Structure of the Airway Mucosa with Particular Emphasis on Secretory Cells

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INTRODUCTION

The epithelium lining the airways of the normal mammalian lung consist of many morphologically distinct cell types often with different but sometimes overlapping functions. In disease the integrity of the epithelium may be compromised such as in symptomatic asthma[1]. In bronchitis there are increased numbers of surface mucus-secreting cells and enlargement of submucosal glands[2]. Malignant transformation of specific epithelial cells may give rise to tumours of differing histologic phenotype[3] and in cystic fibrosis altered movement of ions and macromolecules through and between cells can lead to defective transepithelial water flux and drying of airway secretions[4]. Figure 1 shows that the airway wall comprises epithelial, lymphoid, muscular, vascular and nervous elements interspersed in a pliable connective tissue support arranged as: (i) a lining mucosa of surface epithelium supported by a reticular basement membrane and an ill-defined elastic lamina propria, in which there are bronchial blood vessels, nerve bundles and free cells (including fibroblasts and mononuclear cells), (ii) a submucosa in which lie the bulk of the mucus-secreting glands, muscle and cartilage plates and (iii) a relatively thin adventitial coat.

SURFACE EPITHELIUM

The airway epithelium includes the surface epithelium which lines all airways (nose to alveolus) and which is continuous with that forming the tubulo-acinar submucosal mucus-secreting glands which develop from the surface[5,6]. The stratified squamous epithelium lining much of the larynx gives way to one which is pseudostratified, ciliated and columnar when the trachea is reached. Where it is "pseudostratified" all cells rest on the basement membrane but not all reach the airway lumen (Figure 2). In man, this type of epithelium persists throughout the major bronchi, becoming simple cuboidal more peripherally. Ciliated cells predominate, interspersed by mucus-secreting (goblet) cells which are found regularly in the tracheobronchial tree (Figure 3) but rarely in bronchioles of less than 1 mm diameter[7].

A variety of cell types is recognized in airway surface epithelium: at least eight different epithelial cell types have now been delineated depending on species[8,9]. In addition, cells involved in the immune responses and its reactions may migrate through the epithelial basement membrane: some of these remain within the surface epithelium whereas other are in the process of passing through to the lumenal surface[10].

The terminal processes of sensory nervefibres whose cell bodies lie deep to the epithelium, pierce the epithelial basement membrane and lie surrounded by epithelial cells where they initiate airway reflexes such as bronchoconstriction and cough[11].

These endings may be inappropriately stimulated in conditions such as asthma and chronic bronchitis. The variety of cell types and their putative functions are listed in Table 1. Secretions produced by airway epithelial cells mix with a variety of macromolecules, ions and water whose passage from vascular compartment to airway lumen is largely controlled by the epithelium itself. Thus respiratory

tract fluid comprises a mixture of mucus-glycoproteins, glycosaminoglycans, proteins/peptides, lipids, antiproteases/anti-oxidants, ions and water whose origin is from both epithelial and vascular sources. The secretory cells are now considered in particular detail:

Mucous cell

In human trachea, the normal mean density of surface mucous cells (Figure 4) is estimated at between 6,000-7,000 cells per mm^2 surface epithelium[12]. By electron microscopy, the mucous cell has electron-dense cytoplasm containing electron-lucent, confluent granules of about 800 nm diameter (see Figure 5). Most contain high-molecular-weight glycoprotein which is acidic due to sialic acid or sulphate groups located at the ends of the oligosaccaride side chains, which branch from a backbone of protein[13]. Secretion of the correct amount of mucus with an optimum viscoelastic profile is important in the maintenance of normal mucociliary clearance[14]. Alterations in the predominant histochemical type of mucus have been associated with airway irritation, carcinogenesis chronic bronchitis and cystic fibrosis (see below) but no novel glycoprotein moiety is produced. The numbers of mucus-secreting cells increase in chronic bronchitis and, experimentally in animal models of bronchitis, following inhalation of sulphur dioxide[15] or tobacco smoke[16,17]. Their increase in number and extension to the peripheral bronchioles is one characteristic of small airways disease (see 3). The mucous cell is clearly capable of division and may show stem cell multi-potentiality[18].

