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REVIEW

The role of indoleamine 2,3-dioxygenase in allergic disorders

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Abstract
The amino acid tryptophan (TRP) is critical for the expansion and survival of cells. During the past few years, the manipulation of tryptophan metabolism via indoleamine 2,3 dioxygenase (IDO) has been presented as a significant regulatory mechanism for tolerance stimulation and the regulation of immune responses. Currently, a considerable number of studies suggest that the role of IDO in T helper 2 (Th2) cell regulation may be different from that of T helper 1 (Th1) immune responses. IDO acts as an immunosuppressive tolerogenic enzyme to decrease allergic responses through the stimulation of the Kynurenine-IDO pathway, the subsequent reduction of TRP, and the promotion of Kynurenine products. Kynurenine products motivate T-cell apoptosis and anergy, the propagation of Treg and Th17 cells, and the aberration of the Th1/Th2 response. We suggest that the IDO-kynurenine pathway can function as a negative reaction round for Th1 cells; however, it may play a different role in upregulating principal Th2 immune responses. In this review, we intend to integrate novel results on this pathway in correlation with allergic diseases.

Keywords Allergic diseases · Indoleamine 2 · 3-Dioxygenase · Kynurenine · Tryptophan · Th2-type immunity

Allergic disorders

Allergic disorders are among health issues that create a major economic problem due to the complications of the innate and adaptive immune system [1]. During the last few decades, the prevalence of allergies has dramatically increased. Today, allergies are among the prevalent chronic disorders in most countries [2, 3]. On the other hand, immune regulation is a highly advanced biological response that can create natural immunity and inflammation as well as the adaptive immunity of controlled and self-tolerance development [4, 5].

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IDO structure and characterization

Tryptophan (TRP) is a crucial amino acid and a substrate for numerous proteins used by various cells in the human body [6]. This amino acid exists in low quantities in the body, and it generally flows in the blood and plasma, attached to albumin [7]. Insufficient nutritional consumption of TRP can result in an undesirable nitrogen equilibrium and a decline of muscle mass, weight, and brain mass [8]. The mean serum level of TRP in human blood must be 73 ± 14.9 µmol/l [9].

TRP is significant for cell survival and protein production. Moreover, it is an antecedent for serotonin and other beneficial molecules in the brain tissue, including melatonin and niacin, and it guides immune responses in mammals [10, 11]. Furthermore, it is a valuable backup for the Kynurenine pathway (KYN) [12, 13]. TRP is processed via three diverse biosynthetic paths, i.e., (a) the creation of *KYN* byproducts, (b) the production of serotonin [14], and (c) the biosynthesis of proteins (Fig. 1). The main supervisor enzyme in this path, which is common in several tissues [13], is indoleamine-2,3-dioxygenase (IDO). Current studies show that *KYN* metabolites have immunosuppressive and antimicrobial characteristics [15, 16]. By catabolizing TRP, cells secreting the IDO enzyme can facilitate strong local properties on natural and specific

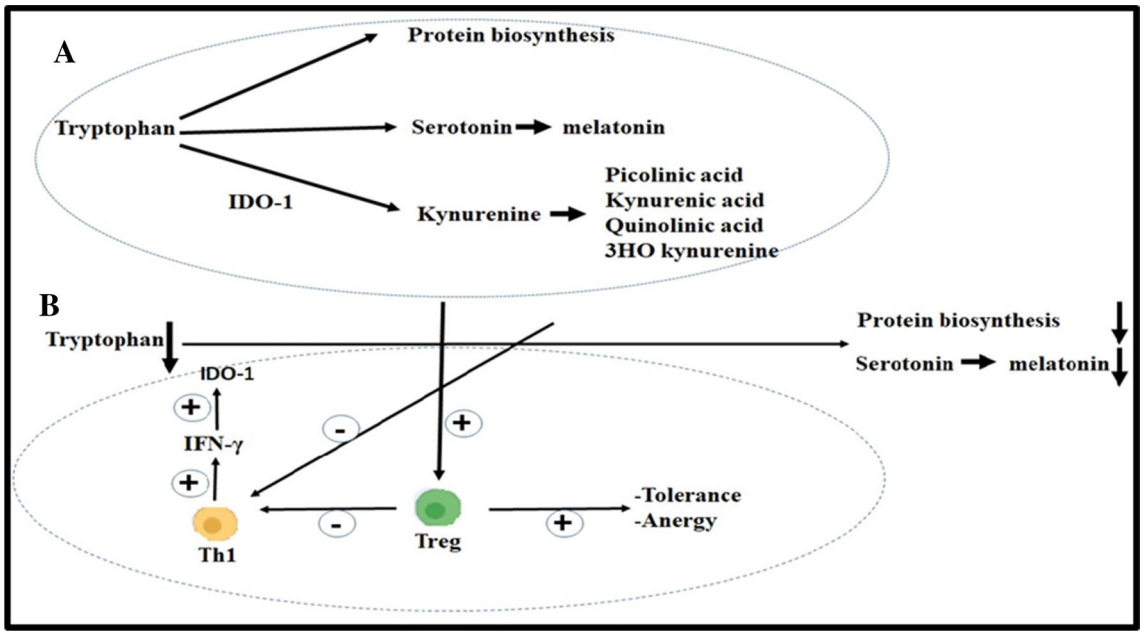

Fig. 1 **A** Normal tryptophan metabolism: Tryptophan degradation through three pathways that result in protein synthesis, melatonin production, and the main product kynurenine. **B** Th1 immune response activation: IFN-γ is the main significant stimulator of IDO1. The decomposition of tryptophan in the kynurenine path results in the addition of products, some of which are created to stimulate Tregs to reduce T cell motivation. Decreasing tryptophan due to degradation by IDO1 restricts protein biosynthesis and melatonin production. (T reg = regulatory T cell; 3HO kynurenine = 3-hyroxykynurenine)

immune responses to inflammatory stimuli [11]. IDO is composed of 407 amino acids, and it is an intracellular monomeric [6] that is responsible for the primary phase in the catabolism of TRP into N-formyl-Kynurenine [17].

The two types of the IDO enzyme are IDO1 and IDO2, both of which change TRP to *KYN* with different levels of activity [18]. IDO2 is less frequently expressed than IDO1, and it only has 3–5% of the enzymatic activity of IDO1 [18, 19]. The IDO enzyme is determined by the IDO1 gene, which is situated on chromosome 8 [20]. IDO1 is expressed in a wide variety of mammalian cells related to immune purpose, as well as specialized immune cells (antigen-presenting cells (APC)), or cells that consult immune concession to tissues. However, the expression of IDO1 is not permanent, and it relates to the immunologic signals mainly engaged via interferons)type I and II((IFNs) [21]. Moreover, IDO is significantly prompted in dendritic cells ($CD123^+$ $CCR6^+$ $CD11b^-$ $CD86^+$ plasmacytoid dendritic cells), which limits infection and avoids overexpressed host responses [17, 22]. IDO also appears to facilitate the switch from natural to specific immunity [23]. In non-inflammatory conditions, IDO appears to facilitate tolerance to self [24].

