Mucus secretion is the first-line defense against the barrage of irritants that inhalation of approximately 500 L of air an hour brings into the lungs. The inhaled soot, dust, microbes, and gases can all damage the airway epithelium. Consequently, mucus secretion is extremely rapid, occurring in tens of milliseconds. In addition, mucus is held in cytoplasmic granules in a highly condensed state in which high concentrations of Ca\(^{2+}\) nullify the repulsive forces of the highly polyanionic mucin molecules. Upon initiation of secretion and dilution of the Ca\(^{2+}\), the repulsion forces of the mucin molecules cause many-hundred-fold swelling of the secreted mucus, to cover and protect the epithelium. Secretion is a highly regulated process, with coordination by several molecules, including soluble N-ethyl-maleimide-sensitive factor attachment protein receptor (SNARE) proteins, myristoylated alanine-rich C kinase substrate (MARCKS), and Munc proteins, to dock the mucin granules to the secretory cell membrane prior to exocytosis. Because mucus secretion appears to be such a fundamental airway homeostatic process, virtually all regulatory and inflammatory mediators and interventions that have been investigated increase secretion acutely. When given longer-term, many of these same mediators also increase mucin gene expression and mucin synthesis, and induce goblet cell hyperplasia. These responses induce (in contrast to the protective effects of acute secretion) long-term, chronic hypersecretion of airway mucus, which contributes to respiratory disease. In this case the homeostatic, protective function of airway mucus secretion is lost, and, instead, mucus hypersecretion contributes to pathophysiology of a number of severe respiratory conditions, including asthma, chronic obstructive pulmonary disease, and cystic fibrosis. Key words: mucin, mucus, asthma, chronic obstructive pulmonary disease, cystic fibrosis. [Respir Care 2007;52(9):1134–1146. © 2007 Daedalus Enterprises]
Introduction

Inhalation of approximately 12,000 L of air a day bombardst the airway epithelium with up to 25 million particles an hour.\(^1\) Cigarette smoking more than doubles that amount.\(^2,3\) As a result, the airway epithelium has developed ways to combat this onslaught of soot, dust, microbes, and allergens. The first-line defense against inhaled insult impinging on and damaging the epithelium is the production of mucus. This mucus is a viscoelastic gel that forms a thin film on the surface of the airways (Fig. 1). It is an important homeostatic defense mechanism with a variety of functions (Table 1) that have evolved to reduce epithelial damage by inhaled irritants. Under normal circumstances, airway mucus protects the epithelial lining by entrapping foreign debris, bacteria, and viruses, and clearing them from the airway by ciliary movement, a process termed mucociliary clearance\(^4\) (Fig. 2). In contrast, in clinical conditions associated with airway mucus hypersecretion, such as asthma,\(^5\) chronic obstructive pulmonary disease (COPD),\(^6,7\) and cystic fibrosis (CF),\(^8\) the mucus shifts from a protective role to one that contributes to respiratory disease (see Fig. 2). Excessive production of airway mucus, termed mucus hypersecretion, and changes in the biophysical properties of the mucus can impair mucociliary clearance, with associated accumulation of mucus in the lungs (Fig. 3), leading to difficulty in breathing, morbidity, and, in severe cases, mortality. The latter aspects are covered in the present article, after a general introduction to airway mucus and the physiology of airway mucus secretion.

Airway Mucus

Airway mucus is a complex dilute aqueous solution of lipids, glycoconjugates, and proteins. It contains electrolytes, enzymes and anti-enzymes, oxidants and antioxidants, exogenous bacterial products, endogenous antibacterial secretions, cell-derived mediators and proteins, plasma-derived mediators and proteins (see Fig. 2), and cell debris such as deoxyribonucleic acid (DNA). Airway mucus is believed to form a liquid bi-layer; an upper gel layer floats above a lower, more watery sol, or periciliary liquid, layer\(^9\) (see Fig. 2). It is likely that a thin layer of surfactant lies between the sol and gel phases\(^10\) (see Fig. 2). The function(s) of the sol layer is debated, but is presumed to include “lubrication” of the beating cilia. The surfactant layer might facilitate spreading of mucus over the epithelial surface. The gel layer traps particles and is moved on the tips of the beating cilia. The inhaled particles are trapped in the sticky gel layer and are removed from the airways—a process termed mucociliary clearance. When the mucus reaches the throat, it is either swallowed and delivered to the gastrointestinal tract for degradation, or, if excessive, as in respiratory disease, it is coughed out as “sputum.”\(^4\)

Respiratory tract mucus requires the correct combination of viscosity and elasticity (viscoelasticity) for optimal efficiency of ciliary interaction.\(^6,11\) Viscosity is a liquid-like characteristic and is the resistance to flow and the capacity to absorb energy when moving. Elasticity is a solid-like property and is the capacity to store energy that moves or deforms the fluid. Viscoelasticity is conferred on the mucus primarily by high-molecular-weight mucous glycoproteins, termed mucins.

