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SURFACTANT PROTEIN A (SP-A) ASSOCIATES WITH IGG VIA THE FC CHAIN.
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Lung surfactant protein A (SP-A), a member of the collectin family of proteins, aids in the clearance of harmful pathogens from the lung. SP-A is also implicated in the classical pathway leading to activation of the complement cascade. Our lab has shown that SP-A inhibits C1 formation by preventing C1q from associating with C1r and C1s subunits. Specifically, SP-A binds C1q. Recently, we’ve tested the hypothesis that interactions occur between SP-A and the antigen-antibody complex. The classical pathway becomes activated upon C1 binding to an antigen-antibody, which is also known as the immune complex. We now show that SP-A can bind to IgG in a both a calcium and dose-dependent manner, but SP-A (0 to 25 ig/mL) cannot compete with antigen for binding to IgG. However, SP-A appears to bind to the Fc chain of IgG rather than the Fab chain. Since C1q must bind to the Fc site in order for a stable C1-immune complex interaction to occur, this suggests SP-A may sterically inhibit C1q binding to antibody, which in turn inhibits complement activity. The interaction of SP-A with the Fc portion of the other immunoglobulins may have important functional consequences since many immunologic responses, including allergic manifestations, are mediated through IgE binding to Fc receptors on mast cells and basophils. Future studies will address this possibility.

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EARLY TREATMENT WITH A RECOMBINANT FRAGMENT OF HUMAN SURFACTANT PROTEIN D REDUCES THE DEGREE OF EMPHYSEMATOUS CHANGE DEVELOPING IN SP-D KNOCK-OUT MICE
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Surfactant protein D deficient mice show a chronic pulmonary inflammation and progressive alveolar proteinosis, characterised by increased numbers of alveolar macrophages in the alveolar space, alveolar lipoidosis, type II cell proliferation and hyperplasia and the spontaneous development of emphysema. We have previously shown that daily intranasal administrations of recombinant human SP-D to SP-D knock-out mice reduced numbers of alveolar macrophages and partially corrected the alveolar lipoidosis (Clark et al, Journal of Immunology, 2002). The aim of the current study was to establish if the partial correction of these indices affected the development of the emphysema phenotype by carrying out detailed lung morphometric studies on treated and untreated SP-D deficient mice. Methods SP-D knock-out mice, aged 3 weeks, 6 weeks and 9 weeks were treated daily for 5 out of 7 days with 10 microgram of recombinant fragment of human SP-D for 9, 6 and 3 weeks respectively. Mice were sacrificed at age 12 weeks and compared to saline treated control 12 weeks old knock-out mice. Lungs were inflation fixed at 17 cm of water in situ and detailed lung morphology carried out according to recently published methodology (Ochs et al, AJRCCM 2003). Results Consistent with our previously reported findings, replacement therapy with recombinant human SP-D reduced the number of alveolar macrophages accumulating in the SP-D deficient lung. The accumulation of excess surfactant phospholipids was similarly much reduced with very scanty foamy macrophages present. The number and volume of Type II cells was also smaller in the treated groups (n=6, p<0.01). Lung volumes were smaller in the treated mice and the number of alveoli was higher in the treated group, with a smaller mean linear intercept of distal air spaces (n=6, p< 0.01). Conclusion Treatment of SP-D deficient mice with a recombinant fragment of human SP-D for as little as 3 weeks from age 9 weeks significantly improved the degree of emphysema normally developing in SP-D knock-out mice.
ROLE OF SURFACTANT IN BLEOMYCIN-INDUCED PULMONARY FIBROSIS
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Idiopathic pulmonary fibrosis is a severe disease characterized by neutrophil, macrophage and lymphocyte infiltration, proliferation of type II pneumocytes and excessive synthesis of extracellular matrix components including collagens, leading to an irreversible distortion of the lung structure and function. Pulmonary fibrosis is the major adverse effect that limits the use of bleomycin in cancer chemotherapy. The molecular mechanisms involved in the extensive structural disorganization as the disease progresses are not clearly understood. The nature of BLM toxicity and its similarity to other injuries and fibrotic processes involving the lung have made BLM treatment of rats a frequently used model system for studying the pathogenesis of pulmonary fibrosis. Recent studies have shown that many aspects of the inflammatory response are regulated by constituents of pulmonary surfactant. Hence we examined the role of surfactant in the pathogenesis of pulmonary fibrosis. Fischer 344 rats were given a single dose of BLM (4U/kg body weight) by intratracheal instillation. Control rats were treated with normal saline. Control and treated rats were sacrificed at various time points from 1-28 days. At least 6 control and 6 BLM-treated rats were studied for each time point. At the time of harvest rats were anesthetized, blood was collected and bronchoalveolar lavage (BAL) was performed on the left lung. Both the lavaged and unlavaged lungs were excised and frozen at -80°C. BAL was analyzed for total cell count, differential cell count, total protein, phospholipid content, SP-A content, oxidized protein content and proinflammatory cytokine (MCP-1 and MIP-2) content. Tissue from the unlavaged lung was used for SP-A and SP-A mRNA content. Hydroxyproline and collagen contents were analyzed in the lung samples of rats at 14 and 28 days. We also carried out histologic evaluation of the lungs for time points 14 and 28 days. The results showed that at early time points following BLM there were increases in a variety of endpoints indicative of lung inflammation. These included increased lung weight, increased protein content of BAL fluid, and an increase in the number of cells in the BAL, many of which were PMNs. We also found increased levels of SP-A at all time points. SP-A is known to enhance production of many proinflammatory cytokines, including MIP-2 and MCP-1, both of which were elevated after BLM. SP-A can also activate macrophages to produce increased levels of reactive oxidants, which may be reflected in the increases in oxidized protein that we observed following BLM. At later time points there was a reduction in endpoints related to inflammation and a rise in levels of collagen and hydroxyproline, indicating increased lung fibrosis. We also found histologic changes and collagen increases consistent with lung fibrosis at 14 and 28 days. In this study we have shown that BLM treatment results in an increase in the levels of SP-A in the BAL fluid and we speculate that the changes in endpoints related to inflammation and fibrosis are the result of the increased levels of SP-A.