IX Reunión de la Red Glial Española

26 al 27 de Septiembre de 2017

Auditorio de la Diputación de Alicante ADDA (Alicante)

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SANOFI GENZYME

IX Reunión de la Red Glial Española
ALICANTE 2017

RED GLIAL ESPAÑOLA RGE-SENC

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SANOFI GENZYME

PROGRAMA DEFINITIVO

Martes 26 de Septiembre (sala CÁMARA)

15:00 Bienvenida e inauguración

15.15 – 16.30 Presentaciones orales

SESIÓN 1: PROGENITORES NEURALES /ASTROCITOS

15:15	*Gertrudis Perea (Instituto Cajal, Madrid)*	Interneuron-Astrocyte Signalling Impact on synaptic transmission
15:30	*Oier Pastor Alonso (Achúcarro B.C.N., Leioa)*	On-Site Generation of the Adult Neural Stem Cell Population in the Postnatal Dentate Gyrus
15:45	*Soraya Martín (Achúcarro B.C.N., Leioa)*	Phenotypical and functional heterogeneity of neural stem cells in the aged hippocampus

SESIÓN 2: MIELINA

16:00	*Mari Paz Serrano Regal (U. País Vasco /EHU)*	A functional role of GABA-B receptors in the maturation of oligodendrocyte precursor cells and remyelination
16:15	*Leyre Mestre Nieto (Instituto Cajal, Madrid)*	Attenuation of progressive disability in a murine model of multiple sclerosis by manipulating gut microbiome
16:30	*Alba Sánchez-Fernández (U. Autónoma, Madrid)*	IL-37 exerts therapeuticeffects in experimental autoimmune encephalomyelitis

16:30-17:00 Café

17:00-18:00 CONFERENCIA PLENARIA. ***Prof. Peter Brophy*** *(University of Edinburgh)*

18:15-19:00 Presentaciones orales

SESIÓN 3: MICROGLÍA

18:15	*Jesús Amo (U. Autónoma, Barcelona)*	Modulating microglia and macrophage plasticity after spinal cord injury
18:30	*Anna Martínez Muriana (U. Autónoma, Barcelona)*	CSF1R blockade slows the progression of amyotrophic lateral sclerosis by reducing microgliosis and invasion of macrophages into peripheral nerves
18:45	*Virginia Sierra (Achúcarro B.C.N., Leioa)*	Microglial phagocytosis of apoptotic cells is impaired by genetic cystatin B deficiency, a mouse model of progressive myoclonus epilepsy (Unverricht-Lundborg disease)

19:00-20:00 Asamblea de socios RGE

Miércoles 27 de Septiembre

9:00:00 Colocación de pósters (VESTÍBULO)

09:30 – 10:30 Premio Laia Acarin (Sala CONFERENCIAS)

	Ane Wyssenbach (Achúcarro B.C.N., Leioa)	Amyloid β-induced astrogliosis is mediated by β1-integrin via NADPH oxidase 2 in Alzheimer's disease

10:30-11:00 Café

11:00-12:30 Sesión de Posters (VESTÍBULO)

LOCALIZACIÓN:

ADDA. Auditorio de la Diputación de Alicante. Paseo de Campoamor, s/n 03010 Alicante
Tel. 965 91 91 00 . GPS coordinates: 38.354494,-0.486183. www.addaalicante.es

COMITÉ ORGANIZADOR

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Diego Gómez Nicola, University of Southampton, UK

Mª Victoria Sánchez Gómez, UPV - Achucarro Basque Center for Neuroscience, Bilbao

SESIÓN PLENARIA

SESIÓN PLENARIA. MYELINATION AND ASSEMBLY OF THE NODES OF RANVIER

Prof. PETER BROPHY

Centre for Neurodegeneration, The University of Edinburgh, UK

COMUNICACIONES ORALES

CO1. INTERNEURON-ASTROCYTE SIGNALLING IMPACT ON SYNAPTIC TRANSMISSION

Gertrudis Perea

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Interneurons are involved in fundamental aspects of brain function playing a key role in the operation of neuronal networks (1). Thus, fast time course of GABAergic signaling controls the neuronal outputs. Astrocytes, considered for decades to play merely supportive roles for neurons, have emerged as active regulatory elements directly involved in synaptic physiology. The GABAergic signaling to astrocytes has been previously shown, being able to activate intracellular Ca^{2+} signaling. However, the impact of the interneuron-astrocyte signaling into neuronal network operation remains unknown. Using the simplest hippocampal Astrocyte-Neuron network, i.e., GABAergic interneuron, pyramidal neuron, single CA3-CA1 glutamatergic synapse, and astrocytes, we found that interneuron-astrocyte signaling dynamically impacts excitatory transmission in an activity- and time-dependent manner that is controlled by astrocytes. While excitatory neurotransmission was inhibited by interneuron single action potentials (APs) through activation of $GABA_A$ receptors (characterized by fast kinetics), it was enhanced by bursts of interneuron APs through additional and concurrent slower mechanisms, i.e., astrocyte $GABA_B$ receptor activation, G-protein-mediated intracellular Ca^{2+} mobilization, astrocytic glutamate release, and presynaptic group I mGluR activation; which persisted after the interneuron burst. Conditional astrocyte-specific $GABA_B$ receptor (GABBR1) knockout mice confirmed the glial source of the interneuron-induced potentiation, and demonstrated the involvement of astrocytes in hippocampal theta and gamma oscillations *in vivo* (2). Therefore, these results show the existence of new mechanisms to fine-tune the output of local synapses by astrocyte activity that might contribute to control the excitation-inhibition balance at the hippocampal circuits.

References

1.Kullmann, D.M. (2011). Interneuron networks in the hippocampus. CurrOpinNeurobiol 21, 709-716.

2.Perea G, Gómez R, Mederos S, Covelo A, Ballesteros JJ, Schlosser L, Hernández-Vivanco A, Martín-Fernández M, Quintana R, Rayan A, Díez A, Fuenzalida M, Agarwal A, Bergles DE, Bettler B, Manahan-Vaughan D, Martín ED, Kirchhoff F, Araque A (2016). Activity-dependent switch of GABAergic inhibition into glutamatergic excitation in astrocyte-neuron networks. Elife. pii: e20362. doi: 10.7554/eLife.20362

CO2. ON-SITE GENERATION OF THE ADULT NEURAL STEM CELL POPULATION IN THE POSTNATAL DENTATE GYRUS

O. Pastor[1,2], J.R.Pineda[1], A. Urbach[3], J. M. Encinas[1,2,4.]
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[2] University of the Basque Country (UPV/EHU), Leioa, Spain.
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[4] Ikerbasque, The Basque Foundation for Science, Bilbao, Spain.

The population of hippocampal neural stem cells (NSCs) decreases markedly with age, as depletion is faster than self-renewal. As the relative proportion of activated NSCs remains constant over time, the neurogenic output throughout adulthood is mainly determined by the size of the initial pool of NSCs. However, how and when the NSCs get established in the subgranular zone (SGZ) of the dentate gyrus (DG) remains mostly unknown.

Using Nestin-GFP transgenic mice, in which NSCs can be readily visualized and analyzed, we observed that adult-like radial NSCs (rNSCs) can be identified, as nestin and GFAP-expressing cells with radial morphology and profuse arborization in the molecular layer, at postnatal day 7 (P7), but not earlier. From then on, the rNSC population increases in size reaching a maximum at P14-21.

Interestingly, using the Lysophosphatidic Acid Receptor 1-enhanced Green Fluorescent Protein (LPAR1-eGFP) transgenic mice, recently shown to selectively label NSCs in the hippocampus, we found that the expression of LPAR1 starts in the NSC population by P7, suggesting a possible functional role of LPAR1 in the establishment of the adult rNSC population in the postnatal dentate gyrus.

