALES ASTRO-NEURONALES selectivas ASOCIADAS A LAS VÍAS DIRECTA E INDIRECTA EN EL ESTRIADO

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Existe comunicación entre neuronas y astrocitos, pero se ignora si existe en el estriado y sus consecuencias fisiológicas.

Utilizando registros electrofisiológicos de pares de neuronas e imagen de calcio en rodajas de estriado dorso-lateral de ratón, hemos estudiado las propiedades de la señal de calcio astrocitaria inducida por actividad neuronal y sus consecuencias sobre la excitabilidad celular y la transmisión sináptica.

La despolarización neuronal, que provoca la liberación de endocannabinoides (ECBs), genera elevaciones de calcio en astrocitos adyacentes acompañadas de corrientes lentas de entrada (SICs) y de una potenciación heteroneuronal de la transmisión. Estos efectos no se observan en presencia de antagonistas del receptor CB1, ni en ratones CB1R<sup>-/-</sup> e IP<sub>3</sub>R2<sup>-/-</sup> (con déficits en señalización de calcio).

Por tanto, los ECBs liberados por neuronas aumentan el calcio astrocitario por activación de receptores CB1 y estimulan la liberación de glutamato por astrocitos, que 1) activa receptores de NMDA postsinápticos generando SICs, y 2) potencia la neurotransmisión glutamatérgica por activación de receptores mGluR tipo I presinápticos.

En neuronas de proyección identificadas (ratones Drd1a-td-Tomato y Drd2-eGFP), la generación de SICs y la potenciación mediadas por activación astrocitaria ocurren en neuronas homotípicas (pertenecientes a la misma vía, directa o indirecta, que la neurona estimulada).

Estos resultados demuestran la presencia de comunicación específica entre astrocitos y neuronas pertenecientes a las vías directa e indirecta, indicando la existencia de redes astro-neuronales funcionales selectivas para cada una de las vías de proyección estriatal.

**GENETIC INDUCIBLE FATE MAPPING TO TRACE THE DIFFERENTIATION OF NEURAL STEM CELLS INTO REACTIVE ASTROCYTES IN A RODENT MODEL OF EPILEPSY**

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A population of radial neural stem cells (rNSCs) that persists throughout adulthood in the dentate gyrus (DG) of most mammals, including humans, is able to generate new neurons that integrate into the hippocampal circuitry. This process referred to as adult hippocampal neurogenesis is important for memory formation, spatial learning, pattern separation, fear conditioning and anxiety.

We have found that in a model of mesial temporal lobe epilepsy (MTLE), the most common form of epilepsy, adult hippocampal neurogenesis results chronically impaired, which in turn implies the loss of the cognitive functions associated with neurogenesis and the loss of the potential to regenerate the neurons that die by excitotoxicity in MTLE.

Based on our previous results we have hypothesized that the main reason to explain the loss of neurogenesis in MTLE might be the massive activation and conversion into reactive astrocytes of rNSCs. We have confirmed our hypothesis by resorting to inducible transgenic Nestin-Cre-ERT2-Rosa26-YFP mice to trace the differentiation of rNSCs in a well-established model of MTLE, the intrahippocampal injection of the glutamatergic agonist kainic acid.

*Keywords:* *Neurogenesis, epilepsy, neural stem cells, gliosis.*

**MOVILIZATION OF PROGENITORS IN THE SUBVENTRICULAR ZONE TO  
UNDERGO OLIGODENDROGENESIS IN THE THEILER'S VIRUS MODEL OF  
MULTIPLE SCLEROSIS: IMPLICATIONS FOR A REMYELINATING PROCESS  
IN LESIONS SITES**

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Pathological loss of myelin in diseases like Multiple Sclerosis (MS) is usually followed by a phenomenon of remyelination, in which oligodendrocytes synthesize new myelin sheaths to envelope exposed around axons in the adult central nervous system (CNS). In this scenario, the mammalian subventricular zone (SVZ) has garnered attention as a potential source of replacement cells after injury. This zone harbours stem cells and supports long-distance migration, and is activated in MS patients to promote gliogenesis. Although NG2<sup>+</sup> precursor cells are the first to react to demyelination and show the highest proliferation rate in comparison with other cells, the relative contribution of the SVZ with respect to the inflammatory demyelination induced by the Theiler's virus infection and oligodendrogenesis has never been addressed. In the present study, we have investigated the behavior of the SVZ in Theiler's Murine Encephalomyelitis Virus – Induced Demyelinating Disease (TMEV-IDD). We report that in this viral model for MS, there is a preclinical phase of the disease with demyelination in the corpus callosum that is followed later by an attempt of remyelination. This phase is accompanied by an activation of the SVZ with no apparent activation of NG2<sup>+</sup> precursors, and a strong and clear staining for GFAP<sup>+</sup> B cells close to the lateral ventricles of the brain that correlate with an increase of the proliferative rate in this area when measured by BrdU incorporation. Finally, we show that Theiler's infection enhances the mobilization of SVZ progenitor cells to the surrounding demyelinated corpus callosum and generate mature APC<sup>+</sup> oligodendrocytes.

