Current Smoker: A Clinical Chronic Obstructive Pulmonary Disease Phenotype Affecting Disease Progression and Response to Therapy

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Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition of the lungs characterized by chronic respiratory symptoms, primarily dyspnea, cough, and sputum production, due to airway and/or alveoli abnormalities that cause persistent, and often progressive, airflow obstruction. Although the underlying mechanisms responsible for COPD remain poorly understood, over the past several decades, clinical phenotypes and endotypes have been suggested. These include frequent exacerbator and eosinophilic groups that guide tailored therapies for patients with that clinical expression. In the developed world, smoking is the main known cause of COPD, responsible for ~80% of cases. Active smokers have more severe disease, with more rapid lung function decline and impaired quality of life, than former smokers. Unfortunately, smoking is still highly prevalent. Rates range between 3% and 37% globally, with factors including sex, age, race, education, and geography influencing the rate of addiction. Importantly, several studies have shown that smoking detrimentally affects treatment efficacy of COPD medications; this is particularly true of inhaled corticosteroids and macrolides. In this review, we discuss the effects of smoking on the pathophysiology of COPD and the clinical impact of smoke exposure in patients with COPD.

Keywords: COPD; smoking; phenotype; endotype

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition of the lungs characterized by chronic respiratory symptoms, such as dyspnea, cough, and sputum production. The disease is due to airway and/or alveolar abnormalities, such as bronchitis, bronchiolitis, and/or emphysema, that cause persistent, often progressive, airflow obstruction (1). Despite a decline in smoking prevalence in developed countries, COPD prevalence and deaths continue to increase (2), particularly in the most densely populated areas of the world. In fact, COPD is currently the third leading cause of death globally, with significant morbidity, mortality, and health-related costs (2).

In the developed world, about 80% of COPD cases are attributable to smoking (3). The incidence of smoking depends on several factors, including sex, age, race, education, and region (4). The global rate of current tobacco use among individuals (male or female) aged 15 years and older dropped from 32.7% (in 2000) to 22.3% (in 2020) (5), and since 1990, there have been significant decreases in the prevalence of smoking by both male (27.5% reduction) and female (37.7% reduction) individuals aged 15 years or more. Nevertheless, population growth has led to a significant increase in the total number of smokers from 0.99 billion in 1990 to 1.14 billion in 2019 (6). Current prevalences of smoking are reported to be 12.5% (an estimated 28.3 million adults) in the United States (7), 25.9% (which extrapolates to 112 million adolescents and

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adults) in Europe (8), 27.7% (about 316 million adults) in China (9), and between 3% and 37% (up to 6 million people) in Latin American countries (10). In India, any form of tobacco (including snuff, chewing, and others) is used by 39% of male and 4% of female individuals aged 15–49 years; tobacco is smoked in a variety of ways by 21.4% of male individuals in this age group (11). In 2021, this percentage represented almost 30 million individuals (12).

Although there are various definitions, smoking status in COPD is generally categorized into three groups: *1*) current smokers, defined as adults who have smoked 100 or more cigarettes in their lifetimes and who currently smoke or have quit in the past 6 months (between 38% and 47% of adults with COPD in the United States report current smoking) (13–17); *2*) former smokers, defined as individuals who have smoked more than 100 cigarettes in their lifetimes but who have quit the habit for more than 6 months (14); and *3*) never-smokers, defined as individuals who have never smoked or who have smoked fewer than 100 cigarettes in their lifetimes (14). Of note, never-smokers with COPD include individuals with exposure to biomass fuel or occupational exposures (18), known risk factors for COPD. According to the CDC, as many as 25% of Americans with COPD are never-smokers (13, 14). This proportion increases in lower income countries around the world, where more than 50% of persons with spirometrically confirmed COPD are classified as nonsmokers (18).

Data show that smoking cessation is the first necessary step to reduce lung function decline and COPD exacerbations among smokers, or even prevent these outcomes if done early enough in the process (1, 17, 19, 20). Despite the benefits of quitting, smoking rates in adults with COPD remain high. This is, perhaps, due mainly to the significant difficulty in quitting a product of the highly addictive properties of nicotine, as well as genetic, social, and/or personal circumstances (15–17, 21, 22). Although smoking cessation can slow the rate of lung function decline and reduce the risk of hospitalization and mortality, former smokers with COPD may continue to experience accelerated lung function decline and COPD exacerbations (1, 19, 23).

