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Title: FOXO transcription factors regulate innate immune mechanisms in respiratory epithelial cells

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Body: Background: Bacterial pathogens are a leading cause of lung infections and contribute to acute exacerbations in patients with chronic respiratory diseases. The innate immune system of the respiratory tract controls and prevents colonization of the lung with bacterial pathogens. FOXO transcription factors are key regulators of cellular metabolism, proliferation and stress resistance. In this study, our aim was to investigate the role of FOXO transcription factors in innate immune functions of respiratory epithelial cells. Methods: Bronchial epithelial cells were transfected with siRNA specific for FOXO1 and FOXO3 and infected with Haemophilus influenza and Pseudomonas aeruginosa. Expression of inflammatory cytokines and antimicrobial peptides were determined. Epithelial uptake of bacteria was examined. FOXO3 was detected in human bronchial tissue. Results: Infection with bacterial pathogens potently activated FOXO transcription factors in respiratory epithelial cells in vivo and in vitro. Active FOXO was also detectable in bronchial tissue of subjects with different infection-related lung diseases. siRNA mediated knock down of FOXO in epithelial cells resulted in reduced expression of factors of the innate immune system such as antimicrobial peptides and proinflammatory cytokines under basal conditions and upon infection. FOXO deficiency further affected internalization of Haemophilus influenzae in bronchial epithelial cells. TLR3 activated innate immune responses in a FOXO-dependent manner. Conclusion: FOXO transcription factors are involved in the cellular responses to bacterial stimuli and possess a central role in regulating innate immune functions of respiratory epithelial cells.