1-O-B2-3 Oral Sessions

Exacerbation of paclitaxel-induced peripheral neuropathy and HMGB1-induced allodynia in ovariectomized mice

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We have demonstrated that macrophage (M ϕ)-derived high mobility group box 1 (HMGB1), a nuclear protein, plays an essential role in the development of chemotherapy-induced peripheral neuropathy (CIPN) in mice treated with paclitaxel (PCT). Our retrospective cohort study in breast cancer patients undergoing PCT-based chemotherapy has shown that 57 years of age or older and endocrine therapy are associated with exacerbation of CIPN. We thus examined the effect of ovariectomy (OVX) on the HMGB1-dependent CIPN in female mice treated with PCT. Repeated i.p. administration of PCT at 1 mg/kg did not affect the mechanical nociceptive threshold in the control mice, but caused CIPN in the mice subjected to OVX, which was prevented by an anti-HMGB1-neutralizing antibody, 17 β -estradiol (E2) or liposomal clodronate, a macrophage depletor. OVX also exacerbated the allodynia following intraplantar administration of HMGB1 or lipopolysaccharide in the control mice. In M ϕ -like RAW264.7 cells cultured in the charcoal-treated medium supplemented with insulin, testosterone and corticosterone, E2 inhibited PCT-induced HMGB1 release. Our findings thus suggest that estrogen protects against CIPN following PCT treatment most probably by reducing the sensitivity to HMGB1 and the PCT-induced HMGB1 release from M ϕ , thereby supporting our clinical evidence.