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REVIEW

Contribution of IDO to human respiratory syncytial virus infection

Felipe M. Benavente[1] | Jorge A. Soto[1] | Magdalena S. Pizarro-Ortega[1] | Karen Bohmwald[1] | Pablo A. González[1] | Susan M. Bueno[1] | Alexis M. Kalergis[1,2]

[1]Millennium Institute on Immunology and Immunotherapy, Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile

[2]Departamento de Endocrinología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Correspondence
Dr. Alexis M. Kalergis, Millennium Institute of Immunology and Immunotherapy. Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Avenida Libertador Bernardo O'Higgins #340, Santiago 8331010, Chile.
Email: akalergis@bio.puc.cl; akalergis@icloud.com

Abstract

IDO is an enzyme that participates in the degradation of tryptophan (Trp), which is an essential amino acid necessary for vital cellular processes. The degradation of Trp and the metabolites generated by the enzymatic activity of IDO can have immunomodulating effects, notably over T cells, which are particularly sensitive to the absence of Trp and leads to the inhibition of T cell activation, cell death, and the suppression of T cell effector functions. Noteworthy, T cells participate in the cellular immune response against the human respiratory syncytial virus (hRSV) and are essential for viral clearance, as well as the total recovery of the host. Furthermore, inadequate or non-optimal polarization of T cells is often seen during the acute phase of the disease caused by this pathogen. Here, we discuss the capacity of hRSV to exploit the immunosuppressive features of IDO to reduce T cell function, thus acquiring relevant aspects during the biology of the virus. Additionally, we review studies on the influence of IDO over T cell activation and its relationship with hRSV infection.

KEYWORDS

indoleamine-2,3-dioxygenase, tryptophan (Trp), hRSV, T cells

1 | INTRODUCTION

IDO is an enzyme that is encoded by the gene *IDO1* (*INDO*) in mammals.[1] In humans, *IDO1* is located in the short arm of chromosome 8 and encodes a ~45 kD polypeptide that is composed of 403 amino acids.[2,3] The primary function of IDO is to catalyze the degradation of tryptophan (Trp), which decreases the availability of this amino acid in the cell and promotes the production of kynurenine (Kyn) and other metabolites (e.g., kynurenic acid, tryptamine) associated to this amino acid in IDO-expressing cells.[4,5] It is known that most human cells have little or no constitutive IDO expression, however, the expression of this enzyme can be induced by IFN-γ-induced signaling pathways in several cell types,[4,5] such as dendritic cells (DCs) and macrophages (Mϕs).[6–8] Other cell types, such as astrocytes, neurons, microglia, and respiratory tract epithelial cells can also express IDO after stimulation by IFN-γ or TNF-α.[9,10]

Trp is necessary within cells for vital cellular functions, including protein synthesis, and the absence of this amino acid can suppress the proliferation of lymphocytes by an arrest of the cell cycle at a mid-G1,[11] which promotes cell apoptosis.[12] Hence, IDO activity is thought to modulate immune response by controlling the proliferation of lymphocytes.[13,14] Another main effect associated with IDO activity is that this enzyme promotes immunological tolerance by inhibiting T cell responses and promoting the proliferation of regulatory T cells (Tregs).[15]

The availability of Trp is also fundamental for the replication of intracellular pathogens such as viruses, as they are obligated parasites and need the host cellular machinery and cellular components to sustain their replication cycle.[16–20] During infections produced by viruses, bacteria, parasites, and fungi, IDO can be activated on antigen-presenting cells (APCs) residing at the infected tissues to reduce Trp availability and deprive pathogens of this amino acid, as an ancient innate host defense mechanism aimed at controlling pathogen proliferation and dissemination (Fig. 1).[21] However, it has been suggested that

Abbreviations: 1MT, 1-methyl-tryptophan; AhR, aryl hydrocarbon receptor; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; DC, dendritic cell; eIF2α, eukaryotic initiation factor 2; HBV, hepatitis B virus; HCV, hepatitis C virus; hRSV, human respiratory syncytial virus; ISG, interferon stimulated gene; Kyn, kynurenine; MFI, median fluorescence intensity; mTOR, mammalian target of rapamycin; PD-L1, programmed cell death 1 ligand 1; Treg, regulatory T cell; Trp, tryptophan; WARS, tryptophanyl-tRNA-synthetase.

