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Symposium

Prevention of chemotherapy-induced peripheral neuropathy by targeting HMGB1

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High mobility group box 1 (HMGB1), a damage-associated molecular pattern (DAMP) protein, is considered to play a role in chemotherapy-induced peripheral neuropathy (CIPN), since an anti-HMGB1-neutralizing antibody prevents CIPN in rodents. Thrombomodulin alfa (TMa), a recombinant human soluble thrombomodulin, is capable of promoting thrombin-dependent degradation of HMGB1. TMa inhibits intraplantar HMGB1-induced allodynia and prevents CIPN caused by distinct chemotherapeutics in rodents. Inhibitors of thrombin, vitamin K or factor Xa attenuate or abolish the preventive effect of TMa on oxaliplatin-induced peripheral neuropathy (OIPN). Repeated administration of those agents aggravates the OIPN and elevates plasma HMGB1 levels. Our retrospective cohort study shows that hepatic dysfunction, possibly due to oxaliplatin therapy, is a risk factor for severe OIPN. Our preclinical study demonstrates that hepatic damage promotes OIPN most probably by promoting HMGB1 release in mice. Together, our data suggest that TMa is available for prevention of CIPN, which requires special attention on co-administration of anti-coagulants, and that careful monitoring of hepatic function is useful to predict severe OIPN.