**Tau binding protein CAPON induces tau aggregation and neurodegeneration**

Shoko Hashimoto *,et al. Nature Communication* **10** (2019)

**Presenter:** Tsung-Yun Liu      **Date/Time:** 2020/03/05, 15:10 -16:00

**Commentator:** Dr.Yu-Min Kuo **Location:** Room 601, Med College Building

**Background:**

Alzheimer’s disease (AD) is the most common neurodegenerative disorder and the major cause of dementia. The neuropathological hallmarks of AD include extracellular deposits of amyloid-β (Aβ), the major component of senile plaques, and neuroﬁbrillary tangles (NFTs) composed of hyperphosphorylated tau protein. In previous study, the authors screened for tau-interacting proteins using Wtau-transgenic (Tg) mice, which express WT human tau tagged with a Flag epitope and isolated tau-binding proteins by immunoprecipitation using a Flag-tag antibody and identiﬁed the tau interactome by LC-MS/MS analysis. The authors focused on one protein, named carboxy-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON). CAPON is an adaptor protein of neuronal nitric oxide synthase (nNOS) and is involved in N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity. Moreover, CAPON also positively regulates spine density and neuronal cell death downstream of the NMDA receptor.

**Objective/Hypothesis:**

In previous study, CAPON is upregulated in CA1 pyramidal cells in the AD brain. These results imply that CAPON may play an important role in the pathogenesis of AD. Accordingly, the authors used hTau-KI mice, AppNL-G-F-KI mice and hTau-KI mice/AppNL-G-F double-KI mice to investigate the effect of CAPON on AD pathogenesis.

**Results:**

The data showed that presence of with Aβ pathology resulted in higher CAPON expression levels in these animals. Immunohistochemical analysis showed a signiﬁcantly stronger CAPON signal in the pyramidal cell layer of AppNL-G-F mice than in the WT mice. On the other hand, the authors used magnetic resonance imaging (MRI) to observe mice after AAV injection. Whereas the AAV-GFP-injected mice did not show any signiﬁcant difference in brain volume, the AAV-CAPON-injected mice exhibited a large decrease in hippocampal volume at 3 months, falling to approximately 77% of the control. They also examined hippocampal atrophy and neuronal cell death using histochemical analysis. Signiﬁcant shrinkage of the hippocampus was conﬁrmed by hematoxylin and eosin staining of brain sections and also observed a signiﬁcant decrease in NeuN-positive neuronal cells and an increase in cleaved caspase 3 signals in the hippocampus of CAPON-expressing mice. CAPON overexpression signiﬁcantly increased the phosphorylation level at all the phosphorylation sites which were tested, without any change in the total tau level. In addition, they isolated a 1% sarkosyl-insoluble fraction of hippocampal protein and detected insoluble tau by immunoblotting using the Tau5 antibody. A greater amount of sarkosyl-insoluble Tau was detected in CAPON-overexpressing mice compared to control mice. The authors also observed a higher amount of soluble tau oligomer, which could be detected by non-reducing SDS-PAGE, in the CAPON-overexpressing mice.

**Conclusion:**

The authors found that Aβ pathology leads to the accumulation of CAPON protein, and that the increase in CAPON induces tau pathology and neuronal cell death. The ﬁndings suggest that CAPON is one of the novel mediators that link Aβ, tau and neurodegeneration.

**References:**

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2. Saito, T. et al. Single App knock-in mouse models of Alzheimer’s disease. *Nat. Neurosci.***17**, 661–663 (2014).