

Review article

Tissue remodelling in upper airways: where is the link with lower airway remodelling?

Tissue remodelling reported in upper airways include epithelial hyperplasia, increased matrix deposition in the nasal or paranasal lining, matrix degradation and accumulation of plasma proteins. Genetic influences, foetal exposures and early life events may contribute to structural changes such as subepithelial fibrosis from an early age. Other structural alterations are related to duration of the disease and long-term uncontrolled inflammation. Structural changes may increase alteration of the protective functions of the upper airways namely by affecting mucociliary clearance and conditioning of inspired air.

The sequences of tissue changes during wound repair of upper airway mucosa after surgery are illustrative of the complexity of tissue modelling and remodelling and could be considered as an important source of information for a better understanding of the complex relationship between inflammatory reaction, of the subsequent tissue damages and fibroblast metabolism of upper airways.

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Several years ago, Bousquet et al. proposed as definition of remodelling 'model again or differently, reconstruct' following the Oxford Dictionary (1).

Remodelling is a critical aspect of wound repair in all organs representing a dynamic process which associates matrix production and degradation in reaction to an

inflammatory insult leading to a normal reconstruction process (model again) or a pathological one (model differently). However, it also appears that some components of remodelling are constitutional and may be genetically driven (2). Finally, this definition stresses the close relationship between the initial inflammation and the subsequent tissue damage.

In asthma, it is now well accepted that, in addition to the classical inflammation, structural changes are always present in the airways and include epithelial disruption and goblet cell hyperplasia, mucous gland hypertrophy, enhanced airway collagen deposition, airway myofibroblasts transformation, increased matrix protein deposition, smooth muscle hypertrophy and hyperplasia and an increased number of collagen IV-positive blood vessels (3, 4). Remodelling may be constitutive but appears to be increased by inflammation (5, 6).

Remodelling in the nose is more complex. In allergic rhinitis, nasal remodelling may exist, but, even if the links between rhinitis and asthma are evident (7, 8), it is far less extensive than in the bronchi of asthmatics. These differences between upper and lower airways could be considered as a consequence of different embryologic origin (9).

After trauma or surgery in airways, a scar may be observed as a pathological consequence of abnormal remodelling. Finally, there are other nasal or paranasal sinus conditions presenting some degrees of remodelling which can significantly interfere with the normal functions of the respiratory mucosa.

Normal nasal and paranasal mucosa

The nasal mucosa is the first physical barrier to foreign materials and a conditioner for inhaled air. The nose and, also probably the paranasal sinuses, also assume largely other functions mainly necessary for conditioning the inspired airflow (10).

The nasal epithelium is separated from the lamina propria by a continuous basement membrane (Fig. 1A). The pseudostratified columnar epithelium (respiratory epithelium) is composed of four major types of cells: ciliated, nonciliated, goblet and basal cells. A functional nasal mucosa can assure mucus production and transport, resorption of surface materials, and formation of new epithelial cells. The proportion of goblet cells was higher in inferior turbinate and lower in the nasal septum (11). Just beneath the basement membrane, lymphocytes and plasma cells form the lymphoid layer of the lamina propria. The supporting connective tissue is of loose type and its extracellular matrix (ECM) component plays an essential role in inflammatory reactions. The subepithelial region also contains two layers of sero-mucous glands: the superficial layer is situated just underneath the epithelium, and the deep layer under the vascular layer. Besides resistant vessels, such as arteries, arterioles or

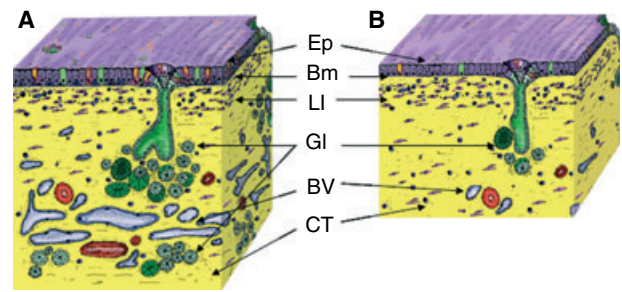


Figure 1. Histomorphological view of normal (A) nasal and (B) paranasal mucosa (Ep: epithelial cells; Bm: basement membrane; LI: lymphoid layer; Gl: glands; BV: blood vessels; CT: connective tissue).