Smoking is the largest contributing risk factor to the development of COPD, affecting almost all, if not all, systems in the body. Approximately one-third of individuals with smoking histories greater than 20 pack-years will develop airflow obstruction leading to COPD, although many more will be symptomatic and exacerbate despite somewhat preserved lung function (24). Because cough and sputum production or the presence of emphysema shown by imaging studies is associated with a higher risk of full clinical COPD, the term "pre-COPD" has been suggested and is supported by the Global initiative for Obstructive Lung Diseases (25). It is proposed that the pathogenesis of COPD is a product of dynamic interactions between genetic predisposition, environmental exposure, and time, coined GETomics (26). COPD clinical presentation, although heterogeneous, does not reflect the substantial pathophysiologic variability in COPD. Unfortunately, inhaled therapies that target the molecular mechanisms underlying COPD are limited. Current therapies predominantly target symptoms (e.g., bronchodilators, antimuscarinic agents, phosphodiesterase-4 inhibitors) or exacerbations. The impact of these drugs on exacerbations or overall disease course is, however, limited. The underlying mechanisms of COPD, and variation among patients, remain only partially identified.

Pathophysiologic Consequences of Smoking in COPD

The inflammatory pathways in COPD involve a complex interaction between innate and adaptive immune responses. In many individuals, increased neutrophils, alveolar macrophages, T lymphocytes, and innate lymphoid cells are identified in the airway lumen (27). However, substantial variability exists in inflammatory responses among individuals and within the same individual across lung regions and airway generations (28).

The direct effects of active cigarette smoke include both proinflammatory and immunosuppressive effects (27). Tobacco smoke can directly activate epithelial cells to produce pro- and antiinflammatory mediators and stimulates airway remodeling (27). Smoke exposure induces the reprogramming of basal cells, the progenitor cells of the airway, leading to squamous and goblet cell metaplasia and loss of ciliated and club cells. This reprogramming can result in mucus accumulation, disordered mucociliary clearance, and a further disordered immune response.

Furthermore, smoke-induced inflammatory signaling in the airway epithelium and by immune cells, including polarized surface macrophages, causes the release of neutrophil chemoattractants as well as other mediators, creating the hallmark neutrophilic inflammation seen in COPD (29). Neutrophils exposed to cigarette smoke display dysfunctional phagocytosis and produce mediators that contribute to tissue degradation. Neutrophilic inflammation leads to mucus secretion and oxidative stress and may also contribute to steroid unresponsiveness, via oxidative stress-induced reductions in histone deacetylase-2 (30). Alveolar macrophages are increased in smokers; however, macrophages exposed to cigarette smoke are dysfunctional, producing more proinflammatory mediators that signal to neutrophils and more matrix metalloproteinases that may contribute to tissue breakdown (29, 31, 32). Although the role of matrix metalloproteinases in human parenchymal destruction resulting in emphysema is controversial, it is accepted that in cigarette smoke–induced animal models of emphysema, MMP-12 appears to play a consistent and important role in lung destruction (33). Finally, alveolar macrophages exposed to cigarette smoke display impaired phagocytosis and are therefore inefficient at both microbial killing and clearing apoptotic neutrophils from sites of inflammation (29, 34).

Adaptive immune cells also contribute to inflammation in COPD. Distinct effector subsets of $CD4^+$ (cluster of differentiation 4) and $CD8^+$ T cells have been shown to participate in the response to cigarette smoke and to COPD pathogenesis. Cigarette smoke increases the proportion of $CD8^+$ T cells but lowers the proportion of $CD4^+$ T cells (35). Subsets of T-helper cell type 1 (Th1) cells, $CD4^+$ T cells primarily expressing IFN-γ, and Th17 cells, $CD4^+$ T cells primarily expressing IL-17, are increased in patients with COPD, and the increase in Th17 cells was found to be predictive of airflow limitation in patients with COPD (36). A similar increase in Th17 cells has been observed in mouse models of chronic cigarette smoke exposure (37–39). $CD8^+$ cells expressing IFN-γ and IL-17 have also been demonstrated in response to cigarette smoke (40, 41). Finally, B-cell responses are particularly relevant in emphysema,

in which tertiary lymphoid structures containing B cells are a common feature (42). Interestingly, nicotine itself can exert immunosuppressive effects through functional impairment of dendritic cell functions (43).

