Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Understanding what happens at a cellular level will lead to more effective treatments. Interleukins and transforming growth factor-β are important inflammatory mediators that may be significant in the evolution of chronic obstructive pulmonary disease.

**Keywords:** bronchitis, chronic obstructive pulmonary disease, emphysema, inflammation, interleukin, transforming growth factor-β

**THE interleukin family is a group of cytokines derived from cells, mostly leukocytes, that play a role in health and disease.**

This review looks at the role of this family in chronic obstructive pulmonary disease (COPD). COPD is a leading cause of morbidity and mortality in this country.

The interleukin family may act independently or in concert with other cytokines to initiate inflammation following an assault by a foreign substance. The inflammatory process normally resolves such situations. However, if the assault is continuous, inflammation may be the underlying cause of the disease.

The number of interleukin family members is growing rapidly. Some of the inflammatory diseases associated with uncontrolled interleukin production include atherosclerosis, inflammatory bowel disease, and rheumatoid arthritis. COPD is an example of a chronic inflammatory response involving cytokines such as the interleukins.

COPD is a generic term and includes chronic bronchitis and emphysema. Asthma is often included in this category, but it tends to be intermittent rather than chronic. COPD is associated with increased mucus production, hypertrophy of glands associated with the respiratory tract, and airway inflammation.

The most common cause of chronic bronchitis and emphysema is tobacco smoke. Tobacco smoke is an irritant that initiates the inflammatory response. Cells that play a role in the respiratory tract inflammation include local phagocytes, alveolar macrophages, and other immune cells responding to cell injury and death.

**INTERLEUKINS AND COPD**

In their work on human subjects, Borish et al. showed that the interleukins play a significant role in the inflammation associated with asthma. Nonasthmatic patients show no evidence of the presence of the interleukins. Interleukins may work synergistically with other cytokines in the inflammatory response. Possible roles for the interleukins include chemotaxis, adhesion of leukocytes to endothelial cells, and leukocytosis.

Others also show increased production of interleukins in response to tobacco smoke, with an imbalance between pro- and anti-inflammatory cytokines.

Destruction of lung tissue by proteases is characteristic of COPD. Two proteases that play significant roles in COPD are collagenase and elastase. Foronjy and D’Armiento suggest that the leukocytes involved with COPD secrete cytokines that promote the production...
of proteases. What follows is an imbalance between the pro- and antiproteases. This imbalance favors the proteases and causes a destruction of the lung tissue.8

Zheng et al9 show that an interleukin plays a pivotal role in promoting protease production in an animal model. More recently, others, also using the animal model, showed that the interleukins promote lung changes consistent with what is seen in humans: increased mucus production, airway inflammation, protease production, fibrosis, and airway remodeling.10,11 Interleukins have been shown to be involved in remodeling cardiac muscle after an acute myocardial infarction to the detriment of the patient. The ability of interleukins to stimulate the production of colony-stimulating growth factors promotes the leukocytosis seen early on in the disease process leading to COPD.1 Tobacco smoke initiates a chronic leukocytosis. This promotes uncontrolled production of cytokines, which have a detrimental effect when secreted in large quantities. Figure 1 summarizes the cellular pathophysiology of COPD.

INTERLEUKINS AND TGF-β

Inflammation is a multifactorial response to a foreign substance. In addition to the interleukins, another player associated with the inflammation of COPD is transforming growth factor-beta (TGF-β). TGF-β is produced by leukocytes and can stimulate the production of the interleukins. TGF-β is known to be an important chemoattractant and may work synergistically with the interleukins.12 Guber et al13 show that TGF-β plays a significant role in chronic immune responses. In this situation, TGF-β recruits mast cells.13 Mast cells are known to be prominent in patients with COPD.14 Others corroborate the role of TGF-β in the recruitment of inflammatory cells in COPD.15 Although TGF-β may initially be involved in repair as in wound healing, large amounts of this cytokine may ultimately lead to destruction.16

Lu et al17 report cross-talking between the interleukins and TGF-β. They suggest that high levels of these cytokines stimulate second messenger systems and genes that promote the production of the interleukins and/or TGF-β. High levels of these cytokines are associated with areas of inflammation.17 Figure 2 speculates how this interaction between the interleukins and TGF-β play a role in COPD.

TREATMENT AND PREVENTION

The present treatment for COPD relies primarily on therapy used for similar diseases such as asthma. However, these therapies are not effective in reversing COPD.18 In their animal model, Lucey et al19 showed that severity of emphysema is diminished when the production of cytokines decreases.

Figure 1. Flowchart showing the cellular pathophysiology of chronic obstructive pulmonary disease (COPD).

Figure 2. Flowchart showing the interaction between interleukins and TGF-β in chronic obstructive pulmonary disease (COPD).
They used mice in which receptors for interleukins and tumor necrosis factor had been knocked out. One can then extrapolate that the use of cytokine antagonists may be beneficial in treatment. DeBoer suggests that drugs specific for the inflammatory process might be useful in the treatment of COPD. These drugs might be specific for the leukocytes and/or the cytokines that control the pathophysiology of COPD. Yamagata and Ichinose suggest that agents directed against cytokine receptors might be beneficial.

We suggest that understanding the cytokines involved in the pathophysiology of COPD will bring about a pharmacologic treatment that will be more effective than what is presently in place. The best prevention is education about the effects of tobacco on the body.

REFERENCES