capillaries, the vasculature of the nose is characterized by capacitance vessels, designated as 'erectile tissue'. This vascular component is mainly concentrated on the middle and inferior turbinates, the septum and may extend posteriorly to the choanal orifices. With these vascular specificities, the nasal mucosa can regulate the airflow, adapt the nasal resistance, filter and condition the inspired air by producing nasal mucus, sustaining a mucociliary transport and serving as support for immune response.

The mucosa isolated from maxillary sinuses is slightly different, mainly thinner and less specialized than nasal mucosa (Fig. 1B). The respiratory epithelium is lower and contains less goblet cells (12). The epithelium contains fewer cilia than the nasal mucosa (13). The basal lamina is always easily identifiable. The glands are fewer and smaller and the venous erectile plexus is absent (14).

The differences in mucosal structures could be explained by differences in flow of inspired air (15) or in extent of mesodermisation during the formation of the mid-face and nasal cavities from *in utero* weeks 4–12. It is probable that other hypotheses will appear when the intrinsic functions of the paranasal sinuses can be better defined.

The inflammation occurring in this region is frequent and many pathological processes could induce chronic types of inflammation. These situations lead regularly to structural changes in epithelium or lamina propria, but the precise relation remains unclear (16).

Model again: wound repair after sinus surgery

A wound is a pathological state in which tissue becomes separated or destroyed after trauma or surgery, and results in loss of body substance and function. Wound healing can be defined as a complex process by which there is restoration of anatomical integrity and of function after injury (Fig. 2).

Wound healing of the nasal and paranasal lining is a highly organized and well co-ordinated process, involving