Respiratory Tract Mucins

In health, mucins comprise up to 2% by weight of the airway mucus.\(^12\) In the airways, mucins are produced by goblet cells in the epithelium\(^13\) (see Figs. 2 and 4) and sero-mucous glands in the submucosa\(^12\) (Fig. 5).
Mucins are long, thread-like, complex glycoconjugates (see Fig. 4). A mucin consists of a linear peptide backbone (termed apomucin), which is encoded by specific mucin (MUC) genes (see below), to which hundreds of carbohydrate side-chains are O-linked, but also with additional N-linked glycans. The glycosylation pattern is complex and extremely diverse,\(^{15}\) and is associated with complementary motifs on bacterial cell walls, which facilitates broad-spectrum bacterial attachment and subsequent clearance.\(^{16,17}\) Within the main protein core are variable numbers of tandemly repeated serine-rich and/or threonine-rich regions, which are unique in size and sequence for each mucin,\(^4\) and represent sites for mucin glycosylation. These complex glycoproteins are polydisperse, linear polymers that can be fragmented, by reduction, to create monomers (see Fig. 4) termed “reduced subunits.”\(^{18–21}\) There are at least 2 structurally and functionally distinct classes of mucin, namely, the membrane-associated mucins (Table 2) and the secreted mucins (either gel-forming or non-gel-forming) (Tables 3 and 4). Membrane-tethered mucins, which have a hydrophobic domain that anchors the mucin in the plasma membrane, contribute to the formation of the epithelial surface.\(^4\) Secretory mucins are stored intracellularly in secretory granules and are released at the apical surface of the cell in response to a stimulus (see below). It would appear that mucus production is such a fundamental homeostatic process that virtually all the interventions that have been investigated trigger airway mucin secretion (Table 5). In addition, many of these same mediators when administered longer-term not only induce mucin secretion but also up-regulate MUC gene expression, with concomitant increases in mucin synthesis and associated goblet cell hyperplasia (see Table 5).

### Mucin Genes and Gene Products

Twenty human MUC genes have so far been identified (see Tables 2–4). Of these, only nine, namely, MUC1, MUC2, MUC4, MUC5AC, MUC5B, MUC7, MUC8, MUC11, and MUC13, are expressed in the human respiratory tract.\(^4\) Of these, only MUC2, MUC5AC, and MUC5B (the classic gel-forming mucins, see Fig. 4), are found in airway secretions. MUC5AC and MUC5B glycoproteins, localized adjacent to each other on chromosome 11p15.5, are considered the major gel-forming mucins in both normal respiratory tract secretions and airway secretions from patients with respiratory diseases.\(^{22–27}\) Interestingly, MUC5B appears to be unique in that it is not polymorphic. Small amounts of MUC2 may, however, be found in secretions from “irritated” airways (see below).

In general, the MUC gene products are poorly characterized biochemically and biophysically.\(^{12}\) The predicted sequences of the MUC1, 3A, 3B, 4, 11–12, 13, 15–18, and 20 gene products suggest they are membrane-bound, with an extracellular mucin domain and a hydrophobic membrane-spanning domain (see Table 2). In contrast, MUC2, 5AC, 5B, 6–9, and 19 gene products are secreted mucins (see Tables 3 and 4). The technology for studying the contribution to physiology and pathophysiology of the individual MUC gene products lags well behind that of in-
vestigation of gene expression. MUC1, 2, and 8 genes are expressed in both the epithelium and submucosal glands, whereas MUC4, 5AC and 13 are expressed primarily in the epithelium. In contrast, MUC5B and MUC7 genes are expressed primarily in the glands. Use of currently available antibodies confirms that the MUC5AC gene product is a goblet cell mucin, whereas MUC5B predominates in

Fig. 3. Mucus obstruction of the airways in asthma and chronic obstructive pulmonary disease (COPD). A: Mucus plugging in asthma. Complete occlusion by mucus (M) plugs of an intrapulmonary bronchus (arrow), cut in longitudinal section, in a patient who died of an acute severe asthma attack. B: Mucus (M) partially obstructing an extrapulmonary bronchus (transverse section: arrow) of an elderly, male, long-term cigarette smoker. C: Bronchoconstriction and luminal mucus in fatal asthma. Intrapulmonary airway (transverse section) of a patient who died of an acute severe asthma attack, showing airway epithelium (arrow) thrown into folds by smooth-muscle contraction, and occlusion by mucus (M) of remaining luminal space. This relatively small amount of mucus would not be expected to significantly reduce airflow in a relaxed, nonconstricted airway. D: Mucus (M) blocking an intrapulmonary airway (transverse section) of an elderly, male, long-term cigarette smoker (a different patient than that in panel B). Note the lack of airway constriction (in contrast to panel B) and the cellular infiltrate in the mucus. The arrow points to the epithelium.