Furthermore, in the postnatal cyclin D2 knock-out mice (D2KO) the population of NSCs fails to expand from P7 to 14, resulting in an almost absent population of adult rNSCs and neurogenesis at P28.

These results put together suggest that the adult rNSC population is established in the postnatal dentate gyrus within a discrete critical period and therefore adult hippocampal neurogenesis cannot be considered a mere continuation of hippocampal development. In addition, we predict that any alterations affecting NSCs around P7 in the DG will strongly alter the adult neurogenic output.

Key words: Development, Neural Stem Cells, Neurogenesis, LPAR1, CyclinD2, Dentate gyrus

CO3. PHENOTYPICAL AND FUNCTIONAL HETEROGENEITY OF NEURAL STEM CELLS IN THE AGED HIPPOCAMPUS

S.Martín-Suárez[1,2], J.Valero[1,2,4], P. Vicente-Munuera[3], P. Gómez-Gálvez[3], LM. Escudero[3], JM. Encinas[1,2,4]

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Adult neurogenesis persists in the hippocampus of most mammals during adulthood, although it declines markedly with age due to progressive loss of neural stem cells (NSCs), although the neurogenic output depends on the actual number of activated NSCs in each given time point.

Using the transgenic Nestin-GFP mice we evaluated 3 different age-points (3, 12 and 18 months) and found two distinct populations of NSCs (Nestin-GFP and GFAP-positive without the astrocytic marker S100β) with different phenotype and properties. An alpha-type cell (α-NSCs) that maintains the classic type-1 radial morphology; and a reactive-like omega-type (Ω-NSCs) of increased morphological complexity and abnormal location. Moreover, the proportion of α-NSCs declines while that of Ω-NSCs increases overtime reaching almost 100% in 18 month-old mice.

Functionally, Ω-NSCs divide with significant lower probability than α-NSCs in normal conditions, as measured by incorporation of the thymidine analog bromodeoxyuridine (BrdU). They also reenter the cell cycle with less frequency than α-NSCs, as measured by colocalization with Ki67. When NSCs are challenged with a pro-activation stimulus (intrahippocampal injection of the glutamate agonist kainic acid, KA), α-NSCs respond by largely increasing the rate of cell division. Although Ω-NSCs are also able to increase their rate of mitosis, most of the KA-induced activation of NSCs corresponds to α-NSCs. Finally, by administration of interferon alpha (IFN- α) we demonstrated that chronic inflammation, one of the hallmarks of brain aging, is able to induce the transformation of α-NSCs into Ω-NSCs.

These results help explain the drastic reduction of hippocampal cell proliferation and neurogenesis in the aged brain and highlight the heterogeneity of NSCs in the adult dentate gyrus.

Keywords: Aging, neural stem cells, neurogenesis, hippocampus.

CO4. A FUNCTIONAL ROLE OF GABA-B RECEPTORS IN THE MATURATION OF OLIGODENDROCYTE PRECURSOR CELLS AND REMYELINATION

M.P. Serrano [1,2,3], M. Canedo-Antelo [1,2,3], A. Palomino [2,3], C. Matute [1,2,3], M.V. Sánchez-Gómez [1,2,3]
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Multiple sclerosis (MS) is a chronic, inflammatory and demyelinating disease of the central nervous system (CNS). Different studies point at oligodendrocyte precursor cells (OPCs) as the main source of remyelination after demyelination, so that OPCs, migrate, proliferate and differentiate into myelinating oligodendrocytes (OLGs). This event may be mediated by neuron-glia interactions that involve several growth factors and neurotransmitter receptors, including GABA. In this context, our aim is to determine the role of the GABAergic system on the differentiation of OPCs into mature oligodendrocytes in different *in vitro* models. Here, we demonstrate that OLGs express GABA and its receptors as well as the GABA synthesizing enzyme $GAD_{65/67}$. The chronic exposure of purified rat OPC cultures to exogenous GABA and other agonists/antagonists of GABA receptors are not toxic for these cells. The selective activation of $GABA_B$ receptors with baclofen in purified rat OLG cultures provokes an enhanced production of myelin associated glycoprotein (MAG) and myelin basic protein (MBP), that is attenuated in the presence of its antagonist CGP55845. Moreover, the function of the GABAergic system in promoting advanced maturation of oligodendrocytes is reproduced in a cerebellar organotypic slice culture where GABA and baclofen induce a remarkable increase of MAG and MBP. Furthermore, GABA receptor agonists reduce lysolecithin-induced demyelination in cerebellar organotypic cultures and promote the subsequent remyelination. These results indicate that GABA, mainly through the $GABA_B$ receptors, regulates OPC maturation and points at these receptors as a possible therapeutic target to enhance remyelination in demyelinating diseases.

Keywords: oligodendrocyte precursor cells, GABA receptors, baclofen, remyelination.

Funded by Basque Government, MINECO and CIBERNED

CO5. ATTENUATION OF PROGRESSIVE DISABILITY IN A MURINE MODEL OF MULTIPLE SCLEROSIS BY MANIPULATING GUT MICROBIOME

L. Mestre[1], FJ. Carrillo-Salinas[1],A. Feliú[1], M. Mecha[1], C. Espejo[3], X. Montalbán[3], JC. Álvarez-Cermeño[2], LM. Villar[2], C. Guaza[1]
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Alterations in the balance of the gut microbioma have been associated with detrimental or protective effects in multiple sclerosis and in experimental autoimmune encephalomyelitis.Recently, we provided evidence of the importance of the gut microbiota in neuroimmune responses during the acute phase of Theiler's virus induced demyelinating disease (TMEV-IDD), a model of progressive MS. Here, we investigated whether oral treatment with a broad spectrum of antibiotics(ABX)or probiotics (Vivomixx®) during the chronic progressive autoimmune phase of TMEV-IDD influence theimmune responses to TMEV and the severity of the disease.
SJL/J mice were provided drinking water supplemented with ABX (1g/L ampicillin, 1g/L neomycin sulfate, 0.5g/L vancomycin, 1g/L metronidazole) for 28days starting 14days before clinical signs. Other group of TMEV-mice was orally treated with Vivomixx®, ($3x10^8$cfu) three times a week for 2weeks once the disease was established. Our results indicate that TMEV-mice subjected to ABX treatment displayed better motor function than TMEV-mice, showing diminished levels of proinflammatory cytokines, IL-1β, IL-6 and TNF-α, and increased levels of the anti-inflammatory cytokines, IL-4 and IL-10, together with elevated expression of Foxp3. The treatment with ABX also modulated spinal cord infiltrates and microglia reactivity. Interestingly, the administration of a mixture of probiotics that include eight beneficial bacterial strains also ameliorated motor disability of TMEV-mice and modulated neuroinflammation.
These results demonstrate that modifications of gut bacterial equilibrium influencecentral immune responses to TMEV infection and the severity of the disease. Further studies are necessary for understanding the causal direction of our findings from a mechanistic perspective.

Key words: Theiler's virus, multiple sclerosis, microbiota, probiotics, antibiotics.

This work was supported by REEM, Red Española de EsclerosisMúltiple[1]RD16/0015/0021; [2]RD16/0015/0001; [3]RD16/0015/0004.

C06. IL-37 exertstherapeuticeffects in experimental autoimmune encephalomyelitis

Alba Sánchez-Fernández[1], Charles A. Dinarello[2,3] and Rubèn López-Vales[1]

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Multiple sclerosis (MS) is achronic, autoimmune and degenerative disorder that causes central nervous system demyelination and axonal injury. MS affects 2.5 million people worldwide and it is highly disabling. Although its ethology remains elusive, several lines of evidence support the concept that autoimmunity plays the major role indisease pathogenesis. The current treatments for MS are unable to prevent disease progression. Interleukin 37 (IL-37)is known to broadly reduce innate inflammation as well as acquired immunity. IL-37 has demonstrated to mediate significant resistance against several inflammatory challenges, including after spinal cord injury. Thus, we hypothesized that IL-37 could mitigate the neurological deficits in MS.