When airway epithelial cells are exposed to cigarette smoke, they also release alarmin cytokines, including IL-33, which can initiate and amplify innate and adaptive immune responses of both type 1 and type 2 inflammation (44). In another preclinical model of COPD exacerbations induced by cigarette smoke and viral infection, cigarette smoke promoted the intracellular accumulation of epithelial-derived IL-33; cigarette smoke decreased the suppressor of tumorigenicity 2 receptor for IL-33 in type 2 innate lymphoid cells but increased receptor expression on macrophages and natural killer cells (45). In response to infection, this leads to an exaggerated type 1 and/or proinflammatory response, suggesting that during exacerbations, which are typically driven by microbes, the IL-33 pathway may contribute to an exaggerated proinflammatory immune response not seen in never-smokers (45).

Multiple factors are altered in the chronic smoking airway microenvironment that likely contribute to microbial dysbiosis (46). For instance, overproduction of pathologic mucus, disrupted mucociliary clearance, and reduced macrophage and neutrophil phagocytosis may all contribute to reduced bacterial killing. Several studies using high-depth sequencing technology have demonstrated differences between smokers and never-smokers, showing an association between smoking and microbial dysbiosis toward more pathogenic communities. One study showed that airway microbial communities in the general population are highly organized networks, with smoking contributing to a loss of diversity, disruption of the network structure, and increases in *Streptococcus* species (47). A study of the bacterial communities of the upper and lower respiratory tracts of healthy current, former, and never-smokers revealed that cigarette smoking resulted in distinct patterns of bacterial response and a higher abundance of opportunistic pathogens in current and former smokers compared with never-smokers (48). In a similar study of the lower respiratory tract microbiome of current, former, and never-smokers, smoking resulted in a loss of diversity and a weakening of the community structure observed in healthy never-smokers (49). Interestingly, the overrepresentation of the genus *Ralstonia* in the lower respiratory tract in both former and current smokers compared with never-smokers suggests that smoking cessation may be insufficient to return the lower respiratory tract to a composition similar to that of never-smokers (49). Future longitudinal studies on the airway microbiome of smokers are needed to address the question of whether cigarette smoke modifies the microbiome in such a way that would predispose smokers to develop COPD.

Clinical Impact of Smoking in COPD

Many former smokers with COPD continue to experience an accelerated rate of lung function decline and remain at risk for exacerbations, with subsequent impacts on morbidity and mortality (1, 19). Although smoking cessation usually improves respiratory symptoms, smoking cessation can induce complete symptom normalization only in the absence of airflow limitation (50).

In data from the ECLIPSE (Evaluation of COPD to Longitudinally Identify Predictive Surrogate Endpoints) observational study, the mean rate of lung function decline was 21 ml per year greater in current smokers than in former smokers (51). This was also observed in a *post hoc* analysis of the TORCH (TOwards a Revolution in COPD Health) study, in which rates of FEV_1 decline were similar in the active treatment arms, and FEV_1 declined fastest in current smokers (52). Compared with those who have never smoked, former smokers have accelerated lung function decline, which continues for many years after smoking cessation (23).

Usually, patients with COPD may present clinically as having chronic productive cough, mucus, and respiratory exacerbations, which are more common in the chronic bronchitis phenotype, whereas a dry cough, dyspnea, air trapping, and hyperinflation usually indicate the presence of emphysema (1) (Figure 1). Chronic bronchitis, independently of having concomitant airway obstruction, is associated with poor quality of life, exacerbations, and increased lung function decline. Among current or former smokers, those with chronic bronchitis had poorer quality of life, reduced exercise capacity, and more frequent respiratory events than those without chronic bronchitis (53). In a multivariate analysis to determine factors associated with

