



# Indoleamine 2,3-dioxygenase expression is associated with chronic rhinosinusitis: review of the evidence

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## Purpose of review

Indoleamine 2,3 dioxygenase (IDO), the key metabolic enzyme implicated in tryptophan catabolism has been studied extensively during the past years in cancer, infections and autoimmunity. This review summarizes the findings of the immunomodulatory effects of IDO. In addition, the possible role of IDO in chronic rhinosinusitis (CRS) is discussed.

## Recent findings

Epithelial and leukocyte IDO expression is pronounced in CRS with nasal polyps and antrochoanal polyps. Although IDO associates with atopic disorders of the lower respiratory tract, we were not able to find an association between IDO and allergic rhinitis in the sinonasal mucosa.

## Summary

IDO might have a distinct role in the upper and lower respiratory tract. Future studies need to identify whether the IDO found in sinonasal mucosa is active and if it is a cause or a reason in the development of CRS with nasal polyps.

## Keywords

asthma, chronic rhinosinusitis, indoleamine 2,3-dioxygenase, kynurenine, tryptophan

## INTRODUCTION

Chronic rhinosinusitis (CRS) is a versatile, multifactorial immunological disease of the nose and paranasal sinuses with a prevalence of about 10%. It is a significant health problem, with a large financial burden on our society and with an increasing incidence [1]. Several diseases have been reported to coexist with CRS by partly unknown mechanisms: asthma, aspirin sensitivity, atopy, chronic rhinitis, depression, anxiety, fatigue, fibromyalgia, immunodeficiency, cystic fibrosis, and primary ciliary dyskinesia [2–4]. CRS can be subdivided into chronic rhinosinusitis with nasal polyps (CRSwNP) and without (CRSSNP). Nasal polyps appear as oedematous masses originating from the middle meatus and affect between 1 and 4% of the general population. CRS may develop in individuals with a certain genetic and/or epigenetic background as an outcome of unbalanced barrier-environment interactions. The exacerbations, triggered by viruses, allergens or other factors, might be both infective and hyperinflammatory in nature. The majority of patients with CRS have mild or moderate disease and can obtain adequate control of symptoms

through conservative therapy, added occasionally by sinus surgery. However, patients with difficult-to-treat CRS might experience considerable morbidity and organ-threatening complications. There is a need to explore biomarkers and tools for preventing progressing of CRS.

Indoleamine 2,3 dioxygenase (IDO) is an intracellular enzyme that initiates the first and rate-limiting step of tryptophan (Trp) breakdown along the kynurenine pathway. The role of IDO has evolved throughout time. IDO is induced in dendritic cells, which restricts infection and prevents exaggerated host responses [5,6]. In noninflammatory states,

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## KEY POINTS

- IDO might have distinct roles in different respiratory diseases.
- IDO might also have a different role in upper and lower airways.
- IDO expression in the sinonasal mucosa seems to be associated with CRS with nasal polyps and antrochoanal polyps.

IDO seems to mediate tolerance to self [7,8]. IDO also seems to mediate the transition from innate to acquired immunity. The role of IDO is traditionally recognized in autoimmunity, infection, cancer and pregnancy in a murine model. The scope of this review is to go over the evidence on the putative role of IDO in CRS and other respiratory disorders.

## TRYPTOPHAN DEGRADATION PATHWAYS

Trp is present in relatively low amounts in the body. Unlike other amino acids, Trp circulates in blood and plasma mainly bound to albumin [9]. Only 10–20% of Trp is present as free form in the plasma. Factors, such as nonesterified fatty acids or some drugs modify the binding of Trp to albumin. Whether or not Trp binding to albumin may modify the availability of Trp for tissue metabolism remains controversial [10,11]. Trp is also the precursor of *N*-formylkynurenine that is converted into kynurenine by kynurenine formamidase. *N*-formylkynurenine and kynurenine are the first metabolites of a complex metabolic pathway ending in quinolic acid, niacin, kynurenic and xanthurenic acid. Two enzymes are able to catalyse the conversion of Trp into *N*-formylkynurenine: Trp 2,3-dioxygenase (TDO) and IDO. These two enzymes differ in their tissue localisation, structure, substrate specificity, cofactor requirement and function. Whereas IDO is widespread in numerous tissues, TDO is mainly located in the liver [12]. The liver through TDO activity is responsible for maintaining Trp homeostasis.