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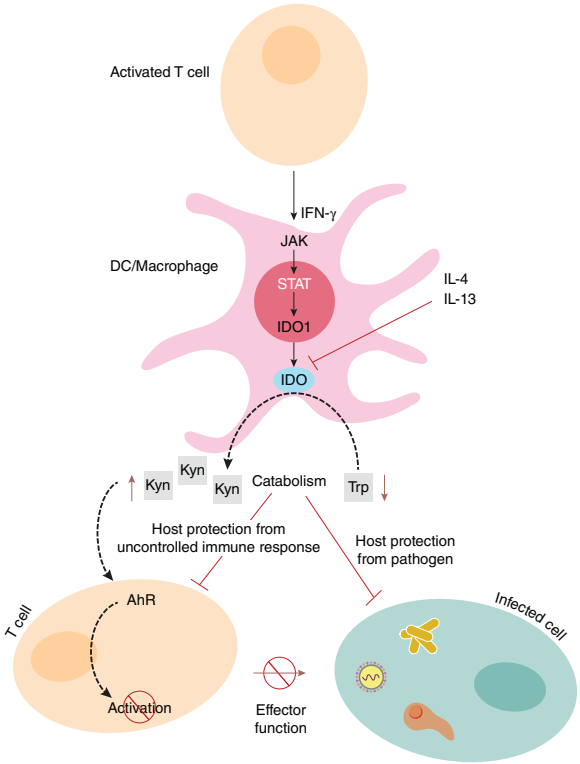

FIGURE 1 **Dual effects of IDO activity in the host**. In response to the presence of a pathogen, activated T cells secrete IFN-γ, which stimulates the expression of IDO in DCs and Mϕs through the JAK/STAT pathway. IDO activity reduces the amount of Trp available to the cell, with a subsequent increase in Kyn. The reduction of Trp protects the host from both, the pathogen and uncontrolled immune responses. However, the decrease in Trp and increase in Kyn prevents the activation and effector functions of T cells, which could benefit the pathogen

some infectious agents,[21] including viruses such as influenza virus, can exploit to their advantage the activity of IDO in host cells and benefit from its immunosuppressive capacity to facilitate their life cycle.[22]

Considering these observations, IDO can contribute to the clearance of pathogens, but also its activity can impact the function of host immune cells, promoting tolerance and chronic infection.[23,24] Thus, opposing biological functions have been attributed to IDO during infections and the final effect of this enzyme activity, either antimicrobial or immunoregulatory, is thought to be dependent on the pathogen specificity.[25] For example, murine models of infection have shown that IDO facilitates, or suppresses microbial clearance of *Toxoplasma gondii* or *Leishmania major*, respectively.[25] Contrarily, according to in an in vivo model of infection with herpes simplex virus type 1 (HSV-1) inhibition of IDO activity does not affect viral replication, virulence, or the induction of latency.[25] Interestingly, the human respiratory syncytial virus (hRSV) has been reported to induce the expression of IDO in human cells in the absence of IFN-γ, although in a viral replication-dependent manner.[26] Thus, the association between hRSV infection and IDO expression is an essential aspect of the study that could help in understanding the host-virus interaction. Here, we discuss as to how IDO activity may contribute to the non-optimal antiviral immune response observed after hRSV infection.

