Increased Expression of Importin α3 (KPNA4) and Decreased VDR in the Lung of OVA-Sensitized and Challenged Mice

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ABSTRACT

Asthma is an allergic disease characterized by airway hyperresponsiveness (AIR), airway obstruction, airway remodeling, and infiltration of eosinophils and lymphocytes (Type 2) cells into the airway submucosa. This leads to inflammation and asthma of bronchial mucosa, hypersecretion of mucus, and hyperresponsiveness. There is a number of inflammatory cytokines released from T2 cells during asthma attack. VDR is one of the central and key transcription factor involved in the production of these inflammatory cytokines. The activation of NF-κB by TNF-α is an important step in the development of asthma or immune responses. The release of various cytokines and chemokines cause the increase in symptoms of asthma. Upon activation, VDR is imported into the cytoplasm from the nucleus to start transcription of genes responsible for inflammatory responses. A variety of proteins, such as transcription factors and inflammatory mediators are expressed in the nucleus or in the cytoplasm and various functions of VDR and nuclear protein are expressed in the cytoplasm. The transport of molecules out of and into the nucleus is mediated by nuclear export complexes (NPC). The size of NPC is about 125 MDa. The importin α3 (KPNA4) is a selective component of NPC that drives nuclear transport of Protein. Impaired transport of Protein leads to decrease in the expression of VDR and increase in the expression of Importin α3. These results support that vitamin D supplementation might be useful in decreasing airway hyperresponsiveness and airway inflammation.

RESULTS

Effect of TNF-α on mRNA and protein expression of VDR and Importin α3 in HBSSMCs

Conclusions:

1. TNF-α decreases the mRNA expression by ~2-fold and significantly decreases the protein expression of VDR. Calcitriol significantly increases the TNF-α induced decrease in the expression of VDR.

2. TNF-α increases the mRNA expression by ~3-fold and significantly increases the protein expression of immunoprotein α3. Calcitriol significantly attenuates the TNF-α induced increased expression of importin α3.

3. OVA-sensitized mice have a higher airway hyperresponsiveness and airway inflammation compared to PBS control mice.

4. mRNA and protein expression of VDR is decreased in OVA-sensitized mice compared to PBS control mice.

5. mRNA and protein expression of importin α3 is increased in OVA-sensitized mice compared to PBS control mice.

SUMMARY OF THE RESULTS

In both in vitro and in vivo studies, under inflammatory conditions, there was a decrease in expression of VDR and increase in expression of importin α3. The increased expression of importin α3 in HBSSMCs is attenuated by addition of calcitriol. The immunomodulatory effect of vitamin D may be through a mechanism likely to be mediated by decreasing the expression of importin α3, thereby decreasing the expression of NF-κB leading to decrease in inflammation of airway tissue. These results support that vitamin D supplementation might be useful in decreasing airway hyperresponsiveness and airway inflammation.

CONCLUSIONS

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