be associated with a lower mortality rate in patients with acute respiratory failure admitted to the ICU. Genotyping was performed as previously reported\(^3,4\) in 96 white patients fulfilling the American European Consensus Committee criteria for ARDS (ARDS group), 88 patients admitted to the ICU for non-ARDS respiratory failure (ICU group), 174 non-ICU patients at risk of ARDS (CABG group), and 1,906 healthy UK men (UK group).

**RESULTS AND DISCUSSIONS**

The frequency of the DD ACE genotype (associated with higher tissue and circulating ACE) was increased in the ARDS group compared to the ICU group (\(p < 0.005\)), CABG group (\(p < 0.005\)), or UK group (\(p < 0.01\)). D allele frequency was also increased in the ARDS group (\(p < 0.0005\) vs CABG group/ICU group, and \(p < 0.005\) vs UK group) and was significantly associated with mortality (Fig 1; \(p < 0.02\)). The strength of this association suggests a major role for renin-angiotensin system in the development and progression of this syndrome.

In relation to IL-6 genotypes, there was no difference in genotype or allele frequencies between the ARDS, ICU, and UK (control male United Kingdom population) groups (C allele frequency of 0.4 for both). However, the C allele and CC genotype frequencies were significantly reduced in both the ARDS group and ICU group nonsurvivors compared to survivors (\(p = 0.023\) and \(p = 0.035\) respectively for both groups). Serum IL-6 levels within 24 h of admission to the ICU were also significantly lower in survivors (median, 17.8 pg/mL; range, 10 to 610 pg/mL) compared to nonsurvivors (median, 1,067 pg/mL; range, 5 to 2,071 pg/mL; \(p < 0.001\)) and correlated with IL-6 genotype (\(p < 0.001\)). These data suggests that the enhanced IL-6 response observed in nonsurvivors of critical illness is, at least in part, genetically determined, and that the C allele is an important prognostic factor in the critically ill.

In conclusion, we provide the first report of genetic factors associated with the onset and severity of ARDS. Confirmation of these results in other ICU populations and the identification of additional polymorphisms could aid both our understanding of pathogenic mechanisms in ARDS, the identification of susceptible individuals, and the targeting of therapies.

**REFERENCES**


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Microarray Analysis Indicates That Pulmonary Edema Fluid From Patients With Acute Lung Injury Mediates Inflammation, Mitogen Gene Expression, and Fibroblast Proliferation Through Bioactive Interleukin-1*

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**Abbreviations:** ALI = acute lung injury; IL = interleukin.

Although the fibroproliferative response to lung injury occurs with a high frequency in patients with acute lung injury (ALI), the mechanisms of this response are largely unknown. This study was undertaken...
to identify alveolar mitogenic factors and to determine the fibroblast gene response profile to pulmonary edema fluid collected early in the course of clinical ALI. Pulmonary edema fluid obtained from ALI patients (as defined by the American-European Consensus Committee) within 4 h of intubation has a direct mitogenic effect on human lung fibroblasts that was 50% greater than that from well-characterized control patients with hydrostatic pulmonary edema. Conditioned media studies revealed that fibroblasts also produce additional soluble mitogenic factors that act in an autocrine manner to stimulate their own proliferation in response to ALI edema fluid. In order to identify the mitogens and inflammation-modulating factors produced in fibroblasts in response to ALI edema fluid, we performed complementary DNA microarray analysis on RNA harvested from human lung fibroblasts that had been exposed either to ALI or hydrostatic pulmonary edema fluids. This analysis revealed that ALI edema fluid induces fibroblast expression of at least 15 inflammation, adhesion, and proliferation-modulating genes at greater than twofold levels in fibroblasts compared with that seen in hydrostatic edema-exposed cells. Interestingly, many of these genes are interleukin-1 (IL)-1-responsive. IL-1 antigen levels were therefore measured and found to be ninefold higher (587 ± 690 vs 71 ± 76 pg/mL; p = 0.009 [Mann-Whitney test]) in edema fluid from patients with ALI (n = 19) compared with that from hydrostatic control subjects (n = 17). Furthermore, IL-1 receptor antagonist abrogates both ALI edema fluid-induced fibroblast proliferation by 30% as well as ALI edema fluid-induced gene expression of individual genes by 50 to 90%, as confirmed by Northern blot analysis. For example, both ALI edema fluid induction of IL-6 messenger RNA (induced 17-fold) and protein (induced fourfold) were abrogated > 90% by IL-1 receptor antagonist in a dose-dependent and specific manner. These novel findings establish that soluble alveolar IL-1 bioactivity is a critical initiator of the early alveolar fibroproliferative response. The spectrum of inflammatory, mitogenic, and adhesion-related genes induced by ALI edema fluid further indicates that fibroblasts are important sources of paracrine and autocrine mediators that are capable of altering the course of ALI.

**Acute Lung Injury**

**Functional Genomics and Genetic Susceptibility**

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Initiated by numerous factors, acute lung injury is marked by epithelial and endothelial cell perturbation and inflammatory cell influx that leads to surfactant disruption, pulmonary edema, and atelectasis. This syndrome has been associated with a myriad of mediators including cytokines, oxidants, and growth factors. To better understand gene-environmental interactions controlling this complex process, the sensitivity of inbred mouse strains was investigated following acute lung injury that was induced by fine nickel sulfate aerosol. Measuring survival time, protein and neutrophil concentrations in BAL fluid, lung wet-to-dry weight ratio, and histology, we found that these responses varied between inbred mouse strains and that susceptibility is heritable. To assess the progression of acute lung injury, the temporal expression of genes and expressed sequence tags was assessed by complementary DNA microarray analysis. Enhanced expression was noted in genes that were associated with oxidative stress, antiprotease function, and extracellular matrix repair. In contrast, expression levels of surfactant proteins (SPs) and Clara cell secretory protein (ie, transcripts that are constitutively expressed in the lung) decreased markedly. Genome-wide analysis was performed with offspring derived from a sensitive and resistant strain (C57BL/6xA F1, backcrossed with susceptible A strain). Significant linkage was identified for a locus on chromosome 6 (proposed as Aliq4), a region that we had identified previously following ozone-induced acute lung injury. Two suggestive linkages were identified on chromosomes 1 and 12. Using haplotype analysis to estimate the combined effect of these regions (along with putative