Response of lung epithelial cells to inflammatory stimuli following exposure to the active form of vitamin D

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The active form of vitamin D (1,25(OH)2D3) is now of huge interest to the scientific community with numerous beneficial effects beyond Ca homoeostasis and rickets. Inflammation plays a central role in the pathogenesis of numerous pulmonary diseases and recent evidence suggests vitamin D exerts immunomodulatory effects in the lung. Serum concentrations of inactive 25(OH)D3 have been shown to directly correlate with FEV1(1) and inversely with upper respiratory tract infection(2). More recent studies have shown potential beneficial effects of high dose vitamin D improving treatment for some tuberculosis patients(3). It is clear from this evidence that vitamin D may play an important role in the lung, but due to the low levels of vitamin D available from the diet, it is unlikely that levels of vitamin D required to be of benefit are achievable through diet alone. However, on a cellular level, respiratory epithelial cells have been shown to be capable of activating vitamin D(4) but as yet it is unknown what concentrations of active vitamin D can be achieved locally given sufficient serum concentrations of 25(OH)D3. Vitamin D inadequacy is a global problem, especially among elderly patients(5) and with an ever increasing ageing population and lifestyles that reduce exposure to sunlight, it is crucial to identify mechanisms by which vitamin D improves function and to identify optimal levels. In this study, the effects of 1,25(OH)2D3 on pro-inflammatory mediator production were investigated in primary human small airway epithelial cells (SAEC). Cells were incubated with 100 nM 1,25(OH)2D3 for up to 48 h and the effects on basal mRNA expression of cytokines (IL-1β, IL-6, IL-8, TNFα, IL-10 and IL-12p70) were investigated using qRT-PCR. 1,25(OH)2D3 treatment significantly reduced the expression of IL-6 mRNA from just 1 h of treatment (results at least in triplicate, one way ANOVA, P<0.001), but had no effect on basal mRNA of the other cytokines. IL-10 and IL-12p70 mRNA and protein were below the limit of detection. Both 10 ng/ml TNFα and 10 μg/ml lipopolysaccharide (LPS)-induced expression of IL-1β, IL-6, IL-8 and TNFα mRNA. Pre-treatment of SAEC with 1, 10 or 100 nM 1,25(OH)2D3 for 1 h before stimulation with TNFα or LPS led to a dose-dependent reduction of IL-6 mRNA induction that was significant at 100 nM with TNFα treatment (results at least in triplicate, t test, P<0.05). Induction of IL-6 protein expression by TNFα was significantly reduced by 1 h pre-incubation with 100 nM 1,25(OH)2D3 as assessed by flow cytometry (results in triplicate, one way ANOVA, P<0.01).

IL-6 is a key cytokine involved in the initiation and extension of the inflammatory response both locally and systemically in lung diseases. This data suggests that vitamin D may be of benefit in reducing IL-6 production by primary human small airway epithelial cells. More research is required into further effects and the mechanism of action of vitamin D on lung epithelium, to determine potential benefits for preventing or treating lung diseases and to define optimum levels.

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