Farnesoid X Receptor Expression in Alveolar Macrophages of Amiodarone-induced Fibrotic Mice Lung Tissue

Fayrouz Merhom, Sheryse Taylor, Andrew Gow
Rutgers, The State University of New Jersey

Up to 9% of patients receiving the oral anti-arrhythmic drug amiodarone develop pulmonary fibrosis (PF). The mechanism of amiodarone toxicity is not known, although direct cytotoxicity to pulmonary cells or induction of phospholipidosis have been suggested. Alveolar macrophages digest pulmonary surfactant lipids and proteins to maintain the lung microenvironment and therefore may be affected by phospholipidosis. In the liver, the nuclear hormone, farnesoid x receptor (FXR), suppresses bile acid synthesis and stabilizes cholesterol and triglyceride levels; and reduced FXR expression has been linked to fibrosis. Recent evidence has found FXR expression in alveolar macrophages to be induced by lung injury. As alveolar macrophages digest phospholipids in the lung lining, we proposed that phospholipidosis resulting from amiodarone administration would negatively affect these cells and that FXR would be critical to this response. To test this hypothesis, we have developed an intranasal administration model of pulmonary fibrosis. Amiodarone was administered at 16mg/kg every 5 days to 8-12 week old C57BL/6 male mice. Mice were euthanized and the lungs collected either 20 or 30 days post-initial administration (IA). At 20 days post-IA, amiodarone-treated lung tissue expressed increased collagen and pro-fibrotic markers (vimentin, TGF-B), and macrophages expressed increased CD206 (marker of alternative activation) relative to the saline control group. By 30 days post-IA, amiodarone-treated lung tissue expressed increased collagen and decreased pro-fibrotic markers compared to the saline group, and CD206-negative macrophages emerge. Immunohistochemistry stains reveal increased FXR expression in the macrophages of amiodarone-treated lung tissue versus saline groups. We concluded that intranasally-administered amiodarone can be used to generate a PF model, and we have early indication that FXR expression is altered in this model.

Amiodarone (A) induces phospholipidosis in alveolar epithelial cells (AEC). Lysosomes (L) store excess phospholipids, forming multi-lamellar bodies

Alveolar type II epithelial cells (AECII) secrete more surfactant lipids and proteins (S) into the alveoli wall. Alveolar macrophages (M) digest excess surfactant and upregulate receptors like FXR to restore lipid levels.

Restore lipid balance
Prevent fibrosis/ lung collapse

↑ Down-stream targets (Fgf15, ERK, cJUN)

↑ FXR?