1725 THE ROLE OF TH2 CYTOKINES IN THE PATHOGENESIS OF ALLERGIC ASTHMA.

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Marked increases in the incidence, morbidity and mortality of allergic asthma have been reported over the last two decades, underscoring the need for a better understanding of the etiology of this disease. As a primary regulator of the inflammatory cascade, CD4+ T-lymphocytes have been implicated in the pathogenesis of this disease. Functional subsets of CD4+ T cells have been distinguished at both clonal and population levels by the unique profiles of cytokines that they produce. The differential presence of these cytokine phenotypes in a variety of allergic and infectious diseases of both mice and humans has provided both descriptive power and theoretical insight into disease pathogenesis. Th1 cells produce interleukin-2, TNF-β , and interferon gamma (IFN-γ), and are critical in the development of cell-mediated immunity. Th2 cells on the other hand produce IL-4, IL-5, IL-13, IL-6, and IL-10 and are important in humoral immune responses. A possible immunopathogenic role for the Th2 cells in asthma has been based on the role that these cytokines play in IgE synthesis and eosinophil regulation. In particular, IL-4 may be of critical importance in allergic inflammatory processes, as it is required for the differentiation an expansion of Th2 lymphocytes and inhibition of the development of Th1 lymphocytes, while both IL-4 and IL-13 regulate IgE syntheses. IL-5 is considered the primary regulator of eosinophil function. Experimental support for this hypothesis is provided by the fact that unique cytokine patterns (i.e. Th2) are expressed in T cells from asthmatic patients. Although considerable inferential evidence supports a role for these cytokines in allergic reactions, the exact mechanisms by which they induce the inflammatory and functional changes associated with allergic asthma are currently debated. Here we will discuss the data derived from both human and experimental animal studies (transgenic and knock-out) which have contributed to our current understanding of the mechanisms leading to the aberrant production of Th2 cytokines in allergic individuals and the mechanisms by which these cytokines induce allergic diseases.

1726 IL-6-TYPE CYTOKINES IN AIRWAYS DISEASE.

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The IL-6-type cytokine family includes IL-6, IL-11, LIF, oncostatin M and cardiotropin-1. IL-11 was initially described as an IL-6-like bioactivity and shown to regulate thrombopoiesis and hematologic recovery. Studies from our laboratory have demonstrated that: (1) IL-11 is produced by a variety of lung epithelial cells, fibroblasts and smooth muscle cells; (2) a variety of stimuli induce IL-11 elaboration by lung stromal cells including TGF-b1, respiratory syncytial virus, rhinovirus and parainfluenza virus type III and (3) TGF-b1 stimulation of stromal cell IL-11 elaboration is mediated, at least partly, via an AP-1-dependent transcriptional mechanism. To begin to address the effector functions of IL-11 in the lung, IL-11 was targeted to the murine lung using the Clara cell 10 kDa (CC10) promoter. These studies demonstrated that the prolonged overexpression of IL-11 caused: (a) enlarged alveoli; (b) peribronchiolar nodules composed of B cells, T cells and rare macrophages; (c) airway remodeling with subepithelial fibrosis and myocyte and myofibroblast hyperplasia. To determine which features of the CC10-IL-11 overexpression mice were development-dependent versus development-independent, an inducible lung-specific airway targeting system using the tetracycline transactivator was produced. When employed with IL-11, the following phenotypes were obtained: (a) short period of IL-11 expression during adulthood Ð no phenotype; (b) expression in utero-14 days of age Ð enlarged alveoli only; (c) expression in utero through 3 months of age Ð phenotype identical to CC10-IL-11 animals. These studies demonstrate that IL-11 is a stromal cell-derived cytokine which can cause development-dependent alveolar enlargement and development-independent peribronchiolar nodules and airway remodeling.

1727 EXPRESSION OF PDGF AND TFGβ1 AT SITES OF LUNG INJURY.

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Inhaled inorganic particles such as silica and asbestos damage the alveolar epithelium leading to the development of interstitial scarring. There is increasing evidence that certain peptide growth factors play a role in the fibroproliferative response that is the hallmark of the fibrogenic process. Thus, we have been studying expression of growth factors that could mediate disease development. Here, we present recent findings on two factors in rats and mice: platelet-derived growth factor (PDGF), A and B isoforms, and transforming growth factor beta1 (TGFβ1). PDGF is the most potent mecenchymal cell mitogen and TGFβ is a powerful inducer of extracellular matrix components. We have shown that during the five hrs. of a single exposure to chrysotile asbestos, both PDGF A and B as well as TFGβ 1 genes and cognate proteins were upregulated at sites of alveolar injury. In situ hybridization (ISH) and immunohistochemistry (IHC) showed that alveolar epithelial cells, interstitial fibroblasts and lung macrophages expressed the protein for at least two weeks post-exposure. Most interesting was our finding that mice with the receptors "knocked out" for tumor necrosis factor alpha (TNFα) were protected from the fibrogenic effects of inhaled asbestos. Since both PDGF and TGFβ1 expression was reduced in these mice, we postulate that TNFα acts as a key factor in controlling production of other molecules that mediate the fibroproliferative response to lung injury. (Supported by NIH Grants #ES06766 and HL60532.)

1728 CHEMICAL-INDUCED ACTIVATION OF NUCLEAR TRANSCRIPTION FACTORS AND THEIR REGULATION OF CYTOKINE SECRETION.

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Non-immune cells from a variety of organs, including the liver, lung and skin, when targeted by toxic agents, secrete pro-inflammatory cytokines and chemokines which participate in pathological as well as repair processes. In particular, tumor necrosis factor alpha (TNFα) and certain members of the neutrophil chemoattractant family of chemokines (CXC), including interleukin-8, play major roles in these responses. This presentation will describe several organ model systems for toxicity including asbestor-induced lung disease, arsenic-induced skin toxicity and heavy metal-medicated hepatotoxicity which demonstrate cytokine participation. In addition to describing the nature of these responses, the molecular events responsible will be detailed. A common pathway responsible for cytokine induction in all of these systems involves chemical-medicated, cellular oxidative stress, which, in turn, activates nuclear transcription factors, such as NF-kB, NF-IL-6 and AP-1. Unraveling the complex mechanism associated with these events may provide novel opportunities for intervention.

1729 CHARACTERIZATION OF THE METABOLIC CAPACITY OF SYRIAN HAMSTER EMBRYO (SHE) CELLS.

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Syrian hamster embryo (SHE) cells are used in the SHE cell transformation assay to predict the carcinogenic potential of chemicals. Unlike other in vitro genetic toxicity assays, the SHE assay efficiently detects carcinogens that act via non-genotoxic mechanisms. In addition, procarcinogens that require metabolic activation to their carcinogenic form are detected by the assay even in the absence of an exogenous metabolic activation system, suggesting that SHE cells possess the ability to metabolize xenobiotics. However, while many of the molecular features of SHE cells have been well characterized, very little is known about the metabolic capacity of these cells. Since cytochromes P450 are the enzyme family primarily responsible for xenobiotic metabolism and procarcinogen activation, the goal of the present work was to characterize cytochrome P450 protein expression in SHE cells. SHE cells derived from several different Syrian hamster embryo isolates were cultured, harvested, sonicated, and microsomes isolated by differential centrifugation. Western blotting with enhanced chemiluminescent detection was used to evaluate SHE cell microsomes for the presence of a battery of cytochrome P450 (CYP) isozymes. The most abundant cytochrome P450

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