*This work has been supported by grants from the MINECO SAF 2010-17501 and REEM (Red Española de Esclerosis Múltiple, RD0700100060)*

*Palabras clave:* *Zona Subventricular, Oligodendrocito, Remielinización, Desmielinización, TMEV-IDD.*

**INHIBITION OF ENDOGENOUS PHOSPHODIESTERASE 7 PROMOTES OLIGODENDROCYTE PRECURSOR SURVIVAL AND DIFFERENTIATION IN MOUSE AND HUMANS: *IN VITRO* REMYELINATION ASSAYS**

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During development, oligodendrocyte precursors (OPCs) are generated in specific sites within the neural tube and then migrate to colonize the entire CNS, where they differentiate into myelin-forming oligodendrocytes. Primary demyelinating diseases, such as multiple sclerosis (MS), are characterized by the death of oligodendrocytes and the consequent loss of myelin. The CNS reacts to demyelinating damage by promoting spontaneous remyelination, an effect mediated by endogenous OPCs, cells that represent approximately 5-7% of the cells in the adult brain. Numerous factors influence oligodendroglogenesis and oligodendrocyte differentiation, including morphogens, growth factors, chemotropic molecules, extracellular matrix proteins and intracellular cAMP levels. In the present work, we demonstrate that, in postnatal and mature cerebral cortex of the mouse, OPCs express phosphodiesterase-7 (PDE7), enzyme which metabolizes cAMP. We investigated the effects of different PDE7 inhibitors (the well known BRL-50481 and two new ones, TC3.6 and VP1.15) on OPC isolated from brain cortex from P0 and P9 mice. While none of the PDE7 inhibitors analyzed altered OPC proliferation, TC3.6 and VP1.15 enhanced both OPC survival and differentiation. These effects were mediated via ERK intracellular signaling pathway. PDE7 expression was also observed in OPCs isolated from adult human brains. The differentiation of these OPCs into more mature oligodendroglial phenotypes was also accelerated under the treatment with both new PDE7 inhibitors.

Moreover, we have performed remyelination assays *in vitro* following demyelination of organotypic cerebellar slices. These new roles for PDE7 may further improve our knowledge of myelination and facilitate the design of therapeutic remyelination approaches for the MS treatment.

**Keywords:** *PDE7 inhibitors, Oligodendrocyte differentiation, Multiple sclerosis.*

*Funded by Ministerio Economía y Competitividad (SAF2009-07842; SAF2012-40023, ADE10-0010, and Red Española de Esclerosis Múltiple -RD07/0060/2007, RD07/0060/0015 “Una manera parcialmente por F.E.D.E.R.; European Union de hacer Europa”-) to FdC. EMMR has a pre-doctoral fellowship from Ministerio Economía y Competitividad (BES-2010-042593 asociado a SAF2009-07842). AB was hired by the Instituto de Salud Carlos III/Ministerio de Economía y Competitividad under Programa Sara Borrell (CD08/0126) and is currently hired by ADE10-0010. FdC is hired by SESCAM.*

**ADMINISTRATION OF A LEPTIN ANTAGONIST DURING THE PHYSIOLOGICAL NEONATAL LEPTIN SURGE INDUCES LONG-TERM SEX DEPENDENT ALTERATIONS IN THE HIPPOCAMPUS AND PREFRONTAL CORTEX OF ADOLESCENT RATS**

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**Objective:** To assess whether interference with the physiological neonatal surge of leptin impairs the development of extrahypothalamic brain regions.

**Material and methods:** Neonatal female and male Wistar rats were treated with rat “mono-pegylated super active leptin antagonist” (mutant D23L/L39A/D40A/F41A), from PND 5 to 9 (5mg/kg/day s.c.; Leptin Antagonist: Lep Ant) or with the corresponding vehicle (Control: Co). Animals were sacrificed at PND43 (males) and PND33 (females) and their brains were removed. Levels of neuronal, glial and neuroplasticity-related proteins were measured in hippocampus (HC) and prefrontal cortex (PCx) by Western Blot.

