Clearing the smoke

Smoke is a solid. Whether from cigarettes, cooking fires or other sources, it is comprised of tiny particles that injure the lung and can lead to lung cancer and chronic obstructive pulmonary disorder, characterized by laborious breathing. Steven D. Shapiro and his colleagues take a look at imaging data in people suggesting that these two conditions have more in common mechanistically than was previously thought. Both diseases seem to stem in part from the ability of inhaled particles to trigger inflammation, a process examined by Robert M. Senior and his colleagues.

■ BEDSIDE TO BENCH

Common origins of lung cancer and COPD

A McGarry Houghton, Majd Mouded & Steven D Shapiro

It should come as no surprise that habitual cigarette smokers frequently develop lung cancer and chronic obstructive pulmonary disease (COPD). It happens so frequently, in fact, that in the US, the two diseases represent the second- and fourth-leading causes of death, respectively[1], and are epidemic worldwide. That both diseases often arise in the same person has been traditionally ascribed to bad luck and one too many cigarettes, with little thought that the two diseases might be linked by more than smoking alone. Yet, in the mid-1980s, Tockman *et al.*[2] and Skillrud *et al.*[3] independently demonstrated that lung cancer incidence increased in individuals with COPD as their forced expiratory volume in one second (FEV1, a measurement of airflow) declined, a relationship that withstood correction for lifetime cigarette smoke dosage. Even so, it is difficult to imagine common mechanisms between two diseases that seem to be diametrically opposed. Lung cancer is a manifestation of uncontrolled cell proliferation, whereas COPD is characterized by inflammation-mediated destruction of the extracellular matrix and cell death.

The past two decades of research have done little to expose the nature of the link between these two diseases. Major obstacles to defining the relationships between them have been their heterogeneous natures and subtle onsets. However, recent use of computed tomography chest imaging has provided a close-up view of the lung, allowing investigators to distinguish between the two major features of COPD—destruction of the tiny air sacs in the lung resulting in airspace enlargement (emphysema) and narrowing of the breathing tubes resulting in obstruction to air flow (airways disease).

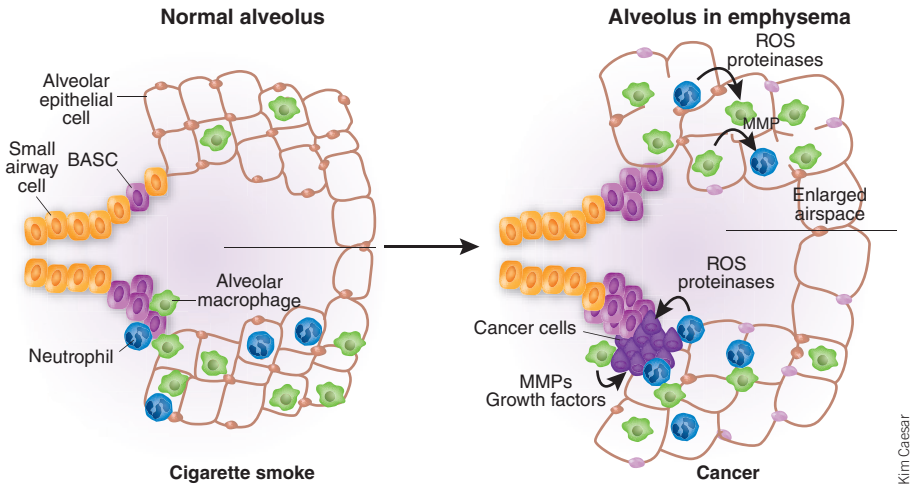

Figure 1 Hypothesized common origins of emphysema and lung cancer. Under normal conditions, lung homeostasis is preserved via low-level cell turnover with alveolar macrophages patrolling the lower airspace to remove invading pathogens and particles. Upon exposure to cigarette smoke, inflammatory cells, particularly neutrophils and macrophages, are recruited and activated, causing them to release serine and matrix metalloproteinases (MMPs) and reactive oxygen species (ROS). Emphysema results when extracellular matrix destruction and cell death exceeds reparative capacity leading to airspace enlargement. BASCs attempt to replace damaged alveolar cells and maintain alveolar integrity. However, repeated induction of BASC proliferation in the context of cigarette carcinogens and inflammatory proteinase-mediated release of growth factors predisposes these cells to become malignant, leading to bronchogenic carcinoma.

Using this approach, de Torres *et al.*[4] asked the following question: does lung cancer risk correlate with airway obstruction, emphysema or both? Their results show that the presence of mild emphysema, even without demonstrable airflow obstruction, confers a substantial risk of developing lung cancer. Although the relative risk of developing lung cancer in individuals with emphysema increased with co-existing airflow obstruction, a reduction in FEV1 alone was not associated with increased risk. The results of de Torres *et al.*[4] have already been validated in a much larger study[5].

The most striking finding is that just a whiff of emphysema—completely independent of cigarette-smoking burden and history of other lung disease—predisposes an individual to lung cancer. This is an entirely new concept and, as such, will require the generation of new mechanistic hypotheses and scientific models to fully understand the clinical findings.

