

REVIEW

Remodelling of the upper airways in allergic rhinitis: is it a feature of the disease?

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Summary

The traditional viewpoint that inflammation, owing to a genetic T-helper type 2 (Th2)-directed imbalance, is the cause of allergic rhinitis has meant that the potential coexistence of other genetic defects and the relevance of any airway remodelling changes to disease pathogenesis and persistence have received scant attention, and as such remain controversial areas. This is particularly so in view of the limited published work in this field, which has so far reported markedly conflicting findings. This review endeavours to outline what is known about the nature of the remodelling response within the upper airway in allergic rhinitis, in addition to highlighting specific areas where further research is warranted.

Keywords allergic, rhinitis, remodelling, upper airway, review

Introduction

Remodelling is defined in the Oxford Concise Dictionary as 'model again or differently, to reconstruct' [1]. Within the lower airways in asthma, it is now well accepted that there are structural changes, in addition to the classical inflammatory infiltration. These changes, which include epithelial disruption, goblet cell hyperplasia, mucous gland hypertrophy, enhanced airway collagen deposition, airway myofibroblast transformation, increased matrix protein deposition, smooth muscle hypertrophy and hyperplasia, and an increase in the number of collagen IV-positive blood vessels, are encompassed within the term airway remodelling [2]. In pathological terms, the remodelled airway in asthma is considered to represent the end product of a dynamic process of wound repair including matrix deposition and degradation in response to insult or injury, leading ultimately to restructuring of the damaged tissue [3, 4]. Usually with repair there is restoration of the normal structure, therefore, this remodelling represents either the consequence of repeated injury that does not permit return to a normal structure resulting in permanent alteration, or an abnormality of the repair process itself that leads to permanency rather than restoration to normality. The strong linkage, recently described, between the gene for the membrane-anchored protein containing a disintegrin and metalloprotease (ADAM) domain 33 (ADAM 33), and asthma with bronchial hyper-responsiveness [5], has focused attention on tissue susceptibility genes that are likely to contribute to directed dysregulation of the repair process with structural and functional sequelae. The initiating stimulus for the development of these structural changes is under debate, particularly as to whether it is a consequence of the allergic inflammatory process, or whether it can arise independently of that process. These are not,

however, mutually exclusive as a range of stimuli, both allergic and non-allergic, can activate epithelial cells, and the local generation of growth factors by these cells can explain many of the mesenchymal changes described [6]. As epithelial cell activation is also a feature of rhinitis, with the elevated levels of nitric oxide in nasal air considered to reflect this indirectly [7], it is surprising that greater attention has not been given to the evaluation of structural changes within the upper airways in allergic rhinitis.

In this review, we aim to address what is already known about the relationship between allergic inflammation and upper airway structural changes, in addition to highlighting particular areas where further research is needed.

Remodelling changes in allergic rhinitis

Epithelium

The limited published work in this field has so far reported conflicting findings. Consistent with the findings of Braunstahl et al. [8], others have also reported that the epithelium in allergic rhinitis is intact with no concomitant shedding [9–11] and that, following allergen challenge out of season, rhinitic epithelial dimensions and integrity are maintained [12]. Other researchers have, however, reported contradictory findings of epithelial damage in the nasal mucosa in allergic rhinitis characterized by enhanced epithelial shedding and intercellular oedema [13–15]. One carefully conducted study revealed not only evidence of epithelial shedding in allergic rhinitis, as compared with that in healthy control subjects, but that this could be demonstrated in relationship to clinical disease expression, through comparison of paired biopsies from the same individuals in and out of a naturally occurring pollen season [15]. This study found a positive correlation between the loss of epithelial integrity and the accumulation of eosinophils, rather than mast cells, at this site [15]. While the discrepancies in the contrasting findings may not be easily reconciled, it is possible that factors such as tissue and sample

