京都大学	博士（　医学　）	氏　名	姜冠華
論文題目	Evaluation of BCAS1-positive immature oligodendrocytes after cerebral ischemic stroke and SVD （脳梗塞と脳小血管病におけるオリゴデンドロサイト前駆細胞分化の BCAS1 免疫組織学的検討）		

(論文内容の要旨)

Background: Ischemic cerebrovascular disease is an important cause of disability and dementia. Brain tissue is especially vulnerable to ischemic insult, and ischemic injury evokes cell deaths which cause active demyelination. Oligodendrocytes, which differentiate from oligodendrocyte precursor cells (OPCs), are crucial for the remyelination of damaged brain and may eventually result in functional recovery. It's been reported that OPCs are abundantly recruited to the ischemic region in ischemic animal models. However, it remains unclear how OPCs gather or distribute to an ischemic area, but fail to mature into functional myelinating oligodendrocytes in human brain. Breast carcinoma amplified sequence 1 (BCAS1) has recently been proved to be highly expressed in newly formed, myelinating oligodendrocytes(pre-mOLGs), and decreases in mature oligodendrocytes, which can be used to segregate them from OPC and mature oligodendrocytes. This study was aimed to explore the changes of pre-mOLGs in the OPC population in human ischemic stroke and small vessel disease (SVD), by using BCAS1 immunohistochemistry.

Methods: In this study, BCAS1 expression was analyzed by immunohistochemical analysis of human post-mortem brain tissue from six stroke patients (death within 2 months after stroke onset) and eight small vessel disease (SVD) patients. Control post-mortem brain tissue was from eight age-matched patients without any obvious central nervous system (CNS) pathology. The Olig2 expression in the area corresponding to the same section of the BCAS1-stained slice was analyzed to determine the total oligodendrocyte lineage. The percentage of differentiating OPCs in the oligodendrocyte lineage was calculated as the ratio of BCAS1+ to Olig2+ cells (BCAS1+%). The stroke and SVD cases showed demyelination with decreased expression of myelin basic protein (MBP, a mature OLG marker).

Result:　During the early stage of differentiation, BCAS1+ cells appeared rounder, with almost no branched processes, and had a larger nucleus, showing a more OPC-like morphology. In the later stage, the cells showed a smaller nucleus and cytoplasm and extended large myelin-like membrane sheets in culture. The stroke cases showed significantly increased numbers of early-stage BCAS1+ cells and Olig2+ cells (pan-oligodendrocyte lineages) in the peri-infarct areas in both the cortex and white matter, but showed no increase in the number of late-stage BCAS1+ cells. In contrast, the SVD cases showed no significant increase in Olig2+ and BCAS1+ cells. In the white matter, the ratio of BCAS1+ to Olig2+ cells (BCAS1+%) increased in the penumbra, but the increase in BCAS1+% in remote areas did not reach significance. Although the cortex BCAS1+/Olig2+ ratio was increased in SVD, it was most likely due to the decrease in the number of Olig2+ cells.

Discussion: While stroke cases showed active OPC recruitment with impaired maturation of early-stage BCAS1+ cells into late-stage BCAS1+ cells, SVD cases showed hindered oligodendrogenesis with neither OLG lineages nor the ratio of BCAS1+/Olig2+ increased. On the basis of these peculiarities of OPC dynamics in stroke and SVD, promoting further maturation of differentiating OPCs or relieving maturation arrest is a possible target for remyelination and functional recovery after stroke, whereas it may be more important to enhance OPC recruitment for SVD.

Conclusion: BCAS1 could be an OPC differentiation marker in ischemic stroke and SVD.

(論文審査の結果の要旨)

本論文では、脳梗塞と脳小血管病においてオリゴデンドロサイト前駆細胞（OPC）から分化する BCAS1 陽性細胞の動態を解析した。

OPC から分化した細胞に高度に発現する BCAS1 マーカーを使用し、ヒト剖検脳を用いた虚血性脳卒中および脳小血管病における OPC 分化の免疫組織的な検討を行った。まず、BCAS1 陽性細胞の分化早期段階と後期段階での形態学的な差異を確認した。さらに、BCAS1 陽性細胞数及びオリゴデンドロサイト(OLG)系譜に占めるその割合を解析した上、急性脳虚血における分化早期の BCAS1 陽性細胞数及びその割合が梗塞辺縁部で著しく増加しているにもかかわらず、分化後期の BCAS1 陽性細胞が減少していることを明らかにした。一方、急性虚血初期状態である脳梗塞遠隔エリアでは分化早期の BCAS1 陽性細胞が増加しているのに対し、脳小血管病における長期慢性脳虚血では OPC の増殖と分化が抑制されていることが示唆された。上記知見より、急性脳虚血時においては分化初期段階の BCAS1 陽性細胞が蓄積しており、分化・成熟が阻害されている一方、慢性脳虚血では OPC の増殖自体が不十分であることが示唆された。

以上の研究はヒト脳虚血における OLG 分化の特徴の解明に貢献し、OLG とその分化過程の細胞を標的とした脳梗塞と脳小血管病の治療法開発に寄与するところが多い。

したがって、本論文は博士（　医学　）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、令和 5 年 12 月 26 日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

要旨公開可能日：　　年　　月　　日　以降