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Inflammatory Diseases of the Lung Induced by Conventional Cigarette Smoke

A Review

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Smoking-induced lung diseases were extremely rare prior to the 20th century. With commercialization and introduction of machine-made cigarettes, worldwide use skyrocketed and several new pulmonary diseases have been recognized. The majority of pulmonary diseases caused by cigarette smoke (CS) are inflammatory in origin. Airway epithelial cells and alveolar macrophages have altered inflammatory signaling in response to CS, which leads to recruitment of lymphocytes, eosinophils, neutrophils, and mast cells to the lungs—depending on the signaling pathway (nuclear factor-κB, adenosine monophosphate-activated protein kinase, c-Jun N-terminal kinase, p38, and signal transducer and activator of transcription 3) activated. Multiple proteins are upregulated and secreted in response to CS exposure, and many of these have immunomodulatory activities that contribute to disease pathogenesis. In particular, metalloproteases 9 and 12, surfactant protein D, antimicrobial peptides (LL-37 and human β defensin 2), and IL-1, IL-6, IL-8, and IL-17 have been found in higher quantities in the lungs of smokers with ongoing inflammation. However, many underlying mechanisms of smoking-induced inflammatory diseases are not yet known. We review here the known cellular and molecular mechanisms of CS-induced diseases, including COPD, respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, acute eosinophilic pneumonia, chronic rhinosinusitis, pulmonary Langerhans cell histiocytosis, and chronic bacterial infections. We also discuss inflammation induced by secondhand and thirdhand smoke exposure and the pulmonary diseases that result. New targeted antiinflammatory therapeutic options are currently under investigation and hopefully will yield promising results for the treatment of these highly prevalent smoking-induced diseases. CHEST 2015; 148(5):1307-1322

ABBREVIATIONS: 8-IP = 8-isoprostane; A1A = α_1-antitrypsin; A1AD = α_1-antitrypsin deficiency; AEP = acute eosinophilic pneumonia; AMP = antimicrobial peptide; CRS = chronic rhinosinusitis; CS = cigarette smoke; DI = deletion/insertion; DIP = desquamative interstitial pneumonia; e-cigarette = electronic cigarette; GM-CSF = granulocyte-macrophage colony-stimulating factor; HBD = human β defensin; ICS = inhaled corticosteroid; ILD = interstitial lung disease; MMP = metalloprotease; NF-κB = nuclear factor-κB; PDE = phosphodiesterase; PLCH = pulmonary Langerhans cell histiocytosis; PP2A = protein phosphatase 2A; RB-ILD = respiratory bronchiolitis-interstitial lung disease; RR = relative risk; SIRT = sirtuin; TLR = Toll-like receptor; TH2 = type 2 helper; TNF = tumor necrosis factor

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Tobacco has been smoked for > 1,100 years, with peak consumption of 4,345 cigarettes per person in the United States in 1963. Over the last 50 years, there has been a dramatic reduction of smokers from 50% of men and 33% of women smoking to 20% and 15%, respectively.[1] However, 61 million Americans actively smoke and are at risk for developing one of many known inflammatory diseases of the lung (Table 1). It is estimated that 600,000 people worldwide die of secondhand smoke exposure every year.[2] In addition, approximately 40% of children worldwide are regularly exposed to secondhand cigarette smoke (CS), which will lead to pulmonary disease in the next generation.

CS contains > 4,000 chemicals, including 100 known carcinogens and 900 suspected carcinogens.[3] Detailed toxicologic studies have revealed a multitude of immunomodulatory chemicals and gases, components that damage lung epithelium.[4] Pulmonary damage from CS leads to inflammation and a compromised immune state, which allows opportunistic pathogens to cause infections, furthering the body's inflammation through generation of inflammatory modulators.[5] CS also increases the virulence of pathogens colonizing the airways, increasing pulmonary infections in that manner.[6] The cycles of smoking-induced damage followed by remodeling and repair involve all compartments of the respiratory system, from the large conducting airways to the single-cell alveolar walls. This repetitive cycle of damage, inflammation, remodeling, and repair leads to destruction (emphysema) and deposition of collagen and elastin (fibrosis). These processes lead to all of the smoking-induced diseases described to date.[7]

Electronic cigarettes (e-cigarettes) are the latest nicotine delivery devices, and their impact on human health remains unknown. During the 12 years since their invention by Hon Lik in China, multiple small studies have been done to evaluate their components, with the findings that e-cigarettes do contain some of the harmful chemicals found in CS,[8,9] and that e-cigarette vapor may impede antimicrobial activities of cells in the airways and promote bacterial virulence.[10] Only three clinical cases of pulmonary disease related to e-cigarette use have been reported to date: acute eosinophil pneumonia (AEP), lipoid pneumonia, and bronchiolitis. All three resolved with cessation of e-cigarette use. Longitudinal studies are needed to evaluate the safety of e-cigarettes and determine whether they will also cause inflammatory diseases and cancer.[11]

We review here the known inflammatory changes in lung cells induced by CS exposure and the inflammatory diseases that result (Table 1). We begin with the latest data on mechanistic pathways, followed by CS-induced diseases in adult smokers, and conclude with inflammatory disorders induced by passive (secondhand) smoke exposure and reported danger from residual smoke particle (thirdhand) exposure.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed for articles published from January 1971, to February 2015, by use of the terms "lung cells AND inflammation AND cigarette," "lung inflammation AND cigarette" (limited to humans), "chronic obstructive pulmonary disease (COPD) AND inflammation AND cigarette (or smoking)," "alpha-1-antitrypsin AND cigarette AND inflammation," "desquamative interstitial pneumonia (DIP) AND inflammation AND cigarette," "Respiratory bronchiolitis-interstitial lung disease (RB-ILD) AND inflammation AND cigarette," "acute eosinophilic pneumonia (AEP) AND inflammation AND cigarette," "chronic rhinosinusitis AND inflammation AND cigarette," "Pulmonary Langerhans cell histiocytosis (PLCH) AND cigarette AND inflammation," "secondhand smoke AND inflammation," and finally, "thirdhand smoke." Articles published in English were included.

Cellular and Molecular Changes Induced by Cigarette Smoke That Lead to Lung Inflammation

Cells

Within the lung parenchyma, multiple cell types are affected by and respond to CS inhalation: small and large airway and alveolar epithelial cells, fibroblasts, WBCs, and endothelial cells. Within the airways, exposure to CS leads to higher BAL cellularity, via increases in both macrophage and neutrophil populations. CS exposure increases leptin expression, a type-1 cytokine expressed in human bronchial epithelial cells, pneumocytes, and lung macrophages. Increased leptin drives further increases in BAL cellularity through recruitment of dendritic cells and $CD4^+$ and $CD8^+$ T lymphocytes into the airways.[12-15]

Cytokines and Proteases

Inflammatory cytokines IL-1β; IL-6; IL-8; monocyte chemoattractant protein-1; macrophage inflammatory protein 1α; regulated on activation, normal T-cell expressed and secreted (RANTES); tumor necrosis factor (TNF)-α; IL-12(p40); and IL-17 are significantly increased in the BAL of smokers. Inflammatory cytokines activate lung endothelial cells to increase adhesion