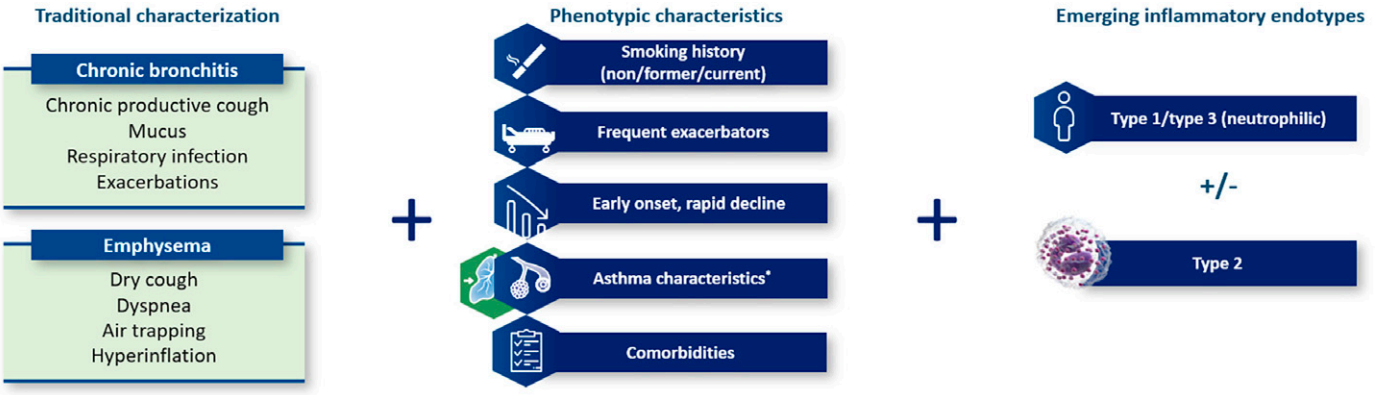

Figure 1. Phenotypes and inflammatory endotypes of chronic obstructive pulmonary disease (COPD). *Global Initiative for Chronic Obstructive Lung Disease guidelines no longer recognize asthma–COPD overlap syndrome and instead emphasize that asthma and COPD are two separate diseases (1).

chronic bronchitis and preserved lung function, current smoking and higher tobacco exposure were significantly associated with nonobstructive chronic bronchitis (53). Furthermore, markers of inflammation are present independently of having obstructive airway disease. In fact, among 830 participants with smoking history (current and former smokers) enrolled in SPIROMICS (SubPopulations and InteRmediate Outcome Measures in COPD Study), the concentrations of an acute phase reactant, C-reactive protein, were elevated in smokers with normal spirometry but clinical symptoms compared with their asymptomatic counterparts and never-smokers (54). Among smokers with normal spirometry, C-reactive protein and sTNFRSF1A were associated with clinical evidence of airway disease, including respiratory symptoms, chronic bronchitis, and exacerbations. These findings suggest that systemic markers of inflammation, including C-reactive protein and sTNFRSF1A, are elevated and inflammation is present among symptomatic smokers with preserved spirometry (54).

Current Smoker Is a Phenotype of COPD

Several studies have attempted to identify phenotypes on the basis of clustering of radiologic and clinical characteristics; however, it has been difficult to link these phenotypes, or clusters, to molecular mechanisms to describe endotypes (55, 56). In 2012, the Spanish COPD guideline (GesEPOC) identified four clinical phenotypes: nonexacerbator, mixed COPD–asthma, exacerbator with emphysema, and exacerbator with chronic bronchitis (57). Common phenotypic characteristics that help characterize patients with COPD include, but are not limited to, smoking history, exacerbation frequency, onset of disease, characteristics of comorbid asthma, and the presence of other comorbidities, such as cardiovascular and metabolic diseases (1) (Figure 1). Identifying endotypes in COPD has proved difficult; however, emerging evidence suggests diverse pathways involved in the severe inflammatory response seen in COPD. As an example, some patients with COPD have elevated eosinophil counts in both sputum and blood, though not always correlated, which can be interpreted as evidence of a type 2 signature or type 2 inflammation (58) (Figure 1).

Importantly, smoking has been proposed as a new clinical phenotype in COPD and not just a risk factor (59). Evidence suggests that phenotypes of COPD developed from smoking may be different than those caused by other environmental insults (57, 60), including differences in where the injury is present: more distal or proximal, respectively (61). Patients with smoking-induced COPD more commonly exhibited an emphysema phenotype, compared with those with biomass smoke–induced COPD, who more commonly exhibit a COPD phenotype with features of airway disease and increased hyperreactivity (60). Current smoking in COPD has been associated with a higher risk of first hospital admission for acute exacerbation of COPD (62); however, other studies have shown no difference in hospital admissions according to smoking status (63, 64). Previous reports have indicated impairment in patient quality of life in current smokers with COPD, both mental and physical, and improved quality of life after smoking cessation (65–68).

Pharmacologic Treatment Effects Differ in Former and Current Smokers

Evidence exists for differential treatment effects in former and current smokers, across a variety of studies, including inhaled corticosteroids, macrolide, and biologic therapies (69–74) (Table 1 and Figure 2). In SUMMIT (Study to Understand Mortality and Morbidity in COPD), inhaled corticosteroids plus long-acting β_2-agonists reduced exacerbations versus placebo by 36% in former smokers and by 19% in current smokers (70). A similar result was observed in the IMPACT (Informing the Pathway of COPD Treatment) study, in which the addition of inhaled corticosteroids to long-acting muscarinic antagonists plus long-acting β_2-agonists reduced exacerbations by 30% in former smokers and by 14% in current smokers (71). The observed steroid resistance in current smokers in these studies may be mediated by a cigarette smoke–induced reduction in histone deacetylase 2, which is required for glucocorticoid receptor interactions and the full antiinflammatory effects of corticosteroids (75, 76).

