Regulation of Human Airway Mucus Hypersecretion

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Mucus is an important component of the innate immune system. Mucus hypersecretion by airway epithelium is a major characteristic of a number of respiratory diseases, such as sinusitis, rhinitis and allergy, and so understanding the basic pathogenic mechanisms that drive mucus overproduction is important. Because bacteria interact with host epithelial cells and activate intracellular signaling pathways resulting in selective regulation of specific mucin genes and mucin production, it is important to clarify the mechanism by which major pathogens like Staphylococcus aureus and Pseudomonas aeruginosa increase mucin gene expression and mucus production. In addition, identifying mechanisms that affect down-regulation of such pathways will be important to better understand processes whereby mucus overproduction can be reversed and mucus obstruction averted or overcome, which is the final goal of our mucin research.

We examined the signal transduction pathway by which bacteria induce mucin production and then tried to find molecules that can suppress mucin gene expression and mucin production.

We found that lipopolysaccharide from P. aeruginosa induced extracellular ATP secretion, and exogenous ATP resulted in the induction of MUC5AC gene expression via Gαq-coupled P2Y2 receptors/ PLCβ/Akt/both ERK1/2 and p38 MAPK sequentially. Interestingly, Regulator of G-protein signaling 4 (RGS4) suppressed ATP-induced MUC5AC production by interacting between the Gαq in vitro and in vivo, suggesting that RGS4 may act as a suppressor of ATP-induced activation of the P2Y2 receptor. Furthermore, LPS also increased MUC5AC production, while its gene expression was negatively regulated by RGS4 in vivo. Inhibition of ATP secretion by glybenclamide decreased MUC5AC production dramatically. In conclusion, LPS from P. aeruginosa induces ATP secretion, and then ATP promotes MUC5AC gene expression, with RGS4 attenuating G protein signaling by GTPase activation. These results give additional insights into the molecular mechanism of negative regulation of mucin production and enhance our understanding of mucus hypersecretion during inflammation.