Here, we discuss the current evolution in understanding immunomodulatory and immunoregulatory characteristics of IDO in allergic responses. The presented developments pinpoint potential new goals for therapy in allergic disorders.

IDO and immune responses

The common task of the immune system is to discriminate among familiar and unfamiliar and to recruit defensive immune responses in the existence of a hurtful, unfamiliar antigen. This equilibrium between the beginning and destruction of the immune response depends on an extraordinary amount of controller mechanisms [25]. Currently, the impact of TRP catabolism via the *KYN* path has been presented in one of the immune tolerance mechanisms. The enzymes that break TRP through this pathway are established in various cells, including the cells of the immune system [6]. IDO expression can be stimulated in the lungs, the brain, the gut, multiple malignancies, kidneys, plasmacytoid dendritic cells (pDCs) inside the spleen, and the draining lymph nodes [26, 27]. In standard physiologic character, IDO is significant in controlling immune motivation to antigenic encounters at mucosal surfaces in the lungs and the digestive tract [28, 29]. Numerous co-stimulators are mandatory for the activation and appearance of IDO-1/IDO-2. They contain cytokines (Tumor necrosis factor-alpha (TNF-α), Transforming growth factor-beta (TGF-β), and interferon (IFN)), lipopolysaccharides similar to amyloid peptides, several human immunodeficiency virus (HIV) antigens, and numerous ligands of Toll-like receptor) TLR [14, 30,

31]. Principally, IFN-γ strongly stimulates the catalytic activity of IDO, reducing TRP and increasing immunoregulatory *KYN*, which will possibly raise regulatory T-cell (Treg) extension. Prompted Treg cells consume TGF-β to preserve an IDO-related regulatory milieu, with the IDO frequently working as an indicating molecule [24]. IFN-γ via co-stimulation molecules stimulated DCs to present practical IDO, decrease TRP, and increase the growth of *KYN* products and consequent Th-cell reticence. Common results show the special stimulation of apoptosis in Th1 cells owing to the improved vulnerability of Th1 cells to *KYN* metabolites [32, 33]. Furthermore, with regard to the impacts of TRP on Th(1, 2, and 17) cells, current data show that TRP catabolites influence natural lymphocytes [34].

IDO is a useful regulator of the active equilibrium among immunity and tolerance, and it is essential for adaptive immunity, immune investigation instruments, and antiviral protection, and in confronting intracellular pathogens [35, 36]. IDO1 prevents the propagation of T cells via the reduction of TRP and/or via manufacturing bioactive catabolites. Therefore, TRP metabolism was revealed to be strongly involved in immunomodulation [37]. A character of stimulated IDO1 was shown through the rise in the *KYN*/TRP ratio since *KYN*/TRP is associated with the density of the immune stimulation, such as autoimmune, infections, and neurodegenerative conditions [38, 39]. Through degrading TRP, IDO1 modifies native and total TRP density and initiates the production of immunoregulatory and neuroactive TRP products. Munn et al. used a mouse model to show that IDO1 stimulation indicates a significant feature in the formation of immune tolerance against the embryo, and they have proven the placenta as an immune-privileged place to avoid denial of the embryo. The known controlling activities of the IDO pathway mainly act on T, Natural killer (NK) cell, macrophages, and dendritic cell (DCs) cells. IDO causes naive T cells to discriminate into T regulatory cells (Treg cells, $CD4^+CD25^+FoxP3^+$) that spread general anergy to the presented antigens (Fig. 1) [40]. These catabolites do not have a similar result on Th2 cells, so improved IDO movement seems to tilt Th- cell divergence to a Th2 phenotype [41]. Moreover, IDO encourages Treg differentiation, the initiation of apoptosis in numerous subgroups, and T cell receptor (TCR) stimulation. IDO's activities on NK cells cause the downregulation of motivating receptors and cell death. Moreover, IDO has been revealed to regulate DCs development and migration [42]. DCs expressing IDO suppress T-cell propagation, distinction, effector functions, and sustainability, either through direct effects on T cells or via affecting IDO on the DCs [37]. In other words, IDO is a general regulator of inflammation [43]. Also, studies suggest the contrasting roles that IDO1 and IDO2 play in immune responses, with IDO1 facilitating T cell suppressive effects and IDO2 working traditionally in B cells as a proinflammatory mediator of B cell responses [44].

Immunomodulatory and immunoregulatory roles of IDO

Set-out immune system by critical amino acid famishment via IDO happens through two separate methods. The first is imitating a natural defensive response against inflammatory harm. Secondly, there is an interaction linking Treg cells and APCs, which results in additional upregulation of IDO, capable of limiting T-cell propagation and endorsing Treg cell extension by infectious tolerance [45–47]. The first detection of immunomodulatory properties of IDO enzyme was prepared in 1984 once IFN-γ stimulated TRP deterioration and obstructed the growth of *Toxoplasma gondii* in human fibroblasts. This revealed the IFN-γ stimulation of IDO and the initiation of the *KYN* path, TRP interruption, and gathering of *KYN* products [48]. This first immunoregulatory role of TRP suggested the role of IDO products in the limited cellular reduction of TRP that plays two main roles: firstly, TRP famishment of microbes, triggering demise, and, secondly, helping Th2 cell polarity. Commonly, a Th2 polarity facilitates both the initiation and preservation of immunity by antibodies. This is different from a Th1 shifting that facilitates cellular immunity and plays a significant role in inflammation and autoimmunity. Previous works have referred to a regulatory subgroup of macrophages and DCs presenting IDO that have the capability to stimulate cell cycle halt in T cells, depending on IDO breakdown [49, 50]. More recent evidence shows that TRP famishment by IDO is not achieved solely by disabling TCR; rather, it occurs together with the stimulation of FAS-correlated cell phase halt in the mid G1 stage of T-cell death, clonal energy, and the prevention of specific cellular responses [50, 51]. The current consensus is that the stimulation of the IDO-*KYN* path causes T-cell apoptosis [52], T-cell anergy [52], Th17 and Tregs cells propagation [53], and the aberration of the Th1/Th2 response [53]. The downstream products of TRP overwhelm immune reactivity via directly interacting with many types of immune cells, especially effector T lymphocytes [54, 55]. The signaling activity of IDO in DCs has been shown, and these DCs are steadily switched into regulatory DCs [4]. The IFN–IDO pivot is also capable of negative regulation of immune responses to reduce damage to immune-dependent tissues and organs in the precise setting of infectious immunity [56], over-reactive inflammatory responses [57], and autoimmunity [58]. This inherited counter-regulatory mechanism has three parts [59]. First, the products of TRP catabolism have developed direct immunoregulatory roles [60]. Second, the collective impacts of TRP famishment and Kynurenines [33] have shown a