## THE IMMUNOREGULATORY ROLE OF INDOLEAMINE 2,3-DIOXYGENASE

IDO is more than a metabolic enzyme. At first, its role seemed to be antimicrobial by restricting Trp availability. Munn showed in mice that inhibition of IDO by 1-methyl-DL-Trp (1-ML) in pregnancy causes rejection of semi-allogeneic, but not syngeneic fetuses [13]. IDO is widely expressed in a variety

of cell types, including leukocytes, antigen-presenting cells and tumour cells [14–16]. IDO is known to be induced by both type I and II interferons (IFN) [17,18]. In a murine model, macrophages and monocytes seem to express IDO messenger RNA (mRNA) transcripts only when activated by IFN- $\gamma$  [19]. On the contrary, IDO is expressed constitutively in CD8<sup>−</sup> and CD8<sup>+</sup> dendritic cells, as well as eosinophils, even in the absence of IFN- $\gamma$ . To date, two isoforms of IDO, IDO1 and IDO2 have been identified. Both differ in local expression, activity and organ specificity [20].

## The putative mechanisms of action

The downstream metabolites of Trp suppress immune reactivity by directly interacting with effector T lymphocytes and other types of immune cells [21,22]; however, not all T cells are susceptible to the toxic effects of Trp metabolites [23]. Kynurenine metabolites regulate the production of type I IFNs by decreasing the number of macrophages [24]. Another hypothesis proposes that the breakdown of Trp suppresses T-cell proliferation by reducing the availability of this essential amino acid in local tissue microenvironments.

## Indoleamine 2,3-dioxygenase in hypersensitivity responses

The function of IDO in eosinophils is either stimulatory or inhibitory on Th1 (T-helper 1 cell) and Th2 (T-helper 2 cell) cells depending on the inflammatory model and previous sensitization [23,25]. IDO induction in eosinophils might mediate a Th2 polarization in-vitro and in-vivo eosinophils displayed intracellular IDO immunoreactivity [26]. The abundance and persistence of IDO-expressing eosinophils in lymphoid tissue may accentuate or, at a minimum, potentiate the apoptotic effect on Th1 cells previously thought to be associated only with IDO-expressing tolerogenic dendritic cells and thus maintain Th2 bias [26].

## Indoleamine 2,3-dioxygenase in induction of tolerance

IDO seems to provide a potential mechanism for the development of dendritic cell-mediated T-cell tolerance [27]. The effects of IDO are selective and narrowly focused on specific forms of acquired peripheral tolerance or unresponsiveness to novel antigens. Classically antigen presentation to resting T cells occurs in draining lymph nodes and this is thought to lead to T-cell activation, but studies have shown that this can also lead to potent,

antigen-specific tolerance induction, particularly when antigens are presented in lymph nodes draining normal uninfamed tissues or mucosal surfaces. These studies emphasize that it is the nature of the lymph node, rather than the antigen, which dictates the choice between tolerance and immunity. Systemic inactivation of IDO does not appear to cause severe autoimmunity [28]. Yet, IDO might mediate tolerance to self by transforming growth factor-beta (TGF- $\beta$ ) [7,8]. In this pathway, IDO is phosphorylated and acts as a signalling mediator [29,30]. IDO also seems to mediate the transition from innate to acquired immunity. IDO has signalling activity in dendritic cells, which are stably turned into regulatory dendritic cells [29]. Dendritic cells have functional plasticity. They can present antigens in an immunogenic or tolerogenic fashion, depending on environmental factors [31]. In certain pathways, antigen-presenting cells and regulatory T cells (Tregs) are involved in an interplay which results in further upregulation of IDO and also four other amino acid-consuming enzymes, capable of restraining T-cell proliferation and promoting Treg expansion [29].

