Pharmacological study by bidirectional approach between bench and bedside: novel evidence from risk factor analysis in cancer patients undergoing chemotherapy

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Chemotherapy-induced peripheral neuropathy (CIPN), a potentially dose-limiting toxicity, impairs the quality of life in cancer patients, whereas there are no effective countermeasures for prevention or treatment of CIPN. Our fundamental studies have demonstrated the critical role of HMGB1, a DAMP molecule, in the development of CIPN following treatment with paclitaxel, vincristine, oxaliplatin, etc. in rodents, and indicated that anti-HMGB1-neutralizing antibodies and thrombomodulin alfa capable of inactivating HMGB1 are useful in inhibiting the development of CIPN. Our retrospective cohort studies in cancer patients undergoing chemotherapy have shown that hepatocellular damage is associated with increased severity of CIPN following oxaliplatin treatment, and that women with breast cancer over menopause age have a higher risk for the incidence of CIPN following paclitaxel treatment. Our animal experiments conducted on the basis of those clinical findings have revealed that experimentally induced hepatocellular damage and ovariectomy aggravate the CIPN caused by oxaliplatin and paclitaxel, respectively, in an HMGB1-dependent manner. Collectively, bidirectional studies between bench and bedside unveil previously unknown risk factors for the incidence and/or increased severity of CIPN, in which HMGB1 might play an essential role.