Abstract

Chronic obstructive pulmonary disease (COPD) is characterized and defined by limitation of expiratory airflow. This can result from several types of anatomical lesions, including loss of lung elastic recoil and fibrosis and narrowing of small airways. Inflammation, edema, and secretions also contribute variably to airflow limitation. Smoking can cause COPD through several mechanisms. First, smoke is a powerful inducer of an inflammatory response. Inflammatory mediators, including oxidants and proteases, are believed to play a major role in causing lung damage. Smoke can also alter lung repair responses in several ways. Inhibition of repair may lead to tissue destruction that characterizes emphysema, whereas abnormal repair can lead to the peribronchiolar fibrosis that causes airflow limitation in small airways. Genetic factors likely play a major role and probably account for much of the heterogeneity susceptibility to smoke and other factors. Many factors may play a role, but to date, only α-1 protease inhibitor deficiency has been unambiguously identified. Exposures other than cigarette smoke can contribute to the development of COPD. Inflammation of the lower respiratory tract that results from asthma or other chronic disorders may also contribute to the development of fixed airway obstruction.

COPD is not only a disease of the lungs but is also a systemic inflammatory disorder. Muscular weakness, increased risk for atherosclerotic vascular disease, depression, osteoporosis, and abnormalities in fluids and electrolyte balance may all be consequences of COPD.

Advances in understanding the pathogenesis of COPD have the potential for identifying new therapeutic targets that could alter the natural history of this devastating disorder.

Introduction

Chronic obstructive pulmonary disease (COPD) is a syndrome characterized and defined by a single physiological parameter: limitation of expiratory air-flow. Most often, the airflow limitation is slowly progressive over years. Several anatomical lesions contribute to airflow limitation, including loss of lung elastic recoil and fibrosis and narrowing of small airways, both of which likely cause fixed airflow limitation. Edema of the airways, accumulation of secretions, and smooth muscle contraction can also lead to airflow limitation that may be partially reversible. The various lesions that contribute to airflow limitation in COPD may be variably present within an individual and may account for some of the clinical heterogeneity that characterizes groups of patients with COPD.

Multiple pathogenetic mechanisms likely contribute to the development of COPD. The most important risk factor is cigarette smoking, which can affect the lungs by a variety of mechanisms. Other exposures also contribute, probably through similar pathways. Factors in addition to exposures, including both genetic and acquired conditions, also play a role and likely account for much of the variable susceptibility of individuals to the effects of smoking.
Over the past 50 years, understanding of the pathogenesis of COPD has advanced significantly, and new concepts continue to emerge. Perhaps most important among these is the recognition that COPD is a systemic disease and that the clinical course is often prominently affected by aspects of the disease other than airflow limitation. This review discusses the pathogenesis of COPD and highlights newly emerging concepts.

Inflammation

Inflammation is characteristically present in the lower respiratory tract in patients with COPD. Acutely worsening inflammation is characteristic of COPD exacerbations (see article elsewhere in this issue on Pathogenesis and Treatment of Exacerbations of COPD). In stable disease, pigment-laden macrophages accumulate in the respiratory bronchioles and alveoli. These macrophages are the most numerous inflammatory cells present, both in the normal lung and in COPD in most circumstances. Macrophage-derived mediators have been regarded as key pathogenetic mediators of COPD. Similarly, neutrophils are present within the airway lumen, within airway glands, and accumulate progressively within pulmonary tissues as the disease worsens. A key emerging concept, however, is that other inflammatory cells likely also play key roles.

Lymphocytes, particularly CD8+ lymphocytes, are also present in the airways, alveolar structures, vessels, and lymph nodes. Increased numbers of CD8+ T-lymphocytes are associated with more severe disease. It has also been shown that the T-lymphocytes found in COPD express the chemokine receptors CCR5 and CXCR3, which are considered to be markers of T helper 1 (Th1) cells. Thus the lymphocytic inflammation in COPD is different from that found in asthma where predominantly Th2 cells are found. Although less well studied, mast cells are also present in the airway wall in COPD and mast cell mediators are present in bronchoalveolar lavage (BAL) fluid of COPD patients, leading to the suggestion that mast cells also play a role. Eosinophils are also present in the airway wall in COPD and can be found in lavage specimens and induced sputum. The presence of eosinophil-derived mediators indicates eosinophil activation. Interestingly, a subset of patients with eosinophilia and mast cell activation has been suggested to represent a subtype of COPD and patients with sputum eosinophils may be more responsive to glucocorticoids. Finally, the structural cells of the lung, including epithelial and mesenchymal cells, are now recognized as producers of inflammatory mediators. It is likely that these cells play key roles in regulating the inflammatory process in COPD.

