

Mucin Expression and Corticosteroid Efficacy in Chronic Rhinosinusitis with Nasal Polyps

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an upper airway respiratory disease of the sinuses which may develop resistance to corticosteroid efficacy. Corticosteroids are the main therapy of this disease and as part of their anti-inflammatory activity they are known to exert an effect in mucin expression. This review aims to describe the current state-of-the-art knowledge regarding mucin expression in CRSwNP and its possible relation with corticosteroid efficacy, by highlighting the differential expression of membrane-tethered versus secreted mucins in different subsets of CRSwNP with an emphasis in corticosteroid non-responder patients. In addition, this review aims to suggest potential interactions between mucins and corticosteroids that could be addressed in future research to ascertain the role of mucins in the corticosteroid resistant mechanisms of this disease. In this sense, among the different mucins, we will highlight the membrane-tethered MUC1 and its potential role in corticosteroid-resistant CRSwNP, as it is currently considered an especially relevant mucin due to its anti-inflammatory properties.

Keywords: Mucins; Corticosteroids; Corticosteroid resistance; Chronic rhinosinusitis with nasal polyps; MUC1

Introduction

Inflammatory phenotypes in chronic rhinosinusitis with nasal polyps (crswnp) and their relation with corticosteroid resistance

CRSwNP is an inflammatory disease of the nose and paranasal sinuses characterized by polyp formation in the latter. The main symptoms of CRSwNP are nasal obstruction or discharge, which are usually accompanied by the presence of other symptoms such as facial pain or pressure and loss of smell. The chronic characteristic of this disease is evidenced by the persistence of these symptoms during 12 weeks or more without their complete resolution [1]. CRSwNP has been associated with different clinical factors, among which asthma and aspirin sensitivity are highlighted due to the estimates that point out that ~10-15% of asthmatics and over 90% with aspirin intolerant asthma (AIA) suffer this disease [1]. This last subset of patients, known as Samter's or aspirin triad, suffer CRSwNP, aspirin sensitivity and asthma and are associated with a particularly persistent and therapy-resistant form of the disease [1]. Moreover, corticosteroid resistant CRSwNP constitute an additional subset of patients that fail to respond to corticosteroids showing a limited clinical response, thus posing a challenge for research as currently their therapeutic options to control the disease only rely in undergoing sinus surgery.

Nasal polyps are formed by a pseudostratified ciliated epithelium with a thickened basal membrane, stromal edema, fibrotic foci, a sparse presence of vascularity, glands and innervations, and exhibit a high infiltration of different cell types such as eosinophils, lymphocytes, and plasma cells [2,3]. Despite eosinophils are historically considered the major cellular infiltrate and hallmark of CRSwNP and are regarded as a differential aspect from other types of CRS without polyps [4,5], it is important to highlight that some subsets of CRSwNP show relatively low eosinophilia with a predominant influx of other cell types. In this sense, nasal polyp mucosa inflammation exhibiting a high eosinophilic infiltration and orchestrated mainly by TH2 cytokines

has been specifically associated with a majority of Caucasian CRSwNP [3,6] while, in contrast, Asian polyps are less eosinophilic, more neutrophilic, and exhibit a Th1/17 cytokine pattern [7,8]. The relevance of the different eosinophilic and neutrophilic CRSwNP phenotypes has been highlighted recently, as they have been linked with a differential response to corticosteroids, the main treatment of this disease. While eosinophilic inflammation is generally considered sensitive to corticosteroid treatment, increased neutrophilia in nasal polyps has been related with a reduced response to corticosteroid therapy [9]. This differential response to corticosteroids depending on the eosinophilic or neutrophilic inflammatory phenotype shows a resemblance with that described in asthma [10], evidencing the close interrelationship between these diseases.

The accumulation of fibroblasts foci in CRSwNP has also been related with the limited clinical response to corticosteroid treatment, result of a relative resistance to the anti-proliferative and collagen deposition inhibitory effects of these drugs. In this sense, previous results have described the relation between the poor responses of non-responder patients with the impaired sensitivity of fibroblasts to the effects of corticosteroids [11].

Our group is currently studying corticosteroid-resistant CRSwNP patients, among other phenotypes, in order to investigate the potential relationship between mucin expression and corticosteroid efficacy and

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establish potential common mechanisms. The following figure shows representative stained sections of nasal polyp from non-asthmatic and corticosteroid-resistant CRSwNP patients that support previous evidences describing the absence of eosinophilic infiltration (Figure 1B) and the presence of abundant fibrotic foci and extracellular matrix deposition (Figure 1D) in nasal polyps from corticosteroid non-responder patients compared to non-asthmatic CRSwNP, which are mainly characterized by eosinophilic inflammation and the absence of fibroblasts (Figure 1A-1C).

Membrane-tethered and secreted mucins and their expression in CRSwNP

The fact that this inflammatory process of the nasal and paranasal sinus mucosa occurs at the interface with the external environment supports the evidences that suggest that this inflammatory response could result from an inappropriate or excessive immune response to foreign agents, such as bacteria, fungi, allergens or viruses [1,12].