vestigation of gene expression. MUC1, 2, and 8 genes are expressed in both the epithelium and submucosal glands, whereas MUC4, 5AC and 13 are expressed primarily in the epithelium. In contrast, MUC5B and MUC7 genes are expressed primarily in the glands. Use of currently available antibodies confirms that the MUC5AC gene product is a goblet cell mucin, whereas MUC5B predominates in the glands, albeit that some MUC5AC (and possibly MUC7) is also usually present. Interestingly, MUC4 mucin localizes to the ciliated cells.

The mucin content of secretions from patients with hypersecretory respiratory diseases may differ from normal. For example, MUC5AC mucin, initially isolated as a tracheobronchial mucin, is found in airway secretions pooled
Fig. 4. Airway mucin and mucin secretion. A: Goblet cell (GC) and ciliated cell (CC) in human bronchus. M = mucin-containing granules. C = cilia. L = lumen. B: Visualization of mucin exocytosis by a guinea pig tracheal goblet cell. Fusion of an intracellular mucin granule (arrow) with the apical membrane of the cell (arrow head) leads to the formation of a bi-membrane-spanning pore that rapidly opens out to form an “omega” (Ω) profile (shown), which allows release of stored mucin (M). In this image the mucin is retained in the granule, due to the use of tannic acid fixation. C: Predominant airway mucin gene products: modular motifs in amino acid backbones. MUC2, MUC5AC, and MUC5B are cysteine-rich secretory mucins. See Reference 4 for details of modular motifs. D: Mucin subunit. Each subunit (approximately 500 nm in length) comprises an amino acid backbone with highly glycosylated (linear) domains and folded regions, stabilized via disulphide bonds, with little or no glycosylation. Glycosylation is via O-linkages and is highly diverse. E: Mature mucin molecule. In secretions, the mucin subunits are joined end-to-end by disulphide bonds (S-S) to form long, thread-like mature mucin molecules.
from healthy individuals, and increased levels are present in the airways of patients with asthma. The expression of many genes, such as MUC5AC, in airway epithelial cells is regulated by various neurohumoral factors and inflammatory mediators (see Table 5). MUC5B mucins are a major component of tenacious mucus plugs from the lungs of a patient who died in status asthmaticus, and in sputum from patients with chronic bronchitis. From the above it appears that, in healthy individuals, MUC5B is mainly expressed in the airway submucosal glands, which are restricted to the more proximal, cartilaginous airways. In contrast, MUC5AC expression is generally restricted to goblet cells in the upper and lower respiratory tracts. Thus, the composition of normal mucus can be altered, depending on the relative contribution to the secretions of these different cellular sources.

In respiratory diseases associated with airway mucus hypersecretion, such as asthma, COPD, and CF, further changes in the composition of the mucus, and in the mucus secretory phenotype in general, are observed (see below).

**Mechanisms of Goblet Cell Exocytosis**

Exocytosis is an evolutionarily conserved and ubiquitous process whereby hormones, mediators, and other molecules are released from cells. For exocytosis of most vesicles to occur, a soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex has to be formed, which links the vesicle (v-SNARE) and the target cell membrane (t-SNARE) together, to facilitate release of vesicle content from the cell.

There are 2 general mechanisms by which exocytosis occurs, and these apply also to mucin exocytosis:

- **Constitutive (basal) secretion:** this secretion is unregulated and of a low level.
- **Stimulated secretion:** regulated exocytosis of granules in response to extracellular stimuli.
Mucin granules are present in the cytoplasm of airway mucin-secreting cells (see Fig. 4). Mucins are first synthesized on the rough endoplasmic reticulum, then oligomerized and sent to the Golgi for glycosylation and subsequent packaging and budding into mature mucin granules. The granules are stored in the cytoplasm, in preparation for release.