Although the lower respiratory tract of COPD patients is characterized by the accumulation of inflammatory cells, these cells also accumulate in the lower respiratory tract of essentially all smokers. The factors that distinguish the inflammatory process among those who are susceptible and will develop more severe fixed airflow limitation remains unclear. Current concepts suggest that the susceptible individual exposed to cigarette smoke has a quantitatively more exuberant or more persistent inflammatory response rather than a response that is qualitatively distinct. The persistent nature of inflammation in COPD is highlighted by the effects of smoking cessation. When normal smokers quit smoking, inflammation in the lower respiratory tract resolves. Alveolar macrophage numbers decrease within months, although it may take several years for the pigment-laden cells to be cleared. Longitudinal studies evaluating inflammation in patients with COPD following smoking cessation have not been performed. Cross-sectional studies of former smokers with COPD demonstrate inflammation comparable to that of current smokers with COPD. This suggests that the inflammatory response may persist once the disease progresses to a certain point.

Smoking cessation has been demonstrated to affect both the symptoms and the progression of the disease and is associated with the reduction in cough and sputum production. The Lung Health Study, which evaluated patients with relatively mild COPD, demonstrated that smoking cessation affected the rate at which lung function was lost. Immediately after cessation, there was a small improvement in lung function after which lung function then declined, but at a rate similar to that of a nonsmoker.

Thus there are some gaps, particularly regarding the natural history of inflammation in well-established COPD.
following smoking cessation. Nevertheless, current concepts suggest that smoking, and likely other exposures, leads to an inflammatory response in the lower respiratory tract. Undoubtedly, cigarette smoke can directly damage the lungs. Mediators released by inflammatory cells, however, are believed to account for most of the alterations in lung structure that characterize COPD (see following sections). If an individual quits smoking early enough, the inflammatory changes may be reversible. However, if the disease has progressed sufficiently far, a concept not rigorously defined, the inflammation may be persistent and the disease may progress even following smoking cessation.

Cytokines and Intracellular Signaling

The presence of inflammatory cells in airways in COPD would suggest that proinflammatory cytokines are active and have drive chemotaxis of these cells. Several investigators have documented increased levels of important neutrophil chemotactic factors in specimens from COPD patients. Interleukin-8 (IL-8), tumor necrosis factor (TNF), C-X-C motif ligand 1 (CXCL1), and monocyte chemoattractant protein (MCP)-1 are found in sputum. It has recently been shown that the levels of cytokines remain elevated over time in COPD. Increased levels of chemotactic factors, chemokines, and their receptors are also found in bronchoalveolar lavage specimens and lung tissue in COPD. Elevated levels of chemotactic factors for inflammatory cells in COPD suggest that antichemotaxis agents may be a therapeutic strategy in COPD. It may be difficult to identify one specific cytokine or receptor for targeting. The chemokines, for example, have significant redundancy so that inhibition of one chemokine may not be clinically effective. Inflammatory cytokines do share some intracellular signaling pathways, suggesting that agents that target signaling systems could have broad effects on inflammation.

Different cytokines stimulate leukocyte chemotaxis through interacting mechanisms. Cyclic nucleotides can serve as a common signaling system. Neutrophil chemotaxis is modulated by cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Elevation of cAMP levels generally reduces leukocyte adhesion and migration functions. Effects on cAMP levels and inflammatory mechanisms may be an important mechanism for the effect of theophylline on inflammation in COPD. Phosphodiesterase (PDE) 4 inhibitors that raise cAMP levels also have anti-inflammatory effects. There are also common signaling systems for the production of cytokines. The expression of many proinflammatory molecules such as IL-8, granulocyte-macrophage-colony stimulating factor (GM-CSF), and RANTES is modulated by the nuclear transcription factor nuclear factor (NF)-kappa B. Several investigations have shown in several cell types that common signaling intermediates are involved the NF-kappa B-dependent effects. Protein kinase C (PKC) has multiple isoforms of which several are implicated in proinflammatory signaling and expression of IL-8. PKC is particularly interesting because it may mediate effects of cigarette smoke on macrophages and epithelial cells and thus provide a direct mechanism for cigarette smoke modulation of inflammation.