### **Indoleamine 2,3-dioxygenase in infection: a tolerogenic pathogen strategy**

When pathogens invade host cells, they activate the innate immune system and elicit the production of cytokines and chemokines, which recruit immune cells that mediate pathogen clearance. Type I IFNs especially are important mediators of innate immunity that limit the adverse effects of many viruses. IFN- $\gamma$ -induced IDO has an antiviral effect in measles virus infection of epithelial and endothelial cells *in vitro* [32]. On the contrary, IFN- $\gamma$  has shown to induce IDO's enzymatical functions in dendritic cells, which restricts infection and prevents exaggerated host responses [5,6]. Hoshi *et al.* [24] found in a murine acute viral myocarditis model that IDO was induced by encephalomyocarditis virus, which promoted viral replication and tissue damage. IDO-deficient and inhibitor-treated mice had higher survival rates and had greater suppression of encephalomyocarditis virus replication. Disadvantageous effects of IDO have also been reported in other viral infections [33,34]. Bacterial infection with *Mycobacterium tuberculosis* strongly upregulated the expression of IDO1 in human monocyte derived dendritic cells and macrophages [35]. In a murine model, Loughman and Hunstad [36] observed that uropathogenic *Escherichia coli* attenuated innate responses to epithelial infection by inducing expression of IDO. Bacteria such as uropathogenic *E. coli* seem to stimulate IDO expression

as a pathogen strategy to create local immune privilege at epithelial surfaces, thus attenuating innate responses to promote colonization and the establishment of infection. Moreover, the authors observed that IFN was not necessary for IDO induction.

### **INDOLEAMINE 2,3-DIOXYGENASE IN AIRWAY DISEASES**

Several studies propose that IDO has a role in the control of atopic and infective airway diseases, as summarized in Table 1 [23,25,26,35,37–53].

#### **Indoleamine 2,3-dioxygenase in asthma**

In a murine asthma model, IDO inhibits eosinophilic inflammation [37]. In an OVA-sensitized mouse model, An *et al.* [38] found that immature dendritic cells (imDCs)-expressing IDO relieved allergic airway inflammation, as measured by decreased eosinophil and total cell counts, as well as by improved pulmonary histopathology. The authors also observed that increased CD4<sup>+</sup> T-cell apoptosis was observed in mice receiving IDO-expressing imDCs, in comparison to the control groups. Paveglio *et al.* [39] showed in a transgenic mouse model that overexpression of IDO in the lungs might cause an antiasthmatic effect by diminishing proliferation, numbers and cytokine production of CD4<sup>+</sup> T cells. It has been shown that IDO in lung dendritic cells promoted Th2-mediated allergic airway inflammation, but was not essential for immune tolerance via inhibition of Th1 response [40,54]. Toll-like receptor-9-ligand-induced pulmonary IDO activity inhibits Th2-driven experimental asthma [37]. When exposing *in vitro* monocyte-derived dendritic cells with house dust mite *Dermatophagoides pteronyssinus* 1, functionally active IDO decreased in cells from patients with house dust mite-sensitive asthma compared with nonatopic asthmatics [41]. In studies with asthmatic patients, von Bubnoff *et al.* [42] showed that after *in vivo* aeroallergen exposure, serum IDO activity was increased in asymptomatic atopics compared with either symptomatic atopic or nonatopic individuals. In an asthma cohort study [55], lower IDO activity has been observed in atopics in comparison to nonatopics. Maneechotesuwan *et al.* [43] showed that asthmatics have low baseline IDO activity in sputum. They also showed that IDO activity could be enhanced by treatment with inhaled corticosteroids [43].

