The featured Research Track from COPD7usa was titled: Genes, Inflammatory Markers & Autoimmunity. The session was Co-Moderated by: Gerard Turino, MD & Robert Senior, MD and featured expert speakers including: Tracy Adair-Kirk, PhD, Steven Shapiro, MD & Edwin Silverman, MD, PhD.

Dr. Steven D. Shapiro M.D. Professor of Medicine and Chief Medical and Scientific Officer, UPMC focused his remarks on new developments in the understanding of chronic Obstructive Pulmonary Disease (COPD) since 2003.

He stated that there is strong evidence, both clinically and mechanistically, that COPD is a chronic inflammatory disease. More recent studies at the cellular level supported this view. The elastase-antielastase hypothesis, which had its origins in the development of emphysema and COPD in individuals born with severe deficiency of alpha-1 antitrypsin, the major inhibitor of neutrophil elastase, was still a viable concept but had to be integrated into newer data on factors causing chronic inflammation.

In COPD, oxidants from cigarette smoke, or inflammatory cells themselves, promote transcription of nuclear factor-KB (NFkB) and inactivation of histone decetylase. This results in intermediate mechanisms which cause unwinding of DNA and chemokines, which result in recruitment of neutrophils and macrophages to the lung. Neutrophils and Macrophages contain injurious enzymes of neutrophil elastase and metalloproteases, which cause parenchymal lung injury resulting in COPD. Oxidative stress may also induce cell death (apoptosis) by release of ceremide, a second messenger lipid.

A major characteristic of COPD is that the inciting cause of COPD and the inflamed lung is exposure to tobacco smoke. However, smoking cessation does not result in resolution of lung tissue inflammation, which persists. Mechanisms responsible for persistent inflammation include bacterial colonization, latent viral infections, residual matrix tissue fragments. An added mechanism which is gaining increasing support is autoimmunity. Exposure to cigarette smoke may activate dendritic cells, which induce adaptive immune responses involving T-helper cells, CD4+T-cells, CD8 cytotoxicity and B-cell responses. Dendritic cells are specialized antigen-presenting cells that link innate and adaptive immune responses.

Matrix fragments resulting from enzymatic degradation of tissue constituents such as elastin and collagen may become antigens perpetuating immune responses and the lung inflammatory state. Other factors which may be playing a role in COPD are senescence of tissue from the aging process.

An especially interesting observation in mouse lung cancer models is evidence that neutrophil elastase promotes lung tumor growth by gaining access to the endosomal compartment within tumor cells, where it degrades the insulin receptor substrate (IRSI).

It is to be noted that co-morbidities in patients with COPD may result from the persistent inflammation. These include cardiovascular disease, osteoporosis, lung CA and depression.

A hope in the development of new therapies moving forward is that they will be better individualized to the specific patient on the basis of their genomic phenotypes. Also to use advances in genomics and computational science to revolutionize the way we understand disease and improve outcomes and decrease cost.

Edwin K. Silverman, MD, PhD of the Channing Laboratory and Brigham and Women’s Hospital in Boston, Massachusetts focused on the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease.
Dr. Silverman explained that although cigarette smoking is a major environmental risk factor for many people who develop COPD, the development and severity of COPD vary widely among smokers. COPD clusters in families, and genetic factors likely cause this familial clustering. Alpha-1 antitrypsin deficiency is a proven genetic risk factor for a small percentage of COPD subjects, but multiple other rare and common inherited influences on COPD risk likely exist.

Genetic studies have been transformed within the past five years by the development of genome-wide association studies, which assess the relationship of hundreds of thousands of common genetic markers across the genome to complex diseases like COPD. COPD genome-wide association studies have convincingly identified several locations within our genetic code that influence COPD susceptibility. These locations include a region near the hedgehog interacting protein (HHIP) gene, which is an important regulator of lung development; the FAM13A gene, a gene which is of currently unknown function; and a cluster of genes on chromosome 15 which include an iron binding gene (IREB2) as well as some genes that encode proteins that bind to nicotine. Further work to identify the key inherited variations within these regions is ongoing. The identification of such inherited risk factors for COPD could lead to improved understanding of the biological mechanisms which lead to COPD and to new pathways for COPD treatment.