**Results:** A baseline sexual dimorphism was found in the levels of glial fibrillary acidic protein (GFAP) and neuronal nuclei (NeuN) , with Co females exhibiting a significant lower content of both proteins when compared with Co males in PCx ( $p<0.05$ ). The Lep Ant treatment induced the following significant ( $p<0.05$ ) effects. Treated males: Decreased levels of synaptophysin and CB2 cannabinoid receptors in HC and PCx and of neural cell adhesion molecule (NCAM) in PCx, and increased levels of Reelin in PCx and of CB1 cannabinoid receptors in HC. Treated females: Decreased levels of NCAM, Reelin and CB1 receptor in PCx and of NG2 (a marker of oligodendrocytes progenitor cells) in HC and PCx.

**Conclusions:** The present results indicate that disruption of leptin actions by administration of a leptin antagonist during the neonatal leptin surge induces long-lasting sex-dependent changes in the developing hippocampus and prefrontal cortex.

*Acknowledgements: Ministerio de Economía y competitividad: BFU2012-38144, BFU2011-27492 and Instituto Carlos III: RD2012/0028/0021and CIBERobn.*

*Keywords: leptin, homeostatic and neuroendocrine systems, development, adolescence.*

**REGROWTH OF TRANSECTED RETINAL GANGLION CELL AXONS DESPITE PERSISTENT ASTROGLIOSIS IN THE LIZARD (*GALLOTIA GALLOTTI*).**

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We analysed the astroglia response that is concurrent with spontaneous axonal regrowth after optic nerve (ON) transection in the lizard *Gallotia galloti*. At different post-lesional time points (0.5 to 12 months), we used conventional electron microscopy and specific markers for astrocytes [GFAP, vimentin (Vim), Sox9, Pax2] and for proliferating cells (PCNA). The experimental retina showed a limited glial response since the increase of gliofilaments was not significant if compared to controls, and proliferating cells were undetectable. Conversely, PCNA<sup>+</sup> cells populated the regenerating ON, optic tract (OTr). Subpopulations of these PCNA<sup>+</sup> cells were identified as GFAP<sup>+</sup> and Vim<sup>+</sup> reactive astrocytes. Reactive astrocytes up-regulated Vim at 1 month post-lesion, and both Vim and GFAP at 12 months post-lesion in the ON-OTr, indicating long-term astrogliosis. They also expressed Pax2, Sox9 in the ON, and Sox9 in the OTr. Concomitantly, persistent tissue cavities and disorganised regrowing fibre bundles reaching the OT were observed. Our ultrastructural data confirm abundant gliofilaments in reactive astrocytes joined by desmosomes. Remarkably, they also accumulated myelin debris and lipid droplets until late stages, indicating their participation in myelin removal. These data suggest that persistent mammalian-like astrogliosis in the adult lizard ON contributes to a permissive structural scaffold for long-term axonal regeneration and provides a useful model to study the molecular mechanisms involved in these beneficial neuron-glia interactions.

*This work was supported by the Spanish Ministry of Education (Research Project BFU2007-67139), the Regional Canary Island Government (ACIISI, Research Projects SolSub200801000281 and ULPAPD-08/012-4).*

## ACTIVATION OF HIPPOCAMPAL RADIAL NEURAL STEM CELLS IN RODENT MODELS OF EPILEPSY AND ELECTROCONVULSIVE SHOCK

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New neurons are generated in the hippocampus throughout the life span of mammals, including humans, due to the persistence in the dentate gyrus of a population of radial glia cells that act as neural stem cells (rNSCs). The integration of newborn neurons into the hippocampal circuitry has been shown to participate in memory formation, spatial learning, pattern separation, fear conditioning and anxiety. Adult hippocampal neurogenesis declines with age and is impaired in neurological disorders such as temporal lobe epilepsy.

Using intrahippocampal injection of the glutamatergic agonist kainic acid (KA), a well-established model of mesial temporal lobe epilepsy, we have observed that seizure-inducing neuronal hyperexcitation induces a massive activation of rNSCs and their differentiation into reactive astrocytes. A subpathological, non-epileptogenic dose of KA also recruits and activates higher numbers of rNSCs, which in turn accelerates the depletion of the rNSC population.

In order to test if this is a common mechanism attributable to different kinds of neuronal stimulation we are investigating if electroconvulsive shock, the experimental model of the increasingly-applied to depression patients electroconvulsive therapy, also promotes the activation of rNSCs. Recruitment and activation of rNSCs to enter cell cycle would accelerate the decline of the population through astrocytic conversion resulting in the long-term reduction of cell proliferation and neurogenesis. Impairment of neurogenesis in turn would imply the loss of the cognitive functions associated with the integration of new neurons into the hippocampal circuitry plus the loss of the potential to regenerate neurons dead by excitotoxicity.