The solubility and viscosity of mucus varies considerably with ionic strength and divalent cations, such as calcium, cause mucus to form a rigid cross-linked gel which may be difficult to clear by mucociliary action or cough. High calcium and sulphate content is reported in tracheobronchial secretions of patients with cystic fibrosis (CF)[19]. In biopsy studies, mucous cells from patients with CF have been shown to contain significantly raised intracellular calcium and

sulphate levels and lower potassium levels than those of patient with chronic bronchitis[20]. The clinical significance of these results is as yet unclear.

Serous cell

Serous cells have electron-dense cytoplasm, much rough endoplasmic reticulum and, in contrast to mucous cells, discrete electron-dense granules of about 600 nm diameter (Figure 6). Morphologically, serous cells of the surface epithelium resemble those present in the submucosal glands.

They have been described in surface epithelium only in the rat, cat, young hamster and fetal humans[21]. In the author's experience they are also found normally in human small bronchi and bronchioli. Many contain neutral mucin and there is evidence that some may also contain a non-mucoid substance, probably lipid[22].

Clara (non-ciliated bronchiolar) cell

Clara cells in man are restricted in location to the terminal bronchioles where they typically bulge into the airway lumen and contain electron-dense granules of about 500-600 nm diameter, ovoid in man but irregular in most other species[23] (Figure 7).

The function of this cell type is as yet undetermined. It may produce a carbohydrate (hypophase) component of surfactant[24] or an antiprotease[25,26] and is known to have ion-absorbing and secreting properties[27]. Furthermore, the Clara cell acts as the stem cell of small airways where basal and mucous cells are normally sparse: both ciliated and mucous cells may develop from the Clara cell subsequent to its division and differentiation (see 18).

Dense-core granulated (DCG) cell (Synonyms: endocrine, Kultchitsky and Feyrter cell)

Argentaffin-positive and argyrophilic cells have been identified within the surface epithelium by light microscopy. By electron microscopy, DCG cells are infrequently found, generally basal in position, but often with a thin cytoplasmic projection reaching the airway lumen (see 3,28). Single cells and clusters of such cells may also be associated with nervefibres (i.e. so-called neuroepithelial bodies or neurite-receptor complexes) (see 3,29). The cytoplasm of DCG cells usually contains large numbers of small (70-150 nm) spherical granules each with an electron-dense core surrounded by an electron-lucent halo. Granule subtypes have been described and the cells may contain biogenic amines[30] or peptides such as bombesin[31] which, when released, may influence vascular and bronchial smooth muscle tone, mucous secretion and ciliary activity. The location of the cell in surface epithelium and its cytoplasmic content make it a prime candidate for sensing hypoxia in the airway lumen. It is likely that, as a consequence, vasoactive substances are released which cause local vasoconstriction and shunting of blood to better ventilated zones of the lung.

Indeterminate and transitional cells

Many non-ciliated cells fall into the category of "indeterminate", a classification category comprising a mixture of cells, none of which is clearly classifiable. In addition, normal epithelium may show a number of cells each of which shows features transitional to two or more morphologically well-defined cell types (see 3). For example:

(i) **Serous-mucous cells** may be rarely found in normal specific-pathogen free (SPF) rats, but are frequent in rats made "bronchitic" by inhalation of cigarette smoke. The may also be found in areas of grossly normal human epithelium in lungs resected for carcinoma. The cells contain secretory granules of the mucous type with electron-dense cores resembling serous granules.

(ii) **Clara-mucous cells** may be found after irritation by sulphur dioxide (see 3) or multiple injections of the beta-adrenergic agonist isoprenaline sulphate. The transitional cell retains the protruding apex, abundance of smooth endoplasmic reticulum and many of the electron-dense granules of the Clara cell but additionally has many large mucous granules.

