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Title: MNK-1 inhibition reduces proliferation and CXCL10 in airway smooth muscle cells

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Body: BACKGROUND: Asthmatic airway smooth muscle cells (ASMC) proliferate faster and secrete more CXCL10 when compared to non-asthmatic ASMC, in vitro. This pathology may be due to the earlier observed faulty mRNA translation control in asthmatic ASMC. A key player in translational control is the eukaryotic translation initiation factor (eIF)-4E, which is directly phosphorylated by the MAP kinase interacting kinases (MNK)-1, downstream of MAPK p38 and ERK. In this study we investigated whether ASMC proliferation and CXCL10 expression is regulated by the MAPK/MNK-1/eIF4E pathway in asthmatic and non-asthmatic ASMC. METHODS: ASMC were pre-treated with MNK-1 inhibitor CGP57380 (1-20 μM), ERK inhibitor PD98059 (30 μM) or p38 inhibitor SB203580 (10 μM) before stimulation with TNF-α (10 ng/ml) or FCS (5%). Total cell lysates and cell supernatants were collected and analyzed by immunoblotting or ELISA. Cell proliferation was measured by direct cell counting. RESULTS: FCS-induced proliferation and TNF-α stimulated CXCL10 secretion was dose-dependently inhibited by CGP57380 (≥ 5 μM) in both asthmatic and non-asthmatic ASMC. TNF-α induced the phosphorylation of MNK-1 after 15-30 min and that of eIF-4E after 15-60 min, which was inhibited by pre-treatment with CGP57380 (5-20 μM), PD98059 or SB203580. Similarly, FCS induced eIF-4E phosphorylation after 15-120 min. CONCLUSION: For the first time, we show that ASMC proliferation and CXCL10 expression depend on the activation of the MAPK/MNK-1/eIF4E pathway in asthmatic and non-asthmatic ASMC. These novel findings may offer new targets for asthma therapy to limit airway remodeling and inflammation in asthma.