Establishment of a new tri-culture system for elucidating crosstalk mechanisms between brain microvascular endothelial system and central nervous system in Alzheimer's disease brains

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Data have accumulated suggesting that angiopathy accelerates brain damage in Alzheimer's disease (AD), but its molecular mechanism remains unclear. We hypothesize that amyloid-beta (Ab) assemblies, termed amylospheroids (ASPD), purified from AD patient brains (Noguchi *et al.* JBC 2009), may be the link between angiopathy and brain damage. We have previously shown that ASPD cause dysfunction of brain microvessel endothelial cells (submitted for publication). This time, to verify that the vascular angiopathy leads to brain damage, a new tri-culture system was constructed (human brain blood microvessel endothelial cells, human pericytes, and rat cerebral cortical neurons). Preliminary validation showed that, interestingly, the effects of blood vessel cells damaged by ASPD tended to increase the production of an N-terminal fragment of Ab precursor protein (APP) (APP1-373) in neurons. This fragment has been reported to be associated with neuronal death (Zhang *et al.* Nat Comm 2015), which should be analyzed in the future. As this preliminary result shows, this tri-culture system is suitable for elucidating the molecular mechanism of the link between angiopathy and brain damage, and detailed analysis using this system will be carried out in the future. I would like to discuss out data in the session.