

Nasosinus mucin expression in normal and inflammatory conditions

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**Current Opinion in Allergy and Clinical
Immunology** 2009, 9:10–15

Purpose of review

Mucin expression in normal nasosinus mucosa is upregulated in inflammatory conditions. However, as the first nine mucin genes are expressed, and as more mucins are expected to be expressed in nasosinus mucosa, the range and pattern of variations in mucin expression in nasosinus mucosa would be wide and complicated. This review discusses current knowledge on mucin expression in normal and pathologic nasosinus mucosa.

Recent findings

Studies on nasosinus mucin expression indicate that mucin genes upregulated in inflamed nasosinus mucosa include *MUCs1, 2, 4, 5AC, 5B* and *8* in different combinations and to various degrees. Nasosinus submucosal glands play a more important role in mucin expression than surface epithelium. However, most of the studies on nasosinus mucin expression are focused on basic science and as yet the clinical implications of nasosinus mucin gene expression are still unclear.

Summary

Nasosinus mucin expression is very complicated. Studies including large numbers of samples are needed to investigate the role of different physiological and pathological variables, including inflammatory mediators, in the control of nasosinus mucin expression. This is essential for better understanding of clinical implications of altered nasosinus mucin expression and for future therapeutic applications.

Keywords

mucin gene, mucin, polyps, rhinitis, sinusitis

Curr Opin Allergy Clin Immunol 9:10–15
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1528-4050

Introduction

Mucus hypersecretion is one of the major symptoms and signs of nasosinus inflammation. It results from increased quantity, altered quality of mucus or both. This can disturb nasal mucociliary transport, which depends, in part, on mucus quantity and quality (gel-like properties). The latter depends solely on mucus content of high-molecular-weight glycoproteins known as mucins, which are normally present in polymeric, oligomeric or both forms [1]. Histological studies showed that secretory elements in nasosinus mucosa, which involve goblet cells of the surface epithelium and mucus and serous cells of submucosal glands (SMGs), produce different types of mucins [2].

The discovery of various mucin genes has stimulated research in the field of airway inflammatory diseases and several studies have looked at nasosinus mucin expression in normal and pathologic conditions. However, the large number of mucins, their complex structure and their widely variable expression patterns make it difficult to assess its clinical relevance. In this article, the current knowledge on mucin expression in normal and inflamed

nasosinus mucosa is presented along with the suggested future research topics.

Mucin genes

To date, 21 human mucin genes named *MUC1, 2, 3A, 3B, 4, 5AC, 5B, 6–9, 11–13, 15–21* have been identified by cDNA cloning [1,3]. *MUCs2, 5AC, 5B, 6, 8* and possibly *19* encode for secretory (gel-forming) mucins, whereas *MUCs1, 3A, 3B, 11–13, 15–18, 20* and *21* encode for membrane-bound mucins. *MUC7* mucin is a secretory but not gel-forming mucin, as it exists as a monomer. There are secreted and membrane-bound forms of *MUCs4* and *9*. All currently known human mucin genes, excluding *MUCs9, 11, 16* and *17*, are expressed in lower airway mucosa [1,3]. As a part of the airway, nasosinus mucosa is expected to express a comparable mucin gene spectrum.

Mucin gene expression in normal nasosinus mucosa

There are five main studies [4–7,8], which investigated the expression of a wide range of mucin genes in normal

and pathological nasosinus mucosa. The first two studies used inferior turbinate mucosa as a control, whereas the third and fourth used posterior ethmoid and sphenoid sinus mucosa, respectively. The fifth study did not define the source of control (normal) nasal mucosa. Other studies [9–14,15**] investigated one or a few nasosinus mucins.

Considering the results of the five studies together, the first nine mucin genes are expressed, at various levels, in normal nasosinus mucosa and the major secretory mucins are *MUC5AC* [4,7,8**, 5B [4,8**] and 8 [5,8**], whereas the major membrane-bound mucin is *MUC4* [4,7,8**].

MUC5AC is mainly an epithelial mucin expressed in goblet cells of surface epithelium and to a lesser extent in the SMGs [4,7], whereas *MUC5B* is mainly a glandular mucin expressed in mucus cells of SMGs and to a lesser extent in surface epithelium [4,7,8**,11]. *MUC8* is highly expressed at both epithelial and glandular levels [8**]. These three mucins could represent the main determinants of viscoelastic properties of normal nasosinus mucus. *MUC2* is mainly expressed in goblet cells [4,8**] and its expression is much lower than *MUC5AC*, which can be as high as 10-fold higher as *MUC2* or *MUC1* [9]. *MUC4* is expressed in the majority of cells along the mucosal border including goblet cells, ciliated cells as well as the basal cells [4,7,8**]. Lower levels of *MUC4* expression are expressed in SMGs. Interestingly, *MUC4* is also expressed in stratified squamous epithelium of normal and inflamed nasosinus mucosa [4,7]. *MUC7* is mainly expressed by the SMGs [4] and to a lesser extent in the epithelium [7,16*]. Similar to *MUC4*, *MUC1* exhibited a diffuse epithelial expression by multiple cell types (goblet and ciliated cells) [4].