potential for motivating T-cell distinction to a Treg phenotype [61]. As a final point, the IDO method has developed essential tools for protective resident homeostasis in the intermediary response from natural to adaptive immunity [62, 63]. Thus, the probable immunoregulatory role of IDO in resisting attacking microbes, counter-regulating extreme immune activation in autoimmunity, decontrolling host immune response via cancer cells expressing it, and prompting graft tolerance in transplantation, and in maternal–fetal tolerance are now well documented.

IDO role in diseases

Once pathogens attack host cells, they stimulate the natural immunity and provoke the production of chemokines and cytokines, i.e., worker cells of the immune system that facilitate pathogen sanction. In particular, IFNs are significant mediators of natural immunity that prevent the harmful impacts of several viruses [64]. Presently, evaluations on the characteristics of IDO in cancer [65], HIV [66], antitumor immunity [67], therapeutic potentials [13], the stimulation of the IDO motion and signaling [4], allogeneic engraftment of skin substitutes [68], and posttranslational modifications [69] have been performed. The pharmacologic dampening of IDO causes noticeable aggravation of inflammation and exacerbates the signs of disorder in a murine model of inflammatory bowel disease [70]. Several pre-clinical and clinical studies are focusing on a number of new mixtures with chemotherapeutics and IDO1, IDO2, or both enzyme inhibitors in cancer therapy. In a tumor, IDO appears to reduce the employment of antitumor immune cells, prompt tolerance to tumor Ags, and thus simplify immune escape [71, 72]. IDO helps generate a tolerogenic situation in the tumor and the tumor-draining lymph nodes, both via the direct destruction of T cells and the improvement of limited Treg-mediated immunosuppression [71] (Fig. 1).

Role of IDO in allergic diseases

A point requiring specific attention is the role of TRP metabolism in allergic disorders. An immune aberration to the Th2-type immune pattern is involved in the pathogenesis of allergic diseases. Inflammation due to allergic reactions is considered by the upregulation of cytokines correlated to Th2 [73]. The latter is a robust stimulator of the IDO enzyme, which destroys the critical amino acid TRP as part of an anti-proliferative approach of immunocompetent cells to stop the development of infected and tumorous cells [74].

The immunosuppressive role of IDO in response to an allergen was first understood in a study by Bubnoff Von et al. [75]. They showed the *KYN*/TRP ratio to be decreased, together with lesser TRP and greater *KYN* amounts, in adults susceptive to aeroallergens who were asymptomatic compared to those who displayed signs. Buyuktiryaki et al. described lesser serum *KYN*/TRP ratios in children with a food allergy that persevered as opposed to healthy children or in food allergic children who had established tolerance [76]. Furthermore, recent data show that the stimulation of the *KYN*-IDO path and the subsequent reduction of serum TRP and the growth of TRP products regulate the allergic situation [52]. The mechanism of the IDO-stimulated tolerance motivation can potentially vary; however, the stimulation of Treg cells may be the main feature of the control role over inflammation due to allergic stimuli [21]. Additionally, the microbial motivation of the IDO pathway by TLR might also help determine the result of allergic inflammation [53, 77]. IDO has also been identified in eosinophils, lung epithelial cells, and endothelial cells, which indicates a role in allergic reactions [78]. The role of IDO in eosinophils (ESOs) is also inhibitory or stimulatory on Th1 and Th2 cells related to the previous sensitization and inflammatory pattern [79, 80]. IDO stimulation in ESOs might mediate in-vitro and in-vivo polarization of Th2 [81]. The quantity and perseverance of IDO-presenting ESOs in lymphoid tissues may emphasize the apoptotic result on Th1, formerly believed to be related only with IDO-presenting tolerogenic DCs, and, therefore, preserve Th2 preference [81] (Fig. 2). It was recently described that the experimentally stimulated intensification of rhinovirus asthma was associated with systemic TRP and quinolinic acid amounts. Moreover, it was established that pulmonary IDO1 actions were lower and serum tryptophan amounts were higher in patients with allergic asthma [82]. In addition, TNF-α in allergic diseases, in combination with IFN-γ, can stimulate IDO1 action [83].

The ligation of the FcεRI through allergens on monocytes cells isolated from atopic people stimulates the TRP breakdown pathway in these cells [75]. The stimulation of IDO via FcεRI restricted inflammatory responses resulting from allergies [84]. The specific communication of nitric oxide (NO•) with IDO1 could be significant since a higher production of NO• has been described in patients with allergic rhinitis and asthma. Significantly, NO• overwhelms the movement of IDO1, which could elucidate the greater TRP points [85]. Furthermore, IDO appears to play a role in the effectiveness of allergen immunotherapy. Tolerance stimulation against allergens is incompletely facilitated via IDO stimulation throughout SIT [86]. The creation of TRP products moderately than TRP scarcity appears to create a tolerance to allergens [86]. Therefore, IDO stimulation appears to be applicable throughout immunotherapy to make TRP products, which will then cause tolerance against the stimulation of airway inflammation due to allergy and help tolerance stimulation regarding Th2-related allergic airway inflammation and the suppression of eosinophilia [87].

