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Title: The chemokine decoy PA401 decreases interleukin-8 and chemotactic activity of cystic fibrosis airway samples

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Body: Introduction: The chemokine interleukin-8 (IL-8) is a key mediator of inflammation in the cystic fibrosis (CF) lung. Glycosaminoglycans (GAGs) possess the ability to influence the chemokine profile of the CF lung by binding IL-8 and protecting it from proteolytic degradation. In this study, we examined the effects of PA401, a recombinant glycan-binding IL-8 decoy, on IL-8/GAG complexes. Objectives: As PA401 lacks chemotactic activity yet has increased (x40) glycan binding affinity we investigated the anti-inflammatory effect of PA401 on IL-8 levels and activity within CF lung samples in vitro. Methods: Degradation of IL-8 in CF bronchoalveolar lavage fluid (BALF) after treatment with PA401 was analyzed by ELISA. The in vitro chemotactic activity of neutrophils was evaluated by use of a Boyden chamber-based motility assay. Results: Exposure of CF BALF to increasing concentrations of PA401 (50-1000pg/ml) over a time course of 2-12 hours in vitro, significantly reduced the level of detectable IL-8 ($p<0.05$). Interestingly, PA401 engendered release of IL-8 from GAGs exposing the chemokine susceptible to proteolysis. A 30% decrease in neutrophil chemotactic efficiency towards CF BALF samples incubated with PA401 was also observed ($p<0.05$). Conclusion: The interaction between chemokines and GAGs plays a role in acute inflammation in the CF lung and offers a potential therapeutic target. The IL-8 decoy PA401 disrupts the interaction between GAGs and IL-8, rendering IL-8 susceptible to proteolytic degradation with subsequent decrease in neutrophil chemotaxis in vitro. Clinical application of an IL-8 decoy may serve to decrease the inflammatory burden in the CF lung in vivo.