molecular basis for the toxicity and exacerbations in susceptible populations to environmental exposures, we are developing a gene expression database for a rat cardiopulmonary disease model exposed to air pollutants. The spontaneously hypertensive (SH) rat with underlying cardiovascular and pulmonary disease risk is being utilized toward these efforts. SH rats with polygenic traits toward hypertension exhibit similar heritable risk factors that are found in patients with COPD. We have shown that SH rats are more susceptible to lung injury/inflammation, and oxidative stress from exposure to combustion source particles, and from experimental induction of pulmonary disease compared to healthy normotensive Wistar rats. SH rats also elicited an inflammatory response to ETS exposure, which is less remarkable in other conventional rat strains used in laboratory studies. To understand the molecular basis for the inflammatory response, we screened for a pulmonary gene expression profile in SH rats exposed to ETS. Male SH rats (12 weeks old) were exposed either to filtered air or ETS at 90 mg/m³ for 6 h/d for 2 consecutive days; on the third day, total RNA was isolated from right lung lobes. Pulmonary gene expression was assayed by hybridizing 32P-labeled complementary DNA generated from total RNA to Atlas Rat complementary DNA expression array filter containing 588 genes (Clontech; Palo Alto, CA). Gene expression profile data indicated strong hybridization signals for 40 genes, including N-myc, p53, transforming growth factor-β, p21, bax-α and cytokine macrophage inflammatory protein-2. Pairwise comparison indicated ETS exposure-associated differential expression in 16 genes: increased expression of CYP1A1, calcium pump, Rhogap, p122, and decreased expression of bile salt-activated lipase precursor, a fatty acid binding protein and fatty acid amide hydrolase. ETS induced a twofold to threefold increase in macrophage inflammatory protein-2 expression, suggesting lung injury and inflammation. Overexpression of matrix metalloproteinase-7 suggests a possible release of proteases from ETS-induced infiltration of neutrophils into the airways, consistent with our earlier observations. Increased expression of p27(Kip1), caspase-1, and Stat3 observed in the present study further supports apoptosis of infiltrating neutrophils in the lungs following exposure to ETS. Efforts are underway to explore whether long-term ETS exposure of SH rats will lead to a chronic disease state. A comprehensive expression database indicating ETS-induced changes in susceptible animal models will provide identification and the role of risk factors in understanding health effects of ETS and other environmental pollutant-induced cardiopulmonary disease.

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**Interleukin-18 Expression in Cystic Fibrosis Lungs**

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(Abbreviations: CF = cystic fibrosis; IFN = interferon; IL = interleukin)

A primary dysregulation of pulmonary inflammation has been proposed as a mechanism leading to airways disease in patients with cystic fibrosis (CF). Proinflammatory cytokines, such as tumor necrosis factor-α and interleukin (IL)-8, are elevated in the BAL fluid and sputum of CF patients. Although only a few reports have examined T-helper 1 vs T-helper 2 cytokine expression in CF patients, they suggest a relative defect in T-helper 1 cytokine response. For example, peripheral blood lymphocytes from CF patients produce significantly lower levels of interferon (IFN)-γ compared to lymphocytes from a control group when stimulated in vitro with anti-CD3. Furthermore, IFN-γ has been shown to inhibit the production of IL-8 and other proinflammatory cytokines. IL-18, a cytokine constitutively produced by macrophages and epithelial cells, induces IFN-γ in T cells. We undertook a study to examine the expression of IL-18 in children with CF. IL-18 levels were measured in the BAL fluid of 17 CF patients (median age, 12 years; age range, 4 months to 25 years) and compared to the levels observed in a control population comprised of 11 subjects with various pathologic conditions. Of the 17 CF subjects, only 3 subjects had detectable IL-18 levels (median, 78 pg/mL; mean, 118 pg/mL) and levels in the non-CF control subjects compared to the control group. The IL-1β levels were significantly elevated in the same BAL fluids of CF patients compared to the control group. The IL-1β levels were 124 ± 37 pg/mL in the CF patients and 11 ± 1 pg/mL in the non-CF control subjects (p < 0.001); the IL-8 levels were 645 ± 149 pg/mL in the CF group and 167 ± 101 pg/mL in the non-CF control subjects (p < 0.01). The addition of protease inhibitors to the BAL fluid at the time of collection did

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not alter IL-18 immunoreactivity, suggesting that neutrophil-derived proteases did not degrade IL-18. In contrast, preliminary results from immunohistochemistry staining of CF lungs for IL-18 revealed abundant expression of IL-18 in the epithelial cells and macrophages compared to lungs from normal control subjects. Ongoing experiments suggest that the BAL of the majority of CF patients contains a factor—not present in the BAL of non-CF patients—that interferes with IL-18 detection. In fact, recovery of exogenous recombinant IL-18 from CF BAL was strongly inhibited compared to non-CF BAL. The presence of this factor would solve the apparent contradiction between reduced levels of IL-18 in the BAL and abundant IL-18 tissue expression in CF patients.

REFERENCES

Intracellular Adhesion Molecule Gly241Arg Polymorphism Has No Impact on ARDS or Septic Shock in Community-Acquired Pneumonia*

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The clinical presentation and outcome following inflammatory stimuli are determined in part by the type and degree of the stimulus as well as host factors. We have previously demonstrated associations between genetic polymorphisms in the regulatory regions of tumor necrosis factor-α with both the severity of community-acquired pneumonia (CAP) and the type of clinical presentation. A recent polymorphism has been described in the gene coding for intracellular adhesion molecule (ICAM) type 1, which alters a glycine at position 241 to an arginine. This polymorphism is associated with polymyalgia rheumatica and giant-cell arteritis, common inflammatory diseases involving the synovium and extracranial branches of the aorta. Both of these disorders have elevated levels of ICAM-1, and it is hypothesized that the G241R mutation might allow for more effective binding of ICAM-1 to Mac-1, thereby enhancing the inflammatory response. We hypothesized that this mutation may be involved in some of the complications of CAP in adults.

A prospective cohort study of 289 adults with CAP was performed. Genotyping of the ICAM-1 G241R site was done using allele-specific polymerase chain reaction. Outcome measures included mortality, septic shock (SS), ARDS, and respiratory failure (RF). Heterozygotes at the G241R site demonstrated a frequency of 8.3% in the entire study group; no RR homozygotes were detected. The frequency of the heterozygotes in patients with SS (6.7%) and RF (5.7%) was not different from patients without these complications of CAP. Ten patients in the cohort had ARDS, and 22 patients died; all had homozygotes for the GG phenotype. We conclude that unlike the associations we have reported between tumor necrosis

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