2 | IFN-γ IS A CRUCIAL INDUCER OF IDO ACTIVITY

IDO1 is an IFN-stimulated gene (ISG), and IFN-γ has been recognized as the most important inducer of IDO in several cell types, as mentioned above.[27,28] According to in vitro experiments with epithelial A549 cells, IFN-γ is a more potent inducer of IDO than type I IFN.[28] Hundreds of ISGs have been described, but only a handful of them have been shown to display an antiviral activity in vivo. Besides IFN-γ, other cytokines can also stimulate IDO expression, such as IL-6 and TNF-α.[7,27–30] On the other hand, IL-4 and IL-13, two cytokines characteristic of Th2 response, are recognized as inhibitors of IDO.[31,32]

IFN-γ induces IDO activity particularly in DCs and Mϕs.[8,33,34] This interferon has been reported to induce the activation of *IDO1* through the JAK/STAT pathway.[27,35–37] Binding of IFN-γ to its receptor results in the phosphorylation and activation of the JAK1 and JAK2, which in turn leads to the phosphorylation and subsequent activation of STAT1. The phosphorylated form of this transcription factor (STAT1) then translocate from the cytosol to the nucleus and binds to IFN-γ activation sites (GAS) promoting the initiation of the transcription of different ISGs, including *IDO1*.[27,38–42] Additionally, it was reported that mature DCs might constitutively express IDO, but its enzymatic activity would be productive only after IFN-γ stimulation, which suggests two different enzymatic states for this protein: one active and another inactive.[43]

Gene expression of IDO can also be induced through a mechanism that is independent of IFN-γ, which depends on the activity of the transcription factors NF-κB and the p38 MAPK. Interestingly, Fujigaki et al. showed that inhibitors of p38 MAPK and NF-κB could inhibit the activity of IDO.[44] Both, p38 MAPK and NF-κB are also necessary for the production of IFN-γ and the subsequent transcriptional regulation of *IDO1*. However, the precise mechanism mediating this regulation is not fully understood yet.[45–47] As IDO activity is up-regulated in APCs in response to IFN-γ secreted by activated T cells (Fig. 1), it has been suggested that a negative feedback loop may exist in which this enzyme might be involved in regulating T cell activation.[48]

3 | IMMUNOMODULATORY FEATURES OF IDO ACTIVITY

As mentioned above, IDO activity impacts the immune system in a "double-branch" manner: first, by decreasing the amount of Trp available to the cell and second by increasing the quantity of Kyn affecting both, IDO-expressing APCs and T cells interacting with them.[13] This immunoregulation mechanism leads to the suppression of T cell function, generating an immunosuppressive microenvironment around the cells that display IDO activity (Fig. 2).[11,49,50]

The lack of Trp caused by IDO activity allows an accumulation of uncharged Trp-tRNAs in the cell, which in turn activates GCN2 (eukaryotic translation initiation factor 2 alpha kinase 4) and inhibits the mammalian target of rapamycin (mTOR).[51,52] GCN2 is one of the 4 stress-sensitive kinases that phosphorylate serine 51 in the α

