200 Prevalence and clinical significance of autoantibodies in 144 adult patients with cystic fibrosis

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Background: The aim of this study was to determine the prevalence of different autoantibodies (aAbs) in adult French cystic fibrosis (CF) patients and to look for a correlation between autoimmunity, patient characteristics and survival.
Methods: The sera of 144 patients were screened for a wide range of Abs. Clinical, biological and bacteriological characteristics and CFTR genotype were recorded and progression of lung disease was examined.
Results: One hundred and thirteen patients (78.5%) displayed one or several aAbs, predominantly IgA anti-Saccharomyces cerevisiae antibodies (ASCA IgA) (43.7%) and anti-neutrophil cytoplasmic antibodies (ANCA) (40%), of which 59% showed bactericidal/permeability-increasing protein (BPI) specificity. The presence of BPI-ANCA was associated with the number of antibiotic courses, low body mass index, P aeruginosa colonisation, presence of resistant P aeruginosa, low FEV1, CF-related liver disease, hypergammaglobulinaemia, male gender and inflammatory syndrome. The presence of ASCA IgA was correlated with male gender and hypergammaglobulinaemia. Forty-one patients presented chronic respiratory failure and/or requested lung transplantation or died during follow-up. These events were more frequent in patients with BPI-ANCA or ASCA IgA.
Conclusion: These findings confirmed the high frequency of aAbs in CF, particularly BPI-ANCA and ASCA IgA, and the link between BPI-ANCA, severity of lung disease and CF prognosis.
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201 CF an Immune Disease?

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CF bronchial infections are accompanied by neutrophil inflammation and elevated IL-8 response. The findings that lungs of CF patients are structurally normal at birth, CF airway epithelia fail to kill bacteria, signs of inflammation are apparent in BAL are suggesting that hyperinflammation is directly related to the lack of the affected gene product, the CFTR protein. However many previous BAL studies classified subjects as "infected" if a certain amount of identified pathogens was exceeded and agents considered to be nonpathogenic, were also associated with increased inflammation. This might explain why inflammation has apparently been documented in the absence of infection.
In 2 recent studies with CF infants without any sign of infection it was found that the BAL profiles for inflammatory parameters was comparable to a control group and that there was no hyperinflammation in CF, suggesting that solely the mechanisms underlying the control of inflammation, as well as responses to infection, may be compromised in CF.
CFBE41o- and its identical stably CFTR corrected counterpart were compared and we found in the corrected cell line that IL-8 and IL-6 secretions were increased after LPS stimulation and that this effect could be specifically inhibited by antibodies and siRNA directed against TLR-4. FACS analysis revealed significantly higher levels of TLR-4 surface expression in corrected cells. In lung sections of healthy controls the TLR-4 expression in the bronchial epithelium was significantly higher compared to CF patients.
We suppose that the loss of CFTR function appears to decrease the innate immune responses in CF, possibly by altering the expression of TLR-4 on epithelial cells. This may contribute to bacterial infection and airway obstruction.
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202 Role of COMMD1 and CSN5 in transcriptional regulation of the *CFTR* gene

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Dysregulation of inflammation pathway observed in CF patient's airways, associated with chronic lung infections, leads to a progressive destruction of pulmonary parenchyma. We have previously identified COMMD1 and CSN5 as new CFTR partners. COMMD1 and CSN5 are involved in multiple cellular processes, including NF-κB and TGFβ pathways. TNFα, IFNγ and TGFβ have been shown to decrease the amount of *CFTR* mRNA. We aimed to study the role of COMMD1 and CSN5 on *CFTR* gene transcription in bronchial epithelial cells, given the three subsequent points:

i. CSN5, also known as Jab 1 (Jun activating binding protein), promotes the production of AP-1 protein, involved in inflammation. Moreover, AP-1 activity is increased in CF cells.
ii. COMMD1 interferes with NF-κB transcriptional activity by destabilizing chromatin/NF-κB interaction and, NF-κB is overexpressed in CF cells.
iii. The *CFTR* gene contains one κB-responsive element and at least four AP-1 binding sites.

We have shown a different COMMD1 and CSN5 nucleocytoplasmic distribution between CF (IB3–1) and non CF cells (S9). 5′ deletion analysis of the *CFTR* promoter was performed using ten different constructs encompassing 4000 bp upstream the transcription start site. Functional assays were performed by luciferase tests in different conditions, over and down-expression of both proteins.
Our results suggest that COMMD1 and CSN5 might be new regulators of *CFTR* transcription and will give clues to CFTR downregulation observed in inflammatory conditions.
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203* Anoxia prolongs the life and functionality of polymorphonuclear leukocytes

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Chronic lung infection with *Pseudomonas aeruginosa* is the most severe complication for patients with cystic fibrosis (CF). This infection is characterized by endobronchial mucoid biofilms surrounded by numerous polymorphonuclear leukocytes (PMNs). The mucoid phenotype offers protection against the PMNs, which are in general assumed to mount an active respiratory burst leading to lung tissue deterioration. Recent evidence for accelerated depletion of molecular oxygen by the respiratory burst of the PMNs in the mucus in infected CF bronchi has inspired our hypothesis that the PMNs are well equipped to survive and perform without oxygen.
To test the hypothesis, normal human PMNs were isolated and incubated for 1 to 4 days in ambient air or in an anaerobic bench before estimating membrane integrety, apoptosis, respiratory burst and migration. Significantly more intact PMNs and less apoptotic PMNs were seen from day 1 in the samples incubated without oxygen. In addition, PMNs incubated without oxygen showed a significantly higher respiratory burst and ability to migrate from day 1.
These results demonstrate that PMNs are well adapted to survive and function without oxygen mitochondrial aerobic respiration and suggests a mechanism that contributes to the dominant accumulation of this particular leukocyte subpopulation in anaerobic compartments such as parts of the mucus in infected CF bronchi.