Studies on amyloid toxicity

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Research Abstract

With described work I aim to clarify by which mechanisms amyloid is initiated, transferred between cells or organs, and how amyloid can be prevented or resolved. Particularly we will study the following points: •What mechanism in islet amyloid formation leads to ?-cell death and this includes studies on mechanisms for intra- and extracellular cytotoxicity. •We will investigate if transfer of IAPP amyloid can be responsible for spreading of amyloid between ?-cells and between islets. •Epidemiological studies support a link between type 2 diabetes (T2D) and Alzheimer's disease (AD). Recently, we showed that IAPP and A? co-exist in A?-plaques in brain of AD patients. We will analyze IAPP content in brain of AD patients with and without T2D and characterize the molecular interaction between IAPP and A?. •IAPP is amyloidogenic and it is assumed that endogenous inhibitors exist. We have shown that chaperone domain BRICHOS affects aggregation of A?. Our research aims to examine if BRICHOS can act as a chaperone

for IAPP aggregation. • The mouse model for AA amyloidosis has been useful for studies on induction and resolution of amyloid. C4 binding protein (C4BP) is an inhibitor of the complement cascade and also binds and stimulates amyloid fibril formation (A? and IAPP). AA-amyloidosis will be induced in C4BP deficient and wild type mice and deposition and clearance processes will be characterized. Amyloidoses are the largest group among protein misfolding diseases, and 30 different human proteins have been shown to make amyloid. Examples are islet amyloid polypeptide (IAPP) that forms islet amyloid in almost all individuals with T2D and A? protein that deposits in brain in Alzheimer's disease (AD). Deposition of IAPP-amyloid causes reduction of ?-cells and A?-amyloid results in loss of neurons and there is an increased risk for AD in patients with T2D. Amyloid fibril formation involves formation of intermediates (oligomers or proto-fibrils), and these exhibit cytotoxicity. Since amyloid load can be massive, the deposit itself can form a physical barrier and influence uptake of nutrients and cell signaling. We use islets isolated from human and hIAPP transgenic mice and our newly developed Drosophila melanogaster model to study amyloid development and pinpoint pathways activated by amyloid. We have established a novel assay for monitoring caspase 3 induction and subsequent apoptosis. This cell culture based system is used for different studies e.g. test of endogenous amyloid inhibitors (Bri2-Brichos), and analysis of designed amyloid peptide inhibitors in collaborations with structure biologists (A. Kapurniotu, Germany and D. Eisenberg, UCLA). We explore transmission of IAPP amyloid between cell using a fluorescent dye and monitor amyloid development over time (weeks). We investigate IAPP and A? in different brain regions of patients with AD and T2D and AD only. A double transgenic mouse that develops islet amyloid and AD will be generated and bi-fluorescence technology will be applied for characterization of IAPP/ A? integration. Factors that influence the endogenous system for amyloid degradation are investigated. AA-amyloidosis will be induced in C4-binding protein (C4BP) deficient mouse and the deposition and resolution of amyloid will be characterized. Significance Formation and deposition of amyloid is part of the disease mechanism for many different diseases, and local amyloid deposits are present in AD and T2D. Earlier amyloid was regarded as an inert bystander, but today we know that the amyloid formation process leads to formation of prefibrillar and toxic aggregates (oligomers) which are of central importance for disease development. AD and T2D are two diseases that cause great problems for the diseased and that are associated with huge costs for the society. Therefore, it is important to increase our understanding about the amyloid formation process and participate in development of anti-amyloid therapy.

Further information available at:

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