The blood cell flow and the vascular responses in arterioles and capillaries after subarachnoid hemorrhage

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Purpose: Immediately after subarachnoid hemorrhage (SAH), brain injury begins and determines the acute phase mortality and the long-term prognosis, but its mechanism is not well understood. When SAH at the skull base induces platelet-leukocyte-endothelial cell interactions in venules, the cerebral blood flow is kept well at the cerebral surface¹⁾. We investigated cerebral microcirculation through a mouse cranial window using two-photon laser scanning microscopy at a depth of about 100 μm ^{2,3)}, after SAH was induced at the skull base.

Methods: Tracheotomy was performed and femoral artery was cannulated in mice (FVB/N-Tg (GFAP GFP) 14Mes/j). Q-dot 655 nanocrystal (Q21021MP; Invitrogen) or rhodamine-6G was injected from the cannulated femoral vein, after a craniotomy at the parietal bone without cutting dura matter. SAH was induced at a prone position by using the endovascular perforation model⁴⁾. Immediately and one hour after SAH, blood cell velocities were measured with a line scan method in precapillary and capillary using two-photon laser scanning microscopy.

Results: A penetrating arteriole branched into a precapillary arteriole at the depth of 85.9 $\pm$ 21.0 μm (n=7). Arterioles dilated immediately after SAH and then gradually constricted (n=5/7) and the blood flow disappeared immediately after SAH in the others (n=2/7). The blood cell velocity of the precapillary arteriole decreased from 10.7 $\pm$ 3.0 mm/s before SAH to 0.9 $\pm$ 0.4 mm/s after SAH. The capillary-velocities of blood cells (red blood cells, platelets and leukocytes) also decreased, and rolling and adherent leukocytes prevented blood cells from flowing in capillaries.

Conclusion: The cerebral blood flow decreases in arterioles and capillaries, when the SAH is induced.

References

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c-Met interaction with Angiogenesis and Stem Cell in *Helicobacter heilmannii*-induced gastric MALT lymphoma: Interaction with VASH-2

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We established a low-grade MALT lymphoma model in C57BL/6 mouse infection of *Helicobacter heilmannii* obtained from cynomolgus monkey (Infect. Immun. 75 (3): 1214-1222, 2007). After long-term infection, we found the MALT lymphoma formation in the liver and lung in addition to gastric MALT lymphoma. Recently, c-MET, the tyrosine kinase receptor for hepatocyte growth factor (HGF) has attracted attention as one of the key players in survival and proliferation of B-cell malignancies.

Thus, we have planned to clarify the difference of c-MET, HGF and HGF activator (HGFA) expression as well as VEGF and its receptors, Flt-1, Flk-1 and vasohibin-2 (VASH2) in gastric, hepatic and pulmonary lesions in the MALT lymphoma by immunohistochemistry. The effect of c-MET antibodies or inhibitor, PHA-665752 (10 mg/kg b.w.) on the formation of liver and lung lesion was also investigated.

As a result, Nine months after the infection, small lymphocyte aggregates mostly composed of B cells were observed in the portal area of the liver and the peribronchial area of the lung as well as the gastric MALT lymphoma in approximately 50% of the infected mice. These lymphocytes were mostly centrocyte-like cells, and lymphoepithelial lesions characteristic of MALT lymphoma were also recognized. PCR and *in situ* hybridization analysis showed the existence of *Helicobacter heilmannii* not only in the fundic mucosa but in the lung and liver. Twelve and eighteen months after the infection, approximately 100% of infected mice had hepatic and pulmonary lesions. c-MET immunoreactivity was found in the lymphocytes composing the MALT lymphoma, and HGF immunoreactivity was recognized mostly in the endothelial cells and macrophages. HGFA was localized on mesenchymal cells other than the lymphocytes. The administration of antibodies against c-MET or a c-Met inhibitor to the infected mice induced the significant suppression of hepatic and pulmonary lesions as well as the gastric MALT lymphoma, while VASH2 immunoreactivity rather increased within the tumor.

In conclusion, HGF and c-MET pathway were suggested to contribute to the lymphomagenesis and the VASH2 has a compensatory effect in the liver and lung after *Helicobacter heilmannii* infection.