MOLECULAR BIOLOGY OF SYNAPTIC DYSFUNCTION IN NEURODEGENERATIVE DISEASES

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PROFILE

The basic objective in our lab has been to study the molecular and cellular mechanism involved in neuronal death, as a direct approach for the understanding of neurodegenerative diseases. Although neuronal death in neurodegenerative diseases is very complex, it seems that certain characteristics are common between them. For example, it seems quite clear that apoptosis contributes to cell death observed in Alzheimer, Parkinson or Hungtinton diseases. We are focused in the study of regulation of neuronal apoptosis. Two questions are being addressed in the lab? 1.- Which is the role of apoptosis in cerebral ischemia-mediated cell death 2.- How synaptic activity and some extracellular factors are able to reduce neuronal apoptosis in neurodegenerative diseases?

RESEARCH

RESEARCH INTERESTS/STRATEGIC OBJECTIVES

During the last years, the basic objective of our research team has been the study of the cellular and molecular mechanisms involved in the synaptic dysfunction and neuronal death as a straight approach for the understanding of neurodegeneration in diverse pathologies. At present, the laboratory is focused in the study of the mechanisms involved in early dysfunction of synaptic activity in Alzheimer's disease.

During the last decade, the idea that the alteration of synaptic function in Alzheimer's Disease (AD) occurs well before neurodegeneration is becoming widely accepted. Moreover, it has been suggested that the progressive accumulation of self-aggregates of Aβ as oligomers (oAβ) would mediate this synaptic dysfunction, leading to the initial cognitive deficits observed in mild cognitive impairment (MCI) and earlier AD stages. In this context, we have found, transient learning and memory deficits in $APP_{Sw,Ind}$ and 3xTg-AD transgenic mice at ages when the presence of oAβ was detected well before the appearance of amyloid plaques (*España et al.,*

Biol Psychiatry, 67:513-21, 2010; España et al., J. Neurosci, 30: 9402-10, 2010). We believe that these early memory deficits are a good model to study the processes occurring during the initial stages of the disease at the MCI level or previous asymptomatic stages of AD.

In this context our main interest is the study of the mechanisms involved in the alteration of synaptic activity and learning and memory dysfunction associated to early stages in Alzheimer's disease as a way to identify novel therapeutic targets and biomarkers for earlier diagnosis and functional recovery. In particular, he is exploring the altered regulation of functional synaptic glutamate receptors in experimental AD models by a combination of different processes including transcriptional and post-transcriptional gene regulation, changes in receptors regulatory proteins or alteration in the neurovascular unit affecting the release of angineurins.

MAIN RESEARCH LINES

Validation of a blood biomarker related to synaptic dysfunction for early Alzheimer's disease diagnostic.

Proyectos Prueba de Concepto 2021 -UE Next Generation - Ministerio de Ciencia e Innovación

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Principal Investigator: José Rodriguez Álvarez

Targeting deficits in synaptic plasticity and learning art early stages of Alzheimer's disease with Nr4a

Programa Nacional de Biomedicina

Ministerio de Ciencia e Innovación

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September 2021 – August 2024

Principal Investigator: José Rodríguez Alvarez

LAB FEATURED PUBLICATIONS:

Siedlecki-Wullich D, Miñano-Molina AJ & J Rodríguez-Álvarez microRNAs as early biomarkers of Alzheimer's disease: A synaptic perspective. *Cells 2021, 10, 113. https://doi.org/10.3390/cells10010113*

Cheng W, Siedlecki-Wullich D, Catala-Solsona J, Fabregas C, Fadó R., Casals N, Sole M, Unzeta M, Saura C.A, Rodríguez-Alvarez J & AJ Miñano-Molina.
Proteosomal-dependent AKAP150 degradation accompanies AMPAR endocytosis during cLTP. *eNeuro 23 March 2020, 7 (2) ENEURO.0218-19.2020*

Solé M, Esteban-Lopez M, Fabregas C, Taltavull B, Fadó R, Casals N, Miñano-Molina AJ, Rodríguez-Álvarez J and Unzeta M. Blood-Brain barrier dysfunction underlying Alzheimer's disease is induced by SSAO/VAP-1 dependent cerebrovascular activation with enhanced Aβ deposition. *Biochem. Biophys. Acta - Mol. Basis Dis. 1865:2189-2202 (2019)*

Siedlecki-Wullich D, Catala-Solsona J, Fabregas C, Hernandez I, Clarimon J, Lleó A, Boada M, Saura CA, Rodriguez-Alvarez J and Miñano-Molina AJ. Alteration of microRNAs related to synaptic function as potential plasma biomarkers for Alzheimer disease. *Alzheimer Res & Ther 11:46 (2019)*

Parra-Damas, A., Chen, M., Enríquez-Barreto, L., Ortega, L., Acosta, S., Camats, J., Fullana, N., Aguilera, J., Rodríguez-Alvarez, J & C.A. Saura. CRTC1 function during memory encoding is disrupted in neurodegeneration. *Biol Psychiatry 81:111-123 (2017)*