

Farnesoid X Receptor: A Novel Therapeutic Target for Nitrogen Mustard-Induced Pulmonary Injury

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Nitrogen mustard (NM; (bis(2-chloroethyl)methylamine) is a cytotoxic alkylating agent that causes macrophage-mediated inflammatory disease that can progress to fibrosis. The nuclear receptor – farnesoid X receptor (FXR) – regulates lipid homeostasis and exhibits anti-inflammatory characteristics. We hypothesize that activation of FXR will reduce macrophage-mediated inflammation and prevent the development of fibrosis following NM exposure. Male Wistar rats were exposed to phosphate-buffered saline (CTL) or NM (0.125 mg/kg) via *i.t.* Percutany Microsprayer™ aerosolization followed by oral administration of the FXR-agonist obeticholic acid (OCA) or vehicle control (peanut butter, 0.13-0.18 g), 1x/ day, 5 days/week. Lung, liver, ileum, and alveolar macrophages were collected 28d post-exposure. Initially, we assessed the effects of OCA on FXR activity by evaluating mRNA expression of the FXR target genes in the liver (*cyp7A1*, *BSEP*, *FXR*) and ileum (*SHP-1*, *FGF15*, *FXR*). OCA administration increased *FXR*, *BSEP*, *FGF15*, and *SHP*, but decreased *cyp7A1* expression when compared to vehicle control. Next, we assessed the FXR pathway in lung macrophages by analyzing mRNA expression of target genes. We found that NM significant upregulated *cyp7A1*, *SREBP2*, and *APOE-1* indicating an inhibition of FXR activity; OCA significantly reduced this response. To determine whether this blunted NM toxicity, we evaluated the effects of OCA activity on NM-induced structural alterations in the lung. Exposure of rats to NM caused pulmonary edema, thickening of the epithelium, and circularization of alveoli. This was blunted by OCA. Taken together, these data demonstrates that FXR plays a central role in regulating NM-induced pulmonary injury and provides a potential target for the development of drugs to treat mustard poisoning. Supported by NIH grants AR055073, R25ES020721, and ES005022.