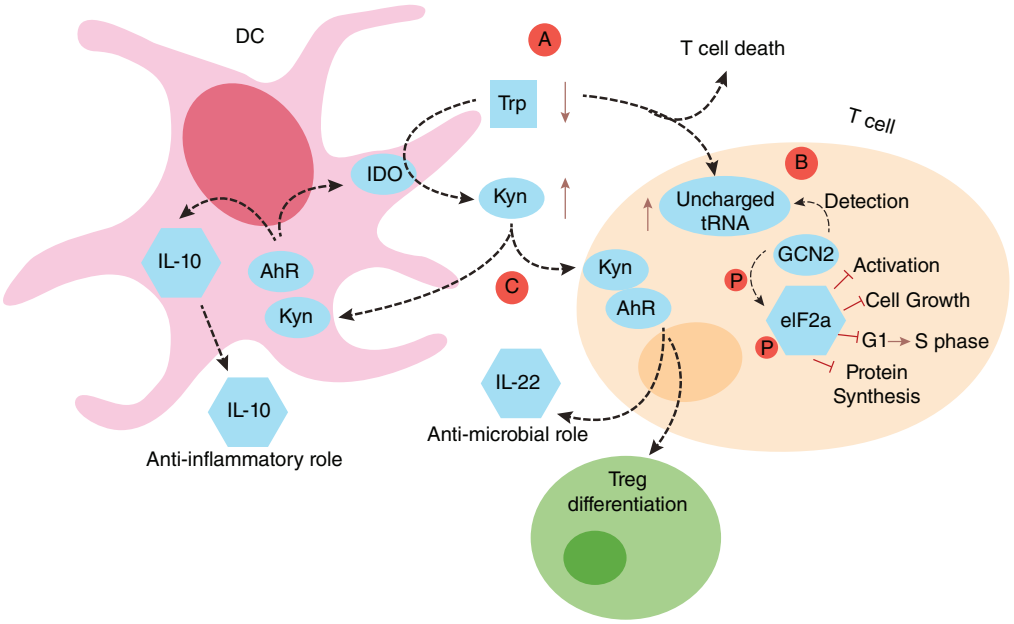

FIGURE 2 **Effect of Trp catabolism on T cells and DCs.** **(A)** Trp in the environment decreases due to the activity of IDO, increasing the amount of Kyn. **(B)** The lack of Trp induces T cell death and an increase in intracellular uncharged tRNA, which is detected by GCN2. In turn, GCN2 phosphorylates eIF2α inhibiting cell growth, protein synthesis, G1-to-S phase transition, and T cell activation. **(C)** In T cells, Kyn acts as a ligand for AhR, which works as a transcription factor, migrating to the nucleus and inducing differentiation toward a Treg phenotype, as well as the transcription of the IL-22 gene. On the other hand, Kyn induces the expression of IDO and IL-10 on DCs

subunit of the translation eukaryotic initiation factor 2 (eIF2α),[53] and this route can prevent the T cell activation.[54] After eIF2α is phosphorylated (and thus inhibited) by GCN2, cell growth and global translation are blocked.[54] This kind of inhibition is thought to protect the cell from a lack of nutrients. It has been reported that the depletion of Trp mediated by IDO in T cells[54] inhibits the G1 to S phase transition.[11] Studies made using in vivo models have shown that T cells with altered GCN2 are not susceptible to this effect.[54]

On the other hand, mTOR is an evolutionarily conserved kinase that can sense the nutritional status of the cell by integrating environmental signals to control cell proliferation, cell homeostasis, and many other cellular functions. Also, it is known that mTOR is necessary for an adequate activation and proliferation of effector T cells, restraining the development of Tregs and other immune functions. Thus, mTOR is an essential regulator of the immune response.[55–57]

Another immune-modulating effect of IDO activity is mediated through Tregs. IDO-expressing plasmacytoid DCs have been shown to activate resting Tregs and thus initiating a potent suppressor activity. In in vitro conditions, naïve CD4$^+$ T cells can differentiate into Foxp3$^+$ Tregs promoted by IDO activity,[58] with such T cells promoting the expression of programmed cell death 1 ligand 1 (PD-L1) and PD-L2 in DCs.[59] Additionally, IDO has been proposed to be a critical controller, keeping an equilibrium between suppressor and effector functions of T cells.[60] Due to the activity of IDO, suppressor Tregs acquire a stable suppressor phenotype that blocks their eventual reprogramming into Th17-like effector T cells.[60]

Different products from the Trp degradation generated by IDO activity such as Kyn, kynurenic acid, and tryptamine participate in other mechanisms of immunomodulation. These metabolites can bind to the aryl hydrocarbon receptor (AhR) and act as ligands for this molecule.[61,62] AhR works as a transcription factor that can modulate the differentiation of immune cells after detecting endogenous ligands.[63–66] Once activated, AhR migrates to the nucleus to regulate the expression of genes, such as CYP1A1, which is a member of the cytochrome P450 superfamily of enzymes.[64] CYP1A1 has an essential role in the metabolism of drugs and chemicals, and polymorphisms in this gene have been associated with different tumors.[67,68]