We induced experimental autoimmune encephalomyelitis (EAE) in transgenic mice expressing the human form of IL-37 (hIL-37tg) or in wildtype littermates.

We firstly assessed the changes in mRNA levels of IL-37 during the disease. qPCR experiments revealed that IL-37 transcriptswere barely detected in the spinal cord of unimmunized and immunized miceat the onset of EAE. However,strong induction of IL-37 was observed at the peak and progression phase of EAE. We also found a reduction in some pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6 and IFN-γ caused by IL-37.We thenevaluated whether IL-37 attenuated the clinical signs of the disease.We found that transgenic expression of IL-37 markedly reduced neurological deficits. Moreover, histological analysis revealed that IL-37 conferred protection against myelin loss.Taking together, this study presents novel data indicating that IL-37 may have therapeutic potential for the treatment ofMS.

Keywords: Interleukin-37, multiple sclerosis,experimental autoimmune encephalomyelitis,neuroinflammation, neuroprotection, cytokines

CO7. MODULATING MICROGLIA AND MACROPHAGE PLASTICITY AFTER SPINAL CORD INJURY

Jesus Amo-Aparicio, Rubèn López-Vales
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Spinal cord injury (SCI) elicits an inflammatory response that comprises mainly microglia and peripheral blood-derived macrophages. These cells contribute to tissue damage and functional loss; however, they can also promote repair. These paradoxically conflicting roles of microglia and macrophages depend on their polarization state: In response to interferon gamma or lipopolysaccharide, macrophages and microglia undergo “classical” M1 polarization. Contrary, upon IL-4 or IL-13 stimulation, macrophages and microglia acquire “alternative” M2 polarization. M1 macrophages and microglia release high levels of pro-inflammatory cytokines and free radicals. These compounds are crucial for killing microbes and tumor cells, but they also induce damage in healthy neighboring cells and are associated with cell loss and secondary damage after SCI. Contrary, M2 macrophages release anti-inflammatory cytokines and are involved in parasite containment, tissue repair and remodelling events after injury. To get insights into the mechanisms that impede microglia and macrophages to acquire an M2-like phenotype after SCI, we found that the expression of IL-13 is detected at very low levels in the contused spinal cord. We hypothesized that inefficient induction of IL-13 expression after SCI favors microglia and macrophages to remain in a M1-like state. We observed that microglia and macrophages induce the expression of the M2 marker Arg1 upon IL-13 administration into the lesion site. Moreover, IL-13 administration reduced the expression of the M1 markers, iNOS and CD16/32, in these immune cell subsets. These results provide evidence that low levels of IL-13 after SCI hamper microglia and macrophages to acquire an M2-like activation state

Key words: spinal cord injury, microglia, macrophages, polarization, interleukin 4, interleukin 13

CO8. CSF1R BLOCKADE SLOWS THE PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS BY REDUCING MICROGLIOSIS AND INVASION OF MACROPHAGES INTO PERIPHERAL NERVES

Anna Martinez-Muriana[1], Renzo Mancuso[2], Isaac Francos-Quijorna[1], Adrian Olmos-Alonso[2], Rosario Osta[3], V. Hugh Perry[2], Xavier Navarro[1], Diego Gomez-Nicola[2], Ruben Lopez-Vales[1]

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Inflammation is a common neuropathological feature in several neurological disorders, including amyotrophic lateral sclerosis (ALS). We have studied the contribution of CSF1R signalling to inflammation in ALS, as a pathway previously reported to control the expansion and activation of microglial cells. We found that microglial cell proliferation in the spinal cord of $SOD1^{G93A}$ transgenic mice correlates with the expression of CSF1R and its ligand CSF1. Administration of GW2580, a selective CSF1R inhibitor, reduced microglial cell proliferation in $SOD1^{G93A}$ mice, indicating the importance of CSF1-CSF1R signalling in microgliosis in ALS. Moreover, GW2580 treatment slowed disease progression, attenuated motoneuron cell death and extended survival of $SOD1^{G93A}$ mice. Electrophysiological assessment revealed that GW2580 treatment protected skeletal muscle from denervation prior to its effects on microglial cells. We found that macrophages invaded the peripheral nerve of ALS mice before CSF1R-induced microgliosis occurred. Interestingly, treatment with GW2580 attenuated the influx of macrophages into the nerve, which was partly caused by the monocytopenia induced by CSF1R inhibition. Overall, our findings provide evidence that CSF1R signalling regulates inflammation in the central and peripheral nervous system in ALS, supporting therapeutic targeting of CSF1R in this disease.

Keywords: ALS, CSF1R, Microglia, Macrophages, Neuroprotection, $SOD1^{G93A}$

CO9. MICROGLIAL PHAGOCYTOSIS OF APOPTOTIC CELLS IS IMPAIRED BY GENETIC CYSTATIN B DEFICIENCY, A MOUSE MODEL OF PROGRESSIVE MYOCLONUS EPILEPSY (UNVERRICHT-LUNDBORG DISEASE)

Virginia Sierra-Torre1, Ainhoa Plaza-Zabala[1], Oihane Abiega[1,2], Víctor Sánchez-Zafra[1,2], Jorge Valero[1,3], Irune Diaz-Aparicio[1,2], Inken Körber[4], Anna Elina Leheshoki[4], Amanda Sierra[1,2,3]

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Microglial phagocytosis of apoptotic cells is an essential component of the brain regenerative response in neurodegenerative diseases. The molecular crosstalk between apoptosis and phagocytosis ensures the coupling of the two processes, resulting in a rapid removal of the neuronal corpses and preventing the spillover of intracellular contents. In addition, phagocytosis triggers an anti-inflammatory response in microglia that further contributes to maintain the brain parenchyma homeostasis. We have recently described that microglial phagocytosis of apoptotic cells is very efficient in adult neurogenic niches in physiological conditions, as well as during apoptotic challenge induced by excitotoxicity or inflammation. Unexpectedly, phagocytosis is impaired in mouse and human mesial temporal lobe epilepsy (MTLE) due to a complex mechanism that involves reduced process motility, reduced expression of phagocytic receptors, and disrupted apoptotic “find-me” molecule ATP gradients due to the widespread release of ATP during seizures. Here we extend our studies to a genetic model of epilepsy induced by deficiency of cystatin B (CSTB), progressive myoclonus epilepsy. CSTB is an inhibitor of cysteine proteases such as cathepsins B, L, and S, which are lysosomal proteins involved in proteolysis. We first demonstrate that the number of apoptotic cells increases while microglial phagocytosis is impaired as early as P14 in CSTB deficient mice, before seizure onset, suggesting alternative mechanisms compared to MTLE mice that may be directly related to the lack of CSTB in microglia. To test this hypothesis, we first show that both CSTB and downstream cathepsins are indeed expressed by microglia acutely purified from the adult hippocampus. Next, we analyze the effect of reduced microglial CSTB expression in an *in vitro* model of phagocytosis of apoptotic cells. Overall, our data suggest that microglial phagocytosis impairment is an early feature of hippocampal damage in epilepsy and opens novel therapeutical approaches for epileptic patients based on harnessing microglial phagocytosis.

