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Absence of tissue transglutaminase delays amyloid-beta deposits in Alzheimer's disease

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Introduction: Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) aggregates in the brain as senile plaques and cerebral amyloid angiopathy. Targeting Aβ aggregates has been one of the major approaches for AD therapies, although these attempts had little to no success so far. Therefore, novel treatment options should focus on blocking the actual formation of neurotoxic Aβ multimers. Evidence is accumulating that the enzyme tissue transglutaminase (tTG) plays a key role in these processes[1]. TTG is abundantly expressed in the human brain and catalyzes post-translational modifications resulting in covalently cross-linked protein complexes[2]. Aβ is a substrate for tTG cross-linking, resulting in stable and neurotoxic Aβ oligomers[3]. As such, tTG activity plays a prominent role in initiating the Aβ cascade in AD. Therefore, *in vivo* absence of tTG in the AD-mimicking mouse model APP23 may provide evidence that tTG is a suitable target in AD to counteract Aβ neurotoxicity.

Methods: Here, we used a crossbreed of the tTG-/- mouse model and the AD-mimicking APP23 mouse model. As a readout, the following analysis were performed: 1)(immuno)histochemical analysis of presence and severity of Aβ pathology, 2) presence of neuroinflammation, 3) mRNA levels of APP and all brain TGs, and 4) amyloid-beta protein analysis.

Results: We found that the absence of tTG in APP23/tTG-/- mice (n=6) resulted in an overall reduction ($p = 0.07$) of Aβ deposits in 12-month-old APP23 mice (n=7), whereas this difference was undetectable in 18-month-old animals (APP23 n=8; APP23/tTG-/- n=10). Analysis of the individual Aβ deposits revealed that the absence of tTG significantly reduced the formation of amyloid plaques ($p=0.03$), small dense plaques ($p=0.049$) and vascular amyloid deposits ($p=0.018$) when compared to aged-matched 12-month-old APP23 mice. This significant difference was undetectable when comparing 18-month-old APP23 mide with APP23/tTG-/- mice. Finally, we found no effects on neuroinflammation associated with the Aβ pathology or beta-pleated sheet formation of the deposited Aβ between APP23 and APP23/tTG-/- mice.

Conclusion: We found that absence of tTG delays the formation of Aβ pathology in the AD-mimicking APP23 mouse model. Therefore, tTG might be a suitable therapeutic target for reducing and/or delaying Aβ deposition in AD.

References:

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