In airway goblet cells, exocytosis of mucin involves the movement of the mucin granule to the apical surface of the goblet cell. This movement is dependent upon many factors, including chaperoning to the plasma membrane via myristoylated alanine-rich C-kinase substrate (MARCKS) protein. Upon stimulation, MARCKS is phosphorylated by protein kinase C, released from the plasma membrane, and de-phosphorylated by protein phosphatase 2A, activated by protein kinase G. This allows MARCKS to be unbound and ready for actin/myosin binding to form an interaction with the secretory vesicle. Targeting to the secretory vesicle is mediated by its chaperone protein, Hsp70. Binding allows MARCKS to chaperone the mucin-containing vesicle to the apical membrane of the goblet cell.
let cell. As a result of MARCKS phosphorylation, the actin/myosin contracts, which allows the vesicle to fuse with the plasmalemma, and release mucin out of the cell. Munc-18 is also required for syntaxin binding to the plasmalemma. Docked granules have to mature to fusion-competence before they can undergo exocytosis. Munc-13--4 participates in this “priming” of airway goblet cell granules. Once at the plasma membrane, the mucin-containing granule forms a SNARE complex, irreversibly tethering the granule. Correct and complete formation of this MARCKS-guided SNARE complex has to occur before mucin exocytosis can take place, which forms an open conformation with the profile of an omega symbol (Ω), that links the mucin granule and apical cell membranes (see Fig. 4).

Once initiated, goblet cell mucin exocytosis obeys first-order kinetics: it is extremely rapid, taking only tens of milliseconds, during which time the released mucin expands many hundred-fold (Fig. 6). Rapid expansion occurs because the mucin is highly condensed within the granules, with the mucin threads bound together by high intragranular concentrations of Ca\(^{2+}\), which acts as a shielding cation. Mucin granules are polyanionic, so without the calcium present within the mucin matrix, such close packaging could not occur. Upon exocytosis, the Ca\(^{2+}\) is progressively diluted, allowing electrostatic expulsion to occur, a process accelerated by water uptake, resulting in expansion of the mucin into the airways. This is a normal, homeostatic process. However, excessive and prolonged exocytosis results in airway mucus hypersecretion, as seen in respiratory diseases such as COPD and asthma.

**Airway Mucus Hypersecretory Phenotype in COPD**

COPD comprises 3 overlapping conditions, namely, chronic bronchitis (airway mucus hypersecretion), chronic bronchiolitis (small airways disease), and emphysema (air space enlargement due to alveolar destruction). The following discussion considers the “bronchitic” component of COPD. The airways of patients with COPD contain excessive amounts of mucus (see Fig. 3), which is markedly increased above that in control subjects. The excessive luminal mucus is associated with increased amounts of mucus-secreting tissue. Goblet cell hyperplasia is a cardinal feature of chronic bronchitis, with increased numbers of goblet cells in the airways of cigarette smokers, either with chronic bronchitis and chronic airflow limitation, or with or without productive cough. Submucosal gland hypertrophy also characterizes chronic bronchitis and the amount of gland correlates with the amount of luminal mucus.

**Airway Mucus Hypersecretory Phenotype in Asthma**

Asthma is a chronic inflammatory condition of the airways, characterized by variable airflow limitation that is at least partially reversible, either spontaneously or with treatment. It has specific clinical and pathophysiological features, including mucus obstruction of the airways. There is more mucus in the central and peripheral airways in patients with chronic or severe asthma than in control subjects. The increased luminal mucus reflects an increase in the amount of airway secretory tissue, due to both goblet cell hyperplasia and submucosal gland hypertrophy, although the latter is not characteristic of all patients with asthma.

Airway mucus obstruction in asthma is particularly evident in a proportion of patients who die in status asthm-
maticus, where many airways are occluded by mucus plugs52–54 (see Fig. 3). The plugs are highly viscous and contain large amounts of plasma proteins (such as serum albumin), as well as DNA, cells, proteoglycans,55 and mucus.30,52,55 The plasma proteins are a result of increased plasma exudation56,57 (Fig. 7), which is a pathophysiological feature of asthma.58 Importantly, incomplete mucus plugs are found in the airways of asthmatic subjects who have died from causes other than asthma,59 which indicates that plug formation is a chronic, progressive process. The increased viscosity of the airway mucus in asthma could be due to an intrinsic abnormality in the secreted mucus30 or to interactions between mucins and plasma, whereby plasma synergistically increases the viscosity of mucin.60,61 (Fig. 8). The mechanisms underlying the latter increased viscosity are unclear, but may be due to plasma-induced rupturing of hydrogen bonds between adjacent mucin molecules, which promotes greater inter-tangling between mucin and albumin molecules, or to plasma limiting the normal hydration and swelling of secreted mucin.62 In addition to its thickening effect on mucin, luminal plasma would directly contribute to the increased amount of airway mucus, and may itself induce mucin secretion,63 leading to further increases in luminal mucus with high viscosity (see Fig. 8).

