Table S1

Aβ induced Tau pathology in in vivo models*

Model	Biological Relevance	References
Transgenic mice with amyloid pathology only (a panoply of models) (APP^{EOFAD}, APP^{EOFAD}x$PS1^{EOFAD}$)	Models with high plaque load display dystrophic neurites containing hyperphosphorylated Tau surrounding amyloid plaques ("senile plaques"). Some models display hyperphosphorylated Tau. None of the models developed full blown NFTs	(Hsiao, 1998, Duyckaerts et al., 2008) [1, 2] (**refs)
Double transgenic mouse model (Tau^{P301L} x $APP^{KM670/671NL}$)	Aggravated Tau-pathology (NFTs) in double transgenic mice compared to the parental Tau strain	(Lewis et al., 2001) [3]
Tau^{P301L} transgenic mice injected with Aβ42 fibrils (Tau^{P301L} + synthetic Aβ42 fibrils)	NFTs develop in neurons projecting to the site of injection of synthetic Aβ42 fibrils in TauP301L mice.	(Gotz et al., 2001) [4]
Triple transgenic mouse model ($APP^{KM670/671NL}$, $PS1^{M146V}$ and Tau^{P301L})	Amyloid pathology preceded tau pathology Aβ immunotherapy reducing extracellular and intracellular Aβ, leads to reduced early tau pathology	(Oddo et al., 2003, Oddo et al., 2004) [5, 6]
Transgenic rat model ($APP^{KM670/671NL}$ and APP^{V717F}) ($APP^{KM670/671NL}$ and $PS1^{M146V}$)	Tau-alterations in APP transgenic rats, without overexpression of Tau	(Echeverria et al., 2004) [7]
Tau^{P301L} mice injected with brain lysate of $APP^{KM670/671NL}$ **Double transgenic mouse model** (Tau^{P301L} x $APP^{KM670/671NL}$)	Induction of Tau-pathology (NFTs) in Tau mice injected with Aβ-containing brain extracts of APP transgenic mice. NFT appear at the site of injection and in remote brain regions. Aggravated tau pathology (NFT) in the double transgenic compared with the parental Tau mice	(Bolmont et al., 2007) [8]
Double transgenic mouse model (APP^{V717I} x Tau^{P301L}) **Double transgenic mouse model** (GSK-3β x Tau^{P301L})	Aggravated Tau-pathology (NFTs) in hippocampus and cortex in double transgenic (APP x Tau) mice compared to the parental Tau strain. Overexpression of constitutive active GSK3β, causes aggravation of Tau-pathology (NFTs) in hippocampus and cortex	(Terwel et al., 2008) [9]
Double transgenic mouse model (Tau^{P301S} x APP^{V717F})	Robustly aggravated Tau-pathology (NFTs) in double transgenic mice compared to parental Tau mice. Development of NFTs followed a spatiotemporal Braak-like pattern	(Hurtado et al., 2010) [10]

Double transgenic mouse model (APP^{E693G} x Tau WT)	Reduction of Aβ (BACE inhibition) rescued cognition and reduced somatic accumulation and phosphorylation wild type Tau.	(Chabrier et al., 2012) [11]
Transgenic rat model ($APP^{KM670/671NL}$ and $PS1^{\Delta E9}$ genes)	Pathological Tau-changes in rats (endogenous Tau), overexpressing mutant APP/PS1	(Cohen et al., 2013) [12]
Double transgenic mouse model ($APP^{KM670/671NL;\ I716V;\ V717I}$, $PS1^{M146L;\ L286V}$ x Tau^{P301S})	Robustly aggravated Tau-pathology (NFT) and neuronal loss in double transgenic mice compared to parental Tau strain	(Saul et al., 2013) [13]
Double transgenic mouse model ($APP^{KM670/671NL;\ I716V;\ V717I}$, $PS1^{M146L;\ L286V}$ x $Tau^{G272V/P301S}$)	Robustly aggravated NFT pathology in double transgenic mice compared to parental Tau strain, associated with increased phosphorylation and truncation of Tau	(Heraud et al., 2014) [14]
Double transgenic mouse model ($APP^{KM670/671NL;\ I716V;\ V717I}$, $PS1^{M146L;\ L286V}$ x Tau^{P301S})	Robustly aggravated Tau-pathology, and increased cognitive deficits, synaptic deficits and hippocampal atrophy in the double transgenic mice compared with parental Tau strain	(Stancu et al., 2014) [15]
Double transgenic mouse model ($APP^{E693\Delta}$ x Tau WT)	Aggravation of Tau-pathology (NFT) in double transgenic mice compared to the parental Tau strain, mildly overexpressing human wild type Tau (3R/4R)	(Umeda et al., 2014) [16]

*We do not claim to provide an exhaustive review of all existing models in this table. We here summarize accumulating evidence in different models demonstrating that Aβ induces Tau-alterations, including pathologically relevant Tau-hyperphosphorylation, somatodendritic accumulation of Tau and full-blown NFT formation. This is not only demonstrated with overexpression of mutant Tau, but also with wild type human Tau, and without Tau overexpression. Furthermore, although some models are based on expression of mutant APP or APP/PS1, injection of extracellular Aβ was sufficient to induce Aβ-induced NFTs. Taken together, these data support Aβ-induced Tau-pathology as a reproducible event in AD models, which must be taken in consideration.

**Multiple APP and APP/PS1 transgenic mice have been generated and characterized in detail (PDAPP, Tg2576, APP23, C3-3 line, CRND8, hAPPH6, J9 hAPP, APP/Ld, J20 hAPP, APP dutch line, ARC6 and ARC48) [9, 17-26]. None of these models displayed full blown NFTs, but dystrophic neurites containing hyperphosphorylated Tau surrounding senile plaques were detected in models with sufficiently high plaque load ("senile plaques"). Some models displayed mild increased levels of hyperphosphorylated Tau [19, 26].

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