An emerging concept regarding cytokines and COPD is that cytokines have direct roles in the processes of lung injury and airway remodeling. Recent experiments with transgenic mice have demonstrated interesting effects of cytokines in the lung. Zheng et al created a transgenic mouse with inducible targeting of IL-13 in the lung. IL-13 is generally considered to be important in asthmatic, Th2-dominated tissue inflammation. However, the investigators found significant alveolar enlargement, an emphysema-like abnormality. IL-13 was shown to increase expression of matrix metalloproteinases, perhaps altering the protease-antiprotease balance in the lung. A transgenic mouse with over-expression of interferon (IFN)-gamma also showed extensive changes of emphysema. IFN-gamma also induced expression of matrix metalloproteinases that are capable of tissue injury. Lung injury and airway remodeling are described in more detail in later sections.

Lung Damage

Emphysema

The characteristic lesion of pulmonary emphysema is destruction of the alveolar wall. The concept that an excess of proteolytic activity can lead to lung destruction, termed the protease-antiprotease hypothesis, now well accepted,
stems from both clinical and experimental observations. Laurell and Eriksson described the association between α-1 protease inhibitor (PI) deficiency and pulmonary emphysema.[52] Concurrent with this clinical observation, experimental studies conducted by Gross and others demonstrated that infusion into the lungs of enzymes with elastolytic activity induced emphysema.[53-56] In contrast, proteolytic enzymes that lack the ability to degrade elastin did not induce emphysema. Consistently, α-1 PI is an inhibitor of many serine proteases, including leukocyte elastase. These observations led to the protease-antiprotease theory of emphysema. Although the initial attention focused largely on α-1 protease inhibitor and neutrophil elastase, other enzymes and inhibitors are now believed to play a role. In this context, several serine proteases in addition to leukocyte elastase, including chymotrypsin and proteinase 3, have elastolytic activity and may contribute to the development of emphysema.[57] Similarly, metalloproteases[58] and cysteine[59] proteases may also have elastolytic activity, have been observed in the lung in COPD.[60,61] and may also contribute to the development of emphysema. Inhibitors of these enzymes are also present in the normal lung, thus expanding the concept of protease-antiprotease balance.

The balance between protease and antiproteases could be modified by several mechanisms in addition to a congenital deficiency of an antiprotease. An inflammatory response, for example, could lead to the increased release of proteases. In this context, increased release of neutrophil-derived enzymes has been reported in the lower respiratory tract of patients with COPD, and the amount of elastase recovered from the lower respiratory tract by BAL has been correlated with the severity of emphysema assessed by computed tomography.[62] Similarly, the levels of matrix metalloproteinase MMP9 and MMP12, metalloproteases with elastolytic activity, are increased in COPD.[60,61] Finally as already noted, cysteine proteases are also present in the lower respiratory tract in COPD. Thus the proteolytic milieu of the lower respiratory tract is characterized by increased levels of a variety of proteases, likely derived from several cell types.

An inflammatory response can also alter the antiprotease screen. In this context, inflammatory responses are characterized by the production of reactive oxidant species. These oxidants are in addition to those directly derived from cigarette smoke. Antiproteases, including α-1 protease inhibitor, are susceptible to oxidation. Oxidation of the methionyl residue at the active site of α-1 protease inhibitor renders it ineffective as an antiprotease.[65] As a result, a smoker or an individual with an active inflammatory response may develop an acquired form of α-1 protease inhibitor deficiency.[66] Interestingly, the oxidative inactivation of α-1 PI may play an important physiological role. Specifically, when released into the extracellular milieu, neutrophil elastase will be present at relatively high concentrations, potentially in excess of the local concentration of protease inhibitor.[67] Until the elastase diffuses and the concentration declines, elastolytic activity could be present at the site of local release. Oxidation of α-1 protease inhibitor within a local milieu could further potentiate local elastase activity. The generation of locally active sites has been suggested to be an important physiological means for regulating elastolytic activity.