This continuous exposure of the upper airways to environmental particles and potential pathogens emphasizes the necessity of diverse fundamental defense mechanisms, such as mucociliary clearance, physical exclusion and the innate and adaptative immune responses, to protect the host by filtering, clearing and eliminating the potential dangers in order to prevent acute or chronic inflammatory processes [13].

The epithelial cell barrier, its motile cilia and the overlying mucus layer are the main constituents of the mechanical barrier of the sinonasal mucosa and contribute to mucociliary transport as first line of defense. Mucins are widely known key components of the airway epithelial mucus layer that contribute to the protection of the epithelium from pathogens and irritants through their participation in

the mucociliary clearance mechanism [14]. However, recent increasing evidence suggests mucin are also involved in other less conventional roles of high interest, such as host defense against airway infection [15].

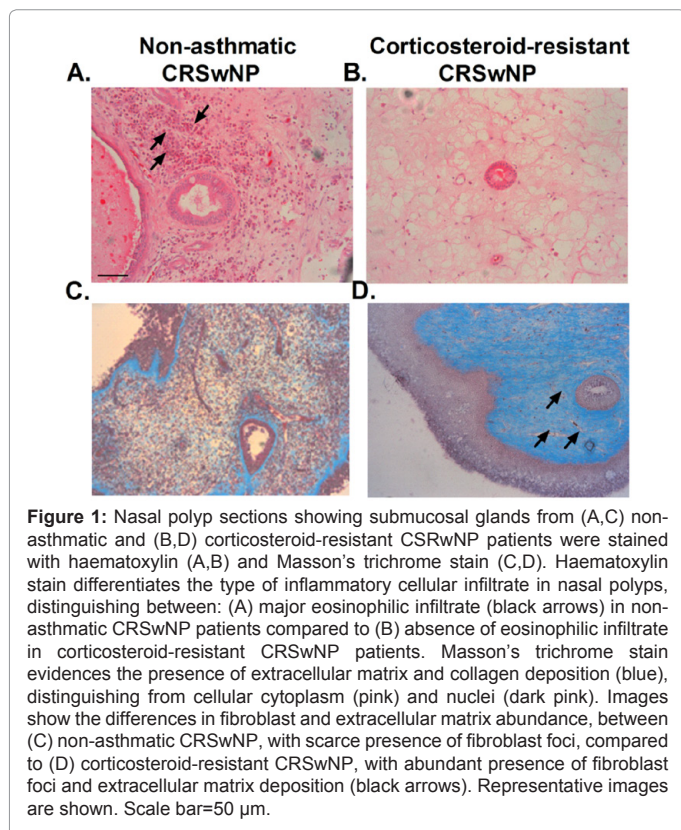
Mucins are heavy weight glycoproteins, produced by surface epithelium goblet cells and submucosal glands, characterized by an extensively glycosylated protein structure with variable number of amino acid tandem repeats, especially rich in serine, threonine and proline, that represent the potential sites for O-glycosilation. The number of human mucin genes identified up to the date is 22, among which 16 are known to be expressed in the respiratory epithelium [14,16]. These mucins are classified in two groups, with different structural and functional properties, considering their secreted or membrane-tethered nature (Table 1).

Membrane-tethered mucins are transmembrane proteins anchored to the apical surface of mucosal epithelial cells, with a highly glycosylated N-terminal domain in contact with the outside environment acting as a sensor receptor and a short cytoplasmic tail (CT) that enables its participation in intracellular signaling [14]. Therefore, these membrane-bound mucins not only modulate extracellular interactions on epithelial cell surfaces but also participate in intra-cellular signaling [17]. In contrast, secreted mucins are the most abundant glycoprotein component in mucus, being directly involved in mucus formation and responsible of its viscoelastic and gel-forming properties [14]. Secreted mucins lack a transmembrane domain, as they are secreted to the extracellular space, and their distinctive feature includes at least five important cysteine-rich domains [18]. However, their importance shouldn't be underestimated as recent publications highlight their essential role in airway defense [19].

Pathological conditions of the upper airways are thought to be a consequence of a dysfunctional capacity of the nasal epithelium to deal with pathogens, being incapable of controlling appropriate and regulated immune responses. As a consequence, the defects in the immune response and in the mechanical barrier defense mechanisms are considered to be related with the establishment of pathologies such as CRSwNP and the development of the characteristic clinical symptoms of these diseases [13]. Mucus hypersecretion in the upper airways, in the form of rhinorrhea, is a common symptom of patients with nasal polyposis and is considered a hallmark of this disease [14].

Previous studies have described a differential mucin expression pattern in nasal polyps compared to healthy upper airway mucosa [20-22]. The mucins MUC1, 2, 3, 4, 5A, 5B, 7, and 8 are known to be expressed in the epithelium of the human airway and focusing exclusively in nasal polyps, the expression of mucins MUC1, 2, 4, 5A, 5B and 8 mRNA [20] and MUC16 [22] has been reported. Among these mucins, the membrane-bound mucin MUC4 and the secreted mucin -5A have been described as the major components of both submucosal glands and epithelial cells in nasal polyps [21].