In a subgroup analysis of a randomized trial of azithromycin therapy in COPD, a significant reduction in the time to first exacerbation was observed in the subgroup of former smokers, with little treatment effect observed in the subgroup of current smokers (69). One potential explanation for these results is that cigarette smoke may interfere with azithromycin effects on mucin production via MUC5AC upregulation (77, 78).

In a proof-of-concept study of the CXC motif chemokine receptor 2 antagonist MK-7123, which targets the IL-8 receptor to reduce neutrophil trafficking, MK-7123 significantly improved lung function and decreased the time to first exacerbation in the subgroup of current, compared with former, smokers (73). In one report, the number of neutrophils in bronchiolar lavage fluid from current smokers was higher than in former smokers (79), suggesting a possible mechanism by which efficacy was observed in current smokers but not former smokers in this trial. In a phase 2b clinical trial, itepekimab, a human monoclonal antibody against IL-33, significantly reduced exacerbations and improved lung function in former smokers with COPD. This significant response was attenuated or not present in current smokers (74). These findings await confirmation in ongoing phase 3 clinical trials. A recent study may provide a biological explanation for the observed differential efficacy of itepekimab in former and current smokers, in which IL-33 expression at the transcriptomic and protein levels was reduced in lung tissue exposed to cigarette smoke, possibly because of a decrease in resting basal cells (80). These observations suggest that itepekimab may be less efficacious in current smokers because of a diminished number of IL-33–containing basal cells in the airway epithelium.

Even though the results from different studies cannot be compared directly, this body of information suggests that former smokers and current smokers with COPD experience different treatment effects, demonstrating the power of phenotyping to identify patients with COPD for tailored treatments. These findings also provide additional motivation for smoking cessation, to maximize the benefits from certain pharmacological therapies.

Table 1. Differential Treatment Effects in Former and Current Smokers with Chronic Obstructive Pulmonary Disease

	Former Smoker	Current Smoker
Azithromycin (antibiotic)[69]	↓ Time to first exacerbation HR = 0.65 (95% CI: 0.55, 0.77) vs placebo; $P < 0.0001$	— Time to first exacerbation HR = 0.99 (95% CI: 0.71, 1.38) vs placebo; $P = 0.95$
	Significant treatment difference between former vs current smokers; $P = 0.03$	
ICS (anti-inflammatory)		
SUMMIT (ICS/LABA)[70]	↑ FEV_1 in former smokers vs current smokers *Mean improvement:* 22 mL (95% CI: 1, 43) in former vs current smokers; $P = 0.038$*	
	↓ Moderate or severe exacerbations in former smokers vs current smokers 36% (95% CI: 27, 43) reduction in former vs 19% (95% CI: 7, 29) in current smokers; $P = 0.013$*	
IMPACT (ICS + LAMA/LABA)[71,72]	↓ Exacerbations 30% reduction (95% CI: 23, 36) vs LAMA/LABA; $P < 0.001$ Regardless of blood eosinophil count	↓ Exacerbations 14% reduction (95% CI: 2, 24) vs LAMA/LABA; $P < 0.05$ With blood eosinophil counts >200 cells/μl
	Significant treatment difference between former vs current smokers; $P = 0.011$	
Anti-CXCR2 (IL-8 receptor); reduces neutrophil chemotaxis[73]	— Post-bronchodilator FEV_1 - change from baseline at 6 months −8 mL (95% CI: −73, 43) vs placebo†	↑ Post-bronchodilator FEV_1 - change from baseline at 6 months 168 mL (95% CI: 84, 252) vs placebo; $P = 0.037$
	— Likelihood of having a first exacerbation HR = 1.55 (95% CI: 0.89, 2.70) vs placebo†	↓ Likelihood of having a first exacerbation HR = 0.51 (95% CI: 0.27, 0.97) vs placebo†
Itepekimab (anti-IL-33)[74]	↑ Pre-bronchodilator FEV_1 - change from baseline 90 mL (95% CI: 20, 150) vs placebo; $P < 0.01$	— Pre-bronchodilator FEV_1 - change from baseline 20 mL (95% CI: −50, 90) vs placebo, NS
	↓ Moderate or severe exacerbations RR = 0.58 (95% CI: 0.39, 0.85) vs placebo, $P = 0.0061$	— Moderate or severe exacerbations RR = 1.09 (95% CI: 0.74, 1.61) vs placebo, $P = 0.65$

