Decreased respiratory burst in circulating neutrophils after initiation of CFTR modulator therapy in cystic fibrosis patients with chronic lung infections

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Objectives: Chronic lung infections constitute major complications for cystic fibrosis (CF) patients and accelerate loss of lung function. This loss of lung function has been linked to the activity of neutrophils in sputum leading to proteolytic and oxidative lesions. Most patients at the Copenhagen Cystic Fibrosis Centre treated with triple combination modulator (CFTRm) therapy experienced large improvements in lung function. To determine if this improvement may relate to reduced neutrophil activity, we compared the respiratory burst of blood neutrophils before and after initiation of CFTRm therapy.

Methods: Blood samples were collected before and after initiation of treatment from 10 CF patients with chronic lung infection and the respiratory burst of the neutrophils was assessed by flow cytometry according to the fluorescence of aminophenyl fluorescein (APF). Since CFTRm may reduce lung inflammation we investigated the effect of TNF-alpha on the respiratory burst of neutrophils from 5 non-CF persons by chemiluminescence.

Reduced respiratory burst after initiation of treatment

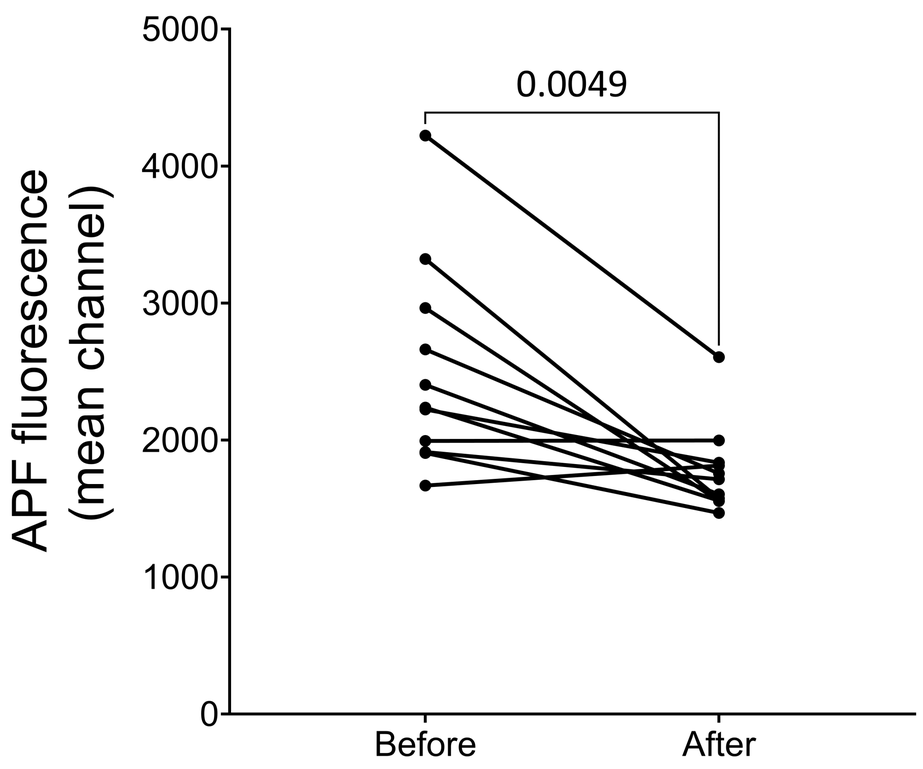

Figure 1. PMA-induced respiratory burst of CF neutrophils before and after initiation of CFTRm therapy.

Priming of the neutrophils' respiratory burst by TNF-α

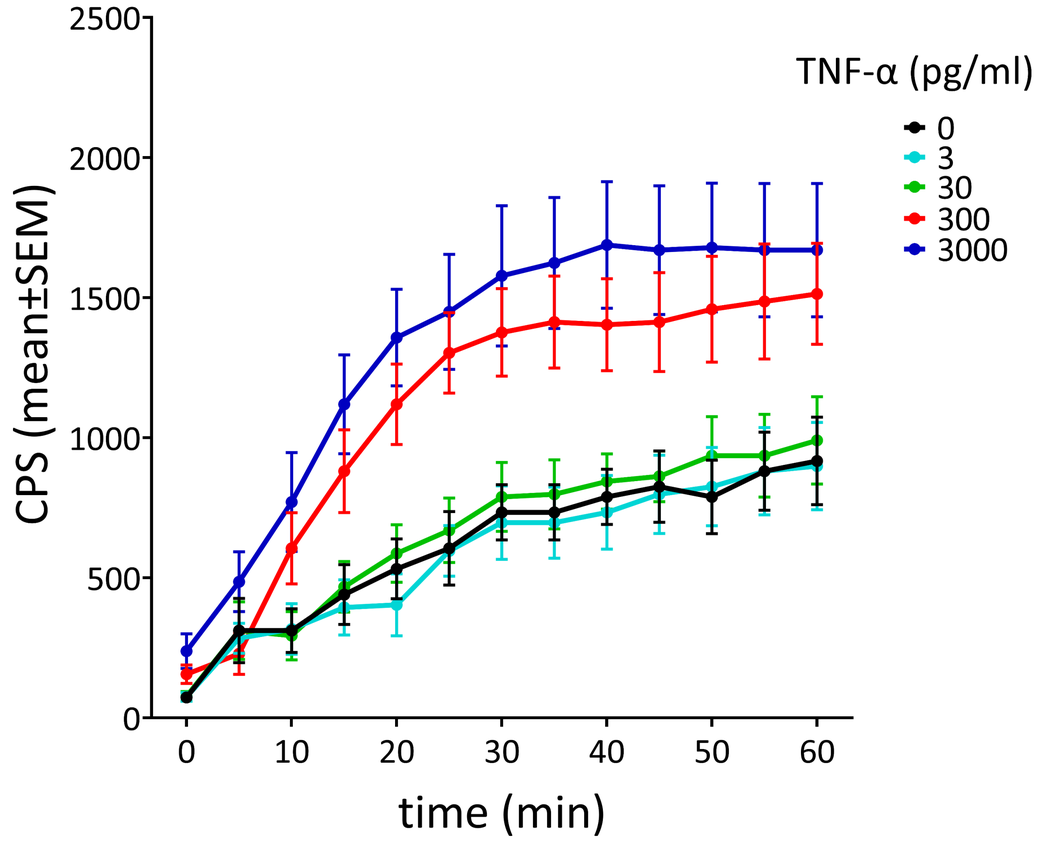

Figure 2. PMA-induced respiratory burst of non-CF neutrophils pretreated with TNF-α.

Results: The intensity of APF fluorescence was significantly lowered by approximately 30% after initiation of treatment ($p<0.01$) indicating a reduction of the respiratory burst in the circulating neutrophils from the CF patients. Addition of TNF-alpha significantly enhanced the respiratory burst of circulating neutrophils from non-CF persons ($p<0.01$) indicating that TNF-alpha may impact the neutrophils' respiratory burst.

Conclusion: Our results demonstrate decreased respiratory burst in circulating neutrophils after initiation of CFTRm therapy in CF patients. Since high levels of the pro-inflammatory cytokine, TNF-alpha, may increase the respiratory burst in neutrophils, our detection of a reduced respiratory burst is suggestive of systemic anti-inflammatory effects of CFTRm therapy, but could also be explained by direct effects of CFTRm on neutrophils.

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