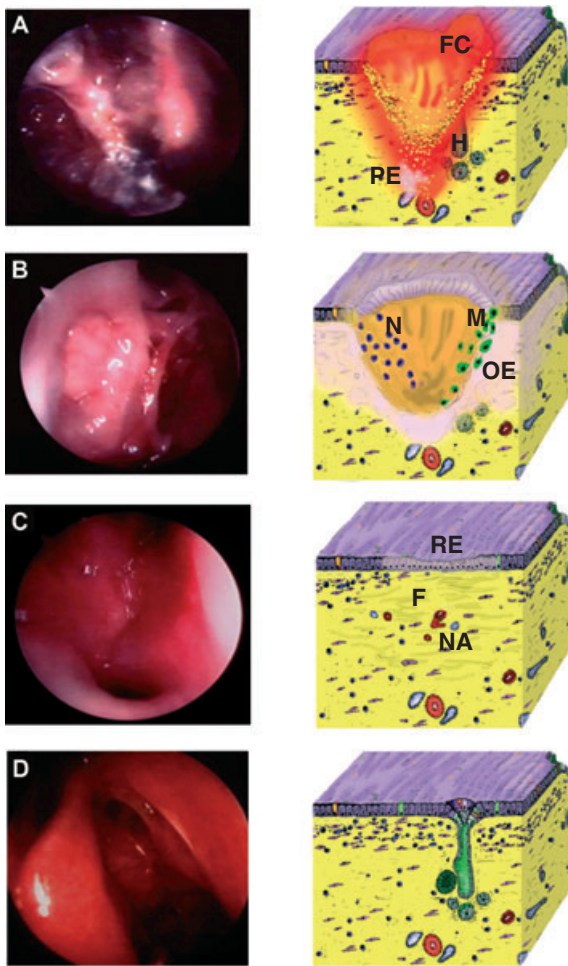


Figure 2. Endoscopic views after sinus surgery (Hopkins endoscope 30°; left column) and their corresponding physio-pathological phases (right column). (A) Phase 1: Endoscopic view – crusts formation inside the wound field; pathological view – massive haemorrhage (H), plasma exudation (PE) and clot formation (FC). (B) Phase 2: Endoscopic view – severe inflammatory reaction with oedema (OE), neutrophil (N) and macrophage (M) recruitment; pathological view – important neutrophilic recruitment and macrophage proliferation. (C) Phase 3: Endoscopic view – residual oedematous and inflammatory reaction; pathological view – active neoangiogenesis (NA), fibroproliferation (F) and re-epithelialization (RE). (D) Phase 4: endoscopic view – normalization of the paranasal mucosa; pathological view – recovery of mucosa structures.

inflammation, cell proliferation, matrix deposition and remodelling, and is regulated by a wide variety of growth factors and cytokines. In this condition, tissue remodelling appears to be essential for recovery of the organ function.

The different phases of wound repair are reflected by different endoscopic features. During the first days after wound healing, massive crust formation is observed within the wound field (Fig. 2A). Since the second week, granulation tissue covered the operated cavities (Fig. 2B)

and is gradually replaced by oedema from week 4 (Fig. 2C). At weeks 6–8, the endoscopic view reveals a normalization of the paranasal lining (Fig. 2D).

The different physiological processes involved in wound repair are proceeding in a sequential manner (17). Following injury to the nasal mucosa the coagulation phase starts with exposure of platelets to the connective tissue. It results in an immediate release of vasoactive substances and the formation of a primary haemostatic plug. Damaged nasal cells release growth factors necessary for secondary chemotaxis of inflammatory cells, while fibrin, in conjunction with fibronectin, acts as a provisional matrix for the influx of monocytes and fibroblasts (18).

In the nasal lamina propria, an intense inflammatory reaction starts simultaneously with the coagulation phase. This inflammation is marked by an infiltration of neutrophils, recruited by tissue debris or fibroblasts (19). This neutrophilic inflammation predominates during the first hours with a simultaneous release of proteases. Three to five days after injury, the neutrophilic population in the wound is replaced by monocytes and macrophages, which contribute to cellular debridement and to amplification and support of the wound-healing process (20). Macrophages of the nasal lamina propria provide a continuing source of cytokines necessary to stimulate proliferation of fibroblast and angiogenesis. Lymphocytes interact with the macrophages during the inflammatory process, linking the immune response to wound healing.

Through a variety of cytokines from platelets and macrophages or through an autocrine regulation, fibroblasts are attracted to the nasal wound and they gradually switch their major function to protein synthesis and cytokine release. Migration of new respiratory cells from the undamaged areas starts within a few hours (21). During angiogenesis, nasal endothelial cells start to proliferate through fragmented basement membranes, through the actions of angiogenic growth factors released from injured nasal cells, platelets and ECM. Furthermore, for diapedesis and migration, most cells produce proteinases able to degrade the ECM (22).

In the remodelling or maturation phase, the inflammatory response and angiogenesis diminish, while the intense fibroblast proliferation starts to attenuate. The composition of ECM changes as the wound matures and the dynamic balance between collagen synthesis and lysis is responsible for the maturation of the wound (23). Typically, poor healers present parallel bundles of fibroblasts and ECM in the recovered connective tissue.

Recently, it was demonstrated that patients with poor-healing reaction after sinus surgery presented significantly more oedema or fibrosis when compared with good healers (24) and significantly higher amounts of matrix metalloproteinase (MMP)-9 in both nasal secretions and connective tissue (25). Interestingly, the changes observed at both endoscopic level and histomorphological level were correlated with significant differences in the MMP

and Tissue Inhibitors of Metalloproteinases (TIMPs) profiles and neutrophilic inflammation (26).