**Mechanisms of Airway Goblet Cell Hyperplasia**

Airway goblet cell hyperplasia is a prominent pathophysiological feature of COPD, asthma, and CF (see above), and is an often-used end point in animal models of respiratory disease.64 The cellular composition of the airway epithelium can alter both by cell division and by differentiation of one cell into another.65 There are at least 8 cell types in the airway epithelium of the conducting airways. In terms of goblet cell hyperplasia, differentiation is the major pathway for production of new goblet cells, and cell division is the major carcinoma pathway. The basal serous and Clara cells are considered the primary progenitor cells, because they have the capacity to undergo division, followed by differentiation into “mature” ciliated or goblet cells. In specific experimental conditions (eg, exposure to cigarette smoke), goblet cell division contributes in part to the hyperplasia. However, differentiation of nongranulated airway epithelial cells is a major route for production of new goblet cells,65–67 In experimental animals, production of goblet cells is usually at the “expense” of the progenitor cells, most notably serous and Clara cells, which decrease in number as goblet cell numbers increase. Serous-like cells and Clara cells are found in macroscopically normal bronchioles in human lung.68 Whether there is a reduction in number in respiratory disease has not been reported, but merits investigation. Reduction in the relative proportion of serous and Clara cells has pathophysiological importance because they produce a number of anti-inflammar
tory, immunomodulatory, and antibacterial molecules vital to host defense. For example, serous cells produce lysozyme, lactoferrin, secretory immunoglobin A, peroxidase, and at least 2 protease inhibitors. Clara cells produce Clara cell 10-kDa protein (also known as uteroglobin), Clara cell 55-kDa protein, Clara cell tryptase, β-galactoside-binding lectin, possibly a specific phospholipase, and surfactant proteins A, B, and D. Thus, in respiratory diseases associated with airway mucus hypersecretion it seems that not only is there goblet cell hyperplasia, with associated mucus secretion, mucin gene expression, and mucin synthesis, which, in turn, are associated with secretory cell hyperplasia, airway mucus hypersecretion and respiratory problems. EGF-R = epidermal growth factor receptor. MAP = mitogen-activated protein (kinases). hCLCA1 = human calcium-activated chloride channel. RAR = retinoic acid receptor.

Some of the mechanisms for development of airway goblet cell hyperplasia and the associated mucus hypersecretory phenotype in asthma and COPD are becoming clearer. Many regulatory and inflammatory mediators and enzymes increase mucus secretion and induce mucin gene expression, mucin synthesis, and goblet cell hyperplasia in experimental systems (see Table 5). These mediators are intermediates in a cascade of pathophysiological events leading from initiating factors (such as allergen exposure in asthma) to a chronic inflammatory/repair response, which in turn leads to mucus hypersecretion and associated airway obstruction and clinical symptoms (Fig. 9). A small number of key molecules may be involved in translating the actions of the different inflammatory mediators into airway mucus hypersecretion, namely, epidermal growth factor and its receptor tyrosine signaling pathway, the mitogen activated kinase and extracellular signal-regulated kinase (MEK/ERK) pathway, calcium-activated chloride channels, and the retinoic acid receptor (RAR)-α signaling pathway. A wide variety of small molecule antagonists and inhibitors of these pathways are currently in pharmacotherapeutic development.

Summary

Secretion of airway mucus is a vital homeostatic mechanism that protects the respiratory tract from a barrage of...
inhaled insult. The mucus has to be of the correct viscosity and elasticity for optimal interaction with the cilia and effective mucociliary clearance of particles from the lungs. Presumably because of the potential damage that inhaled irritants can do to the airway epithelium, the process of secretion is extremely rapid. In addition, because of the marked condensation of intragranular mucins, decondensation and subsequent secretion releases vast amounts of mucin onto the airway surface. However, over and above the rapid secretion in response to temporary inhaled insult, long-term, chronic increased secretion of airway mucus contributes to respiratory disease. In this case, the homeostatic, protective function of airway mucus secretion is lost and, instead, mucus hypersecretion contributes to disease. Airway obstruction by mucus is a common feature of a number of severe respiratory conditions, including asthma, COPD, and CF. To a certain extent, each disease has a particular hypersecretory phenotype, although a number of pathophysiological features are shared (eg, submucosal gland hypertrophy and goblet cell hyperplasia). Goblet cell hyperplasia, and the associated mucus hypersecretion, are particularly important in small airways. Mucus in these airways cannot be cleared by cough and tends to accumulate and cause obstruction. Goblet cell hyperplasia is at the expense of serous cells and Clara cells. The loss of the various anti-inflammatory, immunomodulatory, and antibacterial molecules normally secreted by these cells further compromises host defense.

