that the Arg19 allele, or other polymorphisms of the promoter of the β2-AR gene that are in linkage disequilibrium, may affect the ability of dexamethasone to upregulate β2-AR expression in HASM cells. In addition, our results suggest that β2-AR genotype may be predictive of corticosteroid responsiveness in individuals with asthma.

Reference


The Genetics of Innate Immunity in the Lung*

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Abbreviation: RI = recombinant inbred

Lipopolysaccharide elicits a vigorous inflammatory response and has been linked to the progression of asthma and other forms of airway disease. An improved understanding of the innate immune response to lipopolysaccharide should lead to novel therapies to treat these diseases. Towards this end, we challenged 32 recombinant inbred (RI) strains of (C57BL/6J X DBA/2J) [BXD] mice with aerosolized lipopolysaccharide and compared their biological responses by assaying concentrations of tumor necrosis factor-α and polymorphonuclear cells in the lavage fluid. The biological responses of these RI strains ranged from less than the low-responder parental strain C57BL/6J to higher than the high-responder parental strain DBA/2J. One RI strain was essentially unresponsive to lipopolysaccharide. Phenotypic analysis of F2 offspring from this unresponsive strain suggested these mice have a recessive mutation in a single, unidentified gene.

Spotted complementary DNA microarray analysis was performed on lungs of six selected strains, including the two parental strains and the unresponsive strain. This analysis revealed approximately 50 genes that were consistently induced at least twofold by lipopolysaccharide in the responsive strains. Some, but not all, of these genes have been previously associated with the biological response to lipopolysaccharide. Genes not previously linked to the lipopolysaccharide response might represent novel molecular targets for therapeutic intervention. Most of the genes up-regulated in the responsive strains were unchanged in the unresponsive strain; however, some genes in the latter were also significantly up-regulated, providing clues to the nature of the recessive mutation.

In a parallel study, a quantitative trait locus analysis was performed by relating lipopolysaccharide responses of BXD RI mice to their parental strain DNA distribution pattern using the Jackson Laboratories’ Web site (http://www.informatics.jax.org/searches/riset_form.shtml). Quantitative trait locus analyses of each BXD strain revealed suggestive loci that correlate with the biological response to inhaled lipopolysaccharide. Interestingly, some of these loci contain genes identified in the microarray analysis. These genes represent particularly strong candidates for participants in the innate immune response in the lung.

Macrophage Inflammatory Protein-2 Levels Are Associated With Changes in Serum Leptin Concentrations Following Ozone-Induced Airway Inflammation*

Richard A. Johnston, PhD; Igor N. Schwartzman, BA; and Stephanie A. Shore, PhD

Abbreviations: IL = interleukin; MIP = macrophage inflammatory protein

A positive correlation between obesity and the risk of acquiring asthma has been suggested by epidemiologic studies, but the mechanism underlying this relationship has not been established. The levels of leptin, a proinflammatory, anti-inflammatory cytokine, are increased in the serum of obese individuals; therefore, we hypothesized that obesity promotes the development of asthma through leptin-induced augmentation of airway inflammation. The
Increased Expression of Interleukin-9 Messenger RNA After Segmental Allergen Challenge in Allergic Asthmatics*

Veit J. Erpenbeck, MD; Jens M. Hohlfeld, MD; Marc Discher; Harald Krentel; Andreas Hagenberg; Armin Braun, PhD; and Norbert Krug, MD

(CHEST 2003; 123:370S-371S)

Abbreviations: IL = interleukin; Th2 = T-helper type 2

Inflammation in allergic asthma is mediated by T-helper type 2 (Th2) cytokines. The expression of these cytokines is dependent on specific and nonspecific transcription factors that bind to regulatory sequences in the promoter. GATA-3 is a Th2-specific transcription factor that belongs to the zinc finger family and binds to the interleukin (IL)-5 promoter. It has also binding sites around the IL-4/IL-13 locus. Another Th2 specific tran-