*Keywords:* Neural stem cells, neuronal hyperexcitation, neurogenesis.

**AB OLIGOMERS ACTIVATE INTEGRINS TO PRODUCE OXIDATIVE STRESS THROUGH PI3K/PKC/RAC1/NADPH OXIDASES IN ASTROCYTES**

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Cognitive impairment in Alzheimer disease (AD) is strongly associated with both extensive levels of amyloid beta peptide (A $\beta$ ) and oxidative stress, but the exact role of these indices in the development of dementia is not clear. NADPH oxidase (NOX) is involved in AD pathogenesis as A $\beta$  activates NOX in astrocytes generating oxidative stress that ultimately causes neuronal death. Here, we describe the molecular signaling events mediating NOX activation by A $\beta$  oligomers in cultured astrocytes. First, we found that astrocytes express mRNAs encoding for the regulatory subunit p87phox, NOX1, 2, and 4, and the dual oxidases (DUOX) 1 and 2, but not NOX3 subunits. Then, we observed that A $\beta$  oligomers (5  $\mu$ M) induced a rapid (30-120 min) ROS production which was Ca $^{2+}$ -dependent. A $\beta$ -induced ROS generation was prevented by NOX inhibitors apocynin, DPI and gp91ds-tat peptide. To further investigate the pathway underlying A $\beta$ -mediated ROS generation, we analyzed the activation of NOX-interacting protein Rac by Rac-GTP affinity precipitation and PAK1 phosphorylation assay. We found that A $\beta$  oligomers triggered a sustained Rac activation that was blocked by inhibition of the classic but not by the novel PKC activities. In addition, ROS generation in A $\beta$ -treated astrocytes was reduced by inhibition of integrins as well as of PI3K and PDK activities which in turn blocked the levels of PKC and PDK phosphorylation. Our results demonstrate that A $\beta$  oligomers activate integrins to produce ROS via PI3K/PKC/Rac/NADPH oxidase pathway in astrocytes. These mechanisms may be relevant to AD pathophysiology.

*Supported by CIBERNED, Gobierno Vasco and MINECO.*

*Key words: astrolgia, beta-amyloid, oxidative stress, alzheimer, neurodegeneration*

**PARTIAL RECOVERY OF VISUAL FUNCTION AFTER COMPLETE OPTIC NERVE TRANSECTION IN THE LIZARD *GALLOTIA GALLOTTI***

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Significant regeneration of retinal ganglion cell axons occurs after optic nerve transection through a permissive glial scar in *Gallotia galloti*. Although several of the cellular and molecular events underlying this process have been studied by our group, the functionality of the system has not been tested until now. The pupillary light reflex, accommodation and head orienting have been also used in other reptiles to test visual function (Dunlop et al., 2004). We examined 18 lizards at 3, 6, 9 and 12 months after transection. Our results revealed a tendency of eyelid closing within the first months after operation. Interestingly, by 6 months we detected a significant recovery of pupillary light reflex in two thirds of specimens including a robust response in 17% of them. However, visually guided behaviour recovery was observed only in 2 specimens, yet when presenting a prey (mealworm) in the right, affected eye, most lizards (89%) did not constrict the pupil to focus nor did they follow it as it moved, a behaviour which was detected in the unlesioned side. We conclude that a partial recovery of the visual pathway functionality takes place spontaneously in adult *G. galloti*, which could be enhanced by training or pharmacologically.

*This work was supported by the Spanish Ministry of Education (Research Project BFU2007-67139), the Regional Canary Island Government (ACIISI, Research Projects SolSub200801000281 and ULPAPD-08/012-4).*

*Palabras clave:* regeneration, visual system, visual function, lizard.

## **IL-4 IS INDUCED IN THE BRAIN AFTER ISCHEMIA AND DOWN-REGULATES THE INFLAMMATORY PROFILE OF MICROGLIA**

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**Introduction:** Stroke triggers inflammation that exacerbates brain tissue damage. The inflammatory reaction is naturally set up to clear the necrotic tissue and comprises a complex dynamic process evolving through various steps from initiation to resolution. IL-4 is mainly produced by lymphocytes and promotes an alternative anti-inflammatory M2 phenotype in macrophages. Mice deficient in IL-4 showed worse stroke outcome suggesting that IL-4 plays a role in ischemia. The aim of this study was to find out whether IL-4 was produced in the brain after ischemia and whether IL-4 affected the inflammatory response of microglial cells.