#### **Indoleamine 2,3-dioxygenase in chronic rhinosinusitis**

CRS without nasal polyps (CRSsNP) is characterized by a Th1 polarization with high levels of IFN- $\gamma$  and

**Table 1. Original articles concerning indoleamine 2,3-dioxygenase in airway inflammation or pulmonary infection**

| Reference                          | Patients, number                                                                                                                                                 | Methods                                                                               | Main outcomes                                                                                                                                                                                                                                                                                                |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Swanson <i>et al.</i> [23]         | Mice lung interstitial antigen-presenting cells; mice lung allografts                                                                                            | HPLC; IHC; flow cytometry                                                             | IDO mRNA expression was unique to lung interstitial antigen-presenting cells; they suppressed proliferation of allogeneic T cells. IDO inhibition recovered T-cell proliferation. IDO overexpression in allograft associated with acute rejection                                                            |
| Grohmann <i>et al.</i> [25]        | Mice infected with <i>Aspergillus fumigatus</i> treated with dexamethasone; dexamethasone with 1-MT; no treatment                                                | FACS                                                                                  | Dexamethasone-only treated mice had decreased eosinophils and mucin in BAL, and decreased serum IgE                                                                                                                                                                                                          |
| Odemuyiwa <i>et al.</i> [26]       | Cultured blood eosinophils from atopic patients. Bronchial biopsy from one patient with asthma and Churg–Strauss syndrome                                        | Western blot<br>real time-PCR; IHC                                                    | IDO is expressed in eosinophils obtained from atopic donors. Increased IDO mRNA in eosinophils treated with IFN- $\gamma$ . IDO expressed in eosinophils infiltrating airway tissue                                                                                                                          |
| Weiner <i>et al.</i> [35]          | Serum from patients with latent tuberculosis $N=46$ ; symptomatic pulmonary tuberculosis $N=44$ ; controls $N=46$ ; mice exposed to <i>M. tuberculosis</i> $N=6$ | Nontargeted mass spectrometry<br>IHC; HPLC                                            | Increased IDO1 activity in sera from patients with active tuberculosis. Strong IDO1 expression and activity in mice suffering from experimental tuberculosis                                                                                                                                                 |
| Hayashi <i>et al.</i> [37]         | From OVA-sensitized mice: BAL; Lung tissue; splenic Th1 and Th2 cell lines                                                                                       | Real time-PCR; FACS; airway responsiveness<br>Western blot; histology                 | Toll-like receptor-9-ligand-induced pulmonary IDO protects lung from Th2-driven inflammation and airway hyperreactivity                                                                                                                                                                                      |
| An <i>et al.</i> [38]              | Mice exposed to IDO- imDCs $N=6$ empty plasmid-imDCs $N=6$ ; OVA sensitized mice $N=6$ ; controls $N=6$                                                          | PCR; Western blot<br>flow cytometry<br>histology                                      | IDO-expressing imDCs induced Th2 cell apoptosis, reduced Th2 cell activation and reduced <i>in vivo</i> pulmonary inflammation                                                                                                                                                                               |
| Paveglio <i>et al.</i> [39]        | Mouse transformed airway epithelial cells; mice lung prepares transgenic mice with IDO overexpression                                                            | HPLC; real time-PCR; Western blot                                                     | Overexpression of IDO in airway epithelium diminishes CD4 T cells in lung and their capacity to produce cytokines. Pathophysiological alterations not improved by IDO or pulmonary hyperresponsiveness to methacholine                                                                                       |
| Xu <i>et al.</i> [40]              | Aerosolized OVA-sensitized IDO $^{-/-}$ mice                                                                                                                     | FACS; ELISA; airway responsiveness to methacholine by small-animal ventilator         | IDO $^{-/-}$ mice did not have impairment of airway tolerance. They had attenuated Th2 cytokine production, airway inflammation, mucus secretion, airway hyperresponsiveness, and serum OVA-specific IgE. They had fewer matured DCs in lung-draining lymph nodes after immunization for Th1 or Th2 response |
| Maneechotesuwan <i>et al.</i> [41] | DCs from patients with house dust mite sensitive asthma; nonatopic asthma                                                                                        | Real-time PCR; HPLC<br>coincubation of Der p 1-pulsed DCs, autologous T cells and Trp | Der p 1 suppressed functional IDO in DCs from house dust mite-sensitive asthmatics but enhanced IDO activity in DCs from nonatopic asthmatics                                                                                                                                                                |