Model differently: different pathological conditions

In humans, tissue remodelling in the upper airways cannot be restricted to the very limited tissue damage occurring during allergic rhinitis. Depending on the initial induction (inflammation, trauma), the upper airways can present different types of remodelling: allergic inflammation in allergic rhinitis, persistent oedema and in chronic rhinosinusitis (CRS) with nasal polyps, purely fibrotic tissue like nasal adhesions, or mixed oedema and fibrosis as CRS without nasal polyps.

Allergic rhinitis

Tissue remodelling occurring in nasal mucosa is still a matter of debate and requires more studies (Fig. 3A, B). It mainly concerns the mucosal lining of the nasal cavity with little data on the paranasal sinuses. Important reviews have been recently published (9, 27, 28).

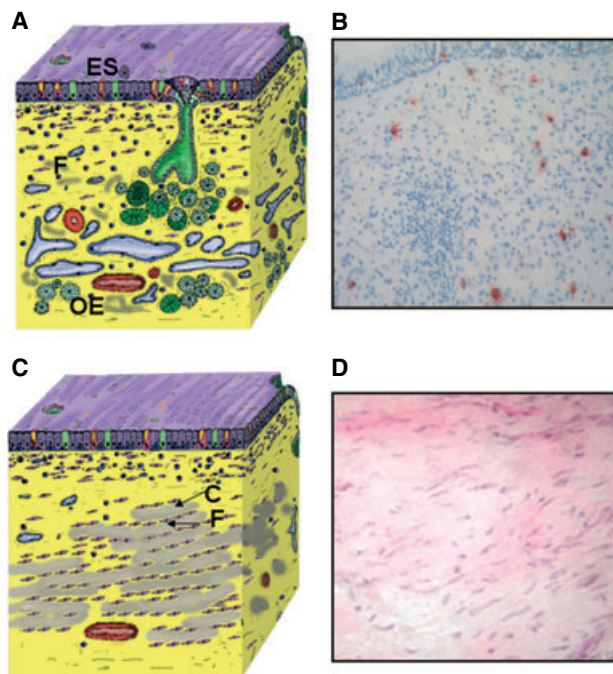


Figure 3. Major types of extracellular matrix remodelling in nasal mucosa. Schemes illustrating the major changes in lamina propria (left column) and corresponding pathological views (right column). (A) Allergic rhinitis: epithelial shedding (ES), mild to moderate fibrosis (F) and oedema (OE). (B) Allergic rhinitis: tryptase staining for mast cells (magnification $\times 200$). (C) Nasal adherence: presence of parallel bundles of collagen-like fibres (C) and active fibroproliferation (F). (D) Nasal adherence: haematoxylin and eosin staining (magnification $\times 400$).

Sanai et al. demonstrated that there is a change in the proportion of different collagens within the nasal airways in perennial rhinitis, with increased amounts of collagen types I and III, in comparison with that in the nonallergic nose (29). By stereological measurement of vascular surface and volume densities in nasal tissue comparing rhinitic and nonrhinitic mucosa, other authors have revealed a lack of vascular remodelling response in the allergic nasal mucosa (30). Only a minor degree of epithelial shedding and limited oedema was noted in the ciliary areas (31, 32). Other authors have not shown significant change in shedding or thickness of basement membrane when comparing controls and perennial allergic nasal mucosa (33). Interestingly, the bulk exudation of plasma into the airway tissue (vascular exudation) and lumen (mucosal exudation) occurring during allergic rhinitis is limited and reversible. The albumin extravasation and consequent remodelling may be different in acute allergen exposure compared with chronic exposure (34). Increased angiogenesis has also been suspected (35, 36).

However, all authors agree on the existence of limited tissue damage in nasal mucosa in allergic rhinitis when compared with the extensive remodelling of the bronchial asthmatic mucosa.

