Title: YKL-40 induces IL-8 expression from bronchial epithelium via MAPK (JNK, ERK1/2) and NF-κB pathways, causing bronchial smooth muscle proliferation and migration

Body: Our previous study, consistent with others, has shown that the serum YKL-40 levels in asthmatics were significantly elevated and were associated with asthma severity. Although these studies raise the possibility that YKL-40 may influence asthma, the mechanisms remain unknown. In this study, we investigated the mechanisms involved in YKL-40-mediated IL-8 production from human bronchial epithelial cells (BEAS-2B) and analyzed the soluble factors (including IL-8) secreted by BEAS-2B exposed to YKL-40 that were responsible for increasing proliferation and migration of primary normal human bronchial smooth muscle cells (BSMCs). We found BEAS-2B treated with YKL-40 resulted in a significant increase of IL-8 expression and release. Moreover, YKL-40 mediated phosphorylation of JNK, ERK, but not p38 in BEAS-2B. Transfection using a NF-κB-luciferase reporter also showed YKL-40 induced IL-8 at the transcriptional level. Furthermore, BEAS-2B pretreated with inhibitors of JNK, ERK or NF-κB decreased IL-8 release upon YKL-40 treatment. In addition, we treated BEAS-2B with YKL-40 and added the conditioned culture media (YKL-40-BEAS-2B-CM) to BSMCs, which led to increased proliferation and migration of BSMCs. By comparison, IL-8-depleted YKL-40-BEAS-2B-CM failed to induce the proliferation and migration of BSMCs. In summary, our data provided the first evidence of YKL-40-induced IL-8 expression in BEAS-2B via MAPK (JNK, ERK) and NF-κB pathways, and the induced IL-8 was found to further stimulate the proliferation and migration of BSMCs. Our results raise the possibility that YKL-40 may play a role in asthma by inducing IL-8 production.