Selective Inhibition of Matrix Metalloproteinase-9 Attenuates Traumatic Brain Injury-Mediated Blood-Brain Barrier Disruption in a Novel Dynamic in vitro Model

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Traumatic brain injury (TBI) is a physical disruption of brain tissue followed by a cascade of inflammatory responses. The responses result in a transient disruption of the blood-brain barrier (BBB). The BBB prevents crossover between the brain's microenvironment and systemic circulation. However, TBI-mediated BBB disruption initiates a chronic cycle of injury exacerbation starting with increased BBB permeability due in part to matrix metalloproteinase-9 (MMP-9) upregulation, which is a modifying enzyme dysregulated by pathophysiological changes. MMP-9 increases permeability by cleaving tight junction proteins that typically seal the endothelium. It currently remains unknown whether MMP-9's role in injury exacerbation is related to previously observed TBI-induced decreased expression of Claudin-5, a tight junction protein. We utilized a novel, in vitro dynamic model of the BBB that can recapitulate the pathophysiology of an injured brain with the goal of evaluating MMP-9's role in increased permeability. Tri-cultures of endothelia, astrocytes, and pericytes were exposed to TNF-a to simulate injury and placed in our platform. They were treated with an MMP inhibitor, anti-MMP-9 antibody, and small interfering RNA. Barrier integrity was assessed by several real-time metrics. Post-lysis, Claudin-5 stability was evaluated via Western blot and MMP-9 and MMP-2 (another CNS MMP) gene knockdown was analyzed with qPCR. Importantly, the most efficacious treatments (MMP inhibitor and siRNA) significantly knocked down the expression of MMP-9 and MMP-2. Previous research has only investigated MMP-9 as a modifier, yet our findings suggest MMP-9 and MMP-2 play critical roles in BBB modification. Ultimately, our results provide insight into the therapeutic potential of MMPs.

Awards Won:
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