Differential Activation of Alveolar Type II Epithelial Cells and Alveolar Macrophages after Nitrogen Mustard Exposure in Rats

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Nitrogen mustard (NM) is a cytotoxic vesicant known to target the lung, causing acute injury which progresses to fibrosis. In previous studies, we demonstrated that alveolar macrophages (AM) are activated following NM exposure and contribute to the pathogenic response. In the present studies, we assessed the effects of NM on alveolar Type II (TII) epithelial cells. Male Wistar rats (150-174 g; 8-10 weeks) were euthanized 3 days after intratracheal administration of NM (0.125 mg/kg) or PBS control. TII cells and AM were collected 3 d later. NM exposure resulted in increases in bronchoalveolar lavage (BAL) cells, protein, IgM, receptor for advanced glycation end products (RAGE), high-mobility group box (HMGB)-1 and surfactant protein (SP)-D; AM and TII cells also increased, indicating damage to the alveolar epithelium and inflammation. This was associated with increased numbers of microparticles in BAL, suggesting activation of inflammatory and cell death pathways. To assess this, we analyzed expression of proteins associated with these pathways in AM and TII cells by western blotting. Expression of inflammatory proteins SP-D, the C-type lectin Dectin-1 and RAGE increased in AM, but not in TII cells after NM exposure. The pro-inflammatory protein, matrix metalloproteinase-9 was also increased in AM, as well as TII cells after NM exposure, while HMGB-1 was decreased. The PI3K/Akt and suppressor of cytokine signaling (SOC)-2 pathways are known to regulate inflammation. NM exposure downregulated expression of PI3K, Akt and SOC-2 in TII cells, with no significant effects in AM. Expression of pro-apoptotic proteins caspase-3 and caspase-9 increased in AM and TII cells, respectively, after NM exposure. In contrast, NM down regulated expression of the pro-apoptotic protein, poly-ADP-ribose polymerase (PARP) in TII cells, with no major effects in AM. Significant increases in the anti-apoptotic protein, Mcl-1 were observed in AM after NM exposure, but decreases in the anti-apoptotic protein, β-catenin was noted in TII cells. These data demonstrate that TII cells, like AM, are highly responsive to NM, and that distinct inflammatory and cell death signaling pathways are activated in these two cell types in rat lung. These findings suggest that TII cells and AM play unique roles in the pathogenesis of pulmonary toxicity caused by mustards. *Support: NIH AR055073, ES004738 and ES005022.*