In summary, mucus secretion is homeostatic, and mucus hypersecretion is not. Where the division lies between secretion and hypersecretion is not clear, but needs to be delineated for more precise and clinically useful diagnosis of airway mucus hypersecretory diseases.

REFERENCES

Discussion

MacIntyre: That was terrific. For somebody who doesn’t deal with this very often, that was very clear, thank you. I have 2 somewhat separate questions. Number one, and this is probably oversimplified, but you described secretions—a normal secretion and a hypersecretion. You say normal is normal and hypersecretion is abnormal. Is there not a state in the middle where a little hypersecretion is appropriate? It’s sort of like the sepsis cascade. You know, we think of these inflammatory mediators as all being bad.

Well, as a matter of fact, we evolved into creatures where this increased inflammatory response in sepsis is probably protective, and it’s only bad when it starts spinning out of control. So there probably is a hypersecretion state that is good, and protects us against viral infections and other infections, and stuff like that. I guess the question is that it’s not normal versus abnormal; it’s like normal at rest, normal hypersecretion, and then abnormal hypersecretion. Does that make sense?

Rogers: I couldn’t agree more with that. That’s the basis of the last question on my final slide. The airway epithelium has got to have mucus on it: mucus is clearly protective. It does all these wonderful things. Not least that it provides a barrier. We’re inhaling about 12,000 liters of air a day. In central London, where I work, it’s bringing millions upon millions of particulate matter into the airways on an hourly basis, and we’ve got to have airway mucus. It’s got viscoelasticity for mucociliary clearance, as well as the other protective mechanisms that it provides. And when, for example, asthmatics inhale pollen or other irritant, acute production of mucus is presumably protection against the inhaled pollen. But then the secretion subsides; so there is only transitory mucus hypersecretion, after which mucus secretion returns to “baseline.” So you’ve got normal mucus secretion, and you’ve got protective, transitory mucus hypersecretion.

MacIntyre: Which is good.

Rogers: Which is good; and absolutely what you want. But at some stage, if your airways are being repeatedly challenged by inhaled particulates, which in turn are setting up a chronic inflammatory response leading to airway remodeling into a mucus hypersecretory phenotype (eg, goblet cell hyperplasia and submucosal gland hypertrophy), you must reach a cutoff point where protective, transitory mucus hypersecretion shifts over into a chronic mucus hypersecretory phenotype, whereby the perpetual presence of excess mucus in the airways is pathophysiological. I don’t know where that cutoff point will be, because the chronic mucus hypersecretion will still be trying to be protective, but will merge into being non-protective: but, where is that merge point?

MacIntyre: Can I ask you another question? I am struck by the fact that emphysema doesn’t have any mucus. As you go down the human tracheobronchial tree, where do you start losing mucus glands? Emphysematous patients are dyspneic, but they certainly don’t cough mucus.

Rogers: This is the thing. You can visualize COPD as 3 interlinked Olympic rings set in a triangle. One is chronic bronchitis, or mucus hypersecretion; one is small airways disease, which is fibrosis, and the resultant stenosis, of the bronchioli; and the third is alveolar destruction, or emphysema. Clearly, in any one patient, you will not necessarily know the relative contribution of those 3 components to the pathophysiology and clinical symptomatology of the patient, unless they are hawking up great quantities of sputum. In the paper by Aikawa et al, the patients just had emphysema; they weren’t producing sputum. They had alveolar destruction, with big holes in their lungs. So, they didn’t seem to have the bronchitic component to their COPD, for whatever reason; but it might be genetic.


MacIntyre: But anatomically, where do you lose mucus glands?

Rubin: You go down until you lose cartilage, so you’ve got mucus glands until you’ve got cartilage.

MacIntyre: And how far down is that? 20. . . ?

Rubin: Not that far down. I’m not sure how far, but I don’t think it’s that far.
Rogers: Terminal bronchioles don’t have cartilage and don’t have glands, so in general you have glands where you have cartilage.

Rubin: The corollary to that is that some of the animal models that are used don’t have submucosal glands—typically, mice, rodents. So one of the reasons we think that there may be no air lung disease in the CF mouse model is the complete lack of submucosal glands, except for a single little submucosal gland right below the vocal cords. So there are very significant species differences, which makes it hard to extrapolate some of these things. Very nicely done, Duncan.

Also, to Neil: There are accumulating data now that there are conditions that are associated with decreased mucus secretion that may lead to more chronic infection inflammation. And primary mucus hyposcretion may actually be pathophysiologic in some of the diseases that we know of. But for asthma, in the last couple of years there’s been an interest in this entity called “secretory hyperresponsiveness” where patients with asthma are given methacholine as a challenge, and some of them clearly get a bronchoconstrictive element and then bronchodilate. Others still get a drop, but don’t respond to bronchodilators.