(iii) **DCG-mucous cells** transitional forms have been found by histochemistry in the gut and by electron microscopy in both gut and bronchi (see 3).

(iv) **Basal-mucous-squamous cell** - tracheobronchial epidermoid metaplasia is a change from an epithelium which is pseudostratified, mucus-secreting and ciliated to one which is stratified and keratinized. McDowell and colleagues[32] have presented evidence and argued convincingly that such an epidermoid change arises subsequent to division of mucous cells rather than arising directly from existing basal cells. Experimentally carcinogens, mechanical trauma and vitamin A deficiency may each induce changes in mucous cells leading to squamous cell metaplasia with or without stratification and keratinization[33].

(v) **Ciliated-secretory cells** have been identified after injections of isoprenaline sulphate in rats and also occasionally in resected human lung (see 3). The cell retains the electron-lucent cytoplasm of the ciliated cell with apical microvilli and ciliary basal bodies, but cilia are absent and there are secretory granules in the cytoplasm.

(vi) **Secretion by ciliated cells** - the surfaces of ciliated cells are densely covered by 200-300 cilia per cell, each normally beating at

about 1,000 times per minute with its effective stroke generally in a cranial direction. Cilia move the overlying mucous sheet only by their tips, the interaction of the ciliary tips and mucus being facilitated by minute terminal hooklets[34]. Long slender microvilli project between the cilia and are associated with an acidic surface mucosubstance, probably a glycosaminoglycan, which may be an important source of mucosubstance[35-38]. The rich microvillar border and associated pinocytotic vesicles may play a role in ion translocation and fluid absorption and thereby control the depth of the periciliary fluid layer in which the cilia beat.

Basement membrane

Seen by light microscopy the basement membrane supporting the surface epithelium consists of at least two morphologically distinct regions: (i) the basal lamina (i.e. the so-called "true basement membrane"), itself composed of three zones, together made up of type IV collagen, laminin, glycosaminoglycans and fibronectin and II a deeper reticular lamina of fine fibrillary type III collagen (i.e. reticulin). In healthy bronchi, the combined thickness of the two zones is about 10μm but this may increase in chronic inflammatory conditions including mild and chronic asthma[1,39].

SUBMUCOSAL GLANDS

The submucosal glands in man are relatively numerous and in the lower respiratory tract are found wherever there is supportive cartilage in the airway wall, i.e. from larynx to small bronchi. The volume, distribution and histochemical composition of gland cells shows considerable species variation[8,40]. It has been estimated that some 4,000 glands are present in the human trachea[41] (Figure 8a). Developing from surface epithelium *in utero*, each gland unit is of the tubulo-alveolar type and in man may be composed of four regions whose lumena are continuous: (i) a relatively narrow ciliated duct in continuity with the surface epithelium, (ii) and expanded collecting duct of cells of indeterminate morphology or of eosinophilic cells (also referred to as "oncocytes") packed with mitochondria, (iii) mucous tubules and mucous acini (Figure 8b) and (iv) serous acini[42]. The movement of ions and water from the vascular compartment to the airway lumen is regulated by both surface epithelium and submucosal glands[43]. In the latter, it is suggested that watery, serous secretions pass from the outermost regions of each gland into the mucous tubules and mix and that the ionic balance to the mixed secretion may be adjusted in the collecting duct before its discharge through the ciliated duct to the bronchial lumen. Discharge is aided by contractile myoepithelial cells which form a basket-like structure around the outer aspects of the acinus.

Both synthesis of intracellular section and discharge are influenced by nerves whose terminals lie adjacent to (in humans) or pierce the secretory unit (as in the cat)[11]. There is evidence that both parasympathetic and sympathetic agonists stimulate secretion although the quantity and quality of the resulting secretion may differ with each[44]. Submucosal glands form a major source of tracheobronchial mucus with the balance contributed to by surface epithelium, the ratio dependent upon the nature of the stimulus. Submucosal gland mass increases in chronic bronchitis, asthma and cystic fibrosis; the increase being due to cell

proliferation within each secretory acinus rather than to an increase in the number of gland units per se[45].