Definition of abbreviations: ↑ = significant increase; ↓ = significant decrease; — = no effect; BD = bronchodilator; CI = confidence interval; CXCR2 = chemokine (C-X-C motif) receptor 2; EOS = eosinophil; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; IMPACT = Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment; ICS = inhaled corticosteroid(s); IL = interleukin; LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; NS = not significant; RR = relative risk; SUMMIT = Study to Understand Mortality and Morbidity in Chronic Obstructive Pulmonary Disease.
The results across different treatments cannot be directly compared as the study designs and populations differ between different trials.
*Results from ICS and/or LABA of former smokers vs placebo compared with ICS and/or LABA of current smokers vs placebo.
†No *P* value was reported.

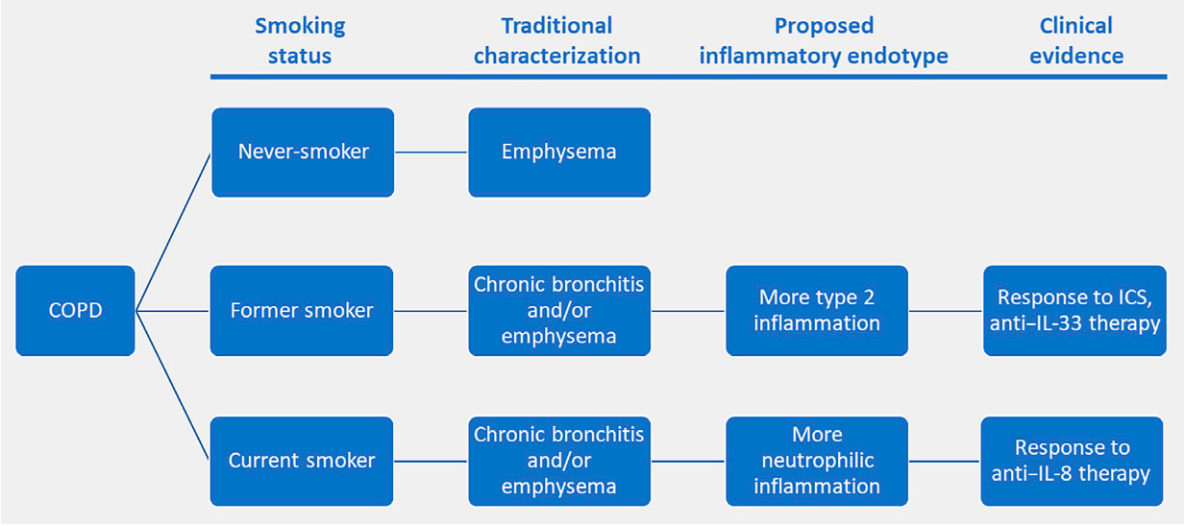

Figure 2. The role of smoking status as a phenotype in COPD. COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid.

Importantly, smoking status is a variable that can change over time. Those who have quit smoking for more than 6 months have an 87% lower risk of smoking resumption compared with those with less than 6 months of abstinence (81), making this an important milestone in becoming a former smoker. Important questions on the transition from current to former smoker remain. How long after smoking cessation can the inflammation and damage from smoking change? Can the lung ever "recover" or "forget" smoking-related changes? Both current smokers and patients who stop smoking continue to have inflammation. Nevertheless, studies have shown that smoking cessation slows the accelerated decline in FEV_1, which strongly indicates that important inflammatory or remodeling processes (or both) are positively affected (50). Although both current smokers and nonsmokers need treatment, these different phenotypes have different responses to therapeutic approaches, providing an opportunity for a more precise treatment.

Conclusions

Smoking status is an important variable for assessing patients in clinical practice, as well as to improve our understanding of the pathophysiology in COPD. This review provides evidence that "current smoker" represents an important clinical phenotype of COPD with therapeutic implications. As 38–47% of patients with COPD may still have tobacco or other smoke exposure, efforts toward helping them quit are warranted. A better understanding of the local and systemic mechanisms implicated in COPD progression are very important to help develop targeted therapies to overcome the devastating disease for both patients and society in general. ■

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