In our current research to ascertain a potential relationship between mucin expression and corticosteroid efficacy, we have studied the expression of different secreted and membrane-tethered mucins in corticosteroid responder and non-responder CRSwNP groups of patients. Nasal polyps from all the CRSwNP patients included in our study were diagnosed according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 guidelines [1] based on endoscopy and/or computerized tomography. All the patients showed extensive nasal polyps, which were classified with the following scoring system according to their size: 1 (small polyps in the middle meatus not reaching below the inferior border of the middle concha), 2 (polyps



Mucin	Type	Location	Physiological & pathological roles	Corticosteroid effect
MUC1	MT	Lung and airways (lining epithelial cells of the lung and alveolar type II cells). Normal nasal mucosa. Nasal polyps. Other: Nearly all epithelium. Hematopoietic cells. Activated T cells (lymphocytes, dendritic cells). Sperm Corneal endothelial cells. Breast. Pancreas.	Responsible for viscoelastic nature of mucus. Role as protective barrier against invading pathogens and chemicals: Aids in mucociliary clearance of foreign bodies. Provides defense to the upper and lower respiratory tracts. Anti-inflammatory role during airway infection, controlling the resolution of inflammation through the inhibition of TLR signaling. Associated with epithelial cell differentiation (in stomach, pancreas, lung, trachea, kidney, salivary and mammary glands and the female reproductive tract). Tumor-associated molecule (frequent over expression and aberrant glycosilation in many cancers including, breast, pancreas, colon, lung and endometrial cancer). Promotes cancer metastasis and tumorigenesis. Functions of the different MUC1 segments: - Ectodomain (anti-adhesive, pro-adhesive, hydration and lubrication of cell surfaces, ERBB signaling). - Cytoplasmic tail (signal transduction, and transcriptional regulation; participation in cell growth and proliferation mechanisms, cell protection from apoptosis).	YES <i>In vitro</i> studies: Dexamethasone increases MUC1 expression in cancer cell lines [60,61]. Dexamethasone upregulates MUC1 expression in human corneal epithelial cells [62]. <i>In vivo</i> studies: Corticosteroid therapy increases MUC1 expression in nasal polyps [64].
MUC2	S	Lung and airways. Normal nasal mucosa. Nasal polyps. Other: Intestines (Jejunum, ileum, colon)	Major mucin secreted in the large intestine. Important role in: host innate defense, regulation of secretion, absorption processes, maintaining colonization resistance that contribute in maintaining the integrity of the protective mucus barrier in the large intestine [78]. The expression of MUC2 correlates with the activity of diseases, such as ulcerative colitis and Crohn's diseases [78].	YES <i>In vitro</i> studies: Budesonide inhibits the induction of MUC2 by inflammatory mediators in airway epithelial cells [58,59].
MUC3	MT	Gastrointestinal epithelium (colon, small intestine, gall bladder)	Major mucin secreted in the large intestine. Important role in: host innate defense, regulation of secretion, absorption processes, maintaining colonization resistance that contribute in maintaining the integrity of the protective mucus barrier in the large intestine [78]. The expression of MUC3 correlates with the activity of diseases, such as ulcerative colitis and Crohn's diseases [78].	YES <i>In vitro</i> studies: Steroids upregulate MUC3 expression in cultured breast cancer cells [79].
MUC4	MT	Lung and airway surface epithelial cells. Normal nasal mucosa. Nasal polyps. Other: Epithelium (eye, oral cavity, lacrimal glands, salivary gland, cervix, prostate gland, stomach, colon and mammary gland).	Responsible for viscoelastic nature of mucus. Role as protective barrier against invading pathogens and chemicals: Aids in mucociliary clearance of foreign bodies. Provides defense to the upper and lower respiratory tracts. Implicated in tumor progression by inducing increased cell growth, proliferation and survival. Aberrant expression in ovarian tumors and premalignant and malignant pancreatic lesions. Frequently overexpressed lung, breast and colon cancers. Functions of the different MUC4 segments: -Ectodomain (anti-adhesive, hydration and lubrication of cell surfaces, ERBB signaling).	YES <i>In vitro</i> studies: Dexamethasone inhibits MUC4 expression in nasal polyps [22]. Dexamethasone downregulates MUC4 expression in human corneal epithelial cells [62]. Inhibitory effect of corticosteroids in MUC4 increased mRNA expression in nasal polyps [63]. <i>In vivo</i> studies: Corticosteroid therapy increases MUC4 expression in nasal polyps [64].
MUC5AC	S	Lung and airway epithelium (goblet cells) Normal nasal mucosa. Nasal polyps. Other: Eyes. Stomach.	Major gel-forming mucin in the respiratory tract. Responsible for viscoelastic nature of mucus. Protection and stabilization of the ciliated surface. Role as protective barrier against invading pathogens and chemicals: Aids in mucociliary clearance of foreign bodies. Provides defense to the upper and lower respiratory tracts. Contribute to the defensive barrier function and the rheology of the airways mucus. Marker for goblet cell metaplasia. Associated with respiratory diseases, mainly with asthma.	YES <i>In vitro</i> studies: Dexamethasone decreases MUC5AC expression in both human epithelial cell lines [55,56,57] and in primary bronchial epithelial cells [57] and in rat primary airway epithelial cells [56]. Budesonide inhibits the induction of MUC5AC by inflammatory mediators in airway epithelial cells [58,59]. <i>In vivo</i> studies: Corticosteroids decrease secreted mucin MUC5AC expression in nasal polyps [64]

