CO-ASSOCIATION OF REELIN AND AMYLOID-BETA IMMUNOREACTIVITY IN RODENT AND HUMAN TISSUE IS ENHANCED IN THE AGED BRAIN

J. Doehner¹, T. Notter¹, D. Krstic¹, M. Neumann², K. Irene¹, Reelin/AD

¹Inst. of Pharmacology and Toxicology/University of Zurich, ²Institute of Neuropathology/University of Zurich, Zurich, Switzerland

Age-dependent changes in Reelin-mediated signaling have been suggested to contribute to the neuropathology of late-onset Alzheimer's disease (AD), albeit the molecular mechanisms remain largely unknown.

Here, we used biochemical and immunohistochemical techniques to characterize the proteomic composition, localization and temporal progression of Reelin-positive plaques, as well as their potential to sequester Aβ-peptides in postmortem human and mouse brain tissue.

In samples of non-demented human subjects, Reelin-positive plaques showed the same layer-specific distribution in the hippocampal formation as described in rodents and primates, demonstrating that the occurrence of Reelin-containing plaques is a highly conserved phenomenon of normal aging. Furthermore, applying optimized immunofluorescence protocols, we were able to detect different proteolytic fragments of amyloid precursor protein (APP) in Reelin-positive plaques in both murine and human brain tissues. This co-association was increased in aged brains. Finally, we observed that Reelin immunoreactivity is overall reduced in AD patients as compared to the control group, though only in fornix and entorhinal cortex this difference reached statistical significance. This is in agreement with our previous results demonstrating that the reduction of Reelin expression aggravates AD-like pathology of transgenic mice (tghAPPswe,arc:Reln⁺⁻). To correlate the neuropathological changes with the Reelin expression in humans, we are investigating putative changes in the methylation status of the Reelin promoter in brains of healthy elderly and AD patients. Taken together, our results support the hypothesis that reduction in Reelin expression below a critical threshold and the perturbation of its signaling accelerates amyloidogenic APP processing and favors both, its own and Aβ-aggregation.