PÓSTERS

P01. ROLE OF UPSTREAM REGIONS IN APOLIPOPROTEIN D GENE EXPRESSION UNDER OXIDATIVE STRESS

Sergio Diez-Hermano[1], Andres Mejias[2], Maria D. Ganfornina[1], Gabriel Gutierrez[2] and Diego Sanchez[1]
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Apolipoprotein D (ApoD) is a glial Lipocalin overexpressed in aging and neurodegeneration. In astrocytes, oxidative stress triggers an early, transient ApoD expression regulated by the JNK MAP-kinase pathway that leads to protective effects. The mechanisms governing the expression of ApoD and its differential spatial distribution under oxidative insults are not known in detail. Transcriptional regulatory elements have been reported in the upstream region of the human Lipocalin ApoD gene, but no study has been performed in the mouse model.
Our *in silica* analysis of the mouse ApoD gene upstream sequence identifies a canonical promoter as well as a plausible alternative promoter region (Prom-β). We have cloned the Prom-β sequence and transfected the IMA2.1 astrocytic mouse cell line. Our results support that Prom-β-driven expression steadily increases in response to oxidative stress, whereas the canonical promoter-driven expression reach saturation and becomes independent of oxidative stimulus concentration. Furthermore, bioinformatic analysis of the 5' and 3'-UTRs sequences of the ApoD gene show the existence of previously unknown alternative splicing variants. The presence of these variants in Lipocalins across different species suggests a conserved translation control mechanism. We assessed the expression levels of mouse ApoD 5'-UTR variants in several tissues, developmental stages, and stress conditions. We have found a nervous system specific variant (5'Var-E) whose expression is dependent on oxidative stress. Further experiments will prove the potential coordination of 5'Var-E expression under Prom-β control, given the prominent role they play as ApoD gene regulatory elements differentially triggered by oxidative stress.

Support: MICINN (BFU2011-23978; BFU2015-68149-R).

Keywords: Apolipoprotein D, glial lipocalin, neurodegeneration, UTR, promoter, gene regulation, oxidative stress

P02. ATTENUATION OF MACROGLIA AND MICROGLIA REACTIVITY BY TUDCA CORRELATES WITH ITS NEUROPROTECTIVE EFFECTS IN RETINITIS PIGMENTOSA.

Laura Fernández-Sánchez[1], Agustina Noaïlles[1], Isabel Ortuño-Lizarán[1], Victoria Maneu[2], Pedro Lax[1], Nicolás Cuenca[1]

[1]Department of Physiology, Genetics and Microbiology, University of Alicante
[2]Department of Optics, Anatomy and Farmacology, University of Alicante

Introduction: In retinitis pigmentosa (RP) photoreceptor death is accompanied by gliosis and reduction of retinal vascularization, which influence the degenerative process. Tauroursodeoxycholic acid (TUDCA) has demonstrated its neuroprotective effect on different animal models of RP. The purpose of this study was to investigate changes in glial cells in the retina of P23H rats, a model of RP, and to evaluate the effect of TUDCAin theglia during degeneration.
Material & Methods: Homozygous P23H line-3 rats aged from P18 to P480 were used to study the evolution of the disease, and SD rats were used as controls. Neuroprotective effects of TUDCA (500 mg/kg, i.p.; P18 - P120) was evaluated at P120. Different glial markers were used to study Müller and astrocyte cells.
Results: During retinal degeneration glial cells were activated, with increasedexpression of GFAP in Müller cells as an early indicator of retinal gliosis.At P120 and P360, the apical processes of Müller cells in P23H rats clustered in firework-like structures, which were associated with ring-like shaped areas of cone photoreceptor cell degeneration. TUDCA treatment prevented the formation of these structures. As the disease progressed, astrocytes increased in number, exhibiting a deteriorated morphology, marked hypertrophy and increased connexin 43 expressions. In P120-TUDCA-treated animals, astrocytes maintained a similar morphology than in control rats. Finally, retinas of TUDCA-treated P23H animalsexhibitedlowermicroglialcellnumber in alllayers.
Conclusions: The effects of TUDCA reducing glial activation could be a key factor in theirneuroprotective actions in retinal degenerative diseases.
Support:MINECO-FEDER (BFU2015-67139-R), Instituto de Salud Carlos III (RETICS-FEDER RD16/0008/0016) and Generalitat Valenciana (PROMETEO/2016/158).

Key words: Müller cells, Astrocytes, Microglia, retina, TUDCA, neuroprotection.

P03. IL-6 AND IL-10 TRANSGENIC CNS OVEREXPRESSION ON GLIAL REACTIVITY AND MOTOR NEURON SURVIVAL AFTER PERIPHERAL NERVE INJURY

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Interleukins have a main role in the regulation of inflammation and tissue damage after an injury. Amongst them, interleukin (IL)-6 acts as a major regulatory cytokine, whereas IL-10 is an anti-inflammatory cytokine. Previous work from our group determined that transgenic mice producing either IL-6 or IL-10 under the GFAP promoter (GFAP-IL6Tg and GFAP-IL10Tg mice) presented important differences in the CNS response after a facial nerve axotomy (FNA). While GFAP-IL6Tg mice showed a decrease in facial motor neuron (FMN) survival compared to wild-type (WT) after FNA, in GFAP-IL10Tg mice FMN survival rate was increased. These differences were importantly correlated with alterations in microglial reactivity. In this work, we aimed to establish the effect of combined astrocyte-targeted production of IL-10 and IL-6 in the CNS response after FNA. Therefore, 3-month-old GFAP-IL6/IL10Tg mice and their respective GFAP-IL6Tg, GFAP-IL10Tg and WT littermates were used. IL-10 concentration in the facial nucleus of these animals was measured in basal conditions. After FNA, FMN survival was quantified in cryostat sections stained with toluidine blue. Glial reactivity was analyzed at 14 and 21 dpi with GFAP and Iba-1 immunohistochemistry, and microglial clusters were counted. Likewise, T-cell infiltration was observed with a CD3 immunohistochemistry. Our results showed that IL-10 basal production increased two-fold in GFAP-IL6/IL10Tg respect to WT mice, while in GFAP-IL6Tg and GFAP-IL10Tg, IL-10 increased four-fold and ten-fold respectively. FMN survival showed no significant differences between GFAP-IL6/IL10Tg and WT mice after FNA; and no appreciable changes in Iba-1 and GFAP immunoreactivity intensity at 14 and 21 dpi were found, as well as in microglial cluster number. Finally, in GFAP-IL6/IL10T there was an important increase in infiltrated T cells in comparison to WT. In conclusion, in GFAP-IL6/IL10Tg mice, the astrocyte-targeted production of IL-10 counteracts the deleterious effect of astrocyte-targeted IL-6 production on FMN survival and glial reactivity after FNA.

Key words: facial nerve axotomy, IL-6, IL-10, GFAP, transgenic mice, T-lymphocyte

P4. ECTOPIC EXPRESSION OF MELANOPSIN DRIVES ASTROCYTE CALCIUM SIGNALS

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The outbreak practice of optical tools to decipher the neuronal circuits' organization and behavioral output has transformed the neuroscience studies. Recently, these approaches have been applied to glial cells, particularly astrocytes, to unmask the consequences of astrocyte signaling in particular brain functions. Here we use a new approach based on melanopsin, a photosensitive G-protein-coupled photopigment expressed by mammalian retinal ganglion cells; which in contrast to those algae-derived opsins that directly form ion channels is coupled to IP3 signaling and elevation of intracellular Ca^{2+} levels. Therefore, we tested whether melanopsin was competent to stimulate Ca^{2+} activity in astrocytes. In order to monitor Ca^{2+} signals, the genetically encoded Ca^{2+} indicator (GECI) Lck-GCaMP6f and melanopsin were fused to the glial fibrillary acidic protein (GFAP) promoter and expressed in hippocampal astrocytes following an adeno-associated virus (AAV)-based strategy. Using two-photon imaging on hippocampal slices, we found that astrocytes co-expressing melanopsin and GCaMP6f showed robust Ca^{2+} increases in fine processes after blue light (473 nm) stimulation. The analysis of Ca^{2+} signals indicated a linear relationship between Ca^{2+} event frequency and light duration, but the amplitude and width of each event were not modified after light pulses. Consequently, viral transfection of melanopsin and GCaMP6f in mice that lack IP3 receptor-2 (*Ip3r2*$^{-/-}$), which is required for IP3-dependent Ca^{2+} release in astrocytes, was evaluated. After blue light stimulation, the number of active domains did not show significant changes at any light pulse tested, as well as the amplitude and width of Ca^{2+} events; indicating that melanopsin selectively activated IP3-dependent Ca^{2+} signals in astrocytes. Therefore, these results describe a previously unidentified method for specific optogenetic activation of astrocytes with melanopsin, which is revealed as a meaningful G-protein signaling mechanism.

