

## Estrogen deficiency aggravates paclitaxel-induced peripheral neuropathy: involvement of HMGB1

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High mobility group box 1 (HMGB1), one of damage-associated molecular patterns (DAMPs), once released to the extracellular space, aggravates inflammation and pain. We have reported that macrophage (M $\phi$ )-derived HMGB1 is involved in chemotherapy-induced peripheral neuropathy (CIPN) following paclitaxel (PCT) treatment. Given our recent clinical evidence for a higher risk for CIPN in PCT-treated breast cancer women over menopause age than younger women, we examined the effect of ovariectomy (OVX) on the development of CIPN in mice treated with PCT. In naïve mice, repeated i.p. administration of PCT at 2 and 4 mg/kg, but not 1 mg/kg, developed CIPN. In contrast, treatment with PCT even at 1 mg/kg caused CIPN on OVX mice. The CIPN in OVX mice treated with PCT at 1 mg/kg was prevented by an anti-HMGB1-neutralizing antibody, recombinant human soluble thrombomodulin capable of promoting HMGB1 degradation, or  $\beta$ -estradiol. Together, our data suggest that estrogen deficiency aggravates CIPN after PCT treatment, and the underlying mechanisms involve HMGB1.