There is controversy regarding *MUC3* (membrane bound) and *MUC6* (secretory) mucins expression in normal nasosinus mucosa. Although mucociliary differentiation in cultured human nasal mucosal cells involved upregulation of these two mucin genes [17], Aust *et al.* [4] studied the expression of the first eight mucin genes in normal inferior turbinates and found no *MUC3* or 6 expression. The other mucin genes included in the study were expressed at various levels. Kim *et al.* [5] studied epithelial expression of the first nine mucin genes, excluding *MUCs3* and 6, in normal inferior turbinates and found that all studied mucin genes were expressed at various levels.

Jung *et al.* [6] studied the expression of first nine mucin genes, excluding *MUC3*, in three normal posterior ethmoid mucosal biopsies and reported epithelial *MUCs5AC* and 8 expression, whereas SMGs were absent in the normal ethmoid mucosa. The small number of mucosal biopsies, individual variations and absence of SMGs could be responsible for lack of expression of other mucin

genes in normal posterior ethmoid mucosa, which, in another study [18], was found to express *MUC2*. A third study [10] revealed sparse *MUC5AC* expression in goblet cells of normal posterior ethmoid mucosa.

We studied the expression of the first eight mucin genes in healthy sphenoid sinus mucosa, which was found to express all the studied mucin genes, except *MUCs6* and 7. The expression was mainly epithelial and mostly involved membrane-bound mucins (*MUCs4* and 3). In SMGs, mucin expression was infrequent and *MUCs4* and 5B expression was generally weak, whereas expression of *MUC5AC* was moderate. No *MUC1*, 2, or 3 expression was detected in the SMGs of healthy sphenoid sinus mucosa [7].

Martínez-Antón *et al.* [8**] studied *MUCs1*, 2, 4–8 expression in normal nasal mucosa. They found that *MUCs1*, 4 and 5AC were highly expressed in the epithelium, whereas *MUC5B* was moderately expressed in SMGs and *MUCs6* and 7 were sparsely expressed. *MUC8* was highly expressed in the epithelium and SMGs of normal nasal mucosa although in a previous study [19] *MUC8* expression was associated with ciliated cells in nasal epithelium and the authors postulated that *MUC8* might be related to the differentiation or function of ciliated cells in nasal epithelium.

Very low expression levels of *MUCs5AC* and 5B mRNA were detected in normal compared with pathologic maxillary sinus mucosa [12,13,15**] along with similar expression levels of *MUC8* [13]. However, the expression profile of the other mucins in normal maxillary sinus mucosa was not explored.

Mucin expression in pathological nasosinus mucosa

The main pathological nasosinus conditions in which mucin expression was studied include the following.

Vasomotor rhinitis

In a study [4] on the expression of the first eight mucin genes in normal and vasomotor inferior turbinate mucosa, the only difference was downregulation of *MUC1* in vasomotor rhinitis (VMR). The authors speculated whether decreased *MUC1* expression might trigger the abnormal neurogenic signal leading to copious nasal secretions in VMR. This has not been further investigated yet.

Allergic rhinitis

Upregulation of *MUC5B* along with expression of *MUC6* was reported in allergic nasal mucosa [20], and in seasonal allergic rhinitis (SAR), there was a significant upregulation [21] of epidermal growth factor receptor (EGFR), which plays an important role in mediating and maintaining

airway goblet cells hyperplasia and stimulating *MUC5AC* expression [22,23]. *MUC5AC* was upregulated in SAR [21], whereas *MUC5B* was downregulated in inferior turbinate scrapings. *MUC5B* downregulation could be due to lack of SMGs in studied samples. Histamine also induced *MUC5AC* production and antihistamines partially suppress histamine-induced *MUC5AC* production in allergic rhinitis [24].

Chronic sinusitis

MUC5AC and *5B* expression is upregulated in chronic sinusitis [12,13,15^{••}] with increased numbers of *MUC5AC* and *5B* staining cells due to goblet cells and SMG hyperplasia [15^{••}]. However, *MUC5AC* upregulation was absent in pediatric chronic sinusitis [25]. This could be due to age-related differences in mucin expression. *MUC8* is also upregulated in chronic sinusitis [13,26]. Quantitative analysis of mucin expression has demonstrated that the majority of mucin produced is of SMG origin [27], and SMG hyperplasia in chronic sinusitis mucosa has been reported in other studies [16[•],28,29].