Palabras clave: optogenetics,astrocytes,intracellular calcium,synaptic transmission, astrocyte-neuron signaling.

P05. PROTECTING THE NERVOUS SYSTEM BY PROTECTING THE VULNERABLE LYSOSOMES: IDENTIFICATION OF A NEW GLIA-DERIVED MECHANISM FOR PRESERVING LYSOSOMAL FUNCTIONAL INTEGRITY UPON OXIDATIVE STRESS.

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Within the nervous system, astrocytes secrete the Lipocalin Apolipoprotein D (ApoD), an extracellular lipid binding protein with antioxidant capacity. ApoD is both an autocrine protective mechanism for astrocytes and a neuroprotector, helping neurons cope with oxidative challenges. Lysosomes are key in this process, because they are particularly sensitive to oxidative-stress triggered permeabilization. Their function depends on intraluminal acidic pH and requires stable membrane-dependent proton gradients. ApoD is one of the few genes consistently over-expressed in the aging brain, and no nervous system disease has been found concurring without ApoD over-expression. The protecting role of ApoD is known from cellular to organism level, and many of its downstream effects, including optimization of autophagy upon neurodegeneration, have been described. However, we still could not assign a cellular mechanism to ApoD that explains how this protection is accomplished. Here we perform a comprehensive analysis of ApoD intracellular traffic, in astrocytes and neurons, and demonstrate its role in lysosomal pH homeostasis upon paraquat-induced oxidative stress. By combining single-lysosome in vivo pH measurements with immunodetection, we demonstrate that ApoD is endocytosed and targeted to a subset of lysosomes in a stress dependent manner. ApoD is functionally stable in this acidic environment, and its presence is sufficient for lysosomes to recover from oxidation-induced alkalinization, both in astrocytes and neurons. This function is accomplished by preventing lysosomal membrane permeabilization. Two lysosomal- dependent biological processes, myelin phagocytosis by astrocytes and optimization of neurodegeneration-triggered autophagy in a Drosophila in vivo model, require ApoD-related Lipocalins.
Our results uncover a previously unknown biological function of the glial protein ApoD. They set the lipoprotein-mediated regulation of lysosomal membrane integrity as a new mechanism, critical for the outcome of a wide variety of neurodegenerative diseases. These results open therapeutic opportunities by providing a route of entry and a repair mechanism for lysosomes in pathological situations. Support: MICINN (BFU2011-23978; BFU2015-68149-R), JCyL (EDU/1883/2013).

Key words: Apolipoprotein D. Lysosomes. Astrocytes. Oxidative stress.

P06. PRODUCTION OF INTERLEUKIN-10 AND INTERLEUKIN-6 IN THE CENTRAL NERVOUS SYSTEM MODIFIES GLIAL CELL RESPONSE ASSOCIATED TO PHYSIOLOGICAL AGING

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Aging is one of the greatest risk factors to develop age-related neurodegenerative diseases. Some of the major hallmarks of aging are increased astrocyte and microglial activation and deregulated cytokine production that can contribute to promote neuronal degeneration and cognitive deterioration. The aim of the present study was to evaluate whether the local production of the anti-inflammatory cytokine interleukin-10 (IL-10) or the pro-inflammatory cytokine interleukin-6 (IL-6) within the central nervous system (CNS), induces changes in the glial response associated to physiological aging. For this purpose, adult (5-7 months old) and aged (19-21 months old) animals from two different lines of transgenic mice with astrocyte-targeted production of either IL-10 (GFAP-IL10Tg) or IL-6 (GFAP-IL6Tg) were used. Major differences regarding astrocytes were found in the cerebral cortex where aged GFAP-IL6Tg animals showed higher levels of GFAP than WT and GFAP-IL10Tg animals.In terms of microglial reactivity, in comparison to their corresponding WT,aged animals from both transgenic lines showed an increased number of Pu.1+ microglial cells together with a more activated phenotype. These microglial cells showed higher Iba1 immunoreactivity as well as alterations in the morphology and in CD68 expression, a marker of phagocytosis.Remarkably, in aged WT mice, CD68 immunostaining was restricted to the microglial soma, whereas in both aged transgenic mice was redistributed along microglial cell branches. In conclusion, these results demonstrate that both IL-10 and IL-6 have a great impact on the glial cell response associated to age, principally altering the phagocytic function of microglial cells. More studies analysing whether these cytokine-induced glial changes affect the neuronal populations are necessary to decipher the implications that microenvironment alterations may exert in physiological aging.

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P07. ASTROCYTES MEDIATE NMDA RECEPTOR-DEPENDENT LONG-TERM DEPRESSION THROUGH p-38α MAPK.

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There is increasing evidence for the existence of bidirectional communication between astrocytes and neurons, which modulates synaptic communication and plays critical roles in the physiology of the nervous system. NMDA receptor-dependent long-term depression (LTD) of synaptic transmission represents an intensely studied form of synaptic plasticity, as it is involved in some aspects of learning and memory. However, LTD is classically considered as a purely neuronal phenomenon, relying on presynaptic glutamate acting on postsynaptic NMDA receptors. We have investigated the involvement of astrocytes in the hippocampal NMDAR-dependentLong Term Depression (LTD) of CA3-CA1 synaptic transmission.Using electrophysiological, optogenetic,chemogeneticand imaging techniques in murineshippocampal slices, we have found that astrocyte activity evoked by electrical stimulation of Schaffer Collaterals stimulates the release of glutamate from astrocytes. On the other hand, direct photostimulation of astrocytes induced LTD of CA3-CA1 synapses. This effect required NMDA receptor activation and was independent of metabotropic glutamate receptors. Additionally, selective hyperpolarization of astrocytes, using viral-mediated delivery of designer receptors exclusively activated by designer drugs (DREADDs), do no prevent hippocampal LTD, indicating that astrocyte depolarization is not needed for NMDAR-dependent LTD in the hippocampus. Finally, we identify astrocytic, and not neuronal, p38α MAPK as a critical signaling molecule responsible for NMDA receptor-dependent LTD. In summary, these resultssuggest that astrocyte activity is sufficient to induce NMDAR-dependent LTD in the hippocampus, contributing to support the idea that astrocytes play an active role in the transfer and storage of synaptic information in the Nervous System.

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Keywords: *Hippocampus, synaptic plasticity, LTD, optogenetics, glutamate, NMDA receptor.*

P08. NEURAL STEM CELLS IN THE ADULT DENTATE GYRUS FOLLOW A DISPOSABLE MODE OF ACTIVATION

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Radial neural stem cells (rNSCs) persist in the hippocampus of most mammals and are able to generate neurons through adulthood, a process known as adult neurogenesis. In normal conditions, only a 2-4% of rNSCs are activated in a given moment. Then, after giving rise to several amplifying neural progenitors (ANPs) in consecutive rounds of cell division, they differentiate into astrocytes. This model implies a sole event of activation, and takes place at least at a population level.