Two hypotheses that might link these anatomic and functionally disparate diseases are related to inflammation and the body's attempt to repair emphysematous airspaces (**Fig. 1**).

Emphysema begins when cigarette smoke induces low-grade inflammation with production of matrix-degrading proteinases, particularly elastases, in excess of antiproteinases[6]. Cell

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death accompanies matrix destruction, which occurs when cells lose their attachment to the scaffold, as well as through oxidative stress. Neutrophils and macrophages, the culprits in emphysema, had been thought to valiantly fight a losing battle against aggressive cancers, but it is now obvious that these cells can be manipulated to work for the wrong side. Responding to bioactive substances within the tumor microenvironment, the same inflammatory cell proteinases responsible for emphysema are capable of releasing growth and other factors from the matrix that tumor cells are anxious to use[7].

The fact that patients with COPD who are treated with inhaled corticosteroids have reduced incidence of lung cancer and death suggests that inhibiting inflammation can retard lung tumor growth. The question is, which specific inflammatory mediators operative in emphysema also promote tumorigenesis and how?

After inflammatory injury, it is likely that progenitor cells attempt to repair the damaged air sacs. Of several candidate cell types, the most intriguing is the bronchoalveolar stem cell (BASC), which, although located in the mouse small airway, has been hypothesized to replenish the peripheral portions of the lung where emphysema develops[8]. Yet because emphysema is not caused by a one-time insult, but rather by chronic, persistent inflammation, the otherwise quiescent BASCs are under constant pressure to proliferate and repopulate damaged areas of the lung. However, it is a fine line between controlled and uncontrolled cell proliferation, particularly in this carcinogen-rich, inflammatory milieu. Indeed, BASC cells give rise to lung adenocarcinoma in the mouse model of K-ras–induced malignancy[8].

Although there is not any direct proof that BASCs can repair lung injury, nor is there proof that they are the sole inducers of bronchogenic carcinoma in mice—let alone in humans—the development of lineage-tagged and lineage-ablated stem cells and their application to mouse models of emphysema and cancer may help elucidate their role. Although cigarette smoke exposure in mice reproducibly leads to both the inflammation and the subsequent airspace enlargement characteristic of human emphysema[9], it does not typically lead to lung cancer. However, combing of this emphysema model with genetically engineered or carcinogen-induced cancer models would allow for the study of tumor growth within an emphysematous microenvironment. Moreover, these same models can be used to dissect inflammatory mediators common to both diseases.

The onus is clearly on the 'bench' side of the equation to uncover the mechanisms responsible for this unexpected 'bedside' observation[4]. Identification of a therapeutic target that links COPD and lung cancer would bolster our treatment strategies for these largely incurable diseases. While searching for better treatment, clinicians must continue to fight an uphill battle against the most addictive substance known and continue to repeat their plea to patients: don't light up.

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■ BENCH TO BEDSIDE

Smoke particulates stress lung cells

Tracy L Adair-Kirk, Jeffrey J Atkinson & Robert M Senior

Inflammation is central to the development of chronic obstructive pulmonary disease (COPD), a disease often triggered by cigarette smoke and smoke from biomass fuels[1]—yet the mechanisms responsible for inflammation in COPD remain undefined. Recent findings by Dostert *et al.*[2] and Kelsen *et al.*[3] provide molecular insight into two pathways that modulate the inflammatory response to inhaled particulates (**Fig. 1**). One pathway involves the 'inflammasome', an intracellular protein complex that mediates the activation of proinflammatory cytokines. The other involves the endoplasmic reticulum (ER) stress–induced unfolded protein response (UPR), which triggers the expression of proinflammatory genes.

Inflammasomes are composed of a member of the nucleotide-binding oligomerization domain (NOD)–like family of pattern recognition receptors (such as NALP3, also called cryopyrin), the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and pro–caspase-1. Stimulation of NALP3 recruits ASC and pro–caspase-1, which results in autocatalytic processing and activation of caspase-1. Active caspase-1 in turn cleaves procytokines, such as interleukin-1β (IL-1β) and IL-18, into their active forms, causing inflammation.

Dostert *et al.*[2] examined the production of IL-1β by human macrophage-like cells in response to various particulates. They found that urate crystals, silica particles and asbestos particles induced the secretion of active IL-1β in a manner dependent on the NALP3 inflammasome. Intracellular reactive oxygen species (ROS) generated by failure of phagocytosis ('frustrated' phagocytosis) of these particles were crucial for the activation of the NALP3 inflammasome. Intriguingly, blood monocytes also showed activation of the NALP3 inflammasome with silica particles, but this activation occurred independently of ROS[4], indicating that the mechanisms by which the same particle activates the NALP3 inflammasome may vary between cell types.

Dostert *et al.*[2] also discovered that cigarette smoke and diesel exhaust, which contain smaller-sized particles than asbestos and silica, did not activate the NALP3 inflammasome in human macrophage-like cells and did not trigger IL-1β production. These studies suggest that, contrary to widespread thinking, the macrophage is not responsible for the initial inflammatory response to inhaled smoke, and that other cell types respond first.

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