Alteration in expression of the rat mitochondrial ATPase 6 gene during Pneumocystis carinii infection

ABSTRACT

The ATPase 6 gene is over expressed during P. carinii infection, and type II pneumocytes and Clara cells are the cell types responsible for this over-expression.

INTRODUCTION

Background Pneumocystis carinii causes pneumonia in immunocompromised patients with a high morbidity and mortality rate. However, the interaction between this organism and the host cell is not well understood. The target cell for P. carinii is believed to be the type I pneumocyte. After contact with the type I pneumocyte, P. carinii trophozoites anchor themselves to the host cell. It was found that the major surface glycoprotein of P. carinii up-regulates the expression of integrins on the surface of cultured lung cells to facilitate this attachment. P. carinii attachment to type I pneumocytes may also be mediated by laminin, vitronectin, or mannose. Alveolar macrophages interact with P. carinii in the lung as the first line of defense against infection. The major surface glycoprotein of P. carinii has been shown to be a chemotactic factor for macrophages and monocytes in vitro. The interaction of alveolar macrophages with P. carinii is mediated by fibronectin. P. carinii organisms are phagocytized when they bind to mannose receptors on the surface of macrophages. Alveolar macrophages have been shown to release TNF-α, prostaglandin E2, and leukotriene B4 upon interaction with P. carinii. These compounds are potent modulators of pulmonary inflammation and lung injury. These are early and important events in the acute response to infection and clearance of P. carinii organisms from the lung. Although it is not certain whether P. carinii organisms attach to type II pneumocytes, type II pneumocytes do respond to P. carinii infections. Type II pneumocytes maintain the structural integrity of alveoli for gas exchange. They produce alveolar surfactant and replicate and differentiate into type I pneumocytes after lung injury. Type II pneumocytes have been shown to increase the production of surfactant protein-A (SP-A) in patients with P. carinii pneumonia (PcP), and the increase of SP-A correlates with the organism load in the lung. The secretion of phosphatidylcholine from type II cells has been found to be inhibited upon P. carinii infection, leading to a deficiency of phosphatidylglycerol and the loss of surfactant function in patients with PcP. The purpose of this study was to detect alterations in host cell gene expression that occur in response to P. carinii infection. We have compared gene expression patterns in P. carinii-infected and mock-infected cells using mRNA differential display and found that the mitochondrial ATPase 6 gene is over-expressed in response to P. carinii infection in rats. We also found that type II pneumocytes and Clara cells are responsible for over-expression of the ATPase 6 gene in P. carinii-infected rat lung.

CONCLUSION

Conclusions The technique of mRNA differential display was used to detect genes that have an altered expression in Pneumocystis carinii-infected hosts. The nucleotide sequence of one differentially displayed fragment was found to be identical to that of the gene encoding the rat mitochondrial ATPase 6, which is a subunit of the F0F1-ATP synthase complex. Northern blot analysis of total RNA extracted from P.

carinii-infected rat lung versus that from mock-infected rat lung revealed that the ATPase 6 gene is over expressed during P. carinii infection. Cells that expressed the ATPase 6 gene were found lining the distal parts of the respiratory tree and in apical areas of alveoli by in situ hybridization. With a two-color fluorescent in situ hybridization, most cells that expressed the ATPase 6 gene were also found to express the SP-B gene, indicating that type II pneumocytes and Clara cells are the cell types responsible for the over-expression of the ATPase 6 gene in P. carinii infection.