It is likely that tissue destruction results from the integrated activity of multiple proteases. In this regard, there are important interactions between the various classes of proteases. First, both cathepsins and metalloproteases are capable of proteolytically cleaving serine protease inhibitors.[58,68] Similarly, serine proteinases can degrade the tissue inhibitor of matrix metalloproteinase (TIMPs), the endogenous inhibitors of the metalloproteinases.[69] These classes of proteinases can alter the relative proteolytic, antiproteolytic balance by affecting inhibitors of other classes. In addition, metalloproteinases are generally released as inactive precursors.[58] Serine proteinases are capable of proteolytic activation of these zymogens. Thus serine proteases may lead to tissue destruction by activating metalloproteinase cascades.

Proteases likely contribute to the pathogenesis of COPD by several mechanisms in addition to destruction of the extracellular matrix. In this context, the proteolytic cleavage of elastin by MMP12 generates peptides that are potent chemoattractants for macrophages.[70] The MMP12-deficient mouse, when exposed to cigarette smoke, does not develop an accumulation of macrophages within the lung, suggesting that MMP12 is essential for this aspect of the inflammatory response.[70] MMPs, moreover, may play a role in the activation of other cytokines, including transforming growth factor (TGF)-β[71] and TNF-α.[72] Similar roles for other proteases in modulating the activity of the inflammatory response seem likely. Similar mechanisms could directly contribute to altered lung structure. In this
context, neutrophil elastase can directly stimulate fibroblast contraction,\[73\] which may account for narrowing of the small airways. Similarly, neutrophil elastase can induce activation of the epidermal growth factor (EGF) receptor and lead to goblet cell metaplasia.\[74\]

That proteases contribute to the pathogenesis of COPD has been well established for some time. The concept that an imbalance between proteases and anti-proteases leads to destruction of extracellular matrix has now been greatly expanded. Interactions among the various classes of proteases and their respective inhibitors will be key. In addition, the concept is emerging that proteases play roles in the pathogenesis of COPD beyond direct degradation of connective tissue matrix, throughout the activation and regulation of cellular activity. For these reasons, inhibition of these pathways remains an appealing approach for therapeutic intervention.

**Oxidants**

Cigarette smoke contains an estimated 6,000 chemical moieties. Many of these are highly reactive, including several highly reactive oxidant species. In addition, the inflammatory response characteristically generates oxygen-free radicals that can lead to tissue damage. In defense against oxidant damage, several endogenous antioxidants are present in the lower respiratory tract. This has led to an oxidant-antioxidant hypothesis analogous to that of the protease-antiprotease hypothesis.\[75\]

That oxidative damage occurs in COPD is established by the presence of several biomarkers of protein and lipid oxidation. In the face of an oxidant stress, antioxidant defenses are initially depleted.\[76\] The enzymes responsible for the generation of antioxidants, however, are rapidly induced, and antioxidant defenses are rapidly restored to normal. The opposite occurs when the oxidant stress is removed. This tight regulation of antioxidant defenses suggests an important physiological role for antioxidants. It may also account for the relative difficulty in showing therapeutic benefits with supplemental antioxidant therapy.

Variations in antioxidants may predispose to COPD, just as variants in antiproteases are believed to. In this context, heme oxygenase 1 may protect against oxidative stress,\[77,78\] and polymorphisms in this gene promoter have been associated with susceptibility to the development of emphysema.\[79\] Interestingly, heme oxygenase 1 levels are increased in normal smokers\[80\] but decreased in patients with COPD.\[81\]

The oxidative stress that likely occurs in the lung in COPD may have important specific pathophysiological effects. Oxidative inactivation of α-1 protease inhibitor was discussed earlier. Oxidative inactivation of histone deacetylase 2 (HDAC2) has been suggested to play a particularly important role.\[82\] HDAC2 functions as a cofactor for glucocorticoid-mediated downregulation of proinflammatory genes.\[83\] Its oxidative inactivation, which may take place in smokers or in COPD patients with persistent inflammation in the absence of smoking, may contribute to the persistent inflammatory response in COPD. It could also account for the inability of glucocorticoids to dramatically alter inflammation in COPD.

