The Role Of Histone Arginine Methylation In Gene Expression Of Airway Smooth Muscle Cells In Asthma

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Introduction and objectives

Asthma is estimated to affect at least 300 million people globally. About 25% of the patients do not respond to therapy; therefore we need to develop novel treatments. ASM cells have a crucial role in asthma, contributing to airway remodelling, inflammation and airflow obstruction. We have previously shown that epigenetic histone modifications, particularly histone lysine acetylation and methylation regulate the secretion of inflammatory mediators from ASM cells. Here we tested the hypothesis that histone arginine changes are also involved. Protein arginine N-methyltransferases (PRMTs) are the enzymes which catalyse histone arginine methylation (HRme, the addition of a methyl group to arginine residues on the N-terminal tails of histones), and inhibiting them represents a strategy to reduce the secretion of inflammatory mediators from ASM cells.

Methods

Studies were performed in cultured human ASM cells from asthmatic and non-asthmatic donors at passage 6. PRMT expression in human ASM cells was investigated by qPCR. Protein levels of four PRMTs in human ASM cells were investigated by western blotting. The effect of inhibiting PRMTs on the secretion of eotaxin, IL-6, CXCL8 and IP-10 from healthy ASM cells, under basal conditions and following stimulation with TNF-α (1ng/ml), was investigated by ELISA.

Results

We found that ASM cells express the PRMT1, PRMT2, PRMT3, CARM1, PRMT5, PRMT6, PRMT7 and FBX011 mRNA and PRMT1, CARM1, PRMT5, and PRMT6 protein. The analysis showed no difference in the levels of expression between cells isolated from asthmatic and non-asthmatic donors. Two PRMT inhibitors, namely TCE5003 – a PRMT1 inhibitor, and 217531 - a CARM1 inhibitor, significantly reduced the secretion of inflammatory mediators from ASM cells.

Conclusions

ASM cells express a number of PRMTs at mRNA and protein levels. The inhibition of PRMTs results in the reduced secretion of inflammatory mediators from ASM cells. PRMTs may have an important role in regulating chemokine production from ASM cells in asthma, and are a promising target for future investigations in asthma.

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