European Respiratory Society
Annual Congress 2013

Abstract Number: 638

Publication Number: 1816

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: ALI (Acute Lung Injury) **Keyword 2:** Animal models **Keyword 3:** Inflammation

Title: The role of vitamin D in regulating the severity and duration of murine lung injury

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Body: Introduction Vitamin D has been shown to modulate both innate and adaptive immune responses. Our research suggests patients with or at risk of developing acute lung injury (ALI) are severely vitamin D deficient/insufficient. As there are no licensed treatments for ALI we investigated the effect of vitamin D deficiency in a murine model of ALI to understand its mechanistic drivers. Methods Vitamin D deficiency in wild type (WT) mice was established using a vitamin D deficient diet. Combining this with intra-tracheal instillations of LPS (50µg) we analysed inflammation within the lungs of these mice compared to those fed on a vitamin D sufficient diet. In addition, systemic vitamin D supplementation was assessed by IP injection of cholecalciferol prior to LPS instillation. Results Compared to WT, vitamin D deficient mice had elevated lung damage at 24 and 48h post IT-LPS; increased Permeability Index ($p=0.007$, $p=0.018$) and RAGE expression ($p=0.007$, $p=0.001$). At 48h post IT-LPS vitamin D deficient mice had a build-up of apoptotic neutrophils ($p=0.038$), increased BALF granulocytes ($p=0.042$), elevated CXCL1/KC ($p=0.012$) and decreased oxygen saturation ($p=0.016$). Furthermore, pre-treatment of mice with normal vitamin D levels, with cholecalciferol reduced lung inflammation - fewer BALF granulocytes ($7.6x10^5$ to $4.3x10^5$, $p=0.135$), and neutrophils (81% to 72%, $p=0.068$) 48h post IT-LPS ($n=6$). Conclusion Our data indicate that vitamin D deficiency significantly augments both the severity and duration of murine lung injury and exogenous vitamin D reduces lung responses to LPS even in mice with normal vitamin D levels. These data support the use of vitamin D to both prevent and potentially treat established ALI.