Nasal adhesions or synechiae

Nasal adhesions are always acquired as the result of trauma, which is usually iatrogenic (Fig. 3C, D). Chemical cautery agents injudiciously applied and virtually any minor nasal surgery, can produce them (37). Fibrotic bridges are seen connecting the turbinates, usually the inferior, to the septum or to the lateral nasal wall. Adhesions often do not produce any symptoms, though if they are extensive they can cause obstruction. However, adhesions in the upper airways, even in middle ear, are likely to obstruct mucociliary clearance and thus enhance the risk of prolonged and recurrent infection (38).

The adhesions are organized into parallel bundles of fibroblasts separated from each other by massive deposition of ECM material. This particular organization of fibroblasts and ECM is common to poor healers at the nose or paranasal sinuses level.

Other nasal fibrotic diseases

Excluding tumours developed from mesenchymal cells or surrounded by collagen deposition, rare diseases such as eosinophilic angiocentric fibrosis (39) can also lead to massive fibrosis in nasal mucosa.

Chronic rhinosinusitis with or without nasal polyps

Recently, the definition of rhinosinusitis has been revised as an inflammation of the nose and the paranasal sinuses characterized by two or more symptoms (blockage, discharge, facial pain, reduction of smell) and either

endoscopic signs (polyps, discharge from middle meatus, oedema/mucosal obstruction in the middle meatus) and/or CT changes within ostiomeatal complex and/or sinuses (40, 41). The presence of nasal polyps distinguishes two subgroups: CRS with or without polyps.

Chronic rhinosinusitis without nasal polyps. The mucosal lining in CRS without polyp is characterized by basement membrane thickening (42), goblet cell hyperplasia, limited subepithelial oedema, prominent fibrosis and mononuclear cell infiltration (43; Fig. 4A, B). Interestingly, the fibrosis is usually limited to collagen deposition mostly in subepithelial regions. In this disease, the MMP and TIMP ratio seems to be balanced (44).

Chronic rhinosinusitis with nasal polyps. In contrast to CRS without nasal polyps, CRS with polyps reveals frequent epithelial damage, a thickened basement membrane, and mostly oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands but virtually no neuronal structure (43; Fig. 4C, D). Recent hypotheses suggested that mammaryglobulin

may contribute to epithelial proliferation in polyp formation (45). Polyps demonstrate increased exudation from vessels, oedema of the lamina propria and bulging of the nasal mucosa. Nasal polyps have been histologically classified into oedematous, glandular and fibrous types (46) according to their stroma remodelling. Among the inflammatory cells, EG2+ (activated) eosinophils, usually located around vessels and glands, are a prominent characteristic in about 80% of patients with nasal polyps. The oedematous nature of nasal polyps consists of fibroblasts and infiltrating inflammatory cells localized around pseudocyst formations. These pseudocysts contain albumin and other plasma proteins, this active exudation being supported by the subepithelial eosinophilic inflammation. Finally, increased aquaporin-1 water channel expression in polyp tissue could influence oedema formation (47). Mostly, in CRS with polyps and aspirin sensitivity, epithelial thickening and eosinophilia was found in inferior turbinates at distance from the polyps (48).

Recently, an imbalance between MMPs and their natural inhibitor TIMP-1 has been reported in CRS with nasal polyps. This imbalance could lead to a local increase of ECM degradation and formation of pseudocysts (44). Like neutrophils and macrophages, mast cells can express MMPs and interact with ECM (49). This view was recently supported by evidence of participation of other MMPs, such as MMP-2 (50–52) in pathogenesis of CRS with nasal polyps. Finally, this clinical entity must be distinguished from the antrochoanal polyp, which presents microscopic similarities with maxillary cyst (53).

In cystic fibrosis (CF), no specific data are available on tissue remodelling in upper airways. However, this disease presents frequently both clinical and radiological expression of CRS with or without nasal polyps (54). The CF airway wall remodelling is consequent to specific changes in tissue vasculature, vessel leakage (55), proteolytic degradation of elastin, collagen and fibronectin fibrils by MMPs (56), increased expression of growth factors (57) and accumulation of airway smooth muscle cells (58). It has been demonstrated that nasal polyps from CF patients present higher expression of innate defence markers (59).