If you look at this, these are the patients who appear to respond more to cholinergic agent by producing these buckets of mucus, presumably something may be related to these patients, whether it’s the presence of neutrophil elastase, which can induce this phenotype, that may lead the really bad asthmatics to end up drowning in their secretions, because you’ve shown that. Have you any more information on what would make somebody have a hypersecretory response to these irritants, as opposed to a bronchospastic response?

Rogers: Yes, that’s a very interesting question. It’s something that fascinates me, and I’ve spoken about it with some of my clinical colleagues. There are clearly patients who have a more bronchospastic response with less secretion. In contrast, other patients produce a lot of mucus compared with the smooth muscle contraction. I’m not sure why that is, because the nerves go to the 2 different structures, to the airway submucosal glands and the smooth muscle. I’m not sure why there should be a difference.

Some patients certainly have “bronchorrhea,” which is a Japanese term, and one we don’t usually use in England or the USA. Bronchorrhea may be associated with excessive water secretion. Submucosal glands secrete water and, in experimental studies, cholinergic stimulation of glands will induce mucus secretion and also water secretion; this is via interaction with mucinergic M3 receptors. It could be that these patients have a polymorphism in the receptor whereby they produce more water in the secretion than mucus. Bronchorrhea secretions are excessive and certainly more watery than a typical mucus secretion, indicating a preferential stimulation of water than of mucus. Why that would be, I don’t know.

One possibility is that there’s a disproportionate change in the glands, whereby you get an increase in serous cells, which produce a more watery secretion, compared with mucous cells, which produce a more viscous secretion. Human glands comprise both serous and mucous acini. In COPD, there are many patients who demonstrate a disproportionate increase in mucus cells compared to serous cells. So there is the possibility of the reverse situation: a disproportionate increase in serous cells. It would be very interesting to make a histological study of the airway glands of patients with bronchorrhea.

Rubin: I know that Ruben Restrepo will be talking about adrenergic agents, but some of us have been interested that as asthmatics have come in with this hypersecretion, they may begin with very watery secretions, very much the way your nose runs during the allergy season. But during severe asthma, they develop these massively viscous secretions, and the concern might be that this may be a result of flogging in the airways with the β agonists. You showed a number of years ago that β-adrenergic stimulation produces a very viscous secretion. And I wonder if some of our asthmatics who are up in the critical care unit are doing so because they’ve been given such massive doses of β agonists.

Rogers: That’s a possibility. One of the things about β agonists is what you’ve alluded to already with your reference to the mouse, is that animals and human beings respond differently to drugs, and β agonists are one example. It’s very easy in research animals to show that β agonists stimulate mucus secretion. β agonists will do it, α-adrenergic agonists will do it, and you can show various interactions. However, in human airways, it’s much more difficult to demonstrate a secretory response to β agonists. It may depend on the distribution of receptors on the cells.

For example, cholinergic stimulation was once considered to induce submucosal gland secretion from both mucous and serous acini. In contrast, β-receptor stimulation would stimulate the mucous cells, whilst α-adrenergic stimulation causes the serous cells to secrete. But it depends on the distribution of the relevant receptors, and that will presumably have a genetic component. So, theoretically,
Physiology of Airway Mucus Secretion and Pathophysiology of Hypersecretion

there is a scenario where there may be preferential stimulation of mucus rather than serous secretion. But I don’t think that’s been systematically looked at.

Homnick: I’m interested in this concept of “tethered mucus” in asthma. I think it’s tethered to the goblet cells, is that correct?

Rogers: Yes, yes. I’m going to be showing a slide of that in my next talk. But we can discuss it now.

Homnick: I’d like to know, what is the mechanism? Is it incomplete exocytosis, or what is it?

Rogers: Well, that’s a very interesting question. In asthma there’s something strange about either the mucus itself, or the secretory process that refuses to release the mucus when it’s being extruded from the goblet cells. There’s continuity of mucus between the lumens and the cells. This incomplete release is not found in the airways of patients with COPD. So there’s something about asthma that leads to this phenotype. And the explanation by the authors was that in asthma the airway inflammatory cell profile comprises Th2 lymphocytes and eosinophils, whereas in COPD, macrophages and neutrophils predominate. The macrophages and neutrophils produce proteases, including elastase and matrix metalloproteases. And the hypothesis is that these proteases cleave the mucus, once it has been secreted, away from the goblet cells.

