European Respiratory Society
Annual Congress 2013

Abstract Number: 4859
Publication Number: P648

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair
Keyword 1: Epithelial cell **Keyword 2:** Animal models **Keyword 3:** Lung injury

Title: Regulation of autophagy in amiodarone induced pulmonary fibrosis

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Body: Rationale: Amiodarone (AD) is a well known anti arrhythmic drug, limited by its potential side effects. Severe pulmonary toxicity is reported in patients receiving amiodarone even at low doses, most common histological finding being chronic interstitial pneumonia. Amiodarone is known to induce autophagy in some cell types. A potential role for autophagy in the development of lung fibrosis has not been elucidated so far. Aims: We aimed to establish a murine model of amiodarone induced pulmonary fibrosis and assess the role of autophagy. Methods: AD or vehicle was instilled intra tracheally into C57BL/6 mice, and sacrificed on days 7, 14, 21 & 28. Lungs were either snap frozen or fixed in formalin. Fibrosis development was shown by hydroxyproline measurement. (MLE)-12 cells and AECII were treated with AD/vehicle and harvested after 8, 16 & 24 hours. Surfactant proteins and markers for autophagy, apoptosis and lysosomal stress were studied by western blotting, immunofluorescence and immunohistochemistry. Results: Lung fibrosis was observed in AD treated mice from day7. Accumulation of surfactant proteins was observed paralleled by an induction of autophagy (LC3B-II) lysosomal stress (Cathepsin D) and apoptosis (cleaved caspase 3) in AECII. MLE12 and AECII treated with AD showed the presence of LC3 positive vacuolar structures as after AD treatment. AD treated cells showed increase in the apoptotic marker cleaved caspase-3. Conclusion: We conclude that the autophagy pathway might be involved in the development of amiodarone inuced pulmonary fibrosis, but its interplay with apoptosis and lysosomal stress has yet to be revealed in this disease.