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processing, patient selection, and evaluation methods may be contributory. Importantly, however, all the above studies define the epithelial abnormality as frank disruption, by analogy with asthma. This may in fact be inappropriate. There are dynamic compressive forces exerted on the epithelium in asthma during bronchoconstriction, which are not reproduced within the upper airways. It is probable that these dynamic changes reveal a pre-existing abnormality and that the more subtle changes in epithelial cell behaviour and cell-cell binding, that underlies such a tendency for disruption, would not be appreciated by light microscopic morphometry and would require more detailed electron microscopic techniques or specific immunohistochemical evaluation. Consistent with this, one study found that while there was no light microscopic evidence of epithelial disruption in perennial allergic rhinitic patients, electron microscopy revealed two characteristic features of epithelial damage in these subjects in comparison with that in healthy controls, namely the presence of cytoplasmic vacuoles in the epithelial cells and a marked widening of the intercellular spaces at this site [16], both consistent with structural airway epithelial cell abnormalities in relationship to disease expression. With this in mind, our studies evaluating epithelial cell activation in allergic rhinitis have clearly identified increased expression of transforming growth factor-beta (TGF- β) and receptors for TGF- β , in particular TGF- β_2 and TGF- β RII, respectively [17], within the nasal epithelium in perennial allergic rhinitis. TGF- β has actions relevant to persistent epithelial cell activation and the maintenance of a repair phenotype [18, 19]. Both TGF- β_1 and TGF- β_2 induce the synthesis of the cyclin-dependent kinase inhibitor p21^{waf}, which causes growth arrest at the G₁ to S phase of transition in the cell cycle, thereby preventing full epithelial repair following damage. Any such effects of TGF- β would be counteracted by the actions of members of the epidermal growth factor (EGF) family acting through the EGF receptor (EGFR). Epidermal growth factor is a mitogen for airway epithelial cells, and our preliminary immunohistochemical analyses also identify enhanced immunoreactivity for EGF and EGFR within the epithelium in rhinitis [17]. As mitogen activated protein kinase (MAPK) activation by mitogens, such as EGF, antagonises TGF- β signalling [20], the overall fate of the epithelium will reflect the integration of survival and proliferative signals provided by EGF-like growth factors and the counterbalancing effect of pro-apoptotic and anti-proliferative signals caused by injury and members of the TGF- β family. In severe asthma the TGF- β signal is dominant within the epithelium, despite increased EGFR expression [21]. The balance within the upper airways in allergic rhinitis is undefined. Over-stimulation by EGF ligands would lead to epithelial hyperproliferation. The thickness of the epithelium is difficult to evaluate using light microscopy, as tangential cutting of the section will give the false impression of epithelial thickening; thus this is best evaluated with electron microscopy, when the orientation can be visualized and optimized. If the sole report of nasal epithelial hyperproliferation in perennial allergic rhinitis can be reproduced [9], this would suggest that at this site the balance favours the EGF ligands and the promotion of epithelial integrity. The enhanced epithelial expression of TGF- β in rhinitis does, however, suggest that this repair is

abnormal, as epithelial cell activation persists, and under such circumstances it would be anticipated that the continued production of TGF- β would promote mesenchymal changes.