**Table 1 (Continued)**

| Reference                          | Patients, number                                                                                                                                                                                                          | Methods                                                                     | Main outcomes                                                                                                                                                                                                                                                                                                                                |
|------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| von Bubnoff <i>et al.</i> [42]     | Serum from subjects with seasonal AR <i>N</i> = 12; asymptomatic atopics sensitized to specific aeroallergens <i>N</i> = 12; controls <i>N</i> = 12                                                                       | HPLC                                                                        | Higher serum kyn/tryptophan-ratio in asymptomatic atopics sensitized to aeroallergens in comparison to controls and seasonal AR                                                                                                                                                                                                              |
| Maneechotesuwan <i>et al.</i> [43] | Induced sputum from asthmatics treated with inhaled short-acting $\beta_2$ -agonists <i>N</i> = 4; inhaled steroids <i>N</i> = 11 inhaled steroids + long-acting $\beta_2$ -agonists <i>N</i> = 17; controls <i>N</i> = 5 | Alkaline phosphatase immunostaining; HPLC                                   | Asthmatics had low baseline IDO activity in sputum. IDO activity enhanced when treated by inhaled steroids with or without long acting $\beta_2$ -agonists                                                                                                                                                                                   |
| Honkanen <i>et al.</i> [44]        | Sinonasal biopsies from: CRSsNP <i>N</i> = 41; CRSwNP <i>N</i> = 68; antroch. polyps <i>N</i> = 10; controls <i>N</i> = 31                                                                                                | IHC                                                                         | Epithelial and leukocyte expression of IDO associated with CRSwNP and antrochoanal polyps                                                                                                                                                                                                                                                    |
| Luukkainen <i>et al.</i> [45]      | Nasal biopsies from pollen AR <i>N</i> = 12; controls <i>N</i> = 15                                                                                                                                                       | IHC                                                                         | No difference in IDO expression between patients with AR and controls both before and after pollen exposure                                                                                                                                                                                                                                  |
| Ciprandi <i>et al.</i> [46]        | Serum from patients with seasonal AR winter <i>N</i> = 56; seasonal AR spring <i>N</i> = 46; controls <i>N</i> = 96                                                                                                       | HPLC                                                                        | No difference in Kyn/Trp-ratio between pollen season and nonexposure. Higher IDO activity in comparison to controls                                                                                                                                                                                                                          |
| Maneechotesuwan <i>et al.</i> [47] | Sputum samples from asthmatics before and 8 weeks after receiving: budesonide + simvastatin <i>N</i> = 22; budesonide + placebo <i>N</i> = 25                                                                             | Real time-PCR; alkaline phosphatase immunostaining; HPLC                    | Budesonide induces IDO activation through the TNF receptor ligand-associated noncanonical nuclear factor $\kappa$ B-pathway with nuclear translocation of p52 and increased IL-10 production. Simvastatin added to Budesonide further increases noncanonical nuclear factor $\kappa$ B-dependent induction of IDO and enhances IL-10 release |
| Taher <i>et al.</i> [48]           | Aerosolized OVA-sensitized, OVA-challenged mice that received subcutaneous immunotherapy with optimal OVA-dosage suboptimal OVA-dosage                                                                                    | ELISA; airway resistance by small-animal ventilator; serum OVA-specific IgE | Inhibition of IDO by intraperitoneal 1-MT during immunotherapy but not during inhalation challenge, partially reversed the suppressive effects of immunotherapy on airway eosinophilia and Th2 cytokine levels                                                                                                                               |
| Kositz <i>et al.</i> [49]          | Serum samples from atopics before specific immunotherapy <i>N</i> = 44; controls <i>N</i> = 38                                                                                                                            | HPLC                                                                        | Higher serum Trp concentrations in atopics, especially in nonresponders to immunotherapy                                                                                                                                                                                                                                                     |
| van der Marel <i>et al.</i> [50]   | Cells isolated from murine lymph nodes. Mice were OVA-sensitized and OVA-challenged or physiological saline-challenged with treatment by 1-MT; placebo                                                                    | Real-time PCR                                                               | Higher IDO expression in DCs from nose draining lymph nodes compared with DCs from other lymph nodes. IDO inhibition during intranasal OVA-challenge lead to abrogated antigen-specific immune tolerance                                                                                                                                     |

