**3070**
**Topic Category:** 4105-ASIP MUCOSAL INFLAMMATION, EPITHELIAL-LEUKOCYTE INTERACTIONS AND EPITHELIAL PATHOBIOLOGY

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**Presentation Preference:** Oral

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**Sponsor's Society:** Pathology - American Society for Investigative Pathology (ASIP) - Host Society
**Keywords:** 1. Colitis 2. PAFR 3. Inflammasome
**Awards:** ASIP Trainee Travel Award

## Platelet Activating Factor Receptor (PAFR) Regulates Colitis-induced Pulmonary Inflammation

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Inflammatory bowel disease (IBD) is a progressive disease that includes Crohn's diseases and ulcerative colitis. Over one third of IBD patients have secondary organ pathologies and pulmonary manifestations are common. The platelet activating factor receptor (PAFR) plays a critical role in regulating inflammation and it is expressed on epithelial cells and neutrophils in both colon and lung. Having identified increased expression of PAFR in both the gastrointestinal (GI) tract and lungs of mice with dextran sulfate sodium (DSS) colitis, we hypothesised that PAFR was a mediator of the pulmonary inflammation associated with colitis. We aimed to elucidate the role of PAFR in gut-lung inflammatory cross-talk using of the DSS-induced experimental model of colitis (7 days). DSS mice were treated with PAFR antagonist CV6209 both intranasally and intravenously and lung, colon and blood were assessed for inflammatory cells and mediators by qPCR, immunoblot, immunohistochemistry and flow cytometry. We demonstrated that DSS-induced colitis resulted in inflammation in mouse bronchoalveolar lavage fluid (BALF) and lungs, as well as increased PAFR protein levels in lungs and colons. Pulmonary neutrophils in DSS animals showed increased PAFR staining. Bacterial *16S* mRNA expression were also increased in mouse lungs after 7 days DSS challenge. Both intravenous and intranasal inhibition of PAFR by CV6209 reduced colitis-induced numbers of neutrophils, but not macrophages, in mouse lungs. Inhibition of PAFR also reduced levels of TNF and IL-1b proteins and bacterial *16S* expression in mouse lungs. Importantly, intravenous administration of CV6209 reduced colitis pathology, TNF and IL-1b protein levels in mouse colons after 7 days DSS challenge. In the DSS model, increased PAFR protein expression was associated with inflammasome activation, characterized by increased NLRP3 and mature caspase-1 proteins, however inhibition of PAFR by CV6209 reduced NLRP3 and caspase-1 levels after DSS challenge in mouse lungs. *In vitro*, NLRP3, activated caspase-1 and secreted IL-1b protein levels were increased in human alveolar epithelial cell culture (A549) after 24h LPS stimulation, and this was inhibited by treatment with CV6209. These data suggest that PAFR regulates colitis-induced lung inflammation by IL-1b protein activation via the NLRP3 inflammasome signalling pathway. PAFR may act as an inflammasome-activating pattern recognition receptor during mucosal inflammation thus is a potential therapeutic target for lung inflammation associated with colitis and bacteraemia.

**Support or Funding Information**
This study was supported by a grant from National Health Medical Research Council (NHMRC) Australia