CONTROL ID: 3008414
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Abstract Details

PRESENTATION TYPE: Poster
CURRENT CATEGORY: AIRWAYS PHYSIOLOGY, PATHOPHYSIOLOGY & DEFENSE
KEYWORDS: IL-1, Human airway epithelial cells, inflammatory response, oxidative stress.
AWARDS:
CF Related Education: No
CF Target Audience: (none)
First Author Information: Yes
Pathogens Exposure - Abstract Submission: I acknowledge that I have read and understand the Foundation's attendance policy for events and will do my part to minimize the spread of germs at NACFC.
Abstract

TITLE: IL-1 IS ASSOCIATED WITH STRUCTURAL LUNG DISEASE IN CHILDREN WITH CYSTIC FIBROSIS
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ABSTRACT BODY:

Abstract Body: Introduction: Neutrophilic airway inflammation in cystic fibrosis (CF) is associated with structural lung damage and decreased lung function, even in absence of infection. Necrosis of airway epithelial cells (AEC) is a characteristic finding in CF has been associated with increased neutrophils and elevated interleukin-1alpha (IL-1α). Here, we aimed to measure IL-1α in human paediatric CF airway, assess for associations with inflammatory markers and structural lung changes, and test in vitro whether necrosis of AEC undergoing anoxia drives IL-1α release. Method: Bronchoalveolar lavage fluid (BALf) obtained from CF children (n=102, mean age: 3.78; range: 0.16 – 7.81 years) with and without respiratory infection was measured for IL-1α, IL-1β, IL-8, neutrophils and neutrophil elastase (NE) activity. Extent of structural lung disease on CT was measured via PRAGMA-CF and associations with IL-1α, IL-1β, IL-8, neutrophils and neutrophil elastase (NE) activity were investigated via multiple linear regression (adjusted for age and sex). CF (AEC_{CF}) AECs were also collected and cultures established. Cells were exposed to anoxia over 48 hours and viability, apoptosis, and necrosis assessed via flow cytometry reported as a percentage of unexposed control (mean ± standard deviation), and IL-1 measured in supernatant. Wilcoxon signed rank test was used to test for significant differences ($p<0.05$). Results: IL-1α and IL-1β were detectable in BALf from young children with CF in absence of detectable infection, were increased in the presence of bacterial infection and correlated with IL-8 (r=0.64 & r=0.64 respectively; $p<0.0001$), neutrophil counts (r=0.71 & r=0.67 respectively; $p<0.0001$) and NE activity (r=0.26; $p<0.01$ and r=0.32; $p<0.001$). When stratified by respiratory infection status, there were associations between IL-1α, IL-1β, IL-8, neutrophil count and NE activity and extent of structural lung disease on CT in children without respiratory infection, however the association between IL-1α and extent of structural lung disease on CT was the strongest (1.20 [0.33, 2.06], p=0.008). Exposure to anoxia for 48 hours resulted in a significant decrease in cell viability (71.97% ± 34.12; $p<0.05$), significant increase in cell necrosis (232.8% ± 174.4; $p<0.05$) but no significant change in apoptosis

(124% ± 31.36). IL-1 was measured in supernatant collected from cells exposed to anoxia. Conclusion: IL-1α is detectable in the CF airway in young children with CF and is associated with structural lung disease on CT, potentially driven by increased necrosis of AEC after exposure to anoxia. Supported by: CFA, CFWA, USCF, German Federal Ministry of Education and Research

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(No Image Selected)