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The purpose of this study was to test this hypothesis by experimentally manipulating endogenous serum leptin levels and assessing their effects on markers of ozone-induced airway inflammation. Serum leptin was increased by feeding weaning C57BL/6J mice chow consisting of either 10 kilocalories or 45 kilocalories percentage fat for 20 weeks and was decreased by fasting mice for 18 h. Mice were subsequently exposed to 2 ppm ozone or filtered air for 3 h. Four hours later, blood was collected for assay of serum leptin and BAL was performed. Serum leptin increased from 6.7 ± 2.3 ng/mL in chow-fed mice to 12.5 ± 2.9 ng/mL and 22.9 ± 3.7 ng/mL (p < 0.005) in mice fed diets of 10% fat and 45% fat, respectively. Compared to air-exposed mice, ozone exposure caused an elevation in BAL protein, interleukin (IL)-6, and macrophage inflammatory protein (MIP)-2 in all three groups of mice. There was no significant effect of diet on BAL protein and IL-6, but MIP-2 levels were significantly higher in mice fed 10% fat (24.9 ± 3.9) or 45% fat (26.4 ± 3.2) than in chow-fed mice (7.5 ± 2.0 pg/mL) [p < 0.001]. Fasting decreased serum leptin from 14.4 ± 2.7 to 6.7 ± 2.2 ng/mL (p < 0.05). There was no significant effect of fasting on ozone-induced increases in BAL protein or IL-6, but fasting reduced BAL MIP-2 from 25.3 ± 8.3 to 6.7 ± 2.1 ng/mL (p < 0.05). The results of this study indicate that serum leptin modulates the levels of the chemokine MIP-2 following acute ozone exposure and suggest that the proinflammatory effects of leptin may contribute to the development of asthma in the obese.

Increased Messenger RNA Expression of c-maf and GATA-3 After Segmental Allergen Challenge in Allergic Asthmatics*

Veit J. Erpenbeck, MD; Jens M. Hohlfeld, MD; Marc Discher; Harald Krentel; Andreas Hagenberg; Armin Braun, PhD; and Norbert Krug, MD

(CHEST 2003; 123:370S-371S)

Abbreviations: IL = interleukin; Th2 = T-helper type 2

Expression of IL-9 messenger RNA after segmental allergen provocation in asthmatics (p < 0.001). This difference did not occur after saline solution provocation or after allergen provocation of healthy control subjects. The increase of IL-9 messenger RNA expression after allergen provocation in asthmatics points to the importance of this cytokine for the pathophysiologic changes in allergic diseases.

Incubation of the cell cultures with 2 ppb ozone for 3 h caused an elevation in BAL protein, interleukin (IL)-6, and macrophage inflammatory protein (MIP)-2 in all three groups of mice. There was no significant effect of diet on BAL protein and IL-6, but MIP-2 levels were significantly higher in mice fed 10% fat (24.9 ± 3.9) or 45% fat (26.4 ± 3.2) than in chow-fed mice (7.5 ± 2.0 pg/mL) [p < 0.001]. Fasting decreased serum leptin from 14.4 ± 2.7 to 6.7 ± 2.2 ng/mL (p < 0.05). There was no significant effect of fasting on ozone-induced increases in BAL protein or IL-6, but fasting reduced BAL MIP-2 from 25.3 ± 8.3 to 6.7 ± 2.1 ng/mL (p < 0.05). The results of this study indicate that serum leptin modulates the levels of the chemokine MIP-2 following acute ozone exposure and suggest that the proinflammatory effects of leptin may contribute to the development of asthma in the obese.

The expression of these cytokines is dependent on specific and nonspecific transcription factors that bind to regulatory sequences in the promoter. GATA-3 is a Th2-specific transcription factor that belongs to the zinc finger family and binds to the interleukin (IL)-5 promoter. It has also binding sites around the IL-4/IL-13 locus. Another Th2 specific tran-

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