

# Farnesoid X Receptor Regulates Macrophage Activation in Nitrogen Mustard-Induced Lung Injury in a Sex-Dependent Manner

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Nitrogen mustard (NM) is a cytotoxic vesicant known to cause acute lung injury which progresses to fibrosis. Following NM exposure, there is a sequential accumulation of pro-inflammatory/cytotoxic M1 and anti-inflammatory/wound repair M2 macrophages in the lung, which we have demonstrated contribute to lung toxicity. In these studies, we analyzed mechanisms regulating macrophage phenotypic activation, focusing on the dysregulation of lung lipids which we hypothesize promotes acute lung injury and fibrosis. Farnesoid X receptor (FXR) is a nuclear receptor involved in regulating lipid homeostasis and inflammation; FXR target genes have been shown to enhance anti-inflammatory M2 macrophage activity and metabolic programming. To analyze the role of FXR in macrophage activation, we used FXR<sup>-/-</sup> mice. Male and female WT and FXR<sup>-/-</sup> mice were treated with PBS (control) or NM (0.08 mg/kg, i.t.). Bronchoalveolar lavage (BAL) and lung tissue were collected 3, 14 and 28 days later. NM caused progressive histopathologic alterations in the lung including inflammatory cell infiltration, septal damage and epithelial thickening; increases in expression of heme-oxygenase-1 (HO-1), a marker of oxidative stress were also noted, along with elevations in BAL protein and cells, markers of alveolar epithelial injury. These changes were more prominent in FXR<sup>-/-</sup> mice at all times examined, especially in males. Additionally, in male, but not female FXR<sup>-/-</sup> mice, there was evidence of foamy macrophages and fibrosis, as assessed histologically and by Gömöri trichrome staining. NM-induced increases in pro- and anti-inflammatory lung macrophages as quantified by flow cytometry, were also more significant in male FXR<sup>-/-</sup> mice, when compared to female FXR<sup>-/-</sup> mice. These findings demonstrate that FXR modulates the response of macrophages to NM and is involved in regulating lung injury, oxidative stress and the development of fibrosis. Our observation that male mice lacking FXR are more sensitive to NM than female mice suggests a potential protective role of estrogen signaling in this model of lung injury. *Supported by NIH Grants AR055073, ES004738 and ES005022.*

