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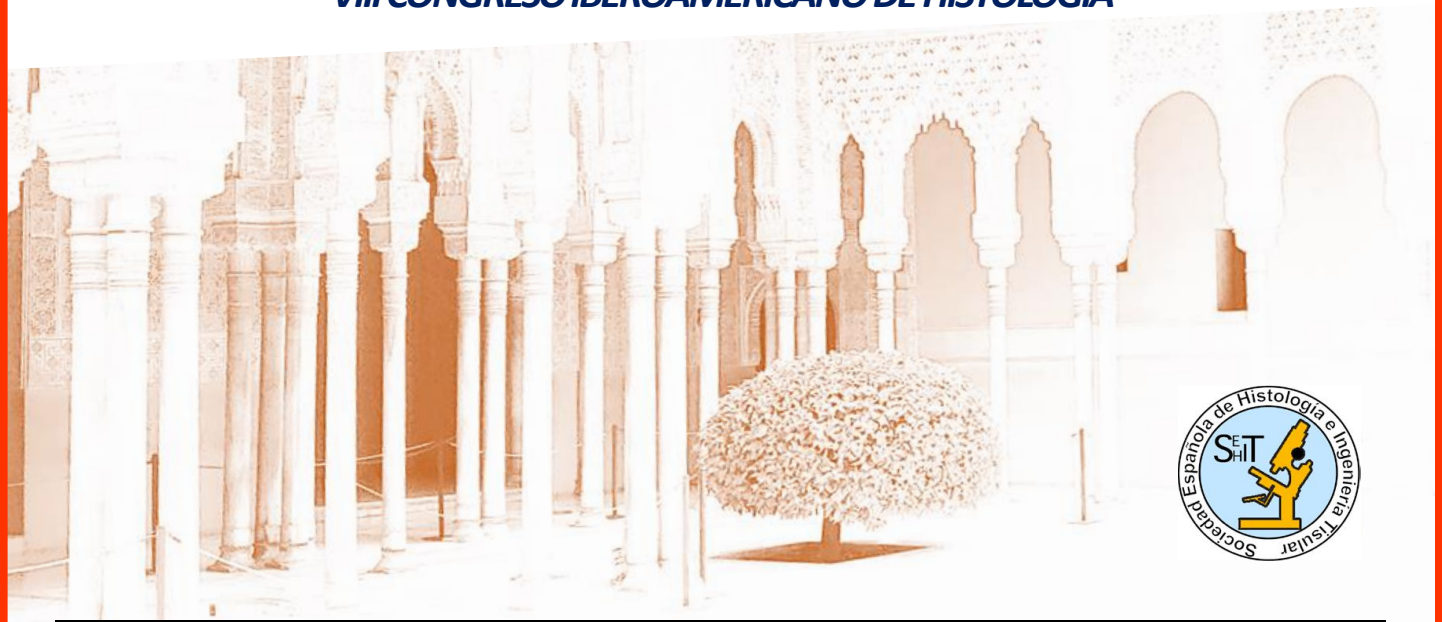

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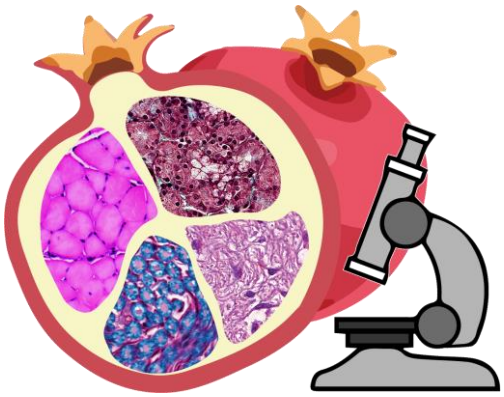

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Histology and Histopathology
From Cell Biology to Tissue Engineering

POSTER PRESENTATION

Protein homeostasis as a therapeutical target for Alzheimer's disease: analysis in the hippocampus of transgenic mouse models

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Introduction: Alzheimer's disease (AD) constitutes the most prevalent form of dementia, being considered one of the global epidemics in the current century, with more than 50 million people affected worldwide. There is neither a cure nor a disease-modifying therapeutic intervention able to slow down the pace of this devastating neurodegenerative condition. Owing to population ageing, it has been estimated that there will be more than 150 million AD patients by 2050. Therefore, there is an urgent need of searching for novel therapeutic targets and treatments.
The main histopathological hallmarks of AD brains are the presence of extracellular amyloid plaques formed by the beta-amyloid (Abeta) peptide, and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau (phospho-tau) protein. In fact, AD is considered a neurodegenerative proteinopathy. The coexistence of these protein aggregates leads to synaptic damage, neuronal loss and cognitive decline in patients. The dysfunction of the intracellular proteolytic systems (autophagy-lysosomal and ubiquitin-proteasome) has been postulated as a pathological mechanism contributing to the cerebral accumulation of these toxic proteins. The aims of the present work are to verify the involvement of these pathways in two different transgenic mice of this disease, and thus, to better understand the differential impact of Abeta and phospho-tau accumulation on the pathological progression in the hippocampus.
Methods: Cerebral sections containing hippocampus from APP- (APPSL/PS1M146L) and tau- (ThyTau22) based mouse models (from 2 to 18 months of age) were analyzed. Age-matched wildtype (WT) animals were used as controls. Immunohistochemical stainings were performed to evaluate the progression of amyloid deposition and phospho-tau accumulation (AT8 antibody) along aging. Autophagic/lysosomal markers and ubiquitin were also assessed by immunohistochemistry at different pathological stages.
Results: In the amyloidogenic model, we have detected a pathological accumulation of autophagic vesicles, lysosomes and ubiquitin in periplaque dystrophic neurites (aberrant axons and presynapses). Conversely, in the ThyTau22 model, only abnormal accumulation of ubiquitin was detected, mainly located in the somas of principal neurons. In any case, the alteration of protein homeostasis pathways was associated to aging and to the progression of both proteinopathies in these models.
Discussion & conclusions: These results demonstrate significant alterations of the proteolytic pathways in both models of proteinopathy. However, amyloidosis and tauopathy transgenic mice were differentially affected. Preclinical studies in transgenic models able to reproduce the pathogenic mechanisms of patients will allow the identification of novel therapeutic targets and to test effective treatments to stop or modify the course of these diseases. Compounds able to reduce the cerebral burden of toxic proteins might be an alternative pharmacological approach to AD and other tauopathies. Finally, clarifying the basic effects of Abeta and phospho-tau over homeostatic mechanisms would indeed enable the development of alternative therapeutic strategies and drugs targeting pathways related to these proteinopathies.

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