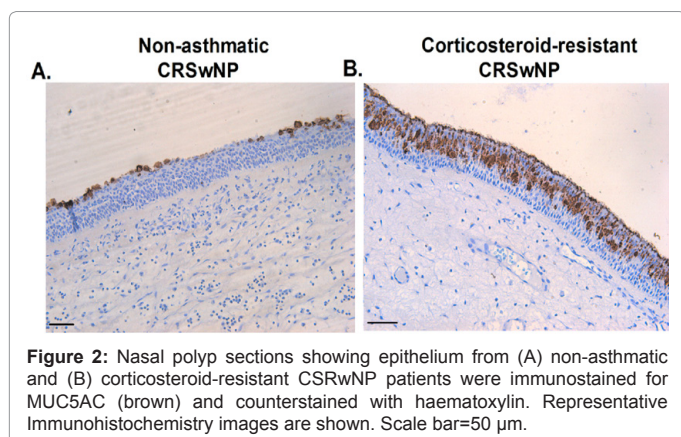
MUC5B	S	Lung and airway epithelium (submucosal glands) Normal nasal mucosa. Nasal polyps. Other: Salivary glands. Submandibular glands.	Major gel-forming mucin in the respiratory tract. Responsible for viscoelastic nature of mucus. Protection and stabilization of the ciliated surface. Role as protective barrier against invading pathogens and chemicals: Aids in mucociliary clearance of foreign bodies. Provide defense to the upper and lower respiratory tracts. Contributes to the defensive barrier function and the rheology of the airways mucus. Associated with respiratory diseases, mainly with COPD. Interaction between MUC5B and different salivary proteins (important in the maintenance of oral physiology by: enhanced physical protection, enhanced enamel integrity, enhanced non-immune host defense).	YES <i>In vivo</i> studies: Corticosteroids decrease secreted mucin MUC5B expression in nasal polyps [64].
MUC6	S	Stomach, ileum, gall bladder. Breast.	MUC6 is expressed in normal, benign and in malignant breast cancer [79].	YES <i>In vitro</i> studies: Steroids upregulate MUC6 expression in cultured breast cancer cells [79].
MUC7	S	Lung and airways. Normal nasal mucosa. Nasal polyps. Other: Salivary glands. Sublingual and submandibular glands. Lacrimal gland acini.	Secreted but not gel-forming mucin. Interaction between mucins and different salivary proteins are important in the maintenance of oral physiology (enhanced physical protection, enhanced enamel integrity, enhanced non-immune host defense).	Unknown.
MUC8	S	Lung and airways. Normal nasal mucosa. Nasal polyps.	MUC8 overexpression in nasal polyps. Upregulation of MUC8 mRNA expression by inflammatory mediators [80]. MUC8 as a ciliated cell marker in human nasal epithelium [81].	YES <i>In vitro</i> studies: Dexamethasone suppressed lipopolysaccharide-induced MUC8 mRNA levels in cultured human nasal epithelial cells [82].
MUC9	S and MT	Ovaries. Fallopian tubes	MUC9 is expressed in malignant epithelial ovarian tumors [83]. MUC9 or oviductal glycoprotein (OVGP1) is present in serum of women with ovarian cancer and has been described as possible serum marker for the detection of ovarian cancer [83].	Unknown.
MUC10		Submandibular mucin.	Salivary mucin.	Unknown
MUC11	MT	Lung Other: Colon Reproductive tract.		Unknown
MUC12	MT	Stomach, colon, pancreas, prostate, uterus.		Unknown
MUC13	MT	Lung and airways. Other: Colon, trachea, kidney, small intestine, conjunctival epithelium.	Aberrantly expressed in gastric, colorectal, ovarian [84], pancreatic, lung ovarian carcinomas. MUC13 overexpression increases cell growth, colony formation, cell migration, and invasion [85].	Unknown
MUC15	MT	Lung and airways. Other [86]: Colon, small intestine, prostate, placenta, salivary gland, thyroid gland, moderately in the kidney, conjunctival epithelium.	Aberrant expression of MUC15 correlates with development of colorectal adenocarcinoma [87]. MUC15 potential marker of malignancy and prognosis in papillary thyroid carcinoma [88].	Unknown
MUC16	MT	Lung and airways surface epithelial cells. Nasal polyps. Other: Epithelium of the ocular surface, reproductive organs and the mesothelium lining body cavities (pleural, peritoneal, and pelvic cavities). Conjunctival epithelium	Role as protective barrier against invading pathogens and chemicals. Overexpressed in ovarian and endometrial cancer. Well-known serum marker for ovarian cancer (CA 125).	YES <i>In vitro</i> studies: Dexamethasone upregulates MUC16 expression <i>in vitro</i> in human corneal epithelial cells [62]. Dexamethasone increases MUC16 expression at both the mRNA and protein levels in nasal polyp epithelial cells [22].