**Table 1 (Continued)**

| Reference                  | Patients, number                                                                              | Methods                                                                  | Main outcomes                                                                                        |
|----------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Suzuki <i>et al.</i> [51]  | Serum from patients with pulmonary tuberculosis<br>N = 174; controls N = 85                   | Liquid chromatography electrospray ionization tandem mass spectrometry   | Higher IDO activity in sera from tuberculosis patients correlates with outcome                       |
| Suzuki <i>et al.</i> [52]  | Serum from patients with community-acquired pneumonia N = 129; controls N = 64                | Liquid chromatography; electrospray ionization; tandem mass spectrometry | Higher IDO activity in sera from patients with community-acquired pneumonia, correlates with outcome |
| Yoshida <i>et al.</i> [53] | Supernatant of lung homogenate from mice before and after exposure to influenza virus aerosol | Incubation with radio-labeled Trp                                        | Increased IDO activity after virus infection                                                         |

1-MT, 1-methyl-D-tryptophan; AR, allergic rhinitis; BAL, Bronchoalveolar lavage; CRSsNP, Chronic rhinosinusitis without nasal polyps; CRSwNP, Chronic rhinosinusitis with nasal polyps; DCs, Dendritic cells; Der p 1, Dermatophagoides pteronyssinus; ELISA, Enzyme linked immunosorbent assay; FACS, Fluorescent activated cell sorting; HPLC, High performance liquid chromatography; IFN- $\gamma$ , Interferon-gamma; IHC, immunohistochemistry; IL-10, Interleukine-10; imDCs, immature dendritic cells; kyn, Kynurenine; mRNA, Messenger RNA; N, number; OVA, Ovalbumin; PCR, Polymerase chain reaction; Th2 cell, T-helper-cell 2-leukocyte; TNF, Tumour necrosis factor; Trp, Tryptophan; Kyn/Trp, Kynurenine/Tryptophan.

TGF- $\beta$  [56]. In comparison to CRSsNP, nasal polyps of Caucasian patients are characterized by pronounced local eosinophilia [57] and systemically by increased blood eosinophilia [58]. CRSwNP is characterised by a Th2 polarization with high interleukin-5 (IL-5) and immunoglobulin E (IgE) concentrations [56]. A deficit in Treg capacity in CRSwNP might lead to a strong increase in Th1 and Th2 effector cell signals [59]. Antrochoanal polyps originate (unilaterally) from the maxillary sinus mucosa and protrude into the choana. They are considered to have a predominance of neutrophils [58].

