Estradiol induces immune dysfunction and reduced wound healing rates after tissue injury

~450,000 people in the USA suffer burn injury each year with ~3,500 deaths, commonly due to infection and impaired wound healing because of severe immune dysregulation. Female burn patients suffer higher mortality rates. Estradiol has been shown to be involved with the regulation of levels of serum interleukin-6 (IL-6), a pleiotropic cytokine which positively correlates with poor outcomes after burn. We hypothesized that estradiol induces reduced rates of wound healing, increased IL-6 expression, and generalized immune dysregulation. We utilized human airway epithelial cells (AECs) and a wound model. AECs were cultured in plastic inserts until confluent. The inserts were removed, simulating a wound, and cells were treated with estradiol (10, 1, and 0.1 nM). Photos taken at 0, 6, 12, and 24 h were analyzed to assess wound closure. mRNA was isolated from cells and immune gene expression was analyzed via Nanostring multiplex gene expression technology (Human Immunology V2 CodeSetTM). We observed decreased rate of wound healing with the highest dose of estradiol (control median 21.2% closure at 6 hours versus 10.7% with 10nM estradiol; p<0.05, n=4). We observed significant differences in immune-associated genes across the range of estradiol concentrations (59-upregulated and 59-downregulated genes with 1nM estradiol versus control; p<0.05, n=3). IL-6 expression was significantly downregulated (√0.3, p<0.005) at 0.1nM estradiol versus control cells but upregulated with 1nM (√1.3) and 10nM (√1.7). These data suggest that estradiol affects the rate of wound healing and may play a role in profound immune dysfunction following burn.