Therapeutic effects of anti-HMGB1 monoclonal antibody on pilocarpine-induced status epilepticus in mice

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Background: High mobility group box-1 (HMGB1) is a representative damage-associated molecular pattern and has been suggested to be involved in many inflammatory diseases. Among the inhibitors of HMGB1, anti-HMGB1 monoclonal antibody (mAb) might have the strongest neutralizing activity against HMGB1. In the previous studies, we demonstrated the beneficial effects of anti-HMGB1 mAb on brain ischemia- and trauma-induced brain injuries in rats through the inhibition of HMGB1 translocation, protection of BBB and suppression of inflammatory responses. In the present study, we focused on whether anti-HMGB1 antibody treatment could relieve status epilepticus-triggered BBB breakdown and inflammation response in addition to the seizure behavior itself.

Methods: Pilocarpine and methyl-scopolamine were used to establish the acute seizure model. The effects of anti-HMGB1 mAb treatment were analyzed with regard to BBB disruption, cytokine expression and behavioral observation. The distribution of therapeutic mAb was also examined immunohistochemically.

Results: Anti-HMGB1 mAb showed inhibitory effects on leakage of the BBB, and on the HMGB1 translocation induced by pilocarpine. The expression of inflammation-related factors, such as MCP-1, CXCL-1, TLR-4, and IL-6 in hippocampus and cerebral cortex were down-regulated by anti-HMGB1 mAb associated with the number of activated astrocytes, microglial cells as well as the expression of IL-1 β . Both hematoxylin & eosin and TUNEL staining showed that the apoptotic cells could be reduced after anti-HMGB1 mAb treatment. The onset and latency of Racine stage five were significantly prolonged in the anti-HMGB1 mAb group. In the analysis of localization of therapeutic mAb, we found that the immunoreactivities of i.v. injected anti-HMGB1 mAb were present on/around vascular endothelial cells of brain in pilocarpine-induced seizure mice. The immunostaining of HMGB1 in vascular endothelial cells in pilocarpine-induced seizure mice revealed the release of HMGB1 from vascular endothelial cells.

Conclusion: These results suggested that anti-HMGB1 mAb prevented the BBB permeability, reduced HMGB1 translocation while inhibiting the expression of inflammation-related factors, protected against neural cell apoptosis and prolonged Racine stage 5 seizure onset and latency, leading to the inhibition of status epilepticus and epileptogenesis.