On the other hand, binding of Kyn to AhR leads to the activation of an AhR-dependent differentiation pathway for T cells, triggering the modulation and proliferation of Foxp3$^+$ Tregs, which can influence the Th1-Th2- or Th17 subsets.[69] Moreover, the Kyn-AhR interaction induced the expression of IDO and IL-10 by DCs, as well as the inhibition of T cell activation (Fig. 2).[70–72] Also, AhR was reported to induce the transcription of IL-22 and mediate the differentiation of Tregs, thus showing antimicrobial and anti-inflammatory roles, respectively, and contributing to immune homeostasis.[73] On the other hand, IL-10 has a crucial role in the maintenance of persistent viral infections (Fig. 2).[74] IL-10 suppresses Ag presentation to CD4$^+$ T cells by DCs and Mϕs,[75] which could increase the overall immunosuppressive effect of IDO activity.

T cells are sensitive to a decrease of Trp. This sensibility can also be considered a condition that promotes viral persistence and disease severity.[7,76,77] However, T cells may be protected from Trp absence and the subsequent stop at the mid-G1 phase through the expression of the IFN-γ-induced enzyme tryptophanyl-tRNA-synthetase (WARS), which produces a reserve of Trp in the form of a complex Trp-tRNA, which IDO cannot catabolize.[12,78] It has been suggested that CD8$^+$ T cells are less sensitive than CD4$^+$ T cells to the lack of Trp, likely

because when stimulated with recombinant CTLA-4 under in vitro conditions, $CD4^+$ T cells express IDO and WARS, but $CD8^+$ T cells only express WARS.[78]

It has been proposed that under physiological conditions, IDO plays different roles in the regulation of Th1 and Th2 responses. In DCs, IDO activity has a suppressive effect over Th1 responses, likely to avoid over-reaction of cellular responses that could damage the host.[79] In vitro and in vivo models have shown that the activity of the enzyme is associated with the apoptosis of proliferating T cells, but this effect occurs preferably in Th1 cells. This phenomenon generates an imbalance in the proportion of Th1/Th2 cells, favoring a Th2, over a Th1 profile of cytokines.[80,81] An example of this cellular imbalance comes from a recent study that has shown that enhanced activity of IDO in human gastric mucosa infected with *Helicobacter pylori* down-regulates Th1 and Th17 but up-regulates a Th2 response.[82] The reason for this selectivity that causes a Th1/Th2 imbalance is still unknown.

Additionally, the proliferation of memory T cells is subject to regulations by the catabolism of Trp mediated by IDO activity. By evaluating allograft survival in mice, along with inhibition and induction of IDO, it has been established that Trp catabolism mediated by IDO controls the generation of memory $CD8^+$ T cells. When IDO activity is up-regulated, central and effector memory $CD8^+$ T cells are diminished, but these cells proliferate when IDO is suppressed.[83]

4 | INHIBITION OF IDO ACTIVITY DURING VIRAL INFECTIONS

Besides hRSV, different viruses such as the human metapneumovirus, adenoviruses, bocaviruses, coronaviruses, and enteroviruses can also cause acute respiratory infections,[84] but to date, there are no studies on the relationship between infection by such pathogens and IDO activity by the host. However, such a relationship has been explored with other viruses that do not cause respiratory disease. For example, IFN-γ and TNF-α induce IDO activity that inhibits HSV-2 and HSV-1 replication, but an increase in Trp abrogates this antiviral effect.[17,19] The same antiviral effect due to IFN-γ and IDO activity was seen against measles virus[18] and vaccinia virus.[16] It has been reported that during HIV infection, IDO activity is also increased due to viral infection and that this alteration may be contributing to the persistence of the virus.[85]