Oxidative stress can initiate numerous signal transduction pathways that are linked to inflammatory mediators already described. Oxidative stress causes activation of epidermal growth factor receptors with subsequent activation of mitogen-activated protein kinases.\[84\] Reactive oxygen species and lipid peroxidation products such as 4-hydroxy-2-nonenal and acrolein activate mitogen-activated protein kinases.\[85\] Takeyama et al also found that the oxidant-mediated signaling led to mucin synthesis.\[86\] Oxidative stress can alter chromatin remodeling and activate NF-kappa B and another nuclear transcription factor activator protein-1 (AP-1), which regulate proinflammatory mediators as already described.\[85,87\]

Several questions remain regarding the species responsible for oxidative damage in the lung, their molecular targets, and the role of specific antioxidants. Nevertheless, because it is likely that inflammatory processes modulate inflammation and damage in the lung, oxidant pathways are also appealing targets for therapeutic intervention in COPD.
**Apoptosis**

Mechanisms independent of inflammation may contribute to the development of emphysema. In this context, the American pathologist Averil Liebow suggested the concept that loss of endothelial cells, which are major structural cells of the alveolar wall, should lead to the development of emphysema. Support for this concept has been generated by Kasahara and colleagues. Their experimental studies were based on the importance of vascular endothelial growth factor (VEGF) for the survival of endothelial cells. In the presence of a VEGF receptor kinase inhibitor administered in a rat model, loss of alveolar wall characteristic of emphysema developed. Importantly, this lesion developed in the apparent absence of an inflammatory response, but with the presence of apoptotic cells. Apoptosis requires the activation of intracellular enzymes termed caspases. In the presence of a caspase inhibitor, VEGF receptor inhibition did not cause emphysema. Further support for this mechanism leading to emphysema has been provided by studies in VEGF-deficient mice. Similarly, mice overexpressing placental growth factor also developed VEGF-deficiency, interpulmonary apoptosis, and emphysema. Finally, mice exposed to a nonspecific serine threonine kinase inhibitor or instilled or transfected with the apoptosis mediator caspase 3 developed both inter-pulmonary apoptosis and emphysema. Such mechanisms may play a role in human emphysema. The lungs of patients with emphysema have been noted to be deficient in VEGF and in the VEGF receptor. Studies have also demonstrated increased numbers of apparently apoptotic cells in the lungs of patients with COPD. Apoptosis, moreover, need not be independent of oxidative or proteolytic damage. In this context, proteolytic disruption of extracellular matrix may lead to cell death through a specialized form of apoptosis termed anoikis. To what degree this may take place in vivo remains undetermined. Oxidative stress has also been reported to contribute to the development of apoptosis. In this context, heme oxidase, which may have antioxidant effects as discussed earlier, can also inhibit apoptosis. Finally, although cigarette smoke has been reported to induce apoptosis, smoke can also inhibit apoptotic pathways.

Thus the role of apoptosis in the development of emphysema remains incompletely defined and likely will be quite complex. The recent advances in describing mechanisms by which altered cell turnover can contribute to emphysema, however, offers novel mechanisms for therapeutic intervention. Therefore, determining to what degree apoptosis plays a role in human disease and defining the specific pathways involved hold great promise.

**Mucous Hypersecretion**

COPD is characterized not only by airflow limitation but also, in many cases, chronic cough and sputum production. This is often associated with metaplasia of the airway epithelium. The normal pseudostratified ciliated epithelium is replaced by goblet cells and, in more severe disease, by squamous metaplasia. In addition, there is associated hypertrophy of mucous glands. These anatomical changes are associated with alterations in the expression of mucin genes. These changes, therefore, lead to the production of mucus that is abnormal in quality and increased in quantity. At the same time, the ciliary apparatus responsible for mucous clearance is disrupted.

The biochemical mechanisms and cellular processes responsible for alteration in epithelial cell populations are incompletely defined. However, inflammatory mediators, including proteases and oxidants, are capable of inducing profound effects on epithelial cells. Activation of the EGF receptor, which may take place either by direct ligand activation or by non-ligand-mediated activation through either oxidant or proteolytic pathways, can lead to altered mucin gene expression. EGF receptor activation also appears to be a key process in goblet cell metaplasia in animal models. Goblet cell metaplasia is characteristically present in smokers but can reverse with smoking cessation. Whether similar benefits can accrue with therapeutic interventions in patients with COPD remains undetermined, but understanding the pathways that lead to altered epithelial cell differentiation holds promise for identifying therapeutic targets.

