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Title: Endoplasmic reticulum stress in circulating cystic fibrosis neutrophils

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Body: Introduction: Cystic fibrosis (CF) is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. A number of studies have been performed to investigate whether neutrophil dysfunction in CF is primarily as a result of the genetic defect or due to chronic bacterial infection and inflammation. Aim: The aim of this study was to provide support for intrinsic alterations in CF, specifically to determine whether accumulation of CFTR within the endoplasmic reticulum (ER) of circulating neutrophils from patients with CF leads to ER stress responses including the release of ER calcium (Ca^{2+}) stores. This study focused on the ER-resident chaperone, GRP78 and ATF6, a transcription factor that coordinates the unfolded protein response (UPR). Methods: Neutrophils were purified from whole blood and the cytosols were analysed using Western blotting for ER stress markers ATF6 and GRP78. Intracellular Ca^{2+} was determined using a fluorometric assay. Results: Western blots revealed that markers of ER stress, GRP78 and cleaved ATF6, were increased in neutrophil cytosols of patients with CF homozygous for the ΔF508 mutation, when compared to healthy controls (n=8 for both groups). In addition, densitometric analysis of immuno-bands confirmed significant up-regulation of both GRP78 and active ATF6 in CF neutrophils compared to control cells ($p<0.05$). Intracellular Ca^{2+} was increased in the CF neutrophils compared to healthy controls. Conclusions: Our data demonstrates for the first time activation of the UPR in vivo in neutrophils isolated from individuals with CF, which may in part explain the exaggerated inflammatory response of these cells.