Hepatic disorder is a risk factor for aggravation of oxaliplatin-induced peripheral neuropathy in humans and mice: Possible involvement of HMGB1

Risa Domoto 1, Tomoyoshi Miyamoto 2, Rika Nishimura 1, Ryotaro Fukuda 1, Fumiko Sekiguchi 1, Maho Tsubota 1, Yuichi Koizumi 2, Masahiro Nishibori 3, Atsufumi Kawabata 1


We have shown a crucial role of HMGB1 in chemotherapy-induced peripheral neuropathy (CIPN). To clarify risk factors for CIPN, we retrospectively analyzed the clinical data of cancer patients undergoing oxaliplatin (OHP) treatment, and then studied the underlying mechanisms using a mouse model for CIPN. Analyses of 150 outpatients treated with OHP in Seichokai Fuchu Hospital identified a significant correlation between the severity of CIPN and plasma ALT, a marker of hepatic disorders. In mice, i.p. OHP at 5 mg/kg caused mechanical allodynia, which was prevented by an anti-HMGB1 antibody (AB) or soluble thrombomodulin (TM) capable of inactivating HMGB1. CCl4 (1%, 5 ml/kg, i.p.) or ethanol (25%, 20 ml/kg x 3 for 2 days, p.o.) significantly increased ALT levels and tended to elevate HMGB1 levels in plasma. CCl4 (every 2 days, 3 times) or ethanol (twice a day, 12 times) did not alter nociceptive threshold in naïve mice, but caused remarkable allodynia in the mice treated with OHP at 1 mg/kg, a subeffective dose, which was blocked by AB or TM. Thus, hepatic disorder is considered a risk factor for aggravation of OHP-induced CIPN in humans and mice, where HMGB1 might play a key role.