Carlos A. Saura

**Neurodegeneration and ageing**

**Neurobiology of Alzheimer's Disease**

**Group leader:**

Carlos A. Saura  
[carlos.saura@uab.es](mailto:carlos.saura@uab.es)  
TEL: +34 93 868 398
Group members:
Paula Conde Rubio
Anna del Ser
Miriam Javier Torrent
Laura Rubió Ferrarons
Carlos Soto Faguás
Ohiane Ussia

Past members:
Dr. Sergi Marco Martín
STRATEGIC OBJECTIVES

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive memory loss caused by early synaptic dysfunction in brain regions essential for memory encoding and storage, such as the hippocampus and entorhinal cortex. Accumulation of amyloid plaques containing ß-amyloid (Aß) peptides, which are generated by presenilin (PS)/ß-secretase-dependent processing of the ß-amyloid precursor protein (APP), and phosphorylated tau are key events in the disease process. Our hypothesis is that cognitive impairment in normal and pathological aging is associated with synaptic dysfunction as a result of changes in gene expression networks. Our investigations combine genetics, transcriptomics and proteomics approaches to better understand the molecular mechanisms by which gene expression changes due to PS and Aß underlie synaptic and cognition dysfunction and neurodegeneration in AD. Progress in understanding the cellular processes regulating gene expression changes in cognition is relevant to develop therapeutic interventions for age-related cognitive disorders.

MAIN RESEARCH LINES

1. Mechanisms of synaptic dysfunction in Alzheimer´s disease
The molecular mechanisms underlying gene expression changes and synapse and cognitive dysfunction in cognitive disorders are largely unknown. Recent studies from our lab indicate that specific gene expression programs induced by synaptic activity are essential for memory processing, whereas deregulation of these programs causes memory impairment in mouse models of AD. We investigate the role of the transcription factor cAMP-response element binding protein (CREB) and its transcriptional coactivators CREB binding protein (CBP) and CREB-regulated transcription coactivator-1 (CRTC1) on regulation of specific gene expression programs in cells and transgenic mice that overexpress mutant APP and presenilin genes. Our results indicate that deregulation of specific CREB-dependent gene expression programs plays a role in synaptic and cognitive dysfunction, and regulation of specific gene networks is relevant to develop therapeutic interventions for age-related cognitive disorders. These signaling pathways are being tested as potential drug targets in AD experimental models.

2. Novel therapeutic strategies in Alzheimer´s disease
The discovery of novel molecular mechanisms underlying synaptic dysfunction and memory loss in transgenic and knockout mouse models of AD allow us to design new therapeutic strategies to prevent and/or reverse cognitive dysfunction in this disease. We have described that inactivation of presenilin-1/ß-secretase reduces age-dependent amyloid pathology and memory deficits in APP transgenic mice, whereas inactivation of both presenilins results in memory deficits and neurodegeneration through deregulation of synaptic proteins and the CREB signaling pathway. Similarly, accumulation of Aß alters expression of CREB target genes required for
memory by deregulating the coactivator CRTC1. We are currently employing novel gene therapy and pharmacological approaches to activate CRTC1 signaling and reverse memory deficits in transgenic mouse models of AD. Finally, we study the cellular mechanisms by which cognitive stimulation has beneficial effects on adult neurogenesis and memory in AD.

FEATURED PUBLICATIONS


- Xifró X, Miñano-Molina A.J, Saura CA, Rodríguez-Álvarez J. Ras protein activation is a key event in activity-dependent survival of cerebellar granule neurons. J Biol Chem. 2014. 289(12):8462-72


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