MUC17	MT	Gastrointestinal tract (duodenum, colon, stomach) Conjunctival epithelium	MUC17 has a role in protecting the intestinal mucosa against luminal pathogens [89]. MUC17 is expressed in select pancreatic and colon cancer cell lines and in intestinal absorptive cells [90]. Aberrant overexpression of MUC17 is correlated with pancreatic ductal adenocarcinomas [91].	Unknown.
MUC18	MT	Lung and airways. Other: Breast.	MUC18 has been shown to promote metastasis in several tumors, such as breast cancer [92] and melanoma [93] by increasing their motility, invasiveness and tumorigenesis. MUC18 amplifies lung inflammation during bacterial infection [94,95].	Unknown.
MUC19	S	Lung and airways (Trachea) Other: Salivary gland.	Major salivary glandular mucin.	Unknown.
MUC20	MT	Lung and airways. Other: Placenta, colon, prostate, liver.	Upregulated in renal injuries [96].	Unknown.
MUC21	MT	Lung and airways.	MUC21 modulates cell adhesion [97]. Marker for lung adenocarcinomas.	Unknown.
MUC22	MT	Lung and airways.		Unknown.

*MT: Membrane-tethered mucin; S: secreted mucin.

*General data in the table reviewed previously in several mucin reviews [14,15,18,21,73,98,99].

Table 1: Mucins, their characteristics and modulation by corticosteroids.



reaching below the lower border of the middle turbinate), 3 (large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha), large polyps causing almost complete congestion/obstruction of the inferior meatus). The different subsets of patients showed similar bilateral nasal polyp endoscopic scores (~5.5 score). All the patients received oral corticosteroid treatment at the moment of recruitment (deflazacort at 1mg/kg/day during 8 days followed by 0.5 mg/kg/day during other 7 days) and corticosteroid resistance was evaluated at day 15 after corticosteroid therapy. Those patients unable to reduce more than 1 nasal polyp endoscopic score after oral corticosteroid treatment were considered resistant, thus were classified in the corticosteroid-resistant group. Representative MUC5AC immunostaining in nasal polyp sections of non-asthmatic and corticosteroid-resistant CRSwNP patients are shown in Figure 2. These images evidence an increased expression of the secreted mucin MUC5AC in corticosteroid-resistant CRSwNP patients (Figure 2B) compared to CRSwNP responder patients (Figure 2A).

Corticosteroid efficacy in chronic rhinosinusitis with nasal polyposis (CRSwNP)

Corticosteroids are the drugs of choice as main treatment for CRSwNP, based on their strong anti-inflammatory activity [1]. Among these, topical intra-nasal corticosteroids constitute the first option due to their effects in maintaining clinical control of the symptoms [23], in reducing the size and extent of nasal polyps [24-27] and the number of recurrence episodes after polyp removal [28,29], thus being considered the most effective drug available. However topical corticosteroids are not always effective, as complete remission of the polyps with this treatment is only achieved in 60-80% of cases [30], leading to the use of systemic corticosteroids as the next available option. Systemic corticosteroids are accepted as an effective therapy in treating severe CRSwNP, demonstrated in a 2-week course of oral corticosteroids study where they reduced significantly the symptoms and polyp size [31]. Nevertheless, there is still a subset of patients that show resistance to the effects of corticosteroids due to cellular mechanistic resistance to this drug. In these cases, sinus surgery is the only available option in order to control the disease.

The mechanisms of action of corticosteroids in CRSwNP have been previously reviewed in the literature [32,33]. Corticosteroid's mechanisms involve corticosteroid receptors, which have been described to be present in all the nasal cell types with greatest numbers in epithelial cells, submucosal glands and leukocytes [34]. These receptors are located in the cellular cytoplasm and they bind corticosteroids with high affinity [35]. The resultant steroid-receptor complex translocates to the nucleus of the cell where it promotes or inhibits gene transcription by diverse mechanisms, such as transactivation or transrepression [36]. Transactivation involves the binding of the complex to DNA sequences known as *glucocorticoid response elements* (GRE), which are found in the promoter regions of corticosteroid regulated genes, and results in the stimulation of anti-inflammatory molecule synthesis. However, their main anti-inflammatory effect is the transrepressor effect, or the influence

of corticosteroids in inactivating inflammatory gene transcription without the direct interaction with DNA. This effect is mediated by the bonding of this complex to transcription factors, such as the nuclear factor kappa beta (NF- κ B) or activator protein-1 (AP-1), which results in the blockage of the transcription of pro-inflammatory cytokines, chemokines, adhesion molecules and inflammatory enzymes induced by these transcription factors [37-39]. Additionally, corticosteroids have also been described to affect histone acetylation through different mechanisms. For instance, corticosteroid's interaction with diverse co repressor molecules attenuating NF- κ B has an effect reversing histone acetylation and chromatin remodeling [40]. Moreover, activated corticosteroids recruit histone deacetylase (HDAC) 2 contributing to the suppression of multiple activated inflammatory genes [41].

