Bing-Chang Chen et al., Biochem Pharmacol (Los Angel) 2017, 6.2 (Suppl)
DOI: 10.4172/2167-0501-C1-007

Thrombin induces IL-8/CXCL8 expression in human lung epithelial cells by mTOR, p70S6K, p300, and NF-κB pathways

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Thrombin plays an important role in lung inflammatory diseases such as asthma. Several studies have shown that thrombin can induce interleukin-8 (IL-8)/CXCL8 in lung epithelial cells, and it plays a critical role in lung inflammation. We previously showed that thrombin induces IL-8/CXCL8 expression via the c-Src- and Rac1/PI3K/Akt-dependent IκB kinase α/β (IKKα/β)/NF-κB signaling pathways in human lung epithelial cells. In this study, we further investigated the roles of mammalian target of rapamycin (mTOR), p70S6K, p300, and NF-κB in thrombin-induced IL-8/CXCL8 expression in human lung epithelial cells. Thrombin-induced IL-8/CXCL8 release was attenuated by rapamycin (a mTOR inhibitor), p70S6K siRNA, and p300 siRNA. Treatment of cells with thrombin caused a time-dependent increase in phosphorylation of mTOR at Ser2448, p70S6K at Thr389, and p300 at Ser1834. Thrombin-induced an increase in p70S6K phosphorylation was inhibited by rapamycin. Thrombin-induced an increase in p300 phosphorylation was inhibited by rapamycin and p70S6K siRNA. Moreover, thrombin-induced phosphorylations of mTOR, p70S6K, and p300 were inhibited by dominant negative mutant of Akt (AktDN). Thrombin caused p70S6K translocation from the cytosol to the nucleus in a time-dependent manner. Treatment of cells with thrombin induced p70S6K, p300, and p65 complex formation. Thrombin caused time-dependent increase p65 Lys310 acetylation and the recruitment of p300 and p65 to the IL-8/CXCL8 promoter. These results indicated that thrombin activates mTOR/p70S6K/p300 signaling pathway to induce NF-κB activation and IL-8/CXCL8 expression in human lung epithelial cells.

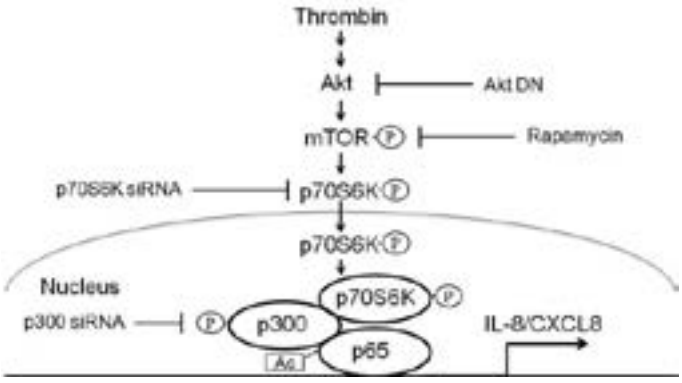

Figure: Schematic summary of the signaling pathway involved in thrombin-induced IL-8/CXCL8 expression in human lung epithelial cells.

Biography

Bing-Chang Chen completed his Graduation in Department of Pharmacy at Chia-Nan Junior College of Pharmacy in 1991 and; PhD at Institute of Pharmacology, College of Medicine, National Taiwan University (NTU), Taiwan in 1999. He completed his Post-doctoral training at Institute of Pharmacology, College of Medicine, NTU from 1999-2001. Currently, he is a Director of Master program of School of Respiratory Therapy at Taipei Medical University (TMU) and also a member of Lung Inflammation Research Group (LIRG) in TMU. His research interests include "Molecular mechanisms of thrombin in chemokine IL-8/CXCL8 expression and lung inflammation; signaling transduction of ADAM17 in pulmonary fibrosis of chronic obstructive asthma (COA) and; pharmacology in respiratory diseases".

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