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Lung inflammation and infection in cystic fibrosis: new concepts for prevention and treatment

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In cystic fibrosis (CF) a variety of innate immune functions have been reported to be dysregulated[1]. These concern the mucociliary clearance system, cationic antimicrobial (poly) peptides, epithelial cells, neutrophils, macrophages and CFTR itself. The inability of mutated CFTR to effectively secrete chloride from respiratory epithelial cells into the airway surface liquid causes excessive water absorption from the airway surface liquid leading to impaired mucociliary clearance (MCC) in individuals with CF. This in turn facilitates the colonization of the viscous mucus layer on the respiratory epithelium with bacterial pathogens. Viscous secretions may obstruct submucosal gland ducts in CF due to mutated CFTR. Consequently, preformed bacteriolytic enzymes and cationic antimicrobial (poly) peptides (CAMPs) such as β-defensins and cathelicidins, produced by submucosal glands may not be secreted onto the epithelium, resulting in facilitated colonization and infection of the respiratory epithelium with bacterial pathogens. The high viscosity of CF secretions also negatively affects migration of neutrophils. The failure of neutrophils to rapidly encounter the pathogens in the viscous mucus may allow bacterial multiplication and profound changes on the bacterial phenotypes which facilitate chronic infection. In the bronchi, the highly viscous mucus generates a microaerobic milieu which may become anaerobic by a rapid oxygen consumption by pathogens such as *P. aeruginosa*. Consequently, the generation of reactive oxygen species by neutrophils and other cells is abolished and bacterial killing impaired. Epithelial cells use CFTR as a receptor for internalization of *P. aeruginosa* via endocytosis and subsequent removal of bacteria from the airway. Thus, CFTR itself can be regarded as a substantial part of the innate immune system and mutant or missing CFTR has been linked to the initiation of *P. aeruginosa* infection, In addition, an abnormal age-dependent accumulation of ceramide in the lungs of *cftr*-deficient mice and in epithelial cells from CF patients has been detected. As a consequence, the rate of cell death increased in respiratory epithelial cells of uninfected CF mice, resulting in the formation of DNA deposits on the respiratory epithelium, which facilitated bacterial adherence. Ceramide accumulation also provoked a pro-inflammatory status in the respiratory tissue of mice with CF, which preceded bacterial infection: an increased synthesis and release of cytokines and a subsequent, age-dependent, recruitment of macrophages and neutrophils had been observed in lungs of uninfected CF mice. The exaggerated inflammatory response to persistent infection not only facilitates tissue destruction but also induces tissue remodelling, in which a number of proteases, growth factors and other compounds from various cells are involved.

The strategy to administer antibiotics against *P. aeruginosa* at a point in time when the microorganisms have not yet switched from a nonmucoid to a mucoid biofilm-forming variant has been largely successful in the recent decade and continues to increase the life expectancy of CF patients word wide. Data from several studies demonstrate that early treatment of *P. aeruginosa* lung colonization effectively eradicates the pathogen and patients with CF may remain free of *P. aeruginosa* for a mean of 2.4 years before a new epidosde of *P. aeruginosa* colonization occurs. Also promising is the vaccination strategy against *P. aeruginosa*, although it becomes more and more difficult to test a new vaccine in this patient group. Finally, the anti-depressive drug amitriptyline which blockes ceramide accumulation, reduces cell death and normalizes the susceptibility of CF mice to *P. aeruginosa* infection is currently under clinical evaluation in patients

with CF. Unravelling dysregulation of innate immunity in CF may allow developing drugs with the aim to normalise innate immune functions. CF provides not only a fascinating insight into biological mechanisms of various innate immune functions, but also into the interplay of host defense functions and survival strategies of opportunistic bacterial pathogens.

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