Finally, tissue damages occurring in other chronic diseases of the paranasal sinuses like fungal balls or mucocoeles remain poorly explored (60).

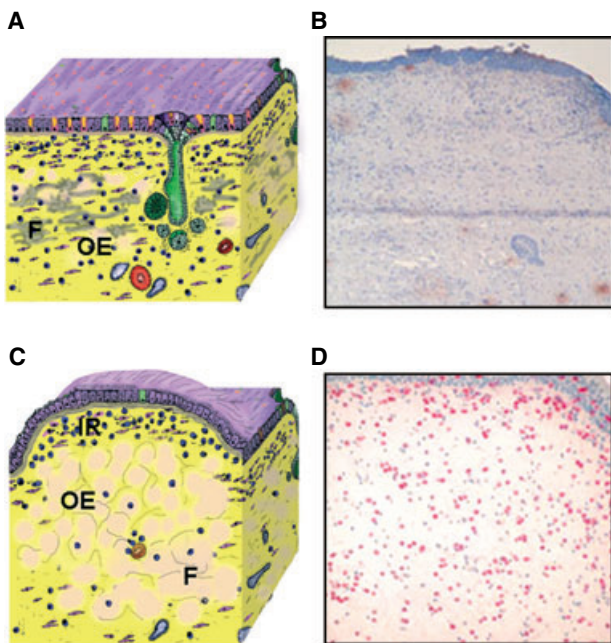


Figure 4. Major types of extracellular matrix remodelling in paranasal diseases. Schemes illustrating the major changes in lamina propria (left column) and corresponding pathological views (right column). (A) Chronic rhinosinusitis without polyps: presence of extensive fibrosis organized in foci (F) and limited oedema (OE). (B) Chronic rhinosinusitis without polyps: transforming growth factor- β 1 staining (initial magnification $\times 100$). (C) Chronic rhinosinusitis with polyps: severe subepithelial inflammation (IR) and massive oedema (OE) in lamina propria with fields of fibrotic foci (F). (D) Chronic rhinosinusitis with polyps: EG2 staining for eosinophils (initial magnification $\times 100$).

Eicosanoid metabolism in upper airway remodelling

Arachidonic acid derivatives (eicosanoids) like cysteinyl leukotrienes (CysLT) and prostaglandins (PG) have been implicated in the lower airway remodelling in chronic asthma (61). In mouse models of asthma CysLT(1) receptor antagonists inhibit the airway remodelling including mucus gland hyperplasia, mucus hypersecretion, smooth muscle cell hyperplasia, collagen deposition

and lung fibrosis (62). On the other hand, PGE₂, the predominant eicosanoid product of the airway epithelium, is a potent inhibitor of mitogenesis and collagen synthesis, expressing potential suppressing activity on remodelling processes.

Some data also suggest the role of eicosanoids in the remodelling of upper airways in patients with rhinosinusitis and nasal polyposis. Increased concentrations of cysteinyl leukotrienes are released from the polypoid upper airway mucosa and enzymes involved in leukotriene production (5-lipoxygenase and LTC₄ synthase) are overexpressed in the mucosa of patients with rhinosinusitis (63, 64). Urinary excretion of LTE₄ in patients with CRS and nasal polyposis is increased in relation to the extend of the disease and decreases after the sinus surgery (65). In contrast, a decreased expression of COX-2 mRNA and diminished PGE₂ production seem to be a feature of nasal polyp tissue suggesting impairment of important regulatory mechanism involved in the growth of nasal polyps and possibly in remodelling.