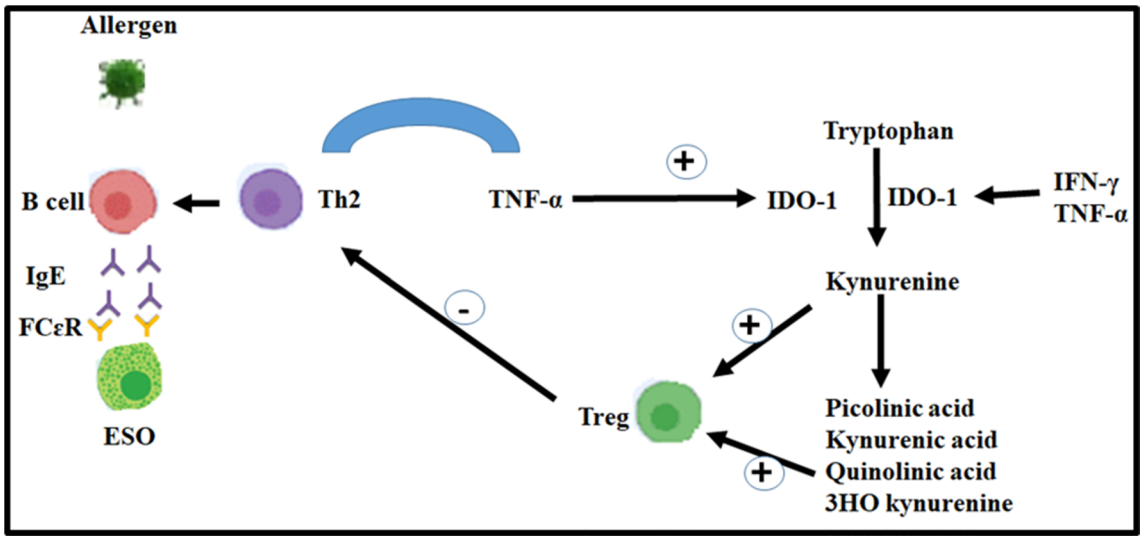

Fig. 2 The production of cytokines, such as TNF-α, in the process of allergic diseases causes the production of IDO enzymes. IDO enzymes play a role in the production of regulatory T cells by metabolizing tryptophan to kanamycin and its metabolites, which negatively regulate Th2 cells and reduce the allergic symptom (T reg = regulatory T cell; 3HO kynurenine = 3-hyroxykynurenine)

Animal and in-vitro studies of IDO in allergic diseases

The role of TRP has extensive immunologic value, and IDO was first separated from rabbits in 1967 [88], and it became quickly obvious that its stimulation helps the mechanism of resistance to microbes. Various studies proving IDO as a proinflammatory enzyme in allergic conditions have been done in IDO knock-out mice [52]. In-vitro, it looks obvious that the lack of TRP definitely motivates the general control nonderepressible 2 (GCN2) kinase in T cells of murine and humans, which results in a pause in the G2 phase of the T-cell subdivision and T-cell suppression [53]. Additionally, a particular blend of TRP products can prevent anti-CD3 antibody-stimulated T-cell propagation and can prompt in-vitro T-cell death [55, 89]. The mixture of little TRP amounts and definite TRP products in-vitro results in the production of Tregs from naive T cells [90]. Adding exogenous *KYN* metabolites to numerous different cells of the immune system indicates that KYN products can optionally prevent dynamic T, B, and NK cells at additional physiologically-related TRP amounts than the TRP diminution theory would suggest [55, 91]. In addition, in pDCs extracted from murine that treated to TGFβ, this enzyme is capable of generating a cellular indication for continuing immune tolerance through the production of Tregs from $CD4^+$ T-cells [24]. Similarly, Mellor and Munn's theory (in-vitro) indicates that KYN encourages the conversion of naive $CD4^+$ T-cells into Tregs that have an important immunosuppressive role [53]. Meanwhile, IDO-stimulated Treg propagation overpowers Th1 and Th2 cells, thus preventing an intense immune response. Xu et al. have suggested that throughout the sequence of a Th1-related response, the death of Th1 cells is favorably prompted. This is different from a Th2-related immune response, where the Th2 cells are targeted via the *KYN*-IDO pathway [41] (Table 1).

The human clinical trial of IDO in allergic diseases

Human studies have established that STI caused by grass pollen or house dust mites allergy contains improved amounts of Treg1 cells that mainly produce IL-10 [100] (Table 2). Firstly, a role of the TRP breakdown pathway in allergic disorders was suggested according to the results of a suppressive subtractive hybridization archive that was shown in high-affinity IgE receptor (FcεRI)-stimulated and unstimulated monocyte cells from a clinically healthy person with atopic family history and numerous sensitizations to shared aeroallergens [75]. This impact is possibly linked to dynamic IDO stimulation and IL-10 production via the activation of Treg throughout immunotherapy in these individuals. In contrast to inflammation due to allergy, particular IgE levels in the blood appear not to be affected by the stimulation of the TRP degradation pathway during SIT in mouse studies [87].

Some of the robust human data for the role of IDO are connected to clinical experiments of specific immunotherapy (SIT) [84]. Primary outcomes from SIT trials confirmed advanced TRP degradation throughout the treatment [75]. IDO has consequently been confirmed to be partially

Table 1 In vitro and animal studies of IDO

Model of study	Effect on immune responses	References
Mouse IDO knock-out	Weakened Th2 cell function	[87]
Mouse (asthma)	Prevent the inflammatory response determined via Th2 cells	[92]
Mouse	Rejection of fetal allograft through T cells of maternal	[93]
Mouse	Products from IDO pathway can inductee tolerogenesis in immunogenic DCs in the nonexistence of IDO	[60]
Mouse	Artificial derivative of the TRP products overwhelm the stimulation of APCs Downregulation of costimulatory molecules such as MHC II	[94]
Mouse	Decline manufacture Th1 cytokine Rise in Th2 cytokine manufacture	[95]
Mouse (asthma)	IDO lacking displayed meaningfully weaker Th2 responses IgE levels in Serum were also lower IDO lack safe against allergic disorder	[52]
Murine (asthma)	Stimulation of IDO expression inhibited Th2-induced asthma	[92]
Mouse IDO knock-out	Weakened Th2 growth in the lung TRP breakdown pathway decreases allergic inflammation	[52]
Mouse (Transgenic)	Overexpression of IDO in the lungs Reducing propagation, numbers and cytokine manufacture of T cells	[96]
Mouse (asthma)	IDO inhibits eosinophilic inflammation	[92]
Mouse	Reduced total and Eso cell counts Enhanced pulmonary histopathology Improved $CD4^+$ T-cell death	[97]
In vitro (In human PBMCs in vitro)	Exposure to IL-4 or IL-10, a lesser stimulatory result of IFN-γ Diminished tryptophan breakdown rate	[98]
In vitro	Sequestered and extremely improved human epidermal $CD1a^+$ LCs, powerfully express IDO Display robust IDO action after IFN-γ promotion in vitro	[99]
In vitro(mDC with house dust mite)	IDO decreased in cells from asthma patients	[29]

