NEURAL DEVELOPMENT, REGENERATION AND NEURODEGENERATION

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Research interests

Brain development is a complex process which involves several sequential steps: regional determination, specification of neuronal cell types, control of cell migration, guidance and formation of neural connective networks, and activity-dependent synaptic plasticity. The correct functioning of all these processes is essential for the construction of the brain. Our research focuses on the identification of new genes involved in these processes, and the characterization of the intracellular signaling pathways activated in growth cones in response to extracellular signals. Moreover, it is known that the adult brain does not regenerate, either after lesions or disease-associated cell-death processes. Studies on the mechanisms that govern the normal development and growth of the nervous system are essential to explain the lack of spontaneous brain repair in adult tissue and to design new regenerative approaches to repair brain lesions.

A second goal of the laboratory is to understand how key developmental genes play a fundamental role in neuronal plasticity in the adult brain, which is crucial for complex neural functions (eg.learning and memory). The rationale is that adult plasticity (adult neurogenesis and synaptic plasticity) is reminiscent of developmental processes. Because dysregulation of adult neurogenesis and synaptic plasticity are implicated in neurological and psychiatric disorders, we aim also to understand how these genes contribute to the pathology of these diseases and whether modelling developmental genes in the adult brain ameliorate these neural disorders.

Research lines

1.-The Armcx Genomic Cluster in Normal and Pathological Conditions (Soriano, Burgaya)

Using a cDNA subtractive hybridization we identified genes that are overexpressed in the developing cortex (García-Frigola, 2004). One of these genes (Armcx3) encoded for Alex3. Genomic analyses provided evidence for a new protein family encoded by an array of Armadillo-domain containing genes located in the X chromosome (Armcx1-6 genes), which are targeted to mitochondria. The Armcx cluster is unique to Eutherian mammals and evolved from a single ancestor gene (Armc10). We have shown that Armcx3/Armc10 genes regulate mitochondrial trafficking in neurons by interacting with the Kinesin/Miro/TRAK2 trafficking complex. Our data provide evidence for a new Eutherian-specific family of mitochondrial proteins regulating mitochondrial dynamics and trafficking (López, 2012; Serrat 2013).

- Mitochondrial dynamics and neurodegeneration: We are investigating the function of the Armcx cluster in mitochondrial dynamics (eg., fusion/fission, autophagy) and in the pathological conditions associated with these processes. We will investigate how Armcx proteins regulate the functions of these key proteins in normal and neuropathological conditions. The impact of Armcx protein levels (knock-down and overexpression) in the pathogenesis of PD will be studied by inducing PD (eg., MPTP; Synuclein overexpression) in Armcx mouse mutants. We have already generated Armcx3, Armcx2 and Armc10-deficient mice.

- Cerebral cortex development and the Wnt/ ß-Catenin pathway:

Proteomic approaches yielded to the identification of several members of the Wnt pathway that interact with Armcx proteins. We are investigating how Armcx proteins regulate the Wnt pathway (we have evidence that Alex3-Armc10 downregulates this pathway), by using in ovo electroporation of the spinal cord.

- Obesity/Diabetes and Cancer: In collaboration with Dr. Francesc Vilarroya (UB) we have

discovered that Armcx3 and Armc10 knock-down mice are obese, accumulate fat in different tissues (eg., liver steatosis and brown adipose tissue), and share features with diabetic mice. We plan extensive biochemical, cell biology (eg., mitochondrial physiological parameters, gene expression arrays), histological and behavioural experiments (eg., food intake and skinner box) to unravel the mechanisms by which the loss-of-function of Alex proteins leads to obesity/diabetes. Furthermore, as hepatic steatosis is clinically linked to hepatocarcinoma, we are exploring the relationship between Armcx gene regulation and hepatic tumors.

2.- SNARE Proteins: Development and Therapeutic Targets for Axonal Regeneration and Cancer (Soriano, Ulloa, Cotrufo)

Directed cell migration is essential step in development and pathology. Netrin-1 is a chemoattractive cue required for the formation of neural pathways. We have shown that the Netrin-1 receptor DCC forms a specific protein complex with the t-SNARE Syntaxin 1 and that blockade of Syntaxin 1 abolishes Netrin-1 attraction (Cotrufo, 2011, 2012). This study underscores a new signaling pathway coupling chemotropic guidance and proteins regulating membrane turnover and exocytosis. Coupling guidance receptors to proteins that regulate stimulus-dependent exocytosis maybe a general mechanism in polarized-cell migration, in both normal and pathological processes. We have recently shown (in collaboration with Dr. Joan Seoane, VHIR) that blockade of SNARE proteins prevents the growth of glioma tumours in mouse xenografts (Ulloa, 2015). Moreover, using a novel in vitro axonal regeneration assay we have demonstrated that blockade of several myelin-associated proteins, incubation with chemical Semaphorin3A inhibitors (identified by us), and altering SNARE protein levels promote axonal regeneration (Montolio, 2009; Del Río and Soriano, 2010; in preparation).