On the basis of its molecular construction, *MUC5B* has been suggested to have a high viscosity [30], and *MUC5B* content was positively correlated with middle ear effusion viscosity [31]. However, such a correlation was lost in chronic sinusitis and it has been postulated that this could be due to the presence, in chronic sinusitis mucus, of other inflammatory factors, which contribute to its viscoelastic properties [14].

In chronic ethmoiditis, more mucin genes (*MUCs1, 4, 5B* and *7*) are expressed with upregulation of *MUC2* [18], whereas normal ethmoid mucosa seems to express a limited number of mucin genes (*MUC2, 5AC* and *8*). This, in addition to goblet cell hyperplasia, explains, in part, mucus hypersecretion in chronic ethmoiditis [6].

Nasal polyps

Mucin expression is upregulated in nasal polyps compared with normal nasosinus mucosa [5,7,8^{••}], and intracellular mucin content is up to three-fold higher than in healthy inferior turbinate mucosa [5,32]. The first nine mucin genes investigated so far have all been found to be expressed in nasal polyps [5,7,8^{••}]. However, the expression pattern of individual mucin genes was widely variable among individual polyps and in different areas within the same polyp. This can be explained by the wide spectrum of local and systemic factors involved in polyp development, progression or both. Variation in mucin gene expression within the same polyp could reflect differences of cell secretory stages and cell cycles at the time of tissue collection [33]. The predominantly expressed mucin genes are *MUCs4* and *5AC* [7,8^{••}] and *MUC8* [5,8^{••}] followed by *MUCs1, 3, 5B* and *7*, whereas the least expressed mucins are *MUCs2* and *6* [7,8^{••}].

MUC1 is upregulated in nasal polyps compared with healthy sphenoid sinus and nasal mucosa [7,8^{••}]. *MUC2* upregulation was detected in nasal polyps compared with normal inferior turbinate epithelium and sphenoid mucosa in two studies [5,7], whereas in a third study [8^{••}] *MUC2* was downregulated in nasal polyps compared with normal nasal mucosa. Epithelial *MUC3* expression was detected in nasal polyps and normal sphenoid mucosa, but glandular expression was only found in nasal polyps [7].

MUC4 was the most predominantly expressed mucin gene in nasal polyps and its expression was upregulated compared with normal sphenoid [7] and nasal mucosa [8^{••},12]. Glandular *MUC5B* was upregulated in nasal polyps compared with normal sphenoid [7] and nasal mucosa [8^{••}]. *MUC6* was expressed at very low levels in normal nasal mucosa [8^{••}] and in nasal polyps but not in normal sphenoid mucosa [7] and glandular *MUC7* was upregulated in nasal polyps compared with normal sphenoid mucosa [7].

MUC5AC is upregulated in nasal polyps compared with normal posterior ethmoid [10], sphenoid [7] and inferior turbinate mucosa [34,35], and *MUC8* is upregulated compared with inferior turbinate mucosa [5,32]. However, *MUC5AC* downregulation in nasal polyps was reported in other studies [8^{••},32]. This contradiction could be related to variation in goblet cell density along inferior turbinate mucosa, which has been found to increase from anterior to posterior [36], lack of SMGs in inferior turbinate epithelial scrapings in the first study [32] or the choice of control nasal mucosa, which was not clearly defined in the second study [8^{••}].

Sources of mucus hyper secretion in inflamed nasosinus mucosa

Increased nasal mucus secretion in inflamed nasosinus mucosa can be due to

- (1) Increased surface area of functioning mucous membrane by mucosal hypertrophy and polyp formation. Even in areas of squamous metaplasia, *MUCs1* and *4* are expressed [4,7].
- (2) Increased number of mucus secretory elements (goblet cells, SMGs or both). The response of goblet cell population to nasosinus inflammation seems to vary from reduced [29] up to increased goblet cell numbers [6,27,35], whereas SMG mass increases [16[•],26,29]. The reduced goblet cell population might be related to disease severity and it could be that in severe inflammation goblet cell numbers decrease due to mucosal damage and increase in less severe inflammation. The expression and activation of EGFR system stimulate goblet cell hyperplasia (cell division) and metaplasia by direct conversion of

