Endothelin-induced astrocytic amyloid production: A neurovascular culprit in the pathogenesis of Alzheimer's disease?

Fung-Kwan Lee[1], Sookja K Chung[2], Paul M Vanhoutte[3], Andrew CK Law[1]. [1]The University of Hong Kong, Dept. of Psychiatry, Hong Kong, [2]The University of Hong Kong, Dept. of Anatomy, Hong Kong, [3]The University of Hong Kong, Dept. of Pharmacology and Pharmacy, Hong Kong.

Astrocytes are known to carry pivotal roles in neuro-inflammation and brain signaling. Moreover, astrocytes participate in cerebral blood flow regulation by interacting with neurons and the endothelia of microvessels together as "neurovascular units" [1]. Alzheimer's disease (AD) is being regarded as the most common neurodegenerative form of dementia. Recent research has increasingly been focusing on the vascular aspects of neurodegeneration, as significant number of AD patients exhibit pathological changes in the cerebral vasculature in addition to having the classical beta-amyloid (Aβ) deposits. Studies have demonstrated changes in endothelin-1 (ET-1) – an important protein in vaso-regulation and vaso-inflammation - and its associating receptors in the AD brains [2]. Exposure of neuroblastoma cells to oligomeric Aβhas been shown to upregulate ET-converting enzyme [3].

Analysis of a previously established clone (C6) derived from the transfection of the astrocytic cell line, DI TNC1, with an ET-1 expression plasmid (pGET) showed thatET-1 over-expression led to an increase of Aβ(1-42) without altering cellsurvival.Treatment of wild-type C57 mouse primary astrocyte-enriched cultures (using DMEM/F12 with 10% fetal bovine serum as media) with exogenous ET-1 (up to 1000nM) increased the level of Aβ(1-42) at 10nM and 100nM. Furthermore, cellular viabilities (assessed by MTT viability assay) were enhanced at all ET-1 concentrations. Experiments were repeated at least three times and Student's t-tests were used for statistical analyses, with $P< 0.05$ being considered statistically significant. All animal-related procedures were conducted in accordance to the university and local government animal care guidelines.

The obtained data demonstrate that Aβ(1-42) is produced in astrocytes upon stimulation by ET-1. Together with the existing literature, our preliminary results suggest a possible astrocytic regulatory mechanism between Aβ processing and the ET system. Furthermore, aberrant ET-1 production as a result of neurovascular unit pathology could be an important upstream event contributing to the eventual Aβ accumulation and toxicity. Further studies into the roles of astrocytes in neurovascular unit dysfunctionassociated with the pathogenesis of AD are warranted.

1. Iadecola, C. Nature Rev.Neurosci. 5: 347-560 (2004).
2. Luo, J. and Grammas, P. J. Alzheimer.Dis. 21(3): 887-896 (2010).
3. Palmer, J.C. et al. Am.J.Pathol. 175(1): 262-270 (2009).