OMICS Group Conferences
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International Congress on
Bacteriology & Infectious Diseases
November 20-22, 2013 DoubleTree by Hilton Baltimore-BWI Airport, MD, USA

FOXA2 inactivation by bacterial pathogens and excessive mucus in chronic airway diseases

Gee W. Lau
University of Illinois at Urbana-Champaign, USA

Airway mucus protects lung epithelial surfaces from inhaled microbial pathogens. However, excessive mucus causes detrimental obstruction of airflow, favoring chronic microbial colonization. Cystic fibrosis (CF) and non-CF bronchiectasis, and chronic obstructive pulmonary disease (COPD) and asthma are airway diseases characterized by abnormal changes of the bronchi with chronic inflammation and infection, goblet cell hyperplasia and metaplasia (GCHM) and mucus hypersecretion. Excessive mucus creates a favorable niche for chronic infection by microbial pathogens. Vicious cycles of pro/anti-inflammatory responses triggered by microbial pathogens progressively damage airways and exacerbate GCHM and mucus hypersecretion. FOXA2 is a major transcriptional repressor of GCHM and mucus biosynthesis. Strikingly, the expression of FOXA2 is depleted in the airways of bronchiectatic and asthmatic patients with GCHM. We examined the mechanism employed by the CF/COPD pathogen *Pseudomonas aeruginosa* and the asthma pathogen *Mycoplasma pneumoniae* to induce GCHM and mucus hypersecretion. Using both primary and immortalized human bronchial epithelial cells as well as mouse models, we found that *P. aeruginosa* secretes a redox-active toxin pyocyanin, which induces STAT6 and EGFR signaling, as well as posttranslational modifications, resulting in the inactivation of FOXA2. Similarly, *M. pneumoniae* induces the expression of airway mucins by activating the STAT3-STAT6 and EGFR signaling pathways to down-regulate FOXA2. Inhibitors of STAT6, STAT3 or EGFR significantly restore the expression of FOXA2 and attenuate the expression of mucins induced by both pathogens. Collectively, these studies demonstrated that *P. aeruginosa* and *M. pneumoniae* induce airway mucus hypersecretion by inhibiting FOXA2 signaling.

Biography

Gee W. Lau completed his Ph.D. at Purdue University, and postdoctoral studies at the Imperial College School of Medicine and Harvard Medical School. Currently, he is an associate Professor of microbiology at the Department of Pathobiology, University of Illinois at Urbana-Champaign. He has published 40 papers in reputed journals in host-pathogen interactions, especially the interplays between pulmonary immunity and bacterial pathogens, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. He also serves as an editorial board member of the journal ISRN Genetics.

geelau@illinois.edu