

Pre-B-cell colony-enhancing factor (PBEF) is a novel candidate gene in acute lung injury

SQ Ye¹, B Simon², RB Easley², B McVerry¹, D Adyshev¹, A Verin, RM Tuder³, R Brower, JGN Garcia¹

Department of Medicine¹, Department of Anesthesiology², Department of Pathology³, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Medicine⁴, Medical College of Wisconsin, Milwaukee, WI.

Rationale The pathogenesis of acute lung injury (ALI), a refractory lung disease with unacceptably high mortality (30-50%), is incompletely understood. Dysregulated expressions of several genes such as IL-8, IL-6, soluble IL-2 receptor, macrophage migration inhibitory factor, von Willebrand factor antigen, soluble intercellular adhesion molecule-1, thrombomodulin, plasminogen activator-1, surfactant proteins and protein C have been associated with the poor outcome or increased risk of death in patients with ALI. Identification of more novel biochemical markers may provide unique insights into mechanism of ALI.

Methods The Affymetrix GeneChip System was used as a gene expression-profiling platform in this study. Briefly, total RNAs of lung tissues of canine or mouse model of ALI induced by high tidal volume ventilation plus either saline lavage injury or LPS treatment and BAL of human ALI patients were isolated for microarray studies according to the Affymetrix standard technical manual. The results were validated by RT-PCR. PBEF protein levels in BAL or serum from canines and mice as well as cytokine stimulated HMVEC-L were determined by western blotting. PBEF interacting proteins were detected by a bacterial 2 hybrid assay or deduced by a novel computer software, PathlinX[®].

Results Microarray-based gene expression profiling in lung tissues of canine and murine model of ALI and BAL of human ALI patient revealed the unexpected findings of marked increase in the expression of PBEF, a relatively obscure cytokine (only 15 papers cited in PubMed so far). These results were validated by molecular cloning/characterization of the canine PBEF cDNA (94% identical to human), by RT-PCR, by immunohistochemistry and by the increased PBEF expression in BAL fluid and serum in both canine and murine models and cytokine-stimulated human lung endothelium. PBEF interacts with proteins in inflammatory, oxidative stress and protein degradation pathways.

Conclusion PBEF may be a novel biomarker for ALI.

Supported by NHLBI HopGene Program in Genomics U01 HL 66583, HL58504 and SCCOR HL 073994.