Table 1 Inflammatory mediators which upregulate airways mucin expression

Inflammatory mediator	Upregulated mucin	References
TNF α	<i>MUC1</i>	[37]
	<i>MUC2</i>	[38]
	<i>MUC5AC</i>	[39–41]
	<i>MUC5B</i>	[39]
IL-1 β	<i>MUC8</i>	[42]
	<i>MUC2</i>	[43]
	<i>MUC4</i>	[44 [•]]
	<i>MUC5AC</i>	[40,44 [•]]
LPS	<i>MUC8</i>	[40]
	<i>MUC4</i>	[44 [•]]
	<i>MUC5AC</i>	[45]
	<i>MUC5B</i>	[45]
IL-9	<i>MUC8</i>	[45]
	<i>MUC2</i>	[46]
	<i>MUC4</i>	[47]
	<i>MUC5AC</i>	[48]
IL-8	<i>MUC5AC</i>	[49]
	<i>MUC5B</i>	[49]
IL-6	<i>MUC5AC</i>	[39]
	<i>MUC5B</i>	[39]
LD4	<i>MUC2</i>	[50 ^{••}]
	<i>MUC5AC</i>	[44 [•]]
PGE2	<i>MUC5AC</i>	[51]
	<i>MUC8</i>	[52]

LD, leukotriene D; LPS, lipopolysaccharide; PGE2, prostaglandin E2.

precursor cells without changing the total number of epithelial cells [23,35].

- (3) Release of inflammatory mediators. Differential regulation of mucin genes by various inflammatory mediators has been reported by several laboratories, and increased mucin gene expression occurs at the level of mucin transcription, translation or both. Table 1 ([37–43,44[•],45–49,50^{••},51,52]) illustrates that several inflammatory mediator upregulate the expression of more than one mucin gene. This appears to be the most important factor, which could, directly or indirectly, upregulate mucus expression in inflamed nasosinus mucosa.

Discussion

Normal nasosinus mucosa expresses small amounts of mucus containing a relatively small number of mucins required for normal mucociliary clearance. As a model of normal nasal mucosa, inferior turbinate [4,5] seems to express more mucins than sinus mucosa [6,7], which is relatively sequestered from environmental insults. Normal sphenoid mucosa, for example, expresses a few secretory mucins with a weak input from the SMGs, whereas membrane-bound mucins seem to have a more important role in maintaining the integrity and sterility of normal sinus mucosa [7].

Inflammatory conditions seem to trigger the recruitment of more mucin genes with upregulation of the already expressed mucins. The wide range of mucin expression profile in inflamed nasosinus mucosa would be reflected

in a wide range of variations of physical and biological properties of mucus secretion. Changes in mucin type could be helpful to adapt the mucus viscoelastic properties to improve mucociliary clearance, whereas mucus hypersecretion could help to dilute and/or eliminate the external and/or internal environmental insults. On the contrary, these alterations in mucus secretion could have a deleterious effect on mucosal protection and predispose to disease development, progression or both. Clinical outcome depends, in part, on the balance between these two situations.

Although the exact biological function of individual mucins is not known yet, it could be that, with the start of the inflammatory process, goblet cell hyperplasia and upregulation of goblet cell-associated mucins (*MUCs*2, 5*AC* and 8) represent the first (epithelial)-line defense in acute inflammatory conditions. With recurrence or chronicity of the inflammatory process or both, the second-line defense comes to work by increased numbers of SMG [16[•],28] along with upregulation of glandular mucins (*MUCs*5*B*, 7 and 8) [8^{••},16[•]]. With these possible variable temporal functions, it is not necessary that SMGs and goblet cells entirely function in isolation from each other. Occasionally, the functions of both secretory elements can be coupled by some physiological mechanisms such as nerve stimulation. Furthermore, sometimes stimulation of the SMGs can induce goblet cell secretion and vice versa. This suggests the occurrence of a bidirectional cross-talk between SMGs and epithelium [53] and might induce other secretory (*MUC8*) and membrane-bound (*MUC4*) mucin expression in both the epithelium and SMGs of inflamed nasosinus mucosa. SMGs seem to have a more active role in mucin expression than surface epithelium and this could possibly be due to exposure of SMGs to more inflammatory stress (cell infiltration and inflammatory mediators) in these conditions.

Conclusion

The clinical relevance of altered mucin expression in inflamed nasosinus mucosa is still unclear. This needs large studies including subgroups of nasosinus inflammatory conditions (nasal polyps, chronic sinusitis, allergic rhinitis etc.) classified according to different clinical (physiological and pathological) variables.

Detailed studies of distribution, ultrastructure and functions of secretory elements in inflamed nasosinus mucosa are needed to advance our understanding of their roles in mucin expression and help targeting these secretory elements with new treatment modalities to control their increased numbers, functions or both.

Characterization of individual mucins in physiological and pathological conditions is crucial to the understanding of

nasosinus mucus biology. Further studies on different mechanisms and pathways by which inflammatory mediators alter mucin expression would facilitate the invention of new therapeutic modalities by blocking control pathways of mucin upregulation in inflammatory conditions. This is the ultimate target for studies on airway mucins and so far, this target seems to be far from being reached.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 79–80).

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