We found that in comparison to control inferior turbinate, IDO is strongly expressed in nasal polyp tissue in the vicinity of the Golgi apparatus of epithelial cells, but not on the supraepithelial mucus [44]. Moreover, IDO is weakly expressed in submucosal leukocytes and intraepithelial glands. Also, epithelial IDO expression seems to correlate with higher eosinophil numbers as well as with leukocyte IDO expression [44]. Epithelial IDO expression associates also with higher amounts of supraepithelial mucus. The maxillary sinus mucosa from patients with CRSwNP showed a higher IDO expression level in leukocytes but not in the epithelium when compared with healthy controls. However, the patients suffering from CRSsNP did not have different expression levels of IDO in the maxillary sinus mucosa in comparison to controls. The findings of IDO expression in sinonasal biopsies were independent of allergic rhinitis, acetyl salicylic acid (aspirin) intolerance, asthma, smoking, use of intranasal or peroral corticosteroids, or antihistamines, previous operations, recurrence of polyps, sex and age [44]. Sekigawa *et al.* [60] showed that the INDO

genotype found in nasal polyp specimens seems to have a role in the genetic risk for aspirin-intolerant asthma. Our unpublished results show that serum IDO activity is significantly lower in patients with nasal polyps (NP), independently of asthma, atopy, aspirin intolerance and smoking. NP might thus affect immunity on a system level independently of asthma, atopy or acetylsalicylic acid intolerance [61–63]. The fact that patients with CRSwNP might have a high level of epithelial IDO locally, but low serum activity of IDO, requires further elucidation. The explanation could partly be that active epithelial IDO does not affect or affects serum kyn/trp concentrations little. Moreover, local and systemically acting IDO probably have different immunoregulatory functions in patients with CRSwNP.

### Indoleamine 2,3-dioxygenase in allergic rhinitis

IDO seems to associate with atopic asthma, yet there is still a lack of evidence whether IDO promotes allergic inflammation also in the upper airways. When we observed patients with CRS, the expression of epithelial and leukocyte IDO was independent of the allergic rhinitis diagnosis [44]. We also took nasal biopsies from controls and patients with birch pollen allergic rhinitis, both in winter and spring. As expected, patients with birch pollen allergic rhinitis had increased serum IgE levels. During spring, atopic patients showed increased mucosal eosinophilia and symptom score. Yet, the expression of IDO in the nasal mucosa remained at the control level [45]. Thus, in the upper airways, IDO could associate with CRSwNP but not with allergic rhinitis.

## INDOLEAMINE 2,3-DIOXYGENASE IN OTHER DISEASES

During the past year, reviews on the role of IDO in allergy [64<sup>■</sup>], cancer [65], antitumour immunity [66<sup>■</sup>], HIV infection [67], the induction of IDO activity and signalling [29<sup>■</sup>], therapeutic potentials [12], posttranslational modifications [30], allogeneic engraftment of skin substitute [68] have been made. In allografts, IDO-mediated T-cell inhibition has shown to be rapidly reversed once IDO activity ceases [69]. The pharmacologic inhibition of IDO causes marked exacerbation of inflammation and worsened symptoms of disease in a murine model of inflammatory bowel disease [70]. In cancer, IDO seems to decrease recruitment of antitumour immune cells, induce tolerance towards tumour antigens and thus facilitate immune escape. In addition, increased IDO expression correlates with diverse tumour progression parameters and shorter patient survival. IDO helps create a tolerogenic milieu in the tumour and the tumour-draining lymph nodes, both by direct suppression of T cells and enhancement of local Treg-mediated immunosuppression. It can also function as an antagonist to other activators of antitumour immunity [71]. Immunologic tolerance to tumours is not simply a passive event; the immune system, in some cases, seems to be aware of tumour antigens but is somehow rendered tolerant to them. Once this acquired tolerance has been established, immunization with tumour-associated antigens can intensify antigen-specific immunosuppression [71]. Preclinical studies with 1-methyltryptophan and other approaches in cancer immunotherapy are in progress [65].

## CONCLUSION

IDO has variable functions in several diseases, such as atopic lower respiratory diseases. By this review, we were able to add a putative role of IDO also in CRSwNP. Before considering IDO as a biomarker or potent tool for management of airways diseases, further studies on the distinct roles of IDO in the respiratory system are needed. Moreover, the elucidation of its role in the pathomechanisms of CRSwNP demands more studies.

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## Conflicts of interest

*There are no conflicts of interest.*

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## 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. 000–000).

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