Table 2 Human trials studies of IDO

Type of study (human)	Effect on immune responses	References
Pollen allergy	– Upper serum clevels of the TRP	[38]
Allergic rhinitis	– Higher tryptophan levels – No changes in *KYN* levels – The *KYN*/TRP proportion was faintly lesser in atopics – Higher levels of tryptophan	[101]
Pollen allergy	– Higher tryptophan levels	[102]
Asymptomatic atopic patients	– Higher *KYN*/TRP levels – Upper IDO-1 motion in asymptomatic persons	[99]
Allergic asthma	– The proportion of KYN to TRP was lesser – Lesser IDO activity in atopic patients	[103]
Airway allergy	– Suppression of ESOs and reduction of inflammation	[87]
Food allergy	– *KYN*/TRP was significantly lower – IL-4 production when induced with casein increased – Rise in IL-10 production – Participation of IDO in progress of tolerance procedure	[76]
Pollen allergy	– Raised serum tryptophan concentrations – Minor alteration of the *KYN*/TRP ratio	[74]
Allergic asthma	– Appearance of IDO was meaningfully lesser No important correlation between IDO levels and asthma sternness	[104]
In-vivo (asthmatic patients)	– Serum IDO action amplified in asymptomatic atopics	[105]
Cohort study (Asthma)	– Lesser IDO action in atopics in contrast to nonatopic	[103]

accountable for tolerance stimulation throughout SIT, with *KYN* products facilitating this influence as opposed to TRP reduction [105, 106]. In contrast, human myeloid dendritic cells (mDCs) have an amplified ability to prompt $CD4^+CD25^-Foxp3^-$ T cells to Tregs with suppressive action [55]. In addition, amplified TRP catabolite levels in low or normal TRP conditions do not change the stimulatory role of human mDCs in-vitro [107].

It has also been found that the expression of IDO is inhibited by Th2 cytokines, such as IL-4 and IL-13, which are well known for their critical role in prompting, preserving, and magnifying inflammatory allergic inflammation [108]. It is imaginable that IDO stimulation throughout SIT produces controlling $ILT3^{+}ILT4^{+}$ DCs via TRP deficiency, which in turn prompts Tregs from $CD4^{+}CD25^{-}$ effector T cells [90].

In-vitro, once $FceRI^{+}$ monocytes (MONs) from asymptomatic atopic individuals are motivated for 24 h, these cells gain the capability to suppress T-cell propagation, depending on their expression of IDO and the breakdown of TRP [109]. By assessing the concentrations of *KYN* and TRP in the plasma, in aeroallergen-sensitized asymptomatic atopic individuals, there was a meaningfully greater universal action of IDO as well as amplified plasma concentrations of IL-10 during allergen season than off-season and symptomatic atopic persons. Consequently, improved general IDO activity may contribute to the control of allergic T-cell reactions and could be involved in the conservation of a state of clinical unresponsiveness regardless of sensitization.

Conclusion

IDO plays various roles in different diseases, including allergic diseases. Most studies confirm that IDO acts as an immunosuppressive, tolerogenic enzyme to decrease inflammation due to allergic disorders, with the stimulation of the IDO-*KYN* pathway, subsequent reduction of TRP, and promotion in *KYN* products. In the allergic situation, this enzyme is triggered in reaction to allergen-stimulated immune activation, with the subsequent production of *KYN* and their products, and the stimulation of tolerance to different allergens. The stimulation of the role of IDO and/or reducing the overall TRP concentrations via the induction of cells of the immune system might be of therapeutic benefit in allergic disorders. Additional studies are essential to determine how each of the *KYN* products acts to create tolerance against numerous allergens.

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Declarations

Conflict of interest The author declares that there are no conflicts of interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ciprandi G, Tosca M, Fuchs D (2011) Nitric oxide metabolites in allergic rhinitis: the effect of pollen allergen exposure. Allergol Immunopathol 39:326–329
2. Isolauri E, Huurre A, Salminen S, Impivaara O (2004) The allergy epidemic extends beyond the past few decades. Clin Exp Allergy 34:1007–1010
3. Sharifi A, Ghadiri A, Salimi A, Ghandil P, Esmaeili S-A (2021) Evaluating the Distribution of (+ 2044G/A, R130Q) Rs20541 and (-1112 C/T) Rs1800925 Polymorphism in IL-13 Gene: An Association-Based Study with Asthma in Ahvaz, Iran. Int J Med Lab 8:62–69
4. Fallarino F, Grohmann U, Puccetti P (2012) Indoleamine 2, 3-dioxygenase: from catalyst to signaling function. Eur J Immunol 42:1932–1937
5. Hajavi J, Esmaeili SA, Varasteh AR, Vazini H, Atabati H, Mardani F et al (2019) The immunomodulatory role of probiotics in allergy therapy. J Cell Physiol 234:2386–2398
6. Moffett JR, Namboodiri MA (2003) Tryptophan and the immune response. Immunol Cell Biol 81:247–265
7. Pardridge W (1979) Tryptophan transport through the blood-brain barrier: in vivo measurement of free and albumin-bound amino acid. Life Sci 25:1519–1528
8. Albay R, Chen A, Anderson GM, Tatevosyan M, Janušonis S (2009) Relationships among body mass, brain size, gut length, and blood tryptophan and serotonin in young wild-type mice. BMC Physiol 9:4
9. Widner B, Werner ER, Schennach H, Wachter H, Fuchs D (1997) Simultaneous measurement of serum tryptophan and kynurenine by HPLC. Clin Chem 43:2424–2426
10. Grohmann U, Bronte V (2010) Control of immune response by amino acid metabolism. Immunol Rev 236:243–264
11. Munn DH, Mellor AL (2013) Indoleamine 2, 3 dioxygenase and metabolic control of immune responses. Trends Immunol 34:137–143
12. Birdsall TC (1998) 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Alternat Med Rev 3:271–280
13. Le Floch N, Otten W, Merlot E (2011) Tryptophan metabolism, from nutrition to potential therapeutic applications. Amino Acids 41:1195–1205
14. Chen Y, Guillemin GJ (2009) Kynurenine pathway metabolites in humans: disease and healthy states. Int J Tryptophan Res 2:S2097
15. Routy J-P, Routy B, Graziani GM, Mehraj V (2016) The kynurenine pathway is a double-edged sword in immune-privileged sites and in cancer: implications for immunotherapy. Int J Tryptophan Res 9:S38355
16. Mehraj V, Routy J-P (2015) Tryptophan catabolism in chronic viral infections: handling uninvited guests. Int J Tryptophan Res 8:S26862
17. Yuasa HJ, Takubo M, Takahashi A, Hasegawa T, Noma H, Suzuki T (2007) Evolution of vertebrate indoleamine 2, 3-dioxygenases. J Mol Evol 65:705
18. Ball HJ, Sanchez-Perez A, Weiser S, Austin CJ, Astelbauer F, Miu J et al (2007) Characterization of an indoleamine 2,3-dioxygenase-like protein found in humans and mice. Gene 396:203–213
19. Prendergast GC, Metz R, Muller AJ, Merlo LM, Mandik-Nayak L (2014) IDO2 in immunomodulation and autoimmune disease. Front Immunol 5:585
20. Najfeld V, Menninger J, Muhleman D, Comings D, Gupta S (1993) Localization of indoleamine 2,3-dioxygenase gene (INDO) to chromosome 8p12→ p11 by fluorescent in situ hybridization. Cytogenet Genome Res 64:231–232