To test this rNSC single activation hypothesis, we administered the thymidine analogue bromodeoxyuridine (BrdU) in drinking water to mice for 1 week or 1 month, and sacrificed them either 1 day or 1 month later. With this approach we labeled even very slow-cycling NSCs which would elude labeling by acute administration methods. We analyzed BrdU incorporation by cell types and evaluated differentiation and cell cycle reentry, by colocalization with Ki67. In the differentiation assays (1 month after either 1 week or 1 month of BrdU), the vast majority of $BrdU^+$ cells were neurons, with a low percentage of oligodendrocyte progenitor cells and astrocytes. Remarkably, an extremely low number of BrdU-labeled rNSCs and ANPs were observed. Cell cycle reentry was high in the proliferation analysis (1 week of BrdU+1 day of survival) but negligible in the differentiation analyses, in which not a single rNSC reentering into the cell cycle was found.

Our results prove that the alternation between quiescence and activation is extremely infrequent in rNSCs. BrdU incorporation analyses suggest rNSCs get activated only once and their progeny originates mostly neurons, and afterwards they differentiate into astrocytes. These results and our previous data strongly support our disposable NSC model in the adult dentate gyrus.

Keywords: Adult neurogenesis, hippocampus, dentate gyrus, neural stem cells.

P09. MORPHOMETRIC VARIABILITY OF ACTIVATED MICROGLIAL CELLS ACCORDING TO IL1B LEVEL EXPRESSION

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Neuroinflammation generated by intracerebroventricular neuraminidase administration results in activation of microglial cells nearby ventricular system. Triggering of cells is identified by IL1B expression. **The aim of this work was founding out if morphological changes of microglia are related to citokines expression degree and also, if there is a brain region especially sensitive for this changes.**

For this purpose, coronal brain slices from injected rats with neuraminidase were immunostaining by Iba1 antibody (green color) and the activated cells by IL1β antibody red color. After image processing for an accurate quantification two cell forms of the same area showed images suitable to quantification of expression of IL1β respect to Iba1; that is: number of pixels of red-channel (IL1β-target) compare to number of pixels of green-channels (Iba1-target), expressed in percent.

Moreover, an accurate morphometric analysis was carried out on these activated cells, only the green-channel cells, which always were more or less targeted by IL1β. Morphometric quantification of **fractal dimension, lacunarity, area, perimeter and density** was carried out on randomly selected cells from caudate putamen, septofimbrial nuclei and hypothalamus.

Linear regression analysis was performed with the aim of modeling the relationship between expression of IL1β on microglial cells as independent variable and each parameter described above as dependent variables.

Our analysis pointed out that there were significant differences between the mean values of lacunarity and density of the different regions of the brain.

The stronger predicted parameters were perimeter, area and density

The region brain with highest correlation was the hypothalamus.

P10. EFFECT OF NEURAMINIDASE-ACTIVATED MICROGLIA ON THE VIABILITY OF EPENDYMOCYTES

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Neuroinflammation generated by intracerebroventricular neuraminidase administration generates ependymal death. Up to now, the factors that determine this death are not well defined. This objective has been raised to investigate the possible role of microglia in this death.

Analysis of viability of isolated ependymocytes in the presence of NA-activated microglia. For this aim, pure cultures of rat ependymal cells and pure cultures of microglia will be obtained. The microglia will be activated by adding to the culture medium NA or other known activating agents (LPS, P3C), and the viability of the ependymal cells will be quantified with the trypan blue vital dye.

Analysis of the efficacy of ependymocytes in lateral ventricle explants in the presence of NA-activated microglia. In this case using unrelated ependymocytes but in its ventricular wall niche. For this purpose, explants from the striatal and septal walls of the rat lateral ventricles will be used. Such explants will be exposed in vitro to NA-activated microglia cultures for 24 hours. Explants will be fixed and ependymal death will be studied by immunohistochemistry

Presence of receptors to cytokines of IL1β and TNFα in ependimocytes. These cytokines, released by activated microglia, could be responsible for the death of ependymal cells. The expression of those genes could be shown by positive detection through PCR of RNA isolated from pure ependymocytes culture.

It has been observed that the activation of the microglia by NA or other agents decreases the viability of the ependymal cells in vivo and in vitro.

Palabras clave:

Ependymocytes, death, microglia, neuraminidase, IL-1β.

P11. THE INFLAMMATORY RESPONSE AND MICROGLIAL ACTIVATION TRIGGER CELL DEATH IN THE RETINITIS PIGMENTOSA DISEASE

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The activation of microglia has been demonstrated in association with several neurodegenerative diseases, producing inflammatory mediators that may contribute to retinal tissue damage during pathological processes.The objective of this work was to study microglial activation in a model of retinal degeneration, to correlate it with changes in inflammatory and apoptotic mediators and visual impairment.Microglial activation was analyzed in homozygous P23H line 3 and Sprague-Dawley rats (controls) at 1, 2 3, 4, 6 and 12 moths of age by immunohistochemistry and flow cytometry, using CD11b, CD45 and MHC class II cell-surface markers. The expression levels of inflammatory and apoptosis-associated geneswas assessed by qPCR. The degeneration of the retinas was analyzed evaluating the number, morphology and connectivity of different neuronal populations, using specific cell markers of retinal cells.Activated microglia were detected at all ages tested in the retinas of P23H but not in Sprague-Dawley rats. Microglial activated population increased with the age, with an apparent plateau from 2 to 6 months of age and exhibited amoeboid morphology in P23H rat retinas. In agreement with that, P23H rat retinas showed increased mRNA levels of TNF-α, IL-1α, IL-1β and caspase-1 compared to SD control rats as well as increased expression levels of Bad, Bax, p53 and Apaf1. These results indicate that increased density and activation of retinal microglia persists in the P23H model of retinal neurodegeneration, even after photoreceptor death,leading to increasedexpression of inflammatory molecules and apoptosis mediators.

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Keywords: Microglia, retina, neurodegeneration, neuroprotection.

P12. THE ROLE OF MICROGLIAL INTERLEUKIN-6 IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Interleukin-6 (IL-6) is a pleiotropic and multifunctional cytokine that controls the immune system and influences the central nervous system (CNS) in normal and pathological conditions. IL-6 plays a crucial role regulating the immune response in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, characterized by demyelinating lesions associated with inflammatory cells (T lymphocytes, B lymphocytes, dendritic cells and mononuclear phagocytes) in the white matter of the CNS. Findings from different research showed that IL-6 deficient mice are resistant to the induction of EAE. However, little is known about the different cellular sources of IL-6 in the CNS and their contribution to EAE. Microglial cells are the main innate immune cells in the CNS and have been extensively described in the pathogenesis of EAE. Here, we focused on studying microglial IL-6 in EAE using a tamoxifen-inducible microglial IL-6 knock-out mouse model (*Il6ΔMic*), generated by crossing *Il6*flox/flox mice with *Cx3cr1*CreER mice, and as a control, their *Il6*flox/flox littermates. Two months after tamoxifen injection, both male and female *Il6ΔMic* and *Il6*flox/flox were induced by active immunization with myelin oligodendrocyte glycoprotein fragment 35-55 (MOG35-55). The clinical score and weight were monitored for 29 days for females and for 15 or 27 days for males. Finally, some inflammatory markers were evaluated by immunohistochemistry and RT-qPCR. Our data provide evidence that microglial IL-6 absence has minor effects on the symptomatology as well as on the animal weights and the histopathological study. However, sex differences could be observed between *Il6ΔMic* and *Il6*flox/flox mice.

