A-kinase anchoring proteins (AKAPs) regulate airway smooth muscle secretory and proliferative functions

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Chronic obstructive pulmonary disease (COPD) is an inflammatory disease mainly caused by cigarette smoke and characterized by neutrophil infiltration, emphysema, increased smooth muscle proliferation and bronchoconstriction. Next to inflammatory cells, airway smooth muscle (ASM) cells regulate such typical features of COPD. Recently, we reported that the main cAMP effectors protein kinase A (PKA) and exchange factor directly activated by cyclic AMP (Epac) reduce cigarette smoke extract (CSE)-induced release of the neutrophil attractant IL-8 from human ASM cells[1]. Current pharmacological treatment relies on cAMP-elevating β_2-agonists and phosphodiesterase inhibitors, notably both drugs relieve a distinct subset of COPD symptoms. This distinction might be due to the existence of A-kinase anchoring proteins (AKAPs) known to compartmentalize cAMP signalling by differentially docking of cAMP effectors. Here we investigated the role of AKAPs in human ASM function. In human ASM, western blots, radio-assays for PKA binding (RII overlay) and RT-qPCR demonstrated the expression of several AKAPs, including AKAP5, AKAP9 and AKAP12. In immortalized human ASM cells, CSE decreased AKAP12 mRNA expression, (fold change±SEM 0.58±0.06 compared to control, $p<0.05$, n=3) whereas expression of AKAP5 was less affected (fold change±SEM 0.66±0.15 compared to control, $p=0.15$, n=3). In primary ASM, mRNA expression for both AKAPs was decreased by 50%, $p<0.01$(n=3). AKAP9 mRNA expression remained unchanged (n=3-4), although, CSE disturbed its cellular localization to the Golgi. Importantly, in lung tissues of COPD patients, expression of all three AKAPs was downregulated compared to control patients (fold change±SEM; 0.25±0.10, 0.27±0.07 and 0.38±0.11 for AKAP5, AKAP9 & AKAP12 respectively, $p<0.05$, n=5 control, n=10 COPD stage II plus IV). Perturbation of AKAP functions with the AKAP inhibitor st-Ht31 augmented CSE-induced IL-8 release from ASM cells, and reduced the inhibition of CSE-induced IL-8 release by the β_2-agonist fenoterol and specific Epac activation. Phosphorylation of ERK has been shown to regulate ASM proliferation as wells as cytokine secretion[1,2]. The AKAP inhibitor st-Ht31 also diminished the inhibitory effect of β_2-agonist fenoterol on ERK phosphorylation in ASM cells. The PKA activity measured by phosphorylation of the PKA effector VASP, however, was not altered. Disruption of AKAP functions by st-Ht31 also reduced platelet-derived growth factor-induced [^{3}H]-thymidine incorporation in human ASM cells. Our studies point to an association between AKAP-dependent and cigarette smoke-pertubated compartmentalized cAMP signalling and COPD. Supported by the Stichting Astma Bestrijding, the Dutch Asthma Foundation and a Rosalind Franklin Fellowship.

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