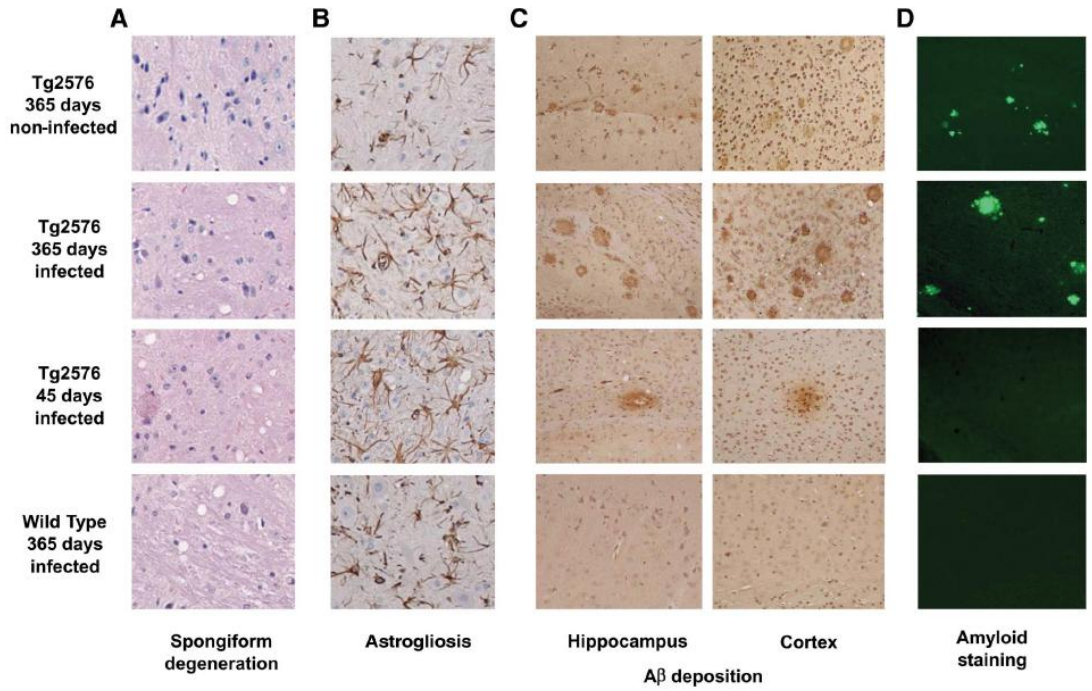
Molecular cross talk between misfolded proteins in animal models of Alzheimer's and prion diseases.

The work whose results suggest an interaction between Alzheimer's and prion pathologies has been published in the March edition of The Journal of Neuroscience, with Joaquín Castilla, the head of CIC bioGUNE's Prion Lab, as one of the authors.

The central event in protein misfolding disorders (PMDs) is the accumulation of a misfolded form of a naturally expressed protein. Despite the diversity of clinical symptoms associated with different PMDs, many similarities in their mechanism suggest that distinct pathologies may cross talk at the molecular level. The main goal of the study was to analyze the interaction of the protein misfolding processes implicated in Alzheimer's and prion diseases. For this purpose, prions were inoculated in an Alzheimer's transgenic mouse model that develop typical amyloid plaques and followed the progression of pathological changes over time. The results show a dramatic acceleration and exacerbation of both pathologies. The onset of prion disease symptoms in transgenic mice appeared significantly faster with a concomitant increase on the level of misfolded prion protein in the brain. A striking increase in amyloid plaque deposition was observed in prion-infected mice compared with their non-inoculated counterparts. Histological and biochemical studies showed the association of the two misfolded proteins in the brain and in vitro experiments showed that protein misfolding can be enhanced by a cross-seeding mechanism. These results suggest a profound interaction between Alzheimer's and prion pathologies, indicating that one protein misfolding process may be an important risk factor for the development of a second one. Our findings may have important implications for understanding the origin and progression of PMDs.

PubMed link: http://www.ncbi.nlm.nih.gov/pubmed/20357103



A–D, Brain histopathological studies. Representative animals from different groups were studied histopathologically for spongiform brain degeneration after hematoxylin– eosin staining (***A***), reactive astrogliosis by GFAP staining (***B***), A_ deposition by immunohistochemistry using the 4G8 anti-A_ antibody (***C***), and staining with the amyloid-specific dye thioflavin S (***D***). It is important to emphasize that the prion deposits in mice affected by RML prions are not thioflavin S positive but are rather diffuse prefibrillar aggregates. The images in ***A*** and ***B*** correspond to the medulla, ***C*** to the hippocampus or cortex as indicated, and ***D*** to the cortex. (See also supplemental Figs. 2, 3, available at www.jneurosci.org as supplemental material.)