Mesenchymal changes

A marker for increased TGF- β bioactivity within the airways is myofibroblast transformation, as a prominent effect of TGF- β is the induction of α -smooth muscle actin filaments within the fibroblast, as part of the transformation into the myofibroblast phenotype [22]. There is evidence for such a transformation in rhinitis. Dr Akiko Sanai and his team in Japan have reported that there is an increase in the numbers of mucosal myofibroblasts within the upper airways in perennial rhinitis [23]. Myofibroblasts also have increased synthetic capabilities, generating interleukin (IL)-6, stem cell factor, and 'released upon activation, normal T-cell expressed and secreted' (RANTES), all factors that will influence the behaviour of infiltrating leukocytes, and generate enhanced amounts of collagen types I and III on activation [24]. Myofibroblast activation would thus lead to increased airway collagen deposition. On initial inspection, the publication by Braunstahl et al. [8] indicates that this is not so within the upper airways in rhinitis and this was also the finding by Sanai et al. [23], who did not find any difference in the total amount of collagen in nasal biopsies from allergic rhinitic and non-allergic subjects. A closer inspection of the Braunstahl data, however, reveals that the upper airway collagen layer beneath the true basement membrane is thickened in all subject groups, as compared with that which is normal within the lower airways. It is thus likely that epithelial mesenchymal signalling is a feature of the upper airways *per se*, with the enhanced epithelial damage that will occur at this site in response to a range of environmental stimuli, such as viral infection, environmental tobacco smoke exposure, ambient air pollution, in addition to allergen-related activation. Measurement of this marker of remodelling, while adequate within the lower airways, is thus insensitive to define allergen-specific remodelling within the upper airways, and the lack of difference between rhinitic and non-rhinitic nasal mucosae cannot be taken as evidence for a lack of airway remodelling in rhinitis. Consistent with this, a more detailed evaluation by Sanai et al. [23] revealed 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 non-allergic nose, indicative of TGF- β directed changes. Furthermore, the finding of evidence of lower airway remodelling changes in non-asthmatic subjects with allergic rhinitis [8] has been echoed by the findings of another study showing a significantly increased deposition of collagens types I and III as well as fibronectin in the sub-basement membrane of these subjects compared with normal controls [25]. These results are suggestive of an active remodelling response in the lower airways in allergic rhinitis similar in nature to that in asthma, but probably not as marked (Fig. 1). Evidently, further work needs to be undertaken in this area, with a better definition of outcome variables and a more refined evaluation of the structural alterations, before firm conclusions can be drawn as to the extent and nature of the remodelling process

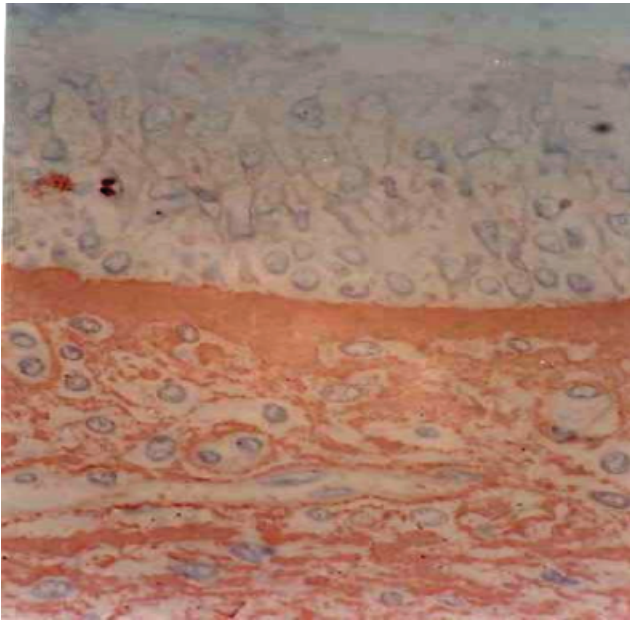


Fig. 1. Immunostaining for type III collagen in the nasal mucosa. Immunoreactivity is clearly identifiable in the lamina reticularis extending deep within the tissue.

within the upper airway. This statement also applies to the evaluation of vascular changes within the tissue.

Vasculature

Although it is well established that increased vascular permeability is a prominent feature of allergic rhinitis [26], there is little evidence for gross structural/morphological changes in the nasal vasculature, albeit this is an area that has received scant attention. One study employing stereological measurement of vascular surface and volume densities in nasal tissue did not reveal any significant differences between rhinitic and non-rhinitic mucosa, indicative of a lack of vascular remodelling response in the allergic nasal mucosa [27]. Such an approach may not, however, properly assess all vessels, which may be collapsed and difficult to evaluate, and more specific immunohistochemical staining may provide more accurate information in this respect. Using a monoclonal antibody directed against CD31 on the vascular endothelium, another study also found no difference in the number of blood vessels within the upper or lower airways between rhinitic or asthmatic volunteers and the healthy controls [8]. However, none of the above-mentioned studies used an antibody directed against collagen IV (Fig. 2). This has been previously used to identify differences between asthmatic and healthy control subjects in the number of mucosal blood vessels in endobronchial biopsies from the lower airways [28, 29], and has been found to be more discriminating in this respect than other endothelial markers. Until studies have been undertaken with this approach, it would be premature to conclude that there is no evidence of angiogenesis, especially as oligonucleotide microarray analysis of nasal tissue has revealed up-regulated transcription of vascular endothelial growth factor (VEGF), an angiogenic growth factor, in allergic rhinitis [30]. Evaluation of other