- SNARE signaling: We will determine whether coupling guidance receptors to proteins that regulate exocytosis is a general mechanism in polarized cell migration and axonal growth. So far, we know that SNARE/receptor interactions are essential for several migration/growth pathways including UNC5H/Netrin1, Robo/Slits and Trk/Neurotrophins. We are characterizing in deep these processes at the biochemical and molecular levels.

- Axonal regeneration: Further, our current data indicate that modelling SNARE protein levels (and associated pathways; eg., lipid rafts, TIMM1) in axotomized neurons may lead to re-growth and regeneration of damaged axons. We will exploit these findings by promoting axonal regeneration in several in vivo models including the spinal cord.

- Cancer: We also aim to dissect the mechanisms by which SNARE blockade reduce glioma tumors: our hypothesis is that SNARE loss-of-function blocks the migration of cancer cells, the secretion of particular proteins, and the gliding along blood vessels. We are also investigating whether SNARE blockade (toxins, dominant negatives or palmitoylated SNARE-like peptides) reduces the growth and/or metastasis in other tumors.

3.- Reelin, Neural Plasticity, Psychiatric disorders and Alzheimer Disease (Soriano, Pujadas)

Reelin is an extracellular protein that is critical for neural migration and synaptogenesis. To unravel the function of this developmental gene specifically in the adult forebrain, we have generated conditional transgenic mice that overexpress Reelin. Using this tool, we have demonstrated that this gene is essential in adult plasticity (both adult neurogenesis and synaptic plasticity) and that its overexpression prevents structural and cognitive deficits in AD and the development of psychiatric-like phenotypes, including cocaine addiction (Pujadas, 2010, 2014; Teixeira, 2011,2012,2013).

- Neural plasticity. We have generated a conditional KO mouse line for the Reelin gene, which has been crossed with Cre-ERT2 lines. We already know that Tamoxifen administration leads to efficient inactivation of the Reelin gene. Taking advantage of this tool we plan to investigate several plasticity-related issues: one is how Reelin controls the development of the connectome and synaptogenesis of adult born neurons, and their recruitment into hippocampal circuits. We will address this issue by injecting retroviral vectors expressing PSD95-GFP (and cre in floxed mice) and performing confocal microscopy and high-throughput 3D EM (FIB/SEM) (Bosch et al., 2015).

- Alzheimer Disease: Our recent work supports strong links between Reelin and AD: we have hypothesized that, by regulating Aß42 metabolism, Tau phosphorylation and adult synaptic plasticity,the Reelin pathway may be an important regulator of adult brain functions whose deregulation may be at the root of AD pathology and that thereby Reelin may be protective against AD. We have recently tested this hypothesis by overexpressing Reelin (conditional Reelin-overexpressing (Reelin-OE) mice) in J20 AD mice. Reelin-OE/J20 mice showed decreased plaque load and a rescue of synapses and cognitive deficits, thereby suggesting that Reelin protects from AD pathology (Pujadas et al., 2014). We plan to extend these findings by: a) To test whether Reelin-OE ameliorates AD in mice once the pathology has been developed and in mice exhibiting Tau-related AD pathology (GSK3-OE and Tau-WLW mice). b) To demonstrate that a downregulation of Reelin specifically in the adult (conditional Reelin KO/AD mice) accelerates AD pathology. c) To understand the physiological and molecular mechanisms by which Reelin may affect AD pathology. d) To develop high-throughput screening strategies to identify compounds that modulate the Reelin pathway.

4.- Novel genetic approaches to AD pathogenesis (Soriano)

Some human diseases, particularly cancer, are caused by somatic mutations that impair the normal function of specific populations of cells. By means of whole exome sequencing we have recently tested the hypothesis that somatic variations and mutations (referred to here as Single Nucleotide Variations-SNVs) are present in the brains of sporadic AD patients. We found a remarkable number of brain-specific SNVs in SAD brains that were not detected in blood of the same donors. Loci with brain-specific SNVs and recurrent SNVs were common to several patients and were not found in the brains of control donors. These findings revealed that adult blood and brain have distinct DNA genomic variations and suggest that somatic, brain-specific genome reshaping contributes to the pathogenesis of AD. We now aim to gain a deeper understanding of brain-specific somatic events in AD pathogenesis.

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Representative Publications

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