Aspirin-sensitive rhinosinusitis

The presence of aspirin hypersensitivity in a patient with rhinosinusitis and nasal polyposis is associated with a particularly persistent and resistant to treatment form of rhinosinusitis, coexisting usually with severe type of asthma and referred to as 'aspirin triad' (66). The unusual severity of the upper airway disease in these patients is reflected by high recurrence of nasal polyps, and frequent need for sinus endoscopic surgery and higher thickness of hypertrophic mucosa as it has been documented with computerized tomography (CT; 67, 68). Higher extend of airway inflammation and remodelling in aspirin-sensitive polyps seems to be related to abnormal arachidonic acid metabolism. A significantly lower generation of PGE₂ by nasal polyps and nasal polyp epithelial cells as well as a decreased expression of COX-2 in nasal polyps of these patients were reported (69, 70).

Nasal polyp tissue from ASA-sensitive patients generate cysteinyl leukotrienes in increased amounts and overexpression of enzymes involved in production of leukotrienes (5-LOX and LTC₄ synthase) and in nasal polyps tissue from these patients was found (64). More recently, other arachidonic acid metabolites generated on 15-LOX pathway have been associated with hyperplastic rhinosinusitis in AA-sensitive patients. In nasal polyp epithelial cells and peripheral blood leucocytes from ASA-sensitive but not ASA-tolerant patients, aspirin triggers 15-HETE generation, suggesting the presence of specific abnormality of 15-LO pathway in these patients (69). Upregulation of 15-lipoxygenase and decreased production of anti-inflammatory 15-LO metabolite lipoxin A₄ found in nasal polyp tissue from ASA-sensitive patients further point to distinctive but not yet

understood role for 15-LO metabolites in nasal polyps (64).

Taking together these data strongly implicate a role for eicosanoids in the remodelling associated with rhinosinusitis and nasal polyposis.

Fibroblasts in upper airways

Fibroblasts in normal airways

Paradoxally, although fibroblasts are found in abundance in the airways, few data are available about their number in nasal diseases, their specific phenotypes and actions in upper airways. These structural cells are derived from mesenchymal progenitors and they orchestrate the continual production and turnover of ECM. Besides their essential functions in ECM production, they can also act as enzyme producers, proinflammatory activators and modulators of the immune response (71). Activation of fibroblasts into myofibroblasts is a key event in many ECM disorders. This transformation into myofibroblasts can occur as consequence of stimulation by growth factors acting in an autocrine or paracrine manner (72), of signalling interactions with ECM proteins, of dynamic cell-cell communications (73), or of changes in physico-chemical gradients in their environment (74).

Fibroblasts are the major and nearly exclusive producers of ECM in airways. They not only secrete collagen fibres, but can also produce other ECM components, such as glycosaminoglycans or glycoproteins (75). They are also known to be able to amplify and sustain the inflammatory reaction through a local release of growth factors or cytokines. Eotaxin can be produced by normal nasal fibroblasts through the synergistic action of interleukin (IL)-13 and tumour necrosis factor (TNF)- α (76). Finally, normal fibroblasts are also able to control the enzymatic balance through production of TIMPs (77).

Fibroblasts in pathological airways

The importance of airway fibroblasts in ECM remodelling has been illustrated in lower airway diseases. Asthma and chronic obstructive pulmonary disease (COPD) are both chronic inflammatory conditions of the conducting airways and lung parenchyma presenting several degrees of ECM deposition (78). However, many other pathological conditions in human airways can also present an intense fibrotic reaction (Table 1). In acute interstitial pneumonia, the acute injury can be massive, involving a large portion of parenchyma and occurring during a single period of time, whereas in usual interstitial pneumonia, the acute injury is usually very focal, affecting widely scattered portions of lung but occurring and recurring over many years (79).