It has been suggested that the inhibition of IDO activity may improve the immune response against some viral pathogens.[86] Inactivation of IDO can reverse the immunosuppressive effects induced by its activity. 1-Methyl-tryptophan (1MT) is a drug that can inhibit IDO activity and has been mainly tested in the treatment of different tumors. However, 1MT has also been reported to be able to restore the host immune response after infections with pathogens. In an in vivo model of influenza virus, the infection was accompanied with an increase in both, a Th1 and a Th17 immune response along with a robust response of specific T lymphocytes against the virus when IDO activity was inhibited.[87]

Similarly, it has been shown that by decreasing the activity of IDO with 1MT during the primary response to influenza virus infection, the response of memory T cells is improved by increasing the production of IFN-γ.[88] After mice were primed with influenza A strain X31 (H3N2), treated with 1MT and challenged with PR8 (H1N1) 28 days p.i., Sage and colleagues evaluated the impact of IDO inhibition on the memory T cell response to influenza virus. The number of memory Th1 (IFN-γ^+) cells and lung virus-specific $CD8^+$ IFN-γ^+ T cells showed to be higher in the bronchoalveolar lavage (BAL) from the group of mice treated with 1MT compared to the control group (without 1MT treatment). Interestingly, all these cellular changes were accompanied by an accelerated repair of the lung tissue. At day 7 post-challenge the authors described less necrosis, alveolar exudate, and neutrophil recruitment in the lungs of mice treated with 1MT compared to control mice. Although the number of Tregs ($CD4^+$ $Foxp3^+$) responding to the virus challenge was not altered by 1MT treatment, the inhibition of IDO resulted in fewer Tregs expressing CTLA-4 on the cell surface according to the median fluorescence intensity (MFI).[88] These data suggest an essential role for IDO during the initial response of the host against the pathogen. This finding could be exploited for the development of vaccines or act as a stimulus for vaccines with weak immune activation to improve T memory responses and reduce disease-associated morbidity.[88,89]

5 | hRSV-INFECTION AND IDO ACTIVITY

hRSV is the most important etiological agent of acute lower respiratory tract infections in infants and young children worldwide, as well as an important pathogen for the elderly.[90] It has been estimated that hRSV infects 50% of children during their first years of life, and 100% of children under 3 years old.[91,92] Usually, 30–75% of infants infected before 12 months of age will be re-infected before the age of 2.[93] This effect is due to an incomplete protective immune response elicited by the host against hRSV because the virus can interfere with the development of both, effector and memory $CD8^+$ T cells in the lungs.[94–96] Furthermore, re-infection can occur throughout life; with the elderly and immunosuppressed patients being a high-risk group.[97–99] Probably, the susceptibility of the host to hRSV-infections in the elderly is due to a low number of specific memory T cells found in this population[100] and could be explained by the fact that hRSV induces IDO expression, which in turn controls the generation of memory $CD8^+$ T cells as discussed above.

During the acute phase of the disease caused by hRSV, systemic $CD4^+$ T cells and $CD8^+$ T cells counts are low while viral loads, neutrophils counts, and disease symptoms reach their peak.[101] Also, there is suppression of memory $CD8^+$ T cell differentiation mediated by mTOR, apoptosis of T cells, and an up-regulation of PD-1 (T cell inhibitory molecule). As neutrophils begin to decrease, pulmonary $CD8^+$ T cells begin to increase along with viral clearance and symptoms decrease.[101]

$CD8^+$ T cells play an essential role in the immune response against viruses and frequently help the host reach complete viral clearance.[102] Consistently, hRSV titers in the lungs of infected mice are reduced

after the adoptive transfer of CD8+ T cells.[103,104] It has been shown that CD8+ T cells induce apoptosis of virus-infected cells by cell-cell contact through the interaction of surface molecules, such as Fas/FasL and TRAIL/DR4,5 or because of the secretion of perforin and granzymes. Also, CD8+ T cells can secrete IFN-γ and TNF-α, which have proinflammatory effects.[105] An essential role for CD8+ T cells is also evidenced by the fact that the absence of CD8+ T cells generates a persistent infection with hRSV.[105] On the other hand, the central antiviral role of CD4+ T cells seems to be supporting the activation of B cells that produce antiviral antibodies as plasma cells.[106]

