Recently, increasing number of experimental studies with using ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13)-gene manipulated mice have shown an important pathophysiological roles of ADAMTS13 in brain [1-3] and heart [4-6] attacks, and thus much attention have been drawn to the possible clinical utility of the ADAMTS13 in patients with such conditions.

Herein, we describe the summarized data from our laboratory of the basic studies on ischemic brain injuries in ADAMTS13-gene knockout (ADAMTS13KO) mice, and discuss the significance of ADAMTS13 in pathological states with brain ischemia caused by acute stroke [1,2], and with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage [7].

A large multimeric adhesive glycoprotein Von Willebrand Factor (VWF) can mediate both platelets and leukocytes activations on the ischemic endothelium. VWF-multimers tether platelets on the injured vascular wall and the platelet-receptor for VWF transmits signals leading to platelet activation [8-10]. The platelet-binding affinity of VWF increases with length of the VWF-multimer-strand [9-11] and with high fluid-shear stress [9,11-13] making the VWF-A1-domain conformation easier to be accessed by platelets. Accordingly, the longest multimer termed ultra-large VWF (ULVWF) would exert the maximum adhesive function especially in the microvasculature or stenosed vessels (high shear-stress) [9,12-15]. The platelets-decorated (UL) VWF-multimer-string bound to endothelium supports leukocytes tethering, rolling and transmigration on the activated vascular endothelial cell surface [16-19]. In addition, VWF can directly adheres to leukocyte-receptors involved in rolling and stable adhesion of leukocytes at the site of endothelial stimulation [16]. Namely, the (UL) VWF-multimer could aggravate ischemia-reperfusion injury in the brain by enhancing post-ischemic inflammation as well as post-ischemic hypoperfusion, by provoking platelet-aggregation and leukocyte-plugging and -extravasation.

ADAMTS13 is an intrinsic von Willebrand factor VWF-deaiving enzyme that was discovered in 2001 as the 13th member of the ADAMTS family of zinc metalloproteinase [20]. Plasma ADAMTS13 inhibits platelet aggregations and leukocytes extravasation by specifically cleaving the VWF. A very-high fluid shear-stress (strong tensile-force) applied to the VWF substrate provokes this cleavage by ADAMTS13 [21,22]. By cleaving the VWF A2 domain, the ADAMTS13 reduces the (UL) VWF physiological activity [23,24]. Therefore, we supposed that plasma ADAMTS13 would protect the brain against ischemia-reperfusion injury, and thereby performed experimental studies with using ADAMTS13KO mice to confirm the possible neuroprotective effects of ADAMTS13 in brain ischemia.

Firstly, to elucidate a significance of the ADAMTS13 in the cerebral microcirculation after brain ischemia-reperfusion, we studied the variation of ischemic brain damage and the modification of the post-ischemic hypoperfusion in ADAMTS13 deficient mice subjected to transient focal ischemia caused by 30minutes’ middle cerebral artery occlusion. Compared to wild type mice, after reperfusion following the arterial occlusion, ADAMTS13KO mice showed 1) reduced regional cerebral blood flow 2) increased VWF-mediated platelet thrombus formation in the cerebral microcirculation, 3) increased damage of the brain tissue subjected to ischemia, and 4) thus deteriorated neurological function [2].

Secondly, we investigated if ADAMTS13-gene-deletion enhances the post-ischemic inflammation associated with cytokine over-expressions as well as the cerebral hypoperfusion and aggravates the ischemic brain damage in mice subjected to brief focal ischemia. The result showed, 1) ADAMTS13KO mice had larger brain infarct and more remarkable cortical-neuronal death in the penumbra compared with WT, 2) the rCBF progressively declined within 30 minutes after reperfusion in ADAMTS13KO mice, 3) the plasma HMGB1 (high-mobility group box1), a potent proinflammatory cytokine secreted by immune cells at a local or systemic level, increased more in ADAMTS13KO mice than in WT after ischemia reperfusion, and 4) brain ischemia induced prominent activation of inflammatory cells co-expressing HMGB1 and MPO (myeloperoxidase) in the ischemic...
cortical-penumbra of ADAMTS13KO mice compared to the WT [1].

These data suggest that ADAMTS13-deficiency enhances systemic- and brain-inflammatory responses, impairs the cerebral blood flow reflow, and aggravates ischemic brain damage in mice after focal ischemia. We therefore concluded that ADAMTS13 could protect the brain from ischemia-reperfusion injury by regulating VWF-dependent inflammation as well as thrombosis. Indeed, the systemic administration of ADAMTS13 ameliorated the ischemic brain damage [1,3].

Thirdly, we have started to investigate if ADAMTS13 would also improve neurological deficits due to delayed cerebral ischemia after experimental subarachnoid hemorrhage (SAH) in mice model. Our preliminary data on this just published in Journal of Thrombosis and Haemostasis [7] show that ADAMTS13 seemingly reduces cerebral neuronal injury after SAH by regulating microthrombosis formation and neuronal inflammation.

We have reported neuronal death and inflammatory response on magnetic resonance imaging, immunohistochemical and neuromembranous sutures in patients and animal models after transient cerebral/brain ischemia [25-33]. These studies show that brain- and systemic-inflammatory reactions and modifications for those factors play important roles in saving the neurons affected and brain functions. ADAMTS13 can regulate both microcirculation and inflammation in the brain after ischemic stroke and thus provide the novel therapeutic approach in the clinical settings.

It is well known that ADAMTS13 can exert its physiological effects only under high-shear stress conditions. Namely, ADAMTS13 does not dissolve the VWF-platelet-primary hemostatic thrombus in the absence of pathologically high fluid shear stress. Therefore, ADAMTS13 may be particularly well suited for acute ischemic stroke without increasing hemorrhagic complications. Further, the data from our laboratory suggest that in future ADAMTS13 may offer a novel therapeutic option for brain injury caused by ischemic stress resulting from not only acute stroke but also secondary brain ischemia due to various hemorrhagic brain diseases including aneurysmal subarachnoid hemorrhage.

REFERENCES


