2-YIA-33 YIA

Anti-HMGB1 mAb therapy for intracerebral and subdural hemorrhage in rats

Dengli Wang[1], Keyue Liu[1], Hidenori Wake[1], Kiyoshi Teshigawara[1], Shuji Mori[2], Masahiro Nishibori[1]

[1]Dept. Pharm., Grad. Sch. Med., Okayama Univ., [2]Sch. Pharm., Shujitsu Univ

High mobility group box-1 (HMGB1) is a ubiquitous and abundant nonhistone DNA-binding protein, and is also an important proinflammatory cytokine once released into extracellular space from the nuclei. In the present study, we examined the effects of anti-HMGB1 mAb on collagenase IV-induced intracerebral hemorrhage(ICH) and autologous blood-induced subdural hemorrhage(SDH) in rats. Here, we show that treatment with neutralizing anti-HMGB1 mAb (1mg/kg, twice) remarkably ameliorated ICH- and SDH- induced brain injuries. Administration of anti-HMGB1 mAb inhibited the release of HMGB1 into the extracellular space and reduced serum HMGB1 levels, thereby decreased the number of activated microglia and the expression of inflammation-related factors including TNF-α, iNOS, IL-1β, IL-6, IL-8R, COX-2 at 24h after ICH and TNF-α, iNOS, IL-1β at 48h after SDH. In chronic phase of ICH, we found that brain tissue loss and vasospasm were apparent, which was alleviated by the treatment of anti-HMGB1 mAb. Moreover, anti-HMGB1 mAb inhibited the body weight loss and improved the behavioral performance of rats. These results strongly indicate that HMGB1 plays a critical role in the development of ICH- and SDH- induced secondary injury through the amplification of plural inflammatory responses. Intravenous injection of neutralizing anti-HMGB1 mAb provides a novel therapeutic strategy for different types of stroke.