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THE ROLE OF FLI-1 IN PERICYTE DYSFUNCTION IN ALZHEIMER'S DISEASE DEVELOPMENT

Brain pericytes regulate cerebral blood flow, maintain the integrity of the blood-brain barrier (BBB), and facilitate the removal of amyloid beta (Ab), which is critical to healthy brain activity. Pericyte loss has been observed in brains from patients with Alzheimer's disease (AD) and animal models. Our previous data demonstrated that friend leukemia virus integration 1 (Fli-1), an erythroblast transformation-specific (ETS) transcription factor, governs pericyte viability in murine sepsis; however, the role of Fli-1 and its impact on pericyte loss in AD remain unknown. Here, we demonstrated that Fli-1 expression was up-regulated in postmortem brains from a cohort of human AD donors and in 5xFAD mice, which corresponded with a decreased pericyte number, elevated inflammatory mediators, and increased Ab accumulation compared with cognitively normal individuals and wild-type (WT) mice. Antisense oligonucleotide Fli-1 Gapmer administered via intrahippocampal injection decelerated pericyte loss, decreased inflammatory response, ameliorated cognitive deficits, improved BBB dysfunction, and reduced Ab deposition in 5xFAD mice. Fli-1 Gapmer-mediated inhibition of Fli-1 protected against Ab accumulation-induced human brain pericyte apoptosis in vitro. Overall, these studies indicate that Fli-1 contributes to pericyte loss, inflammatory response, Ab deposition, vascular dysfunction, and cognitive decline, and suggest that inhibition of Fli-1 may represent novel therapeutic strategy.

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Dr. Hongkuan Fan is an Associate Professor in the Department of Pathology and Laboratory Medicine at the Medical University of South Carolina. He received his Ph.D. degree in Biochemistry at Jilin University. He was trained as a postdoctoral fellow and worked as a junior faculty member in the Department of Neuroscience at MUSC, which built his broad interest and knowledge in the field of vascular biology, immunology, and neuroscience. He has specific expertise in sepsis, Alzheimer's disease, pericyte function, and extracellular vesicle studies. He has published more than 50 peer reviewed publications, some of them are in high impact journals including American Journal of Respiratory and Critical Care Medicine, Critical Care and Molecular Therapy. He published many abstracts and gave numerous invited talks. He has multiple NIH and institutional grant funding and several patent applications. He served on three editorial board and served as grant and journal reviewers.

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