Endotoxin-induced inflammation in healthy human airways

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Abstract

The aim of this thesis was to investigate the innate immune response in healthy human airways *in vivo* after simulation of a Gram-negative infection.

Intrabronchial exposure to the TLR4 agonist endotoxin was used as a model for the innate mechanisms in the immune response that are caused by cigarette smoke and by natural infection with Gram-negative bacteria. Endotoxin is part of the outer cell wall of these bacteria and is one of many components of cigarette smoke. Healthy volunteers were exposed to endotoxin and phosphate buffered saline in contralateral lung segments during bronchoscopy. Bilateral bronchoalveolar lavages (BAL) were then performed at different time points thereafter. Inflammatory cells and soluble mediators involved in the inflammatory response were analyzed in BAL samples.

The exposure of healthy airways to endotoxin led to a prompt increase in proinflammatory mediators as well as to an influx of inflammatory cells, a process that receded within days. In the first study, the proteolytic homeostasis of the healthy human lung was evaluated, where endotoxin induced a net activity of serine proteases, but not of gelatinases. In the second study, an endotoxin-induced increase of the neutrophil recruiting cytokine IL-17 and the presence and endotoxin-induced increase of IL-17-producing memory T-helper cells of a unique phenotype were shown. In the third study, the presence and endotoxin-induced increase of another cytokine, IL-26, was demonstrated. IL-26 was revealed to be expressed by macrophages and to exert chemotaxis on neutrophils. The fourth study analyzed effects of endotoxin on antimicrobial peptides (AMPs), possible candidates for options for new treatment of infectious diseases. Endotoxin did increase the levels of LL-37, but not those of Calprotectin.

In conclusion, the delicate balance of tissue degrading enzymes and their inhibitors is disrupted by a transient stimulus, resembling the initial phase of an inflammation. It is open to speculation as to whether repeated or continuous stimuli of this kind may contribute to the imbalance in proteolytic homeostasis that is a common denominator for chronic inflammatory lung diseases. It can also be concluded that interleukins that are integrated with the innate immunity are involved in the response to endotoxin in healthy human lungs. The findings on interleukins and AMPs may be used to target new drugs for inflammatory diseases and infections.

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Keywords: LPS, bronchoalveolar lavage, neutrophils, human airways, innate immunity

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Increase in net activity of serine proteinases but not gelatinases after local endotoxin exposure in the peripheral airways of healthy subjects. PLoS One. 2013 Sep 23; 8(9):e75032. doi: 10.1371/journal.pone.0075032. eCollection 2013.

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