**Fibrosis**

The small airways of patients with COPD characteristically accumulate mesenchymal cells and the collagenous extracellular matrix these cells produce. This fibrotic response resembles scar tissue at other sites and, like all scars, these lesions likely contract. This process probably accounts for the narrowing of small airways, which is
a major determinant of the fixed airflow limitation present in patients with moderate to severe COPD. It is likely that the processes responsible for peribronchiolar fibrosis resemble the processes responsible for fibrosis in other chronic disorders. In this context, the cytokine-transforming growth factor \( \beta \) is thought to play a central role. This mediator probably plays a key role in wound healing in general. It is a potent activator of fibroblasts, converting them to a myofibroblast-like phenotype and inducing the production of extracellular matrix. TGF-\( \beta \) also stimulates fibroblast recruitment and augments the ability of fibroblasts to contract and shrink their surrounding extracellular matrix. TGF-\( \beta \) activates a receptor that functions as a serine/threonine kinase and phosphorylates mothers against decapentaplegic (smad) proteins, particularly Smad 2 and Smad 3, although other signaling pathways may also play a role. Smad 3 signaling appears to be key in both wound healing and fibroblast activation. The ability to block TGF-\( \beta \) signaling with specific kinase inhibitors opens the possibility of therapeutic intervention.

In addition to TGF-\( \beta \), a variety of other cytokines likely present in the lung in COPD can also modulate fibroblast activity. Most of the many growth factors and cytokines that can modulate fibroblast behavior have not been evaluated in the specific context of COPD. However, increased levels of the Th2 cytokines IL-4 and IL-13, which can stimulate fibroblasts, have been reported in tissues in COPD. It is likely that many mediators, in addition to TGF-\( \beta \), may contribute to the development of fibrosis in COPD. Whether differences in these cytokines account for some of the heterogeneity of COPD remains to be determined.

In contrast to the overexuberant fibrotic scarring that develops in small airways, emphysema may be considered to be a deficient repair response. In this context, alveolar walls in patients with mild COPD have increased amounts of collagen. Similarly, increases in collagen are noted following experimental lung injury capable of inducing emphysema. These observations are consistent with the concept that the lung is capable of repair and that the third type of imbalance; namely, between tissue destruction and tissue repair, can also contribute to the development of emphysema. In this context, cigarette smoke can inhibit fibroblast repair responses, suggesting that smoke may tip the balance toward the development of emphysema by impeding repair as well as by augmenting destruction. Interestingly, the ability of smoke to impair repair responses may depend on cell density. In situations of high cell density, such as may occur in fibrotic airways, smoke may, through the activation of TGF-\( \beta \), have a profibrotic effect.

The concept that the lung can mediate repair has extremely important potential therapeutic implications. Modulation of the fibrotic response in the small airways could have an effect in modifying the natural history of COPD. In this context, agents that elevate cAMP within fibroblasts generally have an inhibitory effect. Several therapeutic interventions are capable of increasing cAMP within fibroblasts and, potentially, could have an antifibrotic effect. In vitro effects on lung fibroblasts consistent with such an action have been demonstrated with \( \beta \) agonists and phosphodiesterase 4 inhibitors.

The concept that alveolar repair may take place offers the exciting possibility of restoring lung function after the development of emphysema. In this context, retinoic acid is a mediator that drives the formation of alveolar wall in the perinatal and postnatal period. Administration of retinoic acid has been found to stimulate the development of new alveolar wall in both rat and murine models, although not all investigators have observed similar effects. In addition, retinoic acid levels may be depleted in cigarette smokers, suggesting another means by which smoke may predispose to the development of emphysema. Although many questions remain, the emerging concept that lung structure can be manipulated medically and that new alveolar wall formation can be induced offers an extremely exciting and potentially novel way to approach treatment of COPD.

