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Letter to the Editor

In vivo Image of Cerebral Amyloid Angiopathy in an Alzheimer's Disease Mouse Model

Jinho Kim, Yong Jeong

Department of Bio and Brain Engineering, KAIST, Daejeon, Korea

Dear Sir:

We would like to share an *in vivo* image of cerebral amyloid angiopathy (CAA) in an Alzheimer's disease (AD) mouse model. In AD, insoluble amyloid beta (Aβ) protein forms plaques in the parenchyma and also accumulates along the vessel walls.[1] The Aβ usually accumulates in the tunica intima and tunica media layers of the vessels. CAA in AD is attributed to the failure of Aβ clearance from the brain through perivascular drainage pathways.[2] In addition, CAA is thought to be responsible for the small vessel pathology that leads to ischemic changes in the white matter in AD. Thus, observation of CAA in regards to white matter lesions or other pathophysiology is important in understanding the development of AD. However, neuropathological studies have typically relied on sections from brain tissues at autopsy, which hampers understanding of the dynamics and topographic distribution of CAA. Cutting-edge optical techniques such as multi-photon laser scanning microscopy enable us to observe CAA in live animals in 3D.[3]

In this study, we used 7-month-old male APPswe/PS1ΔE9 transgenic mice (Jackson Laboratory). One day prior to imaging, methoxy-X04 (5 mg/kg; dissolved in 10% DMSO, 45% propylene glycol, and 45% phosphate-buffered saline) was injected intraperitoneally. This probe has been used for *in vivo* imaging of amyloid plaques in several studies.[4,5] On the day of surgery, the mouse was anesthetized with ketamine and xylazine (0.12 mg/g and 0.01 mg/g, respectively), and a 2×2 mm craniotomy was made over the somatosensory area leaving the dura intact. The cortex was covered with 1% agarose and a glass cover slip. Texas Red-dextran (70 kDa, 100 μL, 5 mg/mL) was injected via the tail vein. All procedures were approved by the KAIST Institutional Animal Care and Use Committee (IACUC). We used a multi-photon laser scanning microscope (LSM510, Zeiss, Germany) and a tunable near-infrared femtosecond pulsed-laser (Chameleon II, Coherent, USA). Images

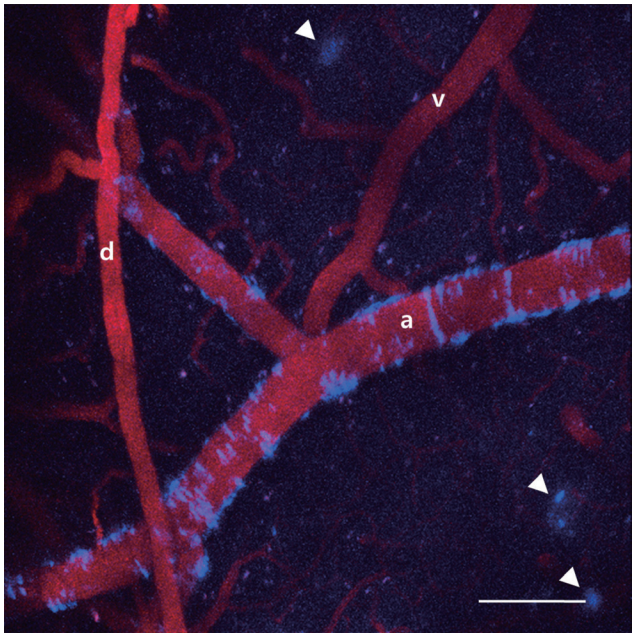

Figure 1. Plaque and cerebral vessel imaging in an APPswe/PS1ΔE9 transgenic mouse (7-month-old; male). Methoxy-X04 (5 mg/kg) was injected intraperitoneally 1 day before the imaging session for plaque imaging. Texas Red-dextran (70 kDa) was injected intravenously on the day of imaging for vessel imaging. Imaging using two-photon laser scanning microscopy was performed up to a depth of 100 μm from the exposed dura. Amyloid aggregates (blue) are deposited on the cerebral arteriole wall (cerebral amyloid angiopathy; CAA) as well as in the brain parenchyma (amyloid plaques). CAA is not observed around the veins or dura vessels. (Red, cerebral blood vessel stained with Texas Red-dextran; a, arteriole; d, dura vessel; v, vein; arrowheads, amyloid plaques; scale bar=100 μm)

were taken using a 20× objective lens (NA 1.0; Carl Zeiss) with a frame rate of 0.5-1 Hz. All images were obtained using the pulsed laser at an excitation wavelength of 800 nm. We discriminated between arterioles and venules based on the direction of red blood cell flow and the morphology of the vessels.

As shown in the Figure 1 (and supplementary movie clip 1 for z-stack image), Aβ deposits were wrapped around the vessel wall in patches. Most plaques did not form complete rings forms at this stage. Seven months is still relatively young, and older mice would have dense Aβ deposits and complete ring forms of CAA. Interestingly, CAA was not observed in either the veins or the dura vessels.[1] This finding supports the concept that CAA is formed by failure of Aβ elimination along the peri-arterial wall, but not along the peri-venous wall.[6]

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Correspondence: Yong Jeong
Department of Bio and Brain Engineering, KAIST, 291 Daehak-ro, Yuseong-gu, Daejeon 305-701, Korea
Tel +82-42-350-4324, Fax +82-42-350-4310
Email: yong@kaist.ac.kr

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