Keyword: INTERLEUKIN-6; EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS ; MICROGLIA

P13. LOSS OF PRESENILIN FUNCTION RESULTS IN AGE-DEPENDENT TAU PHOSPHORYLATION

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Alzheimer's disease (AD), the most common causeof dementia, is pathologically characterized by neuronal loss, amyloid-β (Aβ) deposition and hyperphosphorylated tau protein accumulation in neurofibrillary tangles (NFT). Dominantly inherited mutations in the Presenilin (PS) genes, the catalytic subunit of γ-secretase responsible for Aβ generation, are the major cause of familial AD (FAD) and some cases of frontotemporal dementia, that are characterized by accumulation of aggregated phosphorylated tau. Notably, the molecular mechanisms linking PS and tau phosphorylation are still unknown. Interestingly, loss of PS function in brain-specific PS1/PS2 conditional double knockout (cDKO) mice results in increased tau phosphorylation and neurodegeneration. In this study, we used biochemical and histological approaches to characterize tau phosphorylation and neuroinflammation in PS cDKO mice at 6, 9 and 12 months of age in order to analyze tau pathology and its relationship with astrocytic and microglial activation. Our results show age-dependent tau phosphorylation in the cortex and hippocampus of PS cDKO mice, not only in neurons, but also in glia cells, associated withincreased p25/Cdk5 and decreased GSK3β activity, and elevated microglial activation and astrogliosis. Taken together these results provide further evidence that loss of PS function leads to neurodegeneration by increasing tau hyperphosphorylation, astrogliosis and microglial activation.

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Key words: Alzheimer, Neurodegeneration, Tau, Neuroinflammation, Mice.

P14. ISCHEMIA/STROKE RAPIDLY IMPAIRS MICROGLIAL PHAGOCYTOSIS IN VIVO

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Resumen

Microglial phagocytosis is an essential mechanism to maintain tissue homeostasis. In physiological conditions in the adult hippocampus, apoptotic cells are rapidly and efficiently phagocytosed by microglia. In response to phagocytic challenge induced by excitotoxicity or inflammation, microglia proportionally boost their phagocytic output to counteract the increased number of apoptotic cells, thus maintaining apoptosis and phagocytosis tightly coupled. Conversely, in a mouse model of cerebral hypoxia-ischemia we found the opposite. Using CX3CR1-GFP and CCR2-RFP mice, in which we can discriminate resident microglia from blood-derived monocytes, we have discovered that microglial phagocytosis is strongly uncoupled from apoptosis as early as 1d after ischemia. The phagocytic blockade was the result of reduced microglial surveillance and led to accumulation of non-phagocytosed apoptotic cells. Importantly, we have observed that this impairment occurred before blood-derived monocyte infiltration. Furthermore, while under physiological conditions microglia generally phagocytose by terminal branches (ball-and-chain mechanism), after ischemia the few phagocytic microglia detected engulfed dying cells by direct apposition to the soma. In addition, we also found some cases of phagoptosis, the engulfment of non-apoptotic cells, executed by microglia. Phagoptosis also occurred through the microglial soma and not by their distal processes. These results demonstrate that in the ischemic brain basal microglial phagocytic function is impaired. Accordingly, microglial phagocytic potential is a novel and yet unexplored therapy to promote clearance of apoptotic cells and anti-inflammatory response, in order to accelerate ischemic brain recovery.

Palabras clave: microglia, phagocytosis, apoptosis, phagoptosis, ischemia, stroke

P15. PROMOIJ: A NEW TOOL FOR SEMI-AUTOMATIC ANALYSIS OF CELL PROCESSES MOTILITY

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Microglial cells, the immune cells of the central nervous system, continuously survey the brain parenchyma to detect alterations and maintain tissue homeostasis. The gold standard technique to study motility involves the use of two-photon microscopy to obtain images from living animals. This technique generates large amounts of 4D images (XYZT) which are manually analysed using tedious and time consuming protocols. In addition, motility analysis is frequently performed using Z-projections of image stacks with the loss of 3D information and accuracy.

To overcome these limitations we developed ProMoIJ, an ImageJ tool to perform automatic motility analysis of cell processes in 3D. It includes several ImageJ macros that allow batch processing for registration, background subtraction, and bleaching correction of the images. The main core of the tool is formed by two ImageJ macros, to manually select the process to be analyzed and to automatically reconstruct its 3D skeleton. Several motility data are extracted from each skeleton: process length at each time, length variation per minute, retraction, protraction, tip position, and tip motility.

We have validated the data obtained with ProMoIJ by comparing them with manually obtained data by three different researchers using an assisted reconstruction protocol. Our results show that the use of ProMoIJ presents several advantages compared to manual analysis: 1) it reduces the time required for the analysis, 2) it is less sensitive to experimenter bias, and 3) it produces more consistent data.

To the best of our knowledge, ProMoIJ is the first freely available tool for automated analysis of microglial motility that facilitates the analysis of 3D motility of cell processes by reducing the time required to obtain results, and increasing the accuracy and reproducibility of the data.

P16. INVOLVEMENT OF THE LPA-LPA_2 AXIS IN THE PHYSIOPATHOLOGY OF ALS

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Lysophosphatidic acid (LPA) is a pleiotropic extracellular lipid mediator with many physiological functions that signals through 6 known G protein-coupled receptors (LPA_{1-6}). LPA mediates a wide range of LPA effects in the central nervous system, we have previously shown that microglial cells become cytotoxic upon LPA- LPA_1 activationand lead to myelin loss after spinal cord injury. We have also unpublished data indicating that activation of microglia LPA_2 also leads to demyelination, as well as, to neuronal loss, especially motor neurons, after spinal cord injury.

Since microgliosis is a common hallmark of most neurological conditions, we hypothesized that LPA could be involved in the pathophysiology of neurodegenerative diseases, such amyotrophic lateral sclerosis (ALS). This is a fatal neurodegenerative disease characterized by the loss of upper and lower motor neurons. The underlying mechanisms leading to the degeneration of motor neurons in ALS are diverse and not fully known, however, there is evidence supporting the detrimental action of inflammation in the course of this disease.

Our results revealed that thedecline of the amplitude of the compound muscle action potential of the tibialis anterior muscle was slower in ALS mice lacking LPA_2 as compared to WT littermates, suggesting that the neuro-muscular integrity was better preserved in the absence of LPA_2 activity. Similarly, rotarod testing showed that the lack of LPA_2also resulted in delayed onset and slowed progression of the disease. To our knowledge, these data suggests for the first time the detrimental actions of the LPA-LPA_2 axis in the physiopathology of ALS.

Key words: Amyotrophic lateral sclerosis, microglia, lysophosphatidic acid

P17. MYELIN EXTRACELLULAR LEAFLET COMPACTION REQUIRES APOLIPOPROTEIN-D MEMBRANE MANAGEMENT BY OPTIMIZING LYSOSOMAL-DEPENDENT RECYCLING AND GLYCOCALYX REMOVAL.

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To build a myelin sheath, a series of well-orchestrated processes culminate with myelin compaction. While intracellular leaflet compaction is well understood, that of myelin extracellular sides remains elusive. During the final steps of myelin maturation, an important transition takes place: membrane sliding to build the wraps must be followed by membrane adhesion/compaction of the extracellular sides. In such transition, removal of the negatively charged glycocalyx becomes the limiting factor. What does this membrane zipping process require to be initiated?

We demonstrate that knocking-out the Lipocalin Apolipoprotein D (ApoD), recently discovered to be essential for the maintenance of lysosomal functional integrity in glial cells, results in a specific defect in myelin extracellular leaflet compaction in both CNS and PNS. Myelination initiation and growth, intracellular leaflet compaction, myelin thickness or internodal length remain unaltered. Anomalous extracellular leaflet compaction throughout life results in reduced conduction velocity and suboptimal behavioral outputs: Motor learning is compromised. The absence of ApoD specifically modifies PLP and P0 protein expression, but not MBP or MAG. During late phases of myelin maturation ApoD affects lipogenic and growth-related signaling pathways, but not stress-responsive ones. Without ApoD, the highly sialylated glycocalyx is maintained and ganglioside content remains high. In PNS, Neu3 membrane sialidase and lysosomal Neu1 are coordinately expressed with ApoD in subsets of Schwann cells. ApoD-KO myelin becomes depleted of Neu3 and enriched in Fyn, a kinase with pivotal roles in transducing axon-derived signals into myelin properties. ApoD-dependent lysosomal permeabilization alters Neu1 location as well. Exogenous ApoD rescues ApoD-KO hiper-sialylated glycocalyx in astrocytes, demonstrating that ApoD is necessary and sufficient to control glycocalyx composition in glial cells. ApoD is crucial for myelin extracellular leaflet compaction by ensuring lysosomal functional integrity, adequate recycling of glycolipids and a proper subcellular location of the major effector and regulatory proteins of myelin membrane traffic.