Another important area of investigation in COPD genetics relates to understanding the heterogeneity of COPD. Imaging with chest CT scans can provide valuable measurements of emphysema and airway disease. Large ongoing studies like COPDGene and ECLIPSE are using chest CT analysis combined with genetic studies to generate new insights into COPD.

Dr. Adiar-Kirk explained that the extracellular matrix (ECM) is a complex mixture of proteins, proteoglycans, and glycosaminoglycans. Classically, the ECM has been viewed as a supporting structure for stabilizing the location of cells in tissues and for preserving the tissue architecture. This concept has changed dramatically over the past few decades with discoveries that the ECM has signaling functions that profoundly influence the viability and functions of structural cells. However, there has also been considerable evidence that ECM components and proteolytic fragments of ECM affect multiple functions of inflammatory cells. In many cases, the bioactive ECM fragments have distinct functions from the parent molecule, suggesting that ECM components can have cryptic sites that are exposed only after the ECM is modified. These bioactive ECM domains are called “matricryptins”.

The list of ECM-derived peptides or proteolytic fragments reported to modulate activities of inflammatory cells is lengthy and has predominantly been generated from in vitro studies examining the effects of these fragments/peptides on monocytes, macrophages, and neutrophils. A partial list includes collagen types I and IV, elastin, fibronectin, laminins, entactin/nidogen, thrombospondin, and hyaluronan, which can induce inflammatory cell responses including chemotaxis, phagocytosis, and changes in protease and/or cytokine production. However, to determine whether these findings apply in vivo is difficult. Several pieces of data are needed: 1) induction of inflammation when the ECM peptide/fragment is introduced into tissue; 2) detection of similar fragments in biological samples; 3) demonstration that blocking the ligand-receptor interaction inhibits inflammation and/or tissue injury.

One of the best lines of evidence for a bioactive ECM-derived peptide inducing inflammation is the collagen I-derived peptide ProGlyPro (PGP). The PGP peptide was initially detected in a rabbit model of alkali injury to the eye, which correlated with neutrophils inflammation and corneal ulceration and had chemotactic activity.
in vitro. Weathington et. al. showed that PGP structurally mimics the IL-8 chemokine and that its chemotactic activity is mediated by CXC chemokine receptors CXCR1 and CXCR2 (Nature Medicine 12:317, 2006). In addition, they showed that repeated intrapulmonary exposure to PGP causes inflammation and airspace enlargement in mice, and blocking the ligand-receptor interaction via use of anti-CXCR1/2 blocking antibodies, CXCR1/2 knockout mice, or the co-instillation with a peptide antagonist ArgThrArg (RTR) inhibited PGP-induced inflammation and alveolar damage. Furthermore, PGP was detected in bronchoalveolar lavage (BAL) fluid of COPD patients.

Another example of ECM-derived peptides modulating an inflammatory response in vivo is elastin-derived fragments. Houghton et. al. showed that the BAL fluid of mice exposed to cigarette smoke induced monocyte migration in vitro, and this activity was blocked by anti-elastin antibody (J Clin Invest 116:753, 2006). In addition, instillation of elastin fragments into the lungs of mice induces macrophage accumulation. To prove that the generation of elastin fragments in vivo facilitated the inflammatory response and lung tissue damage, the anti-elastin antibody was given concurrently with cigarette smoke exposure or following instillation of pancreatic elastase (PPE), another mouse model of emphysema. Blocking the ligand-receptor interaction with the anti-elastin antibody prevented the macrophage accumulation in response to cigarette smoke or PPE, and PPE-induced alveolar damage. In addition, several studies have recently reported detection of anti-elastin antibodies in COPD, suggesting that elastin fragments may also affect adaptive immune responses. Because degradation of elastin is a key feature of COPD, investigators have looked for evidence of elastin breakdown in biological samples as an indicator of severity of disease. Desmosine and isodesmosine are specific amino acids of crosslinked elastin, and have been shown to be elevated in the plasma, urine, and sputum of COPD patients. Together, these data indicate that ECM-derived fragments are generated during lung injury, may modulate chronic inflammation, and lead to the progression of COPD. Therefore, ECM ligand-receptor interactions are a potential new area of therapeutic targets.

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Author disclosures and audio of the COPD7usa sessions are available on the COPD7usa conference website: www.copdconferencesusa.org.