In contrast, lymphocytes and eosinophils do not produce appropriate proteases to cleave away the secreted mucus from the goblet cells—hence the tethering. But you would have to look at the kinetics of the system and at how the COPD protease enzymes actually work. For example, are they likely to cleave mucin molecules? Alternatively, it could be something more fundamental, like a difference in the exocytotic mechanism between asthma and COPD. But it hasn’t been explored.

1. Rogers DF. Mucoactive agents for airway mucus hypersecretory diseases. Respir Care; 2007;52(9):1176-1193.

Restrepo: What is the importance of the regional distribution of the serous cells or the mucus secretion? The reason why I ask is because, when you look at the studies for sympathomimetics and anticholinergics, they always talk about these regions of interest. And they will divide these areas of radioaerosol penetration and clearings into peripheral, transitional, and central regions. It looked to me, based on this computerized picture, that the serous cells and the mucus cells don’t have any homogenous distribution.

Rogers: That distribution is theoretically very important. The serous cells are at the periphery of the gland; moving in from there are the mucus cells that are producing mucus; then there is the collecting duct and ciliated duct. Based on this distribution of the different secretory acini, the theory is that on the outside there are the serous cells, which produce a more watery secretion (containing bacterial enzymes). Inside of them are the mucus cells, which produce a more viscous secretion (ie, mucin). And the theory is that the more watery secretion washes the more viscous mucus secretion into the collecting duct and out of the top of the gland. In addition, the glands have got smooth muscle bundles around them, which makes the glands contract, for example, in response to cholinergic stimulation. That contraction, combined with the more watery secretion flooding over the more viscous secretion, would help force the secretions out.

Restrepo: I guess the clinical importance of this distribution is because the sympathomimetics have the tendency to distribute toward the periphery, which actually correlates very well with the pathological changes of patients with COPD or chronic obstructive airway disease.

Rubin: Ruben, I think Dr Rogers was talking about the periphery in the center of an individual gland, distributed throughout the airways . . .

Restrepo: Oh, I’m sorry . . .

Rubin: . . . You’re discussing small airways having greater β agonist receptors and proximal to the trachea having cholinergic receptors, I think, so when we’re talking periphery, we’re using the term differently.

Restrepo: I was actually talking about the lung distribution. When you have this computerized version of the distribution of the . . .

Rogers: That was an individual gland. Professor Bill Whimster cut numerous histological sections through a human airway, and found that he’d also fortuitously cut sections through a submucosal gland. He “reconstructed” the gland using a computer-based image analysis system.1

1. Rogers DF. Physiology of airway mucus secretion and pathophysiology of hypersecretion. Respir Care 2007;52(9):1134-1146.

Restrepo: Well, if that is the case, what is the importance of the lung distribution of these cells? Are they homogenously distributed throughout the lung, or is there any difference on the regional distribution?

Rogers: That’s an interesting question, but it’s not really been addressed because of the magnitude of the task: sampling a whole lung to determine the regional distribution of the glands would be prohibitively demanding. However, many years ago, Restrepo and Heard1,2 did a lot of work with submucosal glands, but not extensive investigation of regional distribution along the airways.

Schechter: I’d like to ask about the proposition that some patients are mucus hypersecretors. That’s an interesting concept, and you even showed a slide indicating that there were differences in mortality, depending upon how these patients were categorized. How does one categorize a patient as a mucus hypersecretor? What criteria do you use for that classification? Are there specific criteria, or is it just a gestalt classification?

Rogers: It was what we might call a gestalt evaluation. There was a questionnaire, and one question asked, “Do you produce a lot of sputum?” They either did or they didn’t. So that was the definition of mucus hypersecretion in the metric. The data from the Copenhagen Heart Study where the population of Copenhagen was sampled. Originally, it was primarily a heart study, and acquired as much information as they could from everybody in Copenhagen, mostly by questionnaire. Professor Jorgen Vestbo and colleagues looked at the data from the perspective of respiratory epidemiologists interested in the respiratory parameters, one of which was chronic mucus hypersecretion, and how it related to parameters such as mortality, infection, hospitalization.1


Schechter: So that creates a problem with interpretation. Even if there was some objective measure of secretion that would allow you to categorize patients as hypersecretors, the problem would still be that the underlying disease process rather that the individual patient characteristics may be the cause of the mucus hypersecretion. So the cause of increased mortality might be the disease that is causing it rather than the presence or absence of the mucus per se.

Rogers: I agree. I’m not an epidemiologist, nor would I want to be; they have a very difficult job—dealing with populations is just too complex.

Schechter: Well, this is the point I am trying to make. We can have interesting discussions that focus at the molecular and at the cellular level, but the jump from the cellular level to the patient outcome level is one that we must make with caution.

Rogers: Absolutely!