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Title: Long-term exposure to TNF-α and IL-1β reduces vitamin D-mediated expression of the antimicrobial peptide hCAP18/LL-37 in primary bronchial epithelial cells (PBEC)

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Body: Vitamin D is a regulator of immunity and inflammation, and vitamin D deficiency is associated with chronic obstructive pulmonary disease (COPD). Its circulating metabolite 25D3 increases epithelial expression of hCAP18/LL-37 via local conversion by CYP27B1 into the active 1,25D3. Concurrently, 25D3 induces negative feedback by increasing CYP24A1, which degrades 1,25D3. We hypothesized that long-term exposure of PBEC to inflammatory stimuli such as TNF-α and IL-1β may alter 25D3-metabolism and expression of hCAP18/LL-37. PBEC were cultured at the air-liquid interface in presence or absence of TNF-α/IL-1β for 14 days and subsequently exposed to 25D3 for 24-48 hrs. Expression of hCAP18/LL-37, CYP27B1, CYP24A1 and vitamin D receptor (VDR) was quantified by qPCR, whereas hCAP18/LL-37 and CYP24A1 protein were also assessed by Western blot. TNF-α/IL-1β reduced 25D3-mediated hCAP18/LL-37 expression compared to control by 3.4 fold ($p = 0.014$), which was confirmed by Western blot analysis. Expression of VDR and CYP27B1 was not affected, whereas CYP24A1 was 9.9 fold increased by TNF-α/IL-1β compared to unstimulated PBEC ($p = 0.007$). After 25D3-stimulation to increase CYP24A1, CYP24A1 mRNA and protein were still elevated in TNF-α/IL-1β exposed cells, although this difference did not reach statistical significance. TNF-α/IL-1β alters 25D3-metabolism resulting in decreased expression of hCAP18/LL-37. This may indicate that supplementation with vitamin D is not always effective in COPD patients, where it might be degraded by CYP24A1. The mechanism underlying the induction of CYP24A1 by TNF-α/IL-1β needs to be further elucidated.