GLYCOPROTEIN HISTOCHEMISTRY

The normal histochemical profile of cellular glycoprotein varies with airway level, stage of maturation and species. In man, the mucus-secreting cells of human airways may produce either neutral, acidic glycoproteins or a mixture of these, the acidity due to sialic acid and/or sulphate esters[46-48]. The majority of surface secretory cells contain a glycoprotein with sugar side chains having terminal sialic acid, penultimate galactose residues and a variable content of sulphate esters. The high iron diamine-alcian blue procedure demonstrates mainly sulphomucin in surface epithelium. The ratio of radioactive sulphate to glucosamine uptake is higher in surface than submucosal gland mucous cells and several studies indicate a highly sulphated acidic secretion from the surface[49,50], particularly in cultured epithelial cells from patients with cystic fibrosis[51].

The cells of mucous and some serous acini of the submucosal glands both contain a glycoprotein with sulphate esters. Serous acini differ from mucous acini in producing a secretion with less carbohydrate, little or no sialic acid and no terminal or penultimate galactose[49]. There is evidence from several studies that serous cells may normally produce secretory component of IgA, lysozyme, lactoferrin, albumin-like molecules and a glycosaminoglycan[52-55]. Alterations in the predominant histochemical type of glycoprotein have been shown in disease and following experimental irritation.

In "fatal" bronchitis there is a reduction in the proportion of sialomucin susceptible to digestion by the enzyme sialidase and an increase in sialomucin resistant to such digestion and of sulphomucin also[56,57].

After experimental irritation by sulphur dioxide or tobacco smoke there is a shift from sialomucin to sulphomucin[15,48] and a similar shift is seen in human smokers[58].

CONCLUSION

The bronchial mucosa comprises epithelial, lymphoid, muscular, vascular and nervous elements interspersed in a pliable connective tissue support.

The tracheobronchial epithelium includes the "surface" lining epithelium and that which forms the submucosal mucus-secreting glands: these are continuous with each other and with the epithelium lining the alveoli and nasal passages. The variety of epithelial secretory cell types and their secretions which have been described herein sever to protect the most distal respiratory portion of the lung from pollutants and infection.

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Table 1

Summary of Cell Functions

a) Epithelium	Function/s	b) Submucosal glands	Function/s	c) Nerve	Function/s
Ciliated	Moves mucus Secretes muco-substance Controls periciliary fluid	Serous	Mucus-secreting (neutral) Secretory piece (component) Lactoferrin Antiprotease Lysozyme	NEB	chemo/mechano-receptor modulation of - growth - vessel & bronchial tone - mucosal secretion
Mucous	Mucus-secreting (acidic) Absorptive Proliferative			nerve terminals	sensory leads to reflex: - bronchoconstriction - secretion - hyperpnoea
Serous	Mucus-secreting (neutral) Secretory piece (component) Periciliary fluid Proliferative	Mucous	Mucus-secreting (acidic) Stimulus-induced proliferation		
Clara	Surfactant-Hypophase Proliferative	Oncocyte	Ionic + water modulation Degenerate acinar cell		motor, modulates - ciliary rate - secretory - endocrine response
DCG/ Endocrine	Secretes amines (5-HT) Peptides (e.g. bombesin)	Myoepithelial	Expulsion of mucus		
Brush	Function unknown	Lymphocyte	Immuno-responsive		
		Endocrine	Secreto-regulatory Vaso-regulatory		
Basal	Proliferative				
Lymphocyte	Immuno-responsive	Intra-acinar nerve	Secreto-regulatory		
Globule leucocyte	Transports immunoglobulins Self-cure phenomenon Release of inflammatory mediators				
Special-type Indeterminate	Function(s) unknown				