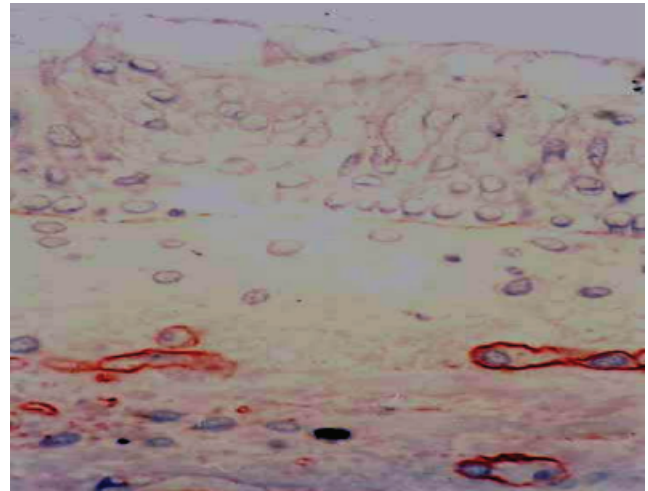


Fig. 2. Immunostaining for type IV collagen in the nasal mucosa showing strong immunoreactivity in the vascular basement membrane and weaker immunoreactivity in the epithelial basement membrane.

indices of vascular change in rhinitis has revealed disease-specific changes in mucosal blood vessels, with thinning and destructive changes in the arteriolar wall [31], deposition of globulins and complement in the vascular wall [32], and vascular dilatation [33].

Glands

The nasal mucosa contains goblet cells, which are unicellular mucus-secreting glands, found above the basement membrane, within the epithelium, and mucosal glands lying deep in the lamina propria. Goblet cells are found most densely in the inferior turbinate and less so within the nasal septum [34]. It has been calculated that the density of goblet cells within the normal nose is approximately 10 000/mm² [35]. There are conflicting findings as to changes in goblet cell numbers in rhinitis. Cytological studies have reported an increased recovery of goblet cells in nasal smears during the grass pollen season in pollen-sensitive rhinitis [36, 37], although this is not a consistent finding [38]. The studies reporting changes were, however, more appropriately powered to detect changes. In perennial rhinitis, while no change in the density of goblet cells could be identified in the inferior turbinate in one nasal biopsy study [39], another reported an increase in the number of sub-epithelial mucous glands in the middle turbinate [40]. Aside from numerical changes to the nasal glands in allergic rhinitis, structural alterations are described in rhinitis including distension of the acini with secretions, degeneration and obstruction of the acini and ducts, as well as cystic dilatation with periglandular round-cell, and eosinophilic cell infiltration of the superficial glands. There is also evidence of compression or dilatation and atrophy of the deeper glands, especially in areas with compact fibrous tissue [41].

Concluding remarks

Although there are conflicting findings and there is currently no clear consensus opinion regarding the nature and extent of

the remodelling response in the upper airway in allergic rhinitis, it is apparent, from a review of the literature, that the structure of the rhinitic nose is not normal. The changes within the upper airway may not be as distinct as those within the lower airways in asthma, and several reasons may exist to explain this. Due to the increased exposure to environmental stimuli in the upper airways, some aspects of structural remodelling may be a feature of the 'normal' nose and thus make comparisons of the rhinitic and non-rhinitic more difficult to discern. On account of this, the evaluation of gross structural change by light microscopy is too blunt an approach and more refined approaches, such as specific immunohistochemical techniques and electron microscopy, are needed. A more detailed evaluation of the biological events underlying structural remodelling is required within the nose in allergic rhinitis, and the relevance evaluated in relation to persistence and chronicity of disease. Only then will it be possible to appreciate more fully differences between upper and lower airway pathology, especially those of particular relevance to disease expression. The work carried out thus far has certainly initiated this process, but clearly further studies will be needed focusing on naturally occurring disease.

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