The most commonly described corticosteroid-resistance mechanisms in CRSwNP have been related either with the ratio between corticosteroid receptor isoforms or with the action of transcription factors. Among the different corticosteroid receptor isoforms, α and β are known as the two principal isoforms. The active isoform α forms a complex with the corticosteroid and interacts with the GRE elements affecting transcription mechanisms. In the other hand, corticosteroid receptor β isoform is considered an inhibitor of corticosteroids as it is able to bind the GRE element on its own, blocking competitively the binding of the corticosteroid-receptor α complex to DNA, but is unable to exert an effect in gene expression [42,43]. Additionally, this isoform β is also capable of binding isoform α , creating a non active complex.

Several molecular mechanisms have been related with steroid resistance in CRSwNP, with close similarities to those mechanisms described in asthma (Table 2). Both of these corticosteroid receptor isoforms play a key role in corticosteroid resistance in CRSwNP, either by the increase of β isoform, the decrease of α isoform or the imbalance of the ratio between these two isoforms [44]. In fact, several studies have described increased expression of isoform β in CRSwNP patients compared to controls [45,46]. In addition, other studies reported a decreased expression of isoform α in CRSwNP compared to controls [47].

Other corticosteroid resistance mechanisms described in CRSwNP involve the direct inhibition of the bonding between the corticosteroid and the receptor by the action of transcription factors, such as NF- κ B or AP-1. Some studies have described NF- κ B activation and expression in CRSwNP and its relation with a worse response to corticosteroid treatment [48-50]. Other possible molecular mechanisms, which have

been described to induce resistance in corticosteroid insensitive or severe asthma, result from the phosphorylation of specific residues of the corticosteroid-receptor α by several kinases. This modifications in the corticosteroid-receptor impair its binding capacity, stability and translocation to the nucleus [51]. Different kinases, such as p38 mitogen activated map kinase (p38MAPK) and others (Table 2), have been described to phosphorylate corticosteroid receptors in asthma, thus inhibiting their nuclear translocation [41,52]. Moreover, microbial superantigens, such as staphylococcal enterotoxin B, have been described to induce corticosteroid resistance through activation of extracellular signal-regulated kinase (ERK) pathways which leads to corticosteroid receptor phosphorylation at Ser²²⁶ [53]. This is especially relevant in the study of corticosteroid resistance in CRSwNP, as the surface of nasal polyps is colonized by multiple pathogenic bacteria that contribute to the inflammatory process through their superantigens and correlate with disease severity [1,54].

Mucin expression and corticosteroid efficacy in chronic rhinosinusitis with nasal polyps (CRSwNP)

There are various *in vitro* studies in the literature that have described the effects of corticosteroids in mucin expression in the airway epithelium (Table 1). These studies mainly focused on secreted mucins although, in the last years, the importance of membrane-bound mucins in airway disease such as CRSwNP is gaining considerable relevance [22].

The corticosteroid dexamethasone has been described to decrease MUC5AC expression in human epithelial cell lines and in primary bronchial epithelial cells [55-57]. Moreover, budesonide has been described to inhibit the induction of major-gel forming mucins by inflammatory mediators in airway epithelial cells [58,59].

Regarding membrane-bound mucins, dexamethasone has been described to affect MUC1 by increasing its expression in cancer cell lines [60,61]. Additionally, this corticosteroid has been described to upregulate MUC1 and MUC16 and downregulate MUC4 expression *in vitro* in human corneal epithelial cells [62].

Few studies have evaluated the effects of corticosteroids in the expression of membrane-tethered mucins in nasal polyps and their potential mechanistic interactions. A recent study described an increase in MUC16 expression at both the mRNA and protein levels in nasal polyp epithelial cells induced by dexamethasone, but no significant effect in MUC4 expression [22]. On the other hand, another previous study described an increased expression of MUC4 in nasal polyps and the inhibitory effect of corticosteroids' in MUC4 mRNA [63].

However, more relevantly, an *in vivo* study evaluated the effects of these drugs in patients with nasal polyps after a course of two weeks of oral corticosteroids and these drugs were described to exert an effect in mucin expression in human nasal polyp epithelium [64]. In this study, corticosteroid therapy was described to increase membrane-tethered mucins (MUC1 and MUC4) and decrease secreted mucins (MUC5AC and MUC5B) expression in nasal polyps, thus evidencing a differential regulatory effect of corticosteroid therapy in mucin expression depending on the nature of the mucin. These results would reinforce the idea that suggests that corticosteroids could be considered a beneficial therapy for mucus hypersecretion in this disease. As the authors point out, the corticosteroid-induced down-regulation of the levels of secreted mucins could result in a decrease of mucus hypersecretion and, in contrast, the up-regulation of membrane-tethered mucins could be related to their participation in epithelial

- Corticosteroid receptor isoforms:
- Decreased corticosteroid receptor α isoform.
- Increased corticosteroid receptor β isoform.
- Imbalance of the ratio between these two corticosteroid receptor isoforms.
- Increased expression of pro-inflammatory transcription factors, such as:
- Nuclear factor kappa beta (NF- κ B)
- Activator protein-1 (AP-1)
- Corticosteroid receptor modifications: Increased phosphorylation of residues decreases nuclear translocation capacity.
GR α phosphorylation at Ser ²²⁶ contributes to steroid resistance by preventing nuclear translocation. This residue has been described to be phosphorylated by:
- Activation of p38 mitogen activated map kinase (p38MAPK).
- Increase in extracellular signal-regulated kinase (ERK).
- Increase in c-Jun N-terminal kinase (JNK)
- Decrease in MKP1.
- Defect in histone acetylation.