**Methods & Results:** Brain ischemia was induced by permanent occlusion of the middle cerebral artery in C57 mice. IL-4 mRNA expression was not detected in control brain, but low levels were found from 6 hours to 4 days post-ischemia, and it strongly increased at day 7. At this time, the expression of several inflammatory markers was attenuated while that of molecules involved in tissue repair increased. Treatment of cultures of murine microglia with IL-4 up-regulated the expression of the M2 markers: arginase-1, IL1RA, and galectin-3 and had anti-inflammatory effects against either LPS or anoxia. IL-4 did not down-regulate TLR-4 expression showing that it did not reduce the cellular capacity to react to LPS or danger signals but it interfered with downstream signaling. The underlying molecular mechanisms are currently under study.

**Conclusion:** These results support that IL-4 contributes to the process of resolution of inflammation after stroke by tuning down the inflammatory profile of microglia.

**Key words:** IL-4, brain ischemia, mice, microglia, M2 markers, inflammation

**COLONIZATION OF THE OPTIC NERVE HEAD AND PECTEN ANLAGE BY MICROGLIAL PRECURSORS DURING QUAIL RETINA EARLY DEVELOPMENT.**

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In the avascular quail retina, microglial cells come from precursors of amoeboid phenotype entering the embryonic retina from the region of the optic nerve head and base of the pecten (ONH/BP) between days 7 and 16 of incubation (E7-E16). By using organotypic cultures of retinal explants, we have previously showed that these microglial precursors are already present in the primordial ONH and pecten anlage, which derive from the fusion of the optic fissure edges, from around E3, i.e., 4 days before they enter the retina. Our aim was to study the colonization pattern of the ONH/BP region of quail embryos between E3 and E6 by microglial precursors and their relationship with the development of other cell types present in this area. For this purpose, whole-mount and cryosectioned retinas of these developmental stages were immunolabeled with the following antibodies: QH1 (which recognizes all developmental phases of macrophage/microglial cells in the quail, as well as endothelial cells), anti-vimentin, TUJ1 (neuron-specific class III beta-tubulin) and anti-active caspase-3. This study revealed that QH1-positive cells with a macrophage phenotype were present in the ONH/BP area from E3. We identified two routes of entry of QH1-positive cells into the ONH/BP area: some cells entered from the meninges surrounding the ONH while others migrated from peripheral retina into the ONH/BP region and entered the optic fissure together with blood vessels contributing to pecten vasculature.

Supported by grant BFU2010-19981 from the Spanish Ministry of Economy and Competitiveness.

*Palabras clave:* Microglia, desarrollo, retina.

**DESACOPLAMIENTO      APOPTOSIS-FAGOCITOSIS      DURANTE      LA  
EXCITOTOXICIDAD ASOCIADA A LA EPILEPSIA**

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La fagocitosis microglial es esencial para el mantenimiento de la homeostasis cerebral, ya que es activamente antiinflamatoria e impide la liberación de contenidos intracelulares tóxicos, al menos *in vitro*. Contrariamente a la bien caracterizada respuesta inflamatoria, la respuesta fagocítica en condiciones neurodegenerativas *in vivo* es una gran desconocida. Como modelo de neurodegeneración utilizamos la inyección intrahipocampal de ácido kaínico (KA), que produce excitotoxicidad y convulsiones. A continuación evaluamos la eficacia fagocítica mediante la determinación del índice fagocítico (porcentaje de células apoptóticas fagocitadas), y el tiempo de eliminación (tiempo medio de degradación de las células apoptóticas), utilizando inmunofluorescencia y microscopía confocal. Al contrario de lo esperado, la eficacia fagocítica microglial se ve drásticamente reducida a las 6-24h tras la inyección de KA. El desacoplamiento entre apoptosis y fagocitosis resulta en la acumulación de células apoptóticas, que tardan hasta 3 días en comenzar a ser eliminadas, mientras que en condiciones fisiológicas su tiempo de eliminación es de 1.2-1.5h. Además el bloqueo de la fagocitosis correlaciona a lo largo del curso temporal con el desarrollo de la inflamación, determinada mediante RT-qPCR de un panel de citoquinas pro- y antiinflamatorias. Dado que en estudios previos no hemos encontrado efecto de la inflamación en la fagocitosis, estos resultados sugieren que la inflamación se desarrolla al menos parcialmente como consecuencia del bloqueo fagocítico, y sugieren que la fagocitosis puede ser una nueva diana farmacéutica para acelerar la recuperación tisular después de una lesión excitotóxica.

*Agradecimientos:* Fundación Ikerbasque; Gobierno Vasco (S-PC12UN014); Ministerio de Economía y Competitividad (BFU-2012-32089).

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