21. Bubnoff D, Bieber T (2012) The indoleamine 2,3-dioxygenase (IDO) pathway controls allergy. Allergy 67:718–725
22. Däubener W, MacKenzie CR (1999) IFN-γ activated indoleamine 2, 3-dioxygenase activity in human cells is an antiparasitic and an antibacterial effector mechanism. Tryptophan, serotonin, and melatonin. Springer, New York, pp 517–524
23. Luukkainen A, Toppila-Salmi S (2013) Indoleamine 2, 3-dioxygenase expression is associated with chronic rhinosinusitis: review of the evidence. Curr Opin Allergy Clin Immunol 13:37–44
24. Pallotta MT, Orabona C, Volpi C, Vacca C, Belladonna ML, Bianchi R et al (2011) Indoleamine 2, 3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells. Nat Immunol 12:870
25. Van der Leek AP, Yanishevsky Y, Kozyrskyj AL (2017) The kynurenine pathway as a novel link between allergy and the gut microbiome. Front Immunol 8:1
26. Batista CE, Juhász C, Muzik O, Kupsky WJ, Barger G, Chugani HT et al (2009) Imaging correlates of differential expression of indoleamine 2, 3-dioxygenase in human brain tumors. Mol Imag Biol 11:460
27. Gao Y-F, Peng R-Q, Li J, Ding Y, Zhang X, Wu X-J et al (2009) The paradoxical patterns of expression of indoleamine 2, 3-dioxygenase in colon cancer. J Transl Med 7:71
28. Ciorba MA, Bettonville EE, McDonald KG, Metz R, Prendergast GC, Newberry RD et al (2010) Induction of IDO-1 by immunostimulatory DNA limits severity of experimental colitis. J Immunol 184:3907–3916
29. Maneechotesuwan K, Wamanuttajinda V, Kasetsinsombat K, Huabprasert S, Yaikwawong M, Barnes PJ et al (2009) Der p 1 suppresses indoleamine 2, 3-dioxygenase in dendritic cells from house dust mite–sensitive patients with asthma. J Allergy Clin Immunol 123:239–248
30. Fujigaki S, Saito K, Takemura M, Fujii H, Wada H, Noma A et al (1998) Species differences inl-tryptophan–kynurenine pathway metabolism: quantification of anthranilic acid and its related enzymes. Arch Biochem Biophys 358:329–335
31. Khakzad MR, Hajavi J, Sadeghdoust M, Aligolighasemabadi F (2019) Effects of lipopolysaccharide-loaded PLGA nanoparticles in mice model of asthma by sublingual immunotherapy. Int J Polym Mater Polym Biomater. https://doi.org/10.1080/00914037.2018.1561453
32. Fallarino F, Grohmann U, Hwang KW, Orabona C, Vacca C, Bianchi R et al (2003) Modulation of tryptophan catabolism by regulatory T cells. Nat Immunol 4:1206
33. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA (2010) An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol 185:3190–3198
34. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G et al (2013) Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 39:372–385
35. Fallarino F, Orabona C, Vacca C, Bianchi R, Gizzi S, Asselin-Paturel C et al (2005) Ligand and cytokine dependence of the immunosuppressive pathway of tryptophan catabolism in plasmacytoid dendritic cells. Int Immunol 17:1429–1438
36. Grohmann U, Fallarino F, Puccetti P (2003) Tolerance, DCs and tryptophan: much ado about IDO. Trends Immunol 24:242–248
37. Mellor AL, Munn DH (2004) IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol 4:762
38. Kositz C, Schroecksnadel K, Grander G, Schennach H, Kofler H, Fuchs D (2008) Serum tryptophan concentration in patients predicts outcome of specific immunotherapy with pollen extracts. Int Arch Allergy Immunol 147:35–40
39. Schröcksnadel K, Wirleitner B, Winkler C, Fuchs D (2006) Monitoring tryptophan metabolism in chronic immune activation. Clin Chim Acta 364:82–90
40. Munn DH, Sharma MD, Hou D, Baban B, Lee JR, Antonia SJ et al (2004) Expression of indoleamine 2, 3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. J Clin Investig 114:280–290
41. Xu H, Zhang G-X, Ciric B, Rostami A (2008) IDO: a double-edged sword for TH1/TH2 regulation. Immunol Lett 121:1–6
42. Wallet MA, Sen P, Tisch R (2005) Immunoregulation of dendritic cells. Clin Med Res 3:166–175
43. Sorgdrager FJ, Naudé PJ, Kema IP, Nollen EA, Deyn PPD (2019) Tryptophan metabolism in inflammaging: from biomarker to therapeutic target. Front Immunol 10:2565
44. Merlo LM, DuHadaway JB, Montgomery JD, Peng W-D, Murray PJ, Prendergast GC et al (2020) Differential roles of IDO1 and IDO2 in T and B cell inflammatory immune responses. Front Immunol 11:1861
45. Belladonna ML, Orabona C, Grohmann U, Puccetti P (2009) TGF-β and kynurenines as the key to infectious tolerance. Trends Mol Med 15:41–49
46. Cobbold SP, Adams E, Farquhar CA, Nolan KF, Howie D, Lui KO et al (2009) Infectious tolerance via the consumption of essential amino acids and mTOR signaling. Proc Natl Acad Sci 106:12055–12060
47. Esmaeili SA, Mahmoudi M, Rezaieyazdi Z, Sahebari M, Tabasi N, Sahebkar A et al (2018) Generation of tolerogenic dendritic cells using *Lactobacillus rhamnosus* and *Lactobacillus delbrueckii* as tolerogenic probiotics. J Cell Biochem 119:7865–7872
48. Pfefferkorn E, Guyre PM (1984) Inhibition of growth of Toxoplasma gondii in cultured fibroblasts by human recombinant gamma interferon. Infect Immunol 44:211–216
49. Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL (1999) Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med 189:1363–1372
50. Munn DH, Sharma MD, Mellor AL (2004) Ligation of B7–1/B7-2 by human CD4+ T cells triggers indoleamine 2, 3-dioxygenase activity in dendritic cells. J Immunol 172:4100–4110
51. Adams S, Braidy N, Bessesde A, Brew BJ, Grant R, Teo C et al (2012) The kynurenine pathway in brain tumor pathogenesis. Can Res 72:5649–5657
52. Xu H, Oriss TB, Fei M, Henry AC, Melgert BN, Chen L et al (2008) Indoleamine 2, 3-dioxygenase in lung dendritic cells promotes Th2 responses and allergic inflammation. Proc Natl Acad Sci 105:6690–6695
53. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D et al (2005) GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2, 3-dioxygenase. Immunity 22:633–642
54. Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB (2002) Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2, 3-dioxygenase. J Exp Med 196:459–468
55. Terness P, Bauer TM, Röse L, Dufter C, Watzlik A, Simon H et al (2002) Inhibition of allogeneic T cell proliferation by indoleamine 2, 3-dioxygenase–expressing dendritic cells: mediation of suppression by tryptophan metabolites. J Exp Med 196:447–457
56. Bozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S et al (2005) A crucial role for tryptophan catabolism at the host/Candida albicans interface. J Immunol 174:2910–2918
57. Romani L, Fallarino F, De Luca A, Montagnoli C, D'Angelo C, Zelante T et al (2008) Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. Nature 451:211