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P18. GRADED ELEVATION OF C-JUN IN SCHWANN CELLS IN VIVO: GENE DOSAGE DETERMINES EFFECTS ON DEVELOPMENT, RE-MYELINATION, TUMORIGENESIS AND HYPOMYELINATION.

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Schwann cell c-Jun has been implicated both in adaptive and maladaptive functions in peripheral nerves. In injured nerves, this transcription factor promotes the repair Schwann cell phenotype and regeneration, and it provides neurotrophic support in in models of peripheral neuropathies. On the other hand, c-Jun is associated with tumour formation in some systems, it potentially supresses myelin genes, and has been implicated in demyelinating neuropathies. To clarify these issues, and determine how c-Jun levels determine its function, we have generated two mouse lines, c-Jun OE/+ and c-Jun OE/OE mice, with graded expression of c-Jun in Schwann cells. We find that Schwann cells are remarkably tolerant of elevated c-Jun, since the nerves of c-Jun OE/+ mice, where c-Jun in elevated about 7 fold, were normal with
the exception of modestly reduced myelin thickness. The stronger elevation of c-Jun in c-Jun OE/OE mice was, however, sufficient to induce significant hypomyelination pathology, which implicates c-Jun as a potential player in demyelinating neuropathies. The tumour suppressor P19ARF was strongly activated in the nerves of these mice, and even in aged c-Jun OE/OE mice, there was no evidence of tumours, in agreement with the fact that tumours do not form after nerve injury, although injured nerves contain proliferating Schwann cells with strikingly elevated c-Jun. We also find that in Jun OE/+ mice, where c-Jun levels are elevated sufficiently to accelerate regeneration,
myelination and nerve function are restored after injury, a precondition for considering therapeutic elevation of Schwann cell c-Jun to promote regeneration.

Keywords: Schwann cells, myelination, Peripheral nervous system, injury, regeneration, senescence, c-Jun

P19. 2-AG, A POTENT REMYELINATING ENDOCANNABINOID IN A PROGRESSIVE MODEL OF MS

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Pathological loss of myelin in the CNS can be followed by a remyelination process to produce new myelin sheaths around naked axons to restore their conduction properties, and occurs in manymultiple sclerosis (MS) lesions.However, this endogenous reparative process often fails in MS due to several factors including immune-mediated damage and oligodendrocyte progenitors (OPCs) depletion over time. Cannabinoids exert anti-inflammatory, antioxidant, anti-excitotoxic, neuroprotective and oligoprotective actions that include oligodendrocyte differentiation, with potential benefits in the treatment of neuroinflammatory, neurodegenerative and demyelinating diseases.We have investigated by immunohistochemistry whether the endocannabinoid 2-arachidonoylglycerol(2-AG) promotes remyelination in Theiler´s murine encephalomyelitis virus- induced demyelinated disease (TMEV-IDD) mice, a primary progressive model of MS with viral etiology. 2-AG was administeredwith subcutaneous miniosmotic pumps (3,5 mg/kg) for 7 daysat 28 days post-infection (dpi).Results show that 2-AG enhanced CC remyelination at 60 dpi compared to vehicle-treated mice, sustained by the activation of local progenitors in the CC and by the mobilization of OPCs (Olig2+/ CC1-) from the adjacent grey matter that differentiate into CC1+ mature oligodendrocytes. Remarkably, cellsproduced in the SVZ also contribute to remyelination as suggested retroviral injections (LentiGO vectors) in the lateral ventricle, that show that proliferating precursors generated in this neurogenic area migrate into the demyelinated CC and generate Olig2+/CC1+ oligodendrocytes. Local and subventricular mobilization of progenitors result in an increase of mature oligodendrocytes in the CC of infected mice that is accompanied by myelin staining restoration as showed by PLP and MBP markers.

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Palabras clave: oligodendrocyte, demyelination, remyelination, microglia, inflammation, subventricularzone, progenitor cell.

P20. MDSCs AS ENDOGENOUS REGULATORS OF OPC BIOLOGY

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Multiple Sclerosis (MS) is the most prevalent primary demyelinating disease of the central nervous system (CNS). The most frequent clinical form of the disease is the relapsing-remitting (RR) variant, characterized by phases with increasing neurological symptoms (relapses) followed by periods of total/partial recovery (remissions). This implies the existence of endogenous regulatory agents that promote the relapsing-to-remitting transition, facilitating the spontaneous reaction of the endogenous population of Oligodendrocyte Precursor Cells (OPCs) in the adult CNS. In the last years, our group unravelled the role of a heterogeneous population of immature myeloid cells, namely the Myeloid-Derived Suppressor Cells (MDSCs), during the clinical course of a MS model, Experimental Autoimmune Encephalomyelitis (EAE). MDSCs are important players on T cell suppression, the subsequent limitation of inflammatory reaction, and symptom recovery in EAE. In all cases, the preservation of MDSC undifferentiated state is crucial for MDSCs to be active. We have found that a first line drug for MS, i.e IFN-ß, is able to preserve the undifferentiated and immunosuppressive phenotype of MDSCs, and increases the already existent inverse correlation between the density of MDSCs and lesion size found in the spinal cord. Moreover, MDSCs were shown to behave as apoptotic inductors of infiltrated T cells, the cells attacking the myelin-forming oligodendrocytes in MS. In this sense, in the current work we show a direct relationship between the abundance of MDSCs and the degree of myelin preservation during EAE. Together, these observations lead us to wonder about the possible direct pro-myelinating role of MDSCs on OPCs. Here we demonstrate by first time that MDSC-conditioned media promote the differentiation in vitro of OPCs towards myelin-forming phenotypes shown as an increase of MBP^+-cells in both in percentage and degree of maturation. Besides, we describe the effects of MDSCs over OPC proliferation and survival. The current data shed more light on the pathophysiological relationship between the immune and nervous systems in order to design pharmacological and/or cell-based therapies to promote effective myelin preservation and repair for MS and eventually other demyelinating diseases.

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P21. CLASS IIA HISTONE DEACETYLASES LINK cAMP SIGNALING TO THE MYELIN TRANSCRIPTIONAL PROGRAM OF SCHWANN CELLS.

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Schwann cells respond to cAMP halting proliferation and expressing myelin proteins. We show here that cAMP-signalling induce the nuclear shuttling of the class IIa Histone Daectylase 4 (HDAC4) in these cells. There, HDAC4 binds to the promoter and blocks the expression of c-Jun, a negative regulator of myelination. Strikingly HDAC4 does not interfere with the transcription factor Mef2. Instead, by interacting with NCoR1/SMRT, HDAC4 recruits a class I HDAC that deacetylates histone 3 in the promoter of c-Jun blocking gene expression. Importantly this is enough to induce Krox20 and start differentiation program and myelin gene expression. Using conditional knock out mice, we also show that class IIa HDACs redundantly contribute to activate the myelin transcriptional program and the development of myelin sheath in vivo and are rate-limiting for c-Jun induction after nerve injury, pivotal for the reprogramming of Schwann cells into the repair cell phenotype. We propose that the nuclear-cytoplasmic shuttling of class IIa HADCs in response to intracellular cAMP controls Schwann cell phenotypic transitions and the establishment of the myelin gene expression program.

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