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W. SKRONSKA-WASEK ET AL.

The antimicrobial peptide S100A8/A9 produced by airway epithelium functions as a potent and direct regulator of macrophage phenotype and function

Wioletta Skronska-Wasek [1,2], Sibel Durlanik[1], Huy Quang Le[2], Victoria Schroeder[2], Kerstin Kitt[1], James Peter Garnett[2] and Stefan Pflanz[1]

[1]Cancer Immunology and Immune Modulation, Boehringer Ingelheim Pharma GmbH and Co KG, Biberach, Germany. [2]Immunology and Respiratory Diseases Research, Boehringer Ingelheim Pharma GmbH and Co KG, Biberach, Germany.

Corresponding author: Wioletta Skronska-Wasek (wioletta.skronska-wasek@boehringer-ingelheim.com)

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Abstract

Background Elevated counts of alveolar macrophages and attenuated phagocytic capacity are associated with chronic obstructive pulmonary disease (COPD). Factors governing macrophage phagocytosis are poorly understood. In this study we aimed to compare the influence of airway epithelial cell secretions from individuals with COPD and without COPD (non-COPD) on macrophage phagocytic activity, and the role of antimicrobial peptides (AMPs).

Methods Supernatants from non-COPD and COPD small airway epithelial cell (SAEC) cultures exposed to non-typeable *Haemophilus influenzae* (NTHi) were applied to human monocyte-derived macrophages (MDMs) to assess their influence on phagocytosis. SAECs were analysed for changes in AMP expression by quantitative reverse transcription PCR, and the influence of select AMPs on macrophage phenotype and function was assessed by flow cytometry and metabolic activity assay.

Results Secretions from the apical and basolateral surface of NTHi-exposed SAECs from non-COPD donors elicited superior phagocytic capacity in MDMs. Moreover, NTHi exposure led to a rapid increase in the expression of a range of AMPs by non-COPD SAECs, but this response was delayed in COPD SAECs. We demonstrate that treatment with AMPs β-defensin 2 and S100 calcium binding protein A8/S100 calcium binding protein A9 (S100A8/A9) improved the phagocytic capacity of MDMs. In-depth analysis of the influence of S100A8/A9 on MDMs revealed a role for this AMP in macrophage phenotype and function. Furthermore, we show that the expression of S100A8 and S100A9 is directly regulated by WNT/β-catenin signalling, a known deregulated pathway in COPD.

Conclusion In conclusion, for the first time, we demonstrate that airway epithelium from patients with COPD has a reduced capacity to support the phagocytic function of macrophages in response to acute NTHi exposure, and we identify the WNT/β-catenin signalling-modulated and epithelium-derived S100A8/A9 as a potent regulator of macrophage phenotype and function.