3-S26-3

Dynamics of HMGB1 in vascular endothelial cells and tumor vessels-targeting therapy using conjugated anti-HMGB1 mAb for cancers

Masahiro Nishibori¹, Shangze Gao¹, Naoko Tomonobu², Masakiyo Sakaguchi²

¹Dept of Pharmacol, Okayama Univ Grad Schl Med, ²Dept of Cell Biol, Okayama Univ Grad Schl Med

High mobility group box-1 (HMGB1), originally identified as a nuclear chromatin DNA-binding protein, plays a very important role in triggering the inflammatory responses in many kinds of diseases once released into extracellular space. HMGB1 directly stimulates RAGE and TLR-4/2, and enhances the signal transduction by forming complexes with CXCL12 and IL-1beta. In the previous studies, we demonstrated that the treatment with anti-HMGB1 monoclonal antibody (mAb) produced the beneficial effects on a diverse range of CNS and PNS diseases including brain ischemia, hemorrhage, trauma, epilepsy and neuropathic pain using animal models. During the studies, we noticed that the treatment with anti-HMGB1 mAb protected blood-brain barrier (BBB) from disruption very efficiently. Then, we focused on the distribution of therapeutic mAb *in vivo* and found that it accumulated around BBB in some types of brain injuries. To further investigate the dynamics of HMGB1 in vascular endothelial cells and the effects of anti-HMGB1 mAb, we used *in vitro* endothelial cell culture. We found that anti-HMGB1 mAb inhibited the stimulation-induced translocation of HMGB1, associated with the reduction of cytokine production. Surprisingly, anti-HMGB1 mAb was incorporated into endothelial cells considerably and we hypothesized that this incorporation could be applicable to DDS of anti-cancer drugs to tumor vessels. We will present *in vivo* data on the effects of conjugated mAb on melanoma in mice.