UKE Paper of the Month November 2021

Ligands binding to the prion protein induce its proteolytic release with therapeutic potential in neurodegenerative proteinopathies

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ABSTRACT:
The prion protein (PrP^C) is a central player in neurodegenerative diseases, such as prion diseases or Alzheimer's disease. In contrast to disease-promoting cell surface PrP^C, extracellular fragments act neuroprotective by blocking neurotoxic disease-associated protein conformers. Fittingly, PrP^C release by the metalloprotease ADAM10 represents a protective mechanism. We used biochemical, cell biological, morphological and structural methods to investigate mechanisms stimulating this proteolytic shedding. Shed PrP negatively correlates with prion conversion and is markedly redistributed in murine brain in the presence of prion deposits or amyloid plaques, indicating a sequestrating activity. PrP-directed ligands cause structural changes in PrP^C and increased shedding in cells and organotypic brain slice cultures. As an exception, PrP-directed antibodies with multiple epitopes do not cause shedding but surface clustering, endocytosis and degradation of PrP^C. Both mechanisms may contribute to beneficial actions described for PrP-directed ligands and pave the way for new therapeutic strategies against currently incurable neurodegenerative diseases.

STATEMENT:
Despite intensive research since decades, there is still no causative treatment or cure for neurodegenerative diseases, such as rare and transmissible prion diseases (e.g. Creutzfeldt-Jakob) or very frequent Alzheimer`s disease. This highlights the need for deeper pathomechanistic insight to enable novel, maybe 'unconventional' therapeutic approaches. We show here for the first time that an apparently protective mechanism already provided by evolution (i.e., the endogenous enzymatic release of the prion protein (PrP) from the neuronal surface) can be further stimulated by treatment with PrP-binding ligands. This substrate-specific approach (limiting severe side-effects to be expected when directly targeting the responsible protease ADAM10 with its multiple substrates in the body) will now allow for better mechanistic knowledge and screening for additional and hopefully therapeutically suitable compounds.

BACKGROUND:
This multidisciplinary team effort involved scientists from different UKE groups (Neuropathology, Neurology, ZMNH), Hamburg`s scientific landscape (Uni Hamburg, EMBL@DESY), Germany (Berlin, Kiel, Bochum, Göttingen), Europe (France, Switzerland, Italy) and overseas (USA, Canada). It greatly profited from technology provided by UKE core services (Mouse Pathology, FACS Sorting and UKE Microscopy Imaging facilities). Major parts of the work were performed in the Institute of Neuropathology, UKE. Key experiments were parts of the PhD and postdoctoral work of the two equally contributing first authors (pictures). Authors are very thankful to the diverse funding institutions and the publication fund 'UKE 10+' of the Dean's office.