

POSTER 26

MATRIX METALLOPROTEINASE PROTEOLYSIS AFTER STROKE: A SURROGATE INDICATOR FOR EARLY DIAGNOSIS AND VALIDATION OF TREATMENT

Gregory Blair (M2)
Chunyang Zhang (Research Specialist)
Rong Hu (Graduate Student)
Fanjun Meng (Research Specialist)
Mayland Chang, PhD
Shahriar Mobashery, PhD
Jiankun Cui, MD

(Zezong Gu, MD, PhD)
Department of Pathology and Anatomical Sciences

Matrix metalloproteinases (MMPs) are a family of endoproteases that have various functions from development to disease. They are also believed to play critical roles in the central nerve system for the pathogenesis of stroke. In ischemic stroke, MMP 9 is involved in neuronal apoptosis, edema, and hemorrhagic transformation. In stroke models, MMPs degrade ECM components and disrupt neurovascular integrity, resulting in blood-brain barrier (BBB) disruption and hemorrhage which further damage to the ischemic area.

There are experimental pharmacological treatments with MMP inhibitors that decrease the extent of neuronal apoptosis and hemorrhage. Recently we tested a new class of mechanism-based MMP-9 specific inhibitors SB-3CT. Our hypothesis is that MMP-9 causes proteolytic changes resulting in neurovascular damage after focal cerebral ischemia in mice. Inhibition of MMP proteolysis with SB-3CT, should result in decreased apoptosis of neurons and improved behavioral outcomes.

In two stroke paradigms in mice, we examined MMP-9 proteolysis of ECM components and the neuroprotective effects of the highly selective inhibitor, SB-3CT. SB-3CT dramatically blocks MMP-9 activity and decreases MMP-9-mediated laminin cleavage, rescuing neurons from apoptosis and ameliorating neurobehavioral outcomes. Treatment with SB-3CT attenuates brain MMP-9 activity and protects against delayed neuronal cell death in the embolus-induced permanent MCAo in mice. We conclude that MMP-9 is a highly promising drug target and that the mechanism-based MMP-9 inhibitors have significant therapeutic potential in stroke patients.