58. Zelante T, Fallarino F, Bistoni F, Puccetti P, Romani L (2009) Indoleamine 2, 3-dioxygenase in infection: the paradox of an evasive strategy that benefits the host. Microbes Infect 11:133–141
59. Mellor AL, Munn DH (1999) Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today 20:469–473
60. Belladonna ML, Grohmann U, Guidetti P, Volpi C, Bianchi R, Fioretti MC et al (2006) Kynurenine pathway enzymes in dendritic cells initiate tolerogenesis in the absence of functional IDO. J Immunol 177:130–137
61. Fallarino F, Grohmann U, You S, McGrath BC, Cavener DR, Vacca C et al (2006) The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor ζ-chain and induce a regulatory phenotype in naive T cells. J Immunol 176:6752–6761
62. Lanzinger M, Jürgens B, Hainz U, Dillinger B, Raberger J, Fuchs D et al (2012) Ambivalent effects of dendritic cells displaying prostaglandin E2-induced indoleamine 2,3-dioxygenase. Eur J Immunol 42:1117–1128
63. Trinchieri G, Sher A (2007) Cooperation of Toll-like receptor signals in innate immune defence. Nat Rev Immunol 7:179
64. Heseler K, Spekker K, Schmidt SK, MacKenzie CR, Däubener W (2008) Antimicrobial and immunoregulatory effects mediated by human lung cells: role of IFN-γ-induced tryptophan degradation. FEMS Immunol Med Microbiol 52:273–281
65. Godin-Ethier J, Hanafi L-A, Piccirillo CA, Lapointe R (2011) Indoleamine 2,3-dioxygenase expression in human cancers: clinical and immunologic perspectives. Clin Cancer Res 17:6985–6991
66. Boasso A (2011) Wounding the immune system with its own blade: HIV-induced tryptophan catabolism and pathogenesis. Curr Med Chem 18:2247–2256
67. Munn DH (2012) Blocking IDO activity to enhance anti-tumor immunity. Front Biosci (Elite Ed) 4:734–745
68. Bahar MA, Nabai L, Ghahary A (2012) Immunoprotective role of indoleamine 2,3-dioxygenase in engraftment of allogenic skin substitute in wound healing. J Burn Care Res 33:364–370
69. Fujigaki H, Seishima M, Saito K (2012) Posttranslational modification of indoleamine 2,3-dioxygenase. Anal Bioanal Chem 403:1777–1782
70. Gurtner GJ, Newberry RD, Schloemann SR, McDonald KG, Stenson WF (2003) Inhibition of indoleamine 2,3-dioxygenase augments trinitrobenzene sulfonic acid colitis in mice. Gastroenterology 125:1762–1773
71. Hou D-Y, Muller AJ, Sharma MD, DuHadaway J, Banerjee T, Johnson M et al (2007) Inhibition of indoleamine 2,3-dioxygenase in dendritic cells by stereoisomers of 1-methyl-tryptophan correlates with antitumor responses. Can Res 67:792–801
72. Metz R, DuHadaway JB, Kamasani U, Laury-Kleintop L, Muller AJ, Prendergast GC (2007) Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2, 3-dioxygenase inhibitory compound D-1-methyl-tryptophan. Can Res 67:7082–7087
73. Feng Z, Yi X, Hajavi J (2021) New and old adjuvants in allergen-specific immunotherapy: with a focus on nanoparticles. J Cell Physiol 236:863–876
74. Engin A, Engin AB (2015) Tryptophan metabolism: implications for biological processes, health and disease. Humana Press, Totowa
75. von Bubnoff D, Matz H, Frahnert C, Rao ML, Hanau D, de la Salle H et al (2002) FcεRI induces the tryptophan degradation pathway involved in regulating T cell responses. J Immunol 169:1810–1816
76. Buyuktiryaki B, Sahiner U, Girgin G, Birben E, Soyer O, Cavkaytar O et al (2016) Low indoleamine 2,3-dioxygenase activity in persistent food allergy in children. Allergy 71:258–266
77. Khorasani S, Mahmoudi M, Kalantari MR, Lavi Arab F, Esmaeili SA, Mardani F et al (2019) Amelioration of regulatory T cells by *Lactobacillus delbrueckii* and *Lactobacillus rhamnosus* in pristane-induced lupus mice model. J Cell Physiol 234:9778–9786
78. Curti A, Trabanelli S, Salvestrini V, Baccarani M, Lemoli RM (2009) The role of indoleamine 2,3-dioxygenase in the induction of immune tolerance: focus on hematology. Blood 113:2394–2401
79. Grohmann U, Volpi C, Fallarino F, Bozza S, Bianchi R, Vacca C et al (2007) Reverse signaling through GITR ligand enables dexamethasone to activate IDO in allergy. Nat Med 13:579
80. Swanson KA, Zheng Y, Heidler KM, Mizobuchi T, Wilkes DS (2004) CDllc+ cells modulate pulmonary immune responses by production of indoleamine 2,3-dioxygenase. Am J Respir Cell Mol Biol 30:311–318
81. Odemuyiwa SO, Ghahary A, Li Y, Puttagunta L, Lee JE, Musat-Marcu S et al (2004) Cutting edge: human eosinophils regulate T cell subset selection through indoleamine 2,3-dioxygenase. J Immunol 173:5909–5913
82. van der Sluijs KF, van de Pol MA, Kulik W, Dijkhuis A, Smids BS, van Eijk HW et al (2013) Systemic tryptophan and kynurenine catabolite levels relate to severity of rhinovirus-induced asthma exacerbation: a prospective study with a parallel-group design. Thorax 68:1122–1130
83. Werner-Felmayer G, Werner ER, Fuchs D, Hausen A, Reibnegger G, Wachter H (1989) Tumour necrosis factor-α and lipopolysaccharide enhance interferon-induced tryptophan degradation and pteridine synthesis in human cells. Biol Chem 370:1063–1070
84. Grohmann U, Orabona C, Fallarino F, Vacca C, Calcinaro F, Falorni A et al (2002) CTLA-4–Ig regulates tryptophan catabolism in vivo. Nat Immunol 3:1097
85. Gostner JM, Becker K, Kofler H, Strasser B, Fuchs D (2016) Tryptophan metabolism in allergic disorders. Int Arch Allergy Immunol 169:203–215
86. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, Van Overtvelt L (2006) Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy 61:151–165
87. Taher YA, Piavaux BJ, Gras R, van Esch BC, Hofman GA, Bloksma N et al (2008) Indoleamine 2, 3-dioxygenase–dependent tryptophan metabolites contribute to tolerance induction during allergen immunotherapy in a mouse model. J Allergy Clin Immunol 121:983–991
88. Yamamoto S, Hayaishi O (1967) Tryptophan pyrrolase of rabbit intestine D-and L-tryptophan-cleaving enzyme or enzymes. J Biol Chem 242:5260–5266
89. Fallarino F, Grohmann U, Vacca C, Bianchi R, Orabona C, Spreca A et al (2002) T cell apoptosis by tryptophan catabolism. Cell Death Differ 9:1069
90. Fallarino F, Grohmann U, You S, McGrath BC, Cavener DR, Vacca C et al (2006) Tryptophan catabolism generates autoimmune-preventive regulatory T cells. Transpl Immunol 17:58–60
91. Lee S-M, Lee Y-S, Choi J-H, Park S-G, Choi I-W, Joo Y-D et al (2010) Tryptophan metabolite 3-hydroxyanthranilic acid selectively induces activated T cell death via intracellular GSH depletion. Immunol Lett 132:53–60
92. Hayashi T, Beck L, Rossetto C, Gong X, Takikawa O, Takabayashi K et al (2004) Inhibition of experimental asthma by indoleamine 2, 3-dioxygenase. J Clin Investig 114:270–279
93. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B et al (1998) Prevention of allogeneic fetal rejection by tryptophan catabolism. Science 281:1191–1193
94. Platten M, Ho PP, Youssef S, Fontoura P, Garren H, Hur EM et al (2005) Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science 310:850–855
95. Molano A, Illarionov PA, Besra GS, Putterman C, Porcelli SA (2008) Modulation of invariant natural killer T cell cytokine