IFN-γ has significant antiviral activity and is related to the modulation of Th1- or Th2-like immune responses, as IFN-γ affects the differentiation of naïve T cells into either Th1 or Th2 cells.[107] Importantly, it is known that a Th1 response is characterized by the activation of CD8+ T cells.[96]

A Th1 or a balanced Th1/Th2 immune response is necessary for an adequate response by cytotoxic T cells (CTL) and IFN-γ secreting CD4+ T cells, which are demonstrated to contribute to hRSV clearance.[108] However, during the acute phase of hRSV infection, the immune response of the host is biased towards a Th2 type, which is not able to eliminate the infection caused by hRSV, on the contrary, it can be harmful to the host.[108] This bias would be contributing to the disease pathogenesis.[96,109,110] As discussed earlier, hRSV-induced IDO activity contributes to a Th1/Th2 imbalance seen during the hRSV infection and probably participates in a potential mechanism by which the virus escapes a Th1 immune response.[26] Additionally, it has been suggested that this Th1/Th2 imbalance generated by IDO could be part of a mechanism that promotes the development of allergic diseases in children who were infected with hRSV at an early age.[26]

The data discussed above indicate that the degradation of Trp, mediated by IDO and its influence on T cell activation and proliferation is likely crucial in the context of hRSV infection as this pathogen requires a T cell-based cellular immune response from the host to be eliminated. However, it is important to highlight that IDO shows opposing biological functions that suppress or facilitate the replication of pathogens. In the case of hRSV-infection, both effects have been described.

As mentioned at the beginning of this review, *IDO1* is an ISG, and some of these genes display antiviral activity.[111,112] Rajan and colleagues showed in both, human lung cells and BALB/c mice that IDO expression is induced by hRSV infection; the results suggest that IDO and IFN-γ would affect viral replication and host cellular responses upon infection. The authors indicated that IDO contributed to the inhibition of viral replication associated with IFN-γ, and the inhibition of specific inflammatory cytokines and chemokines (IL-6, IL-8, CCL4, and CXCL10) that were induced by IFN-γ. The study also reported that IDO was able to decrease CXCL10 levels induced by infection and was not associated with IFN-γ.[113]

In a recent study oriented to counteract the lack of Trp and the subsequent antiviral effects of IDO, Rabbani et al. showed that it is possible to restore viral growth in cells infected with hRSV, as well as parainfluenza virus type 3, through the restoration of Trp levels. The results indicate that the cause of the inhibitory effect over viral growth would be due to a lack of Trp, rather than the products of catabolism of this amino acid.[28] Also, several hRSV proteins, such as N, P, M, and M2-1, were affected by IDO, and the restitution of Trp restored such viral protein levels. The inhibition of viral replication due to IDO up-regulation, as well as the suppression of this effect by the addition of Trp, has also been observed for several other viruses, including vaccinia virus,[16] HSV-2,[17] and measles virus.[18]

Regarding the immunosuppressive effects of IDO, it has been shown that epithelial cells can suppress antigen-specific and antigen-non-specific T cell activation (i.e., T cell proliferation and IFN-γ production) through IDO activity.[114] The immunomodulatory activity of IDO has been shown to affect immune responses associated with hRSV.[26,86] In 2015, it was reported for the first time that hRSV induces the expression of IDO in human monocyte-derived DCs, which depended on viral replication but was independent of IFN-γ (Fig. 3). These results describe a direct relationship between the replication of the virus and the expression of IDO. Likely, hRSV induces IDO activity through the