Table 2: Corticosteroid resistance molecular mechanisms in chronic rhinosinusitis with nasal polyposis (CRSwNP). Similarities with asthma [41].

repairing and remodeling processes. However, this study highlighted that AIA patients would require a special consideration as they showed a trend of resistance to this treatment. In fact, future research in corticosteroid resistance mechanisms is necessary to understand the particularly complex situation of therapy-resistance in AIA and corticosteroid non responder patients.

Our group has explored the expression of both membrane-tethered and secreted mucins in different cohorts of CRSwNP patients, which were selected according to relevant clinical factors that have been associated to this disease. In this sense, we have distinguished the following phenotypes: non-asthmatic CRSwNP, aspirin-tolerant asthmatic CRSwNP, aspirin-intolerant asthmatic CRSwNP and corticosteroid-resistant CRSwNP patients. Our results [65] (data not shown) evidence a down-regulation in the expression of MUC1, MUC4 and MUC16 in asthmatic, AIA and corticosteroid resistant CRSwNP patients compared to non-asthmatic CRSwNP patients, which was most evident in the corticosteroid resistant group. In contrast, the expression of secreted mucins MUC5AC and MUC5B was increased in the corticosteroid resistant CRSwNP group, as shown previously in Figure 2. These results would evidence the failure of the corticosteroid's mechanisms to control clinical symptoms of this disease, particularly mucus hypersecretion, in corticosteroid-resistant CRSwNP patients.

The significance of these results is highlighted as they evidence an opposite pattern of mucin expression in the groups of patients studied, especially in corticosteroid-resistant patients, than that described previously in the literature due to the effects of these drugs. These results could point out towards a clinical implication of mucins in corticosteroid non-responder patients and provide a model to study the potential participation of mucins in the corticosteroid resistant mechanisms in CRSwNP due to a possible interaction between mucins and corticosteroids or their receptors.

During the last years there has been an increasing awareness of the importance of membrane-tethered mucin expression in different diseases. Focusing particularly in respiratory diseases, their expression has been linked to protective functions against different inflammatory or infectious agents [15], thus research in mucins has been directed towards investigating their potential anti-inflammatory benefits. Both their presence at the cell surface, conferring them a high accessibility, and their interaction with multiple proteins, conferring them an ability to regulate different signaling pathways, underline their biological significance and their potential implication in therapeutic strategies.

Among the different membrane-tethered mucins, MUC1 stands out as an anti-inflammatory molecule that has potential clinical applications. MUC1 has been extensively linked with intracellular signal transduction in cancer cells [66] however, it is MUC1's anti-inflammatory role in the airways [67] which could imply a potential key role of this mucin in CRSwNP.

The anti-inflammatory role performed by MUC1 in the airways is evidenced by its participation in defense during airway infection, by inhibiting toll like receptor (TLR) signaling triggered by bacteria and virus [67-71]. The anti-inflammatory effect of MUC1 on TLR has been described to be mediated through its cytoplasmic MUC1-CT component [69,71]. This is especially relevant in the study of CRSwNP, as the surface of nasal polyps is colonized by multiple pathogenic bacteria that, by either forming biofilms or through their superantigens, contribute to the inflammatory process and correlate with disease severity [1,54].

MUC1 is located on the apical surface of mucosal epithelial cells

and hematopoietic cells [72], where it acts as a sensor receptor able to participate in cellular signaling due to its characteristic structure [17]. As a member of the membrane-tethered mucin family, MUC1 is composed by three distinct subunits: a large heavily glycosylated extracellular ectodomain, a single-pass transmembrane region, and an intracellular cytoplasmic tail (CT) that contains several evolutionally conserved tyrosines (Figure 3). The phosphorylation of these tyrosine residues mediates the binding of different kinases and adapter proteins and modulates multiple intracellular signals [67].

As mentioned earlier, the increasing relevance of membrane-bound mucins is due to their ability to interact with multiple and different extracellular and intracellular proteins which constitute a large and diverse family of different proteins, known as mucin-interacting proteins [73]. Among these, the group of proteins that interact with MUC1-CT are the best characterized and, due to their diversity, MUC1-CT is known to be able to unchain multiple downstream signaling events [74].

In addition to the interaction of MUC1-CT with different proteins that act as signal transducers, MUC1-CT has been described to translocate to the nucleus of the cell where it mediates different biological responses. As an example, a previous study has described the interaction between MUC1-CT and the estrogen receptor (ER) α , forming a MUC1-CT-ER α transcription complex that translocates to the nucleus [75]. In addition, another transcription complex involving MUC1-CT, β -catenin-MUC1-CT, has been described to modulate morphogenesis [76,77]. In both cases, the formation of these transcription complexes has been described to exert a protective role against degradation [75,76].