**Systemic Effects**

It is now becoming clear that COPD is not only characterized by airflow limitation and symptoms due to cough and sputum production but is also associated with systemic effects. Often these systemic effects are the major clinical problems affecting patients. These systemic effects include generalized weakness and an increased propensity for the development of cardiovascular disease. The most likely cause of death for patients with...
COPD, in fact, is cardiovascular disease.[139] This is true both for patients with mild disease and for those with more severe COPD. Interestingly, COPD increases cardiovascular risk at all levels of disease.[137] The mechanisms that account for this increased risk are not well defined. However, they do not appear to be simply a measure of smoking because the relationship is present even when epidemiological studies are adjusted for smoking behavior. It is possible that airflow limitation indicates a generalized susceptibility to the effects of cigarette smoke and, therefore, serves as a "marker" of risk for the development of cardiovascular disease, which, in turn, accounts for mortality. Alternatively, inflammatory processes in the lung could lead directly to increased cardiovascular risk.[138] Production of inflammatory mediators within the lung TNF-α and GM-CSF, for example, could lead to vascular damage and increased leukocyte counts, accounting for progressive atherosclerosis. Patients with COPD characteristically have increased C-reactive protein levels,[138] a known risk factor for the development of atherosclerotic vascular disease. Inflammation within the lung can also lead to circulating cytokines such as IL-6,[140] which can lead to a hypercoagulable state through the induction of fibrinogen production and could predispose to thrombotic complications. Finally, pulmonary inflammation, by activating autonomic reflexes, could lead to instabilities of cardiac rhythm.

The weakness that is present in COPD patients is often more important in limiting performance than is airflow limitation.[141] It is likely that several mechanisms contribute to skeletal muscle weakness in COPD, including deconditioning and the effect of medications such as glucocorticoids.[136] The inactivity of COPD patients, however, is likely multifactorial. Dyspnea that occurs with exertion can lead to restricted activity which, in turn, leads to muscle dysfunction, ineffective exercise, and worsening dyspnea on exertion. This vicious cycle likely leads to progressively more severe restriction of activity and more severe deconditioning.[24,142] Abnormality of skeletal muscle, however, has also been suggested.[143,144] In this context, apoptosis of skeletal muscle has been reported.[145] Whether circulating cytokines such as TNF-α can drive this process is unknown. However, increased circulating levels of TNF-α have been associated with weight loss in COPD patients in most,[146-151] but not all, studies.[152,153] Underweight in COPD is independently associated with increased mortality.[154,155] Taken together, these observations suggest that skeletal muscle dysfunction may result from the inflammatory process present in COPD.

Although incompletely defined, it is possible that circulating cytokines produced in the lung contribute to other systemic manifestations of COPD. In this context, circulating cytokines can have important effects on mood and, therefore, could contribute to depression, which has been reported to be more common among COPD patients.[156] Similarly, osteoporosis is common in COPD patients.[157,158] Again, many factors likely lead to reduced bone density in COPD patients, including inactivity, cigarette smoking, diet, and treatment with agents such as glucocorticoids. In addition to these, however, circulating cytokines may also play a role.

Other Factors

Several other factors also contribute to risk for the development of COPD. Lifelong asthma has been associated with a progressive loss of lung function with age in several epidemiological studies.[159-161] It appears that a subset of asthmatics may be particularly susceptible to the development of fixed airflow limitation.[161] It has been suggested that inflammatory mediator-driven airway remodeling in small airways is responsible for increased airways resistance in this setting. In vitro[112,113] and animal studies[50] suggesting that IL-4 and IL-13 can modulate airway repair and remodeling support this concept.

It is also likely that early life events can alter COPD risk. Individuals with low birth weight appear to be at increased risk for the development of COPD as they age.[162,163] Although the mechanisms are unclear, it appears that low birth weight is associated with a reduced maximally attained lung function in young adulthood.[163] Maximally attained lung function, in turn, appears to be related to the development of COPD; specifically, individuals with less maximally attained lung function are at increased risk.[164,165] In addition to low birth weight, other early life events that affect lung development in growth may have a similar impact on COPD risk.

Conclusion

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Understanding of the pathogenesis of COPD has advanced dramatically over the past 50 years. The major risk factor for the development of COPD is exposure to toxic dusts and fumes, the most important of which is cigarette smoke. These exposures likely directly damage lung, but more importantly initiate a complex cascade of inflammatory events. This inflammation further damages the lungs by a variety of mechanisms. The lung, in turn, responds to these injuries by activating repair mechanisms. Alteration in lung structure, therefore, results from the consequence of these complex interacting processes. Further complicating the clinical setting, similar but distinct lesions develop at various sites along the airway and within the alveolar structures. As a result, COPD is characterized by heterogeneous tissue alterations. Inflammatory processes in the lung, moreover, likely lead to systemic effects. As a result, COPD is clinically heterogeneous, with varying processes within and outside the lung accounting for clinical features in individual patients. Current studies delineating the pathogenetic mechanisms in COPD offer great potential not only for understanding disease mechanisms but also for identifying novel therapeutic strategies to treat this condition.

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