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Title: Cigarette smoke upregulates IL-8/CXCL8 expression by augmenting mRNA stability via p38 MAPK/MK2 signalling in normal human pulmonary cells

Dr. Nadia 6589 Moretto n.moretto@chiesi.com [1], Dr. Giorgia 6590 Volpi g.volpi@chiesi.com [1], Dr. Manminder 6591 Kaur manminder.kaur@manchester.ac.uk [2], Dr. Claudia 6592 Iadicicco c.iadicicco@chiesi.org [1], Dr. Serena 6593 Bertolini s.bertolini@chiesi.org [1], Dr. Gessica 6597 Marchini g.marchini@chiesi.org [1], Dr. Dave 6598 Singh DSingh@meu.org.uk MD [2] and Dr. Fabrizio 6603 Facchinetti f.facchinetti@chiesi.org [1]. [1] Department of Pharmacology and Toxicology, Chiesi Farmaceutici S.p.A., Parma, Italy, 43122 and [2] Manchester Academic Health Science Centre, NIHR Translational Research Facility, University Hospital of South Manchester Foundation Trust, Manchester, United Kingdom, M23 9LT .

Body: Interleukin-8 (IL-8/CXCL8) is an important neutrophil chemoattractant known to be elevated in the airways of cigarette smokers and in patients with chronic obstructive pulmonary disease (COPD), a syndrome associated with chronic cigarette smoking. We examined the acute effect of aqueous cigarette smoke extract (CSE) on IL-8 expression in normal human bronchial smooth muscle cells (HBSMC) and alveolar macrophages. CSE upregulates IL-8 mRNA levels in a concentration and time-dependent manner and such an effect was accompanied by IL-8 secretion into the extracellular medium. CSE-evoked elevation of IL-8 mRNA was mimicked by its component acrolein at concentrations (3-30μM) found in CSE. Both CSE and acrolein induced p38 mitogen-activated protein kinase (MAPK) phosphorylation which was accompanied by the phosphorylation of MAPK-activated kinase 2 (MK2), a known downstream substrate of the p38 MAPK. In both HBSMC and human alveolar macrophages, pharmacological inhibition of p38 MAPK or MK2 strongly accelerated the decay of IL-8 mRNA levels upon stimulation with CSE or acrolein and subsequent blockade of mRNA neosynthesis with actinomycin D. Conversely, pharmacological inhibition of extracellular-signal-regulated kinases 1/2 (ERK1/2) signalling did not affect mRNA stability but inhibited both CSE- and acrolein-induced steady-state levels of IL-8 mRNA, suggesting a transcriptional effect. In sum, p38 MAPK/MK2 signalling appear to be an important post-transcriptional mechanism underlying CSE-induced IL-8 mRNA upregulation.