Our data concerning the decreased expression of MUC1 in corticosteroid resistant CRSwNP patients [65] has guided our current research to focus in evaluating the mechanistic link between MUC1 and corticosteroid's anti-inflammatory efficacy. The anti-inflammatory properties of MUC1 in airway inflammation are known to be related with its capacity to inhibit several TLR [69], particularly through MyD88 recruitment [71]. This inhibition prevents various downstream signaling cascades which would lead to the transcription of different pro-inflammatory genes (Figure 4). In addition, as described previously, MUC1 is also known due to its capacity to mediate the translocation of several transcription factors to the nucleus, where these exert their

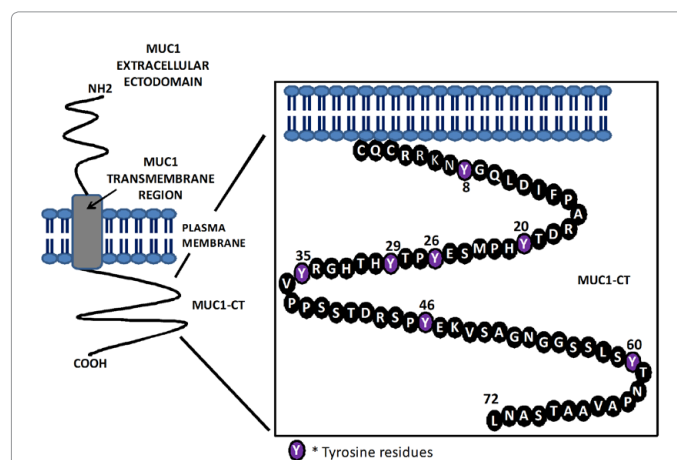


Figure 3: MUC1 structure. The membrane-tethered mucin MUC1 is composed by three distinct subunits: a large heavily glycosylated extracellular ectodomain, a single pass transmembrane region, and an intracellular cytoplasmic tail (CT) that contains several evolutionally conserved tyrosines (Y).

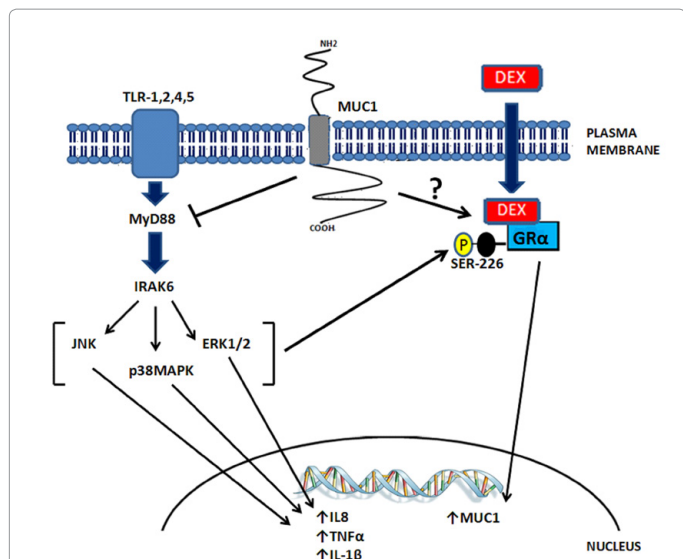


Figure 4: Mechanistic diagram that shows MUC1's anti-inflammatory properties. MUC1 is known to inhibit several toll-like receptors (TLR) through MyD88 recruitment. This results in preventing various downstream signaling cascades, such as c-Jun N-terminal kinase (JNK), p38 mitogen activated map kinase (p38MAPK) and extracellular signal-regulated kinase (ERK1/2), which would lead to the transcription of different pro-inflammatory genes. Dexamethasone (DEX), among other corticosteroids, is known to increase the expression of membrane-tethered MUC1 which would result in increasing its anti-inflammatory capacity. However, corticosteroid receptor (GR) modifications, such as an increased GR α phosphorylation (P) at Ser226, mediated by JNK, p38MAPK and ERK1/2, contributes to steroid resistance by preventing nuclear translocation, thus could have an effect in MUC1 expression. Additionally, the possibility of a potential interaction between MUC1 cytoplasmic tail (MUC1-CT), corticosteroids and their receptors is currently unknown.

function [75-77]. However, up to now, the possibility of a potential interaction between MUC1-CT and corticosteroids and their receptors is unknown. In our opinion, the relevance of studying a potential interaction between mucins, particularly MUC1, and corticosteroids is due to the possibility of providing a mechanistic explanation that would contribute to understand why these drugs are not able to repress inflammation in this particular subset of CRSwNP patients, which are characterized by exhibiting a reduced expression of MUC1.

Conclusion

This review aims to draw attention to the potential involvement of mucins in corticosteroid mechanisms in CRSwNP, specially focusing in membrane-tethered mucins. We postulate the hypothesis that mucin expression is not a consequence of corticosteroids' actions but a contributor to corticosteroid's mechanisms, thus, should be regarded as a potential mediator in the response to corticosteroids, particularly in CRSwNP. Therefore, future research is required to better address the role of mucins in corticosteroid resistance mechanisms in this disease in order to increase the knowledge regarding the loss of efficacy of corticosteroids in CRSwNP patients. Understanding the corticosteroid resistance mechanisms is crucial in contributing to alleviate and improve the situation of this especially difficult and challenging subset of therapy-resistant CRSwNP patients.

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