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The pathophysiologic mechanisms causing inflammation in cystic fibrosis (CF) remain obscure. The effects of proapoptotic agents on pancreatic and tracheal cell lines expressing wild-type CFTR (PANC-1 and NT-1, respectively) or the homozygous CFTRdeltaF508 mutation (CFPAC-1 and CFT-2, respectively) were assessed. An increased susceptibility to apoptosis was observed in CFPAC-1 and CFT-2 cells. Apoptosis was reduced by treatment with a pan-caspase inhibitor and by incubation at 27 degrees C, allowing recruitment of CFTR deltaF508 at the plasma membrane. Inhibition of CFTR function in wild-type cells induced an increase of apoptosis. Apoptosis in CFPAC-1, but not in CFT-2 cells, was associated with overexpression of the proinflammatory mediators interleukin-6 and interleukin-8. In CF cells, apoptosis was linked to NF-kappaB pathway activation. Conditioned medium from actinomycin D-treated CFPAC-1 cells produced an increase in apoptosis of wild-type cells, suggesting that proinflammatory mediators secreted by mutant cells promote apoptosis. This was confirmed through the induction of apoptosis in wild-type cells by exogenous interleukin-6 and interleukin-8. These results suggest that CFTR deltaF508 mutation, apoptosis, and activation of the NF-kappaB pathway contribute to the self-perpetuating inflammatory cycle, at least in pancreatic cells, and provide evidence that excessive apoptosis may account for the exaggerated proinflammatory response observed in CF patients.

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