In chronic sinus diseases, similar types of fibrosis can be found in the submucosa. The amount of subepithelial collagen deposition was significantly greater in adults and

Table 1. Major disorders of matrix remodelling in upper and lower airways

Upper airways	Lower airways
Chronic rhinosinusitis without nasal polyps	Idiopathic pulmonary fibrosis
Chronic rhinosinusitis with nasal polyps	Adult respiratory distress syndrome
Eosinophilic angiocentric fibrosis	Fibrosis with collagen vascular disease
Granulomatous diseases	Cryptogenic organizing pneumonia
Nasal/sinus adhesions	Bronchiolitis obliterans, transplant associated
Rhinitis medicamentosa	Sarcoidosis
Nose/sinus irradiation	Histocytosis X
	Hermansky-Pudlak syndrome
	Asbestosis
	Hypersensitivity pneumonitis
	Drug-induced lung disease
	Asthma and emphysema
	Lung irradiation

children suffering from CRS without polyps, when compared with normal tissue (80). In CRS without polyps, extracellular endogenous proteases, as well as exogenous proteases from mites and moulds are suspected to promote maturation, proliferation and collagen production of fibroblast precursors and mature fibroblasts (81). Fibroblasts can also act as a sustainer of inflammatory reaction. They may play an important role in initiating antiviral responses and inflammation by producing chemokines leading to enhance inflammatory cell recruitment (82). Nasal fibroblasts from patients with CRS produce higher production of vascular endothelial growth factor (VEGF) under hypoxic condition and this production is enhanced in the presence of TNF- α or endotoxins (83). Viral infections are able to induce VEGF and basic fibroblast growth factor (bFGF) production by both epithelial cells and fibroblasts (84). The production of eotaxin by nasal polyp fibroblasts is highly sensitive to the synergistic action of IL-4 and lipopolysaccharide (85). They can constitutively express lysophosphatidic acid (LPA) receptor-1 and, when stimulated by IL-4, can express LPA receptor-2 (86). Connexin 43, abundant in the subepithelial fibroblast, was found inversely correlated with eosinophil infiltration in nasal polyps (87). Increased fibroblast activity was suspected to influence the expression of IL-6 (88, 89), IL-8, growth-related oncogene (GRO)- α (90) or chemokines like C-C chemokine ligand 2, spontaneously or under influence of TNF- α (91).

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In CRS with polyps, fibroblasts embedded in the oedematous framework, present abundant interdigitating cytoplasmic processes and solitary cilia (92). Their activation induced significantly higher rate of proteoglycan synthesis (93). In nasal polyps, the increased number of myofibroblasts in asthmatics may be responsible for the ECM accumulation, polyp formation and recurrence (94). Compared with normal nasal tissue, collagen types I, III and V were significantly more abundant in the submucosal connective tissue and in the basement zone on nasal polyps, this deposition being irreversible after treatment with topical glucocorticosteroids (95).

Furthermore, recruited inflammatory cells and activated epithelial cells in nasal polyps are the major source of cytokines sustaining the inflammatory reaction and activation, proliferation of fibroblasts and myofibroblast differentiation (96, 97). Nitric oxide stimulates collagen expression in human nasal polyp-derived fibroblasts (98). Basic fibroblast growth factor, a potent angiogenesis agent and mitogenic factor for fibroblasts, was not correlated with polyp recurrence or association with asthma (99). Its expression is decreased after administration of topical nasal steroids in nasal polyps (100, 101). Topical application of glucocorticosteroids or antihistamines in nasal polyp patients suppresses the proliferation of nasal fibroblasts (102, 103), while ibuprofen and nimesulid do not influence fibroblast proliferation in nasal polyp (104). Finally, the suppressive activity of roxithromycin and fluticasone propionate has been demonstrated on MMP-2 and MMP-9 production by nasal polyp fibroblasts (105, 106).

Conclusions

From a clinical point of view, a crucial issue in managing patients with disorders of matrix remodelling is predicting which patients will develop more progressive disease. Recent classifications in upper and lower diseases have focused on this issue.

Intriguing similarities in the cellular nature of remodelling inductors and in the severity of initial airway inflammation could serve as a basis for further comparisons between airways spectrum and the recognition of common pathogenesis principles.

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