responses by indoleamine 2, 3-dioxygenase. Immunol Lett 117:81–90
96. Paveglio SA, Allard J, Foster Hodgkins SR, Ather JL, Bevelander M, Campbell JM et al (2011) Airway epithelial indoleamine 2, 3-dioxygenase inhibits CD4+ T cells during *Aspergillus fumigatus* antigen exposure. Am J Respir Cell Mol Biol 44:11–23
97. An X, Bai C, Xia J, Dang T, Qian P, Qian G et al (2011) 4 immature dendritic cells expressing indoleamine 2, 3-dioxygenase suppress ovalbumin-induced allergic airway inflammation in mice. J Investig Allergol Clin Immunol 21:185
98. Weiss G, Murr C, Zoller H, Haun M, Widner B, Ludescher C et al (1999) Modulation of neopterin formation and tryptophan degradation by Th1-and Th2-derived cytokines in human monocytic cells. Clin Exp Immunol 116:435
99. von Bubnoff D, Bausinger H, Matz H, Koch S, Häcker G, Takikawa O et al (2004) Human epidermal langerhans cells express the immunoregulatory enzyme indoleamine 2, 3-dioxygenase. J Investig Dermatol 123:298–304
100. Francis JN, Till SJ, Durham SR (2003) Induction of IL-10+ CD4+ CD25+ T cells by grass pollen immunotherapy. J Allergy Clin Immunol 111:1255–1261
101. Kofler H, Kurz K, Grander G, Fuchs D (2012) Specific immunotherapy normalizes tryptophan concentrations in patients with allergic rhinitis. Int Arch Allergy Immunol 159:416–421
102. Ciprandi G, De Amici M, Tosca M, Fuchs D (2010) Tryptophan metabolism in allergic rhinitis: the effect of pollen allergen exposure. Hum Immunol 71:911–915
103. Raitala A, Karjalainen J, Oja SS, Kosunen TU, Hurme M (2006) Indoleamine 2, 3-dioxygenase (IDO) activity is lower in atopic than in non-atopic individuals and is enhanced by environmental factors protecting from atopy. Mol Immunol 43:1054–1056
104. Hu Y, Chen Z, Jin L, Wang M, Liao W (2017) Decreased expression of indolamine 2, 3-dioxygenase in childhood allergic asthma and its inverse correlation with fractional concentration of exhaled nitric oxide. Ann Allergy Asthma Immunol 119:429–434
105. Von Bubnoff D, Fimmers R, Bogdanow M, Matz H, Koch S, Bieber T (2004) Asymptomatic atopy is associated with increased indoleamine 2, 3-dioxygenase activity and interleukin-10 production during seasonal allergen exposure. Clin Exp Allergy 34:1056–1063
106. Von Bubnoff D, Bezold G, Matz H, Hanau D, Salle HDL, Bieber T (2003) Quantification of indoleamine 2, 3-dioxygenase gene induction in atopic and non-atopic monocytes after ligation of the high-affinity receptor for IgE, FcεRI and interferon-γ stimulation. Clin Exp Immunol 132:247–253
107. von Bubnoff D, Wilms H, Scheler M, Brenk M, Koch S, Bieber T (2011) Human myeloid dendritic cells are refractory to tryptophan metabolites. Hum Immunol 72:791–797
108. Chaves AC, Cerávolo IP, Gomes JA, Zani CL, Romanha AJ, Gazzinelli RT (2001) IL-4 and IL-13 regulate the induction of indoleamine 2, 3-dioxygenase activity and the control of *Toxoplasma gondii* replication in human fibroblasts activated with IFN-γ. Eur J Immunol 31:333–344
109. Von Bubnoff D, Matz H, Cazenave J-P, Hanau D, Bieber T, De La Salle H (2002) Kinetics of gene induction after FcεRI ligation of atopic monocytes identified by suppression subtractive hybridization. J Immunol 169:6170–6177