学位の種類	博士（医学）
報告番号	甲第１９５９号
学位記番号	第１３８９号
氏名	中村 知寿
授与年月日	令和5年 3月 24日
学位論文の題名	Aβ42 treatment of the brain side reduced the level of flotillin from endothelial cells on the blood side via FGF-2 signaling in a blood-brain barrier model （血液脳関門モデルにおける脳側へのAβ42投与はFGF-2シグナルを介して内皮細胞から血液側へのフロチリン分泌を低下させる） Molecular Brain, 16(1):15,2023
論文審査担当者	主査：　松川 則之 副査：　斎藤 貴志，飛田 秀樹

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is the most common type of dementia. It is clinically characterized by the loss of cognitive function accompanied by the deposition of extracellular amyloid β-protein (Aβ) aggregates called amyloid plaques, and the formation of intracellular neurofibrillary tangles that consist of phosphorylated tau.
It is well-known that markers of Aβ and tau protein in the cerebrospinal fluid and brain Aβ deposition on positron-emission tomography (PET) are the most promising diagnostic markers. However, cerebrospinal fluid and PET examinations are very invasive and/or expensive, and their clinical use is limited to only a few specialized centers. To facilitate the diagnosis of AD, many studies have been performed to identify markers, including blood-based biomarkers, for clinical diagnosis. In addition, promising results have been reported from clinical trials of disease-modifying drug candidates, mainly immunotherapies targeting the Aβ pathology, thus the use of biomarkers has become more important than ever in terms of ensuring that AD patients have access to the appropriate therapies available and for an accurate prognosis in the early stages of their disease.
We recently showed that the flotillin level is decreased in the blood of patients with AD when compared to that of patients with non-AD and vascular dementia; however, the molecular mechanism remains to be determined. In this study, to elucidate whether Aβ accumulation in the brain has an effect on the blood flotillin level, we used our previously established blood-brain barrier (BBB) culture model using microvascular endothelial cells obtained from human induced pluripotent stem cells (iBMECs) and astrocytes prepared from rat cortex. In this BBB model with iBMECs plated on the upper compartment (blood side) and astrocytes plated on the lower compartment (brain side), the trans-endothelial electrical resistance values are high and stable during experiments. We found that the addition of Aβ42 to the brain side significantly reduced the level of flotillin secreted by iBMECs on the blood side. The level of basic fibroblast growth factor (FGF-2) in the brain side was significantly reduced by Aβ42 treatment, and was accompanied by a reduction in the level of phosphorylation of the fibroblast growth factor receptor in iBMECs. The brain-side Aβ42 treatment-induced reduction of flotillin secretion into the blood side was restored in a dose-dependent manner by the addition of FGF-2 into the brain side. These results indicated that Aβ accumulation in the brain side reduced FGF-2 release from astrocytes, which attenuated FGF-2-mediated iBMECs signaling via the FGF-2 receptor, and thereby reduced flotillin secretion from iBMECs on the blood side. Our findings revealed a novel signaling pathway crossing the BBB from the brain side to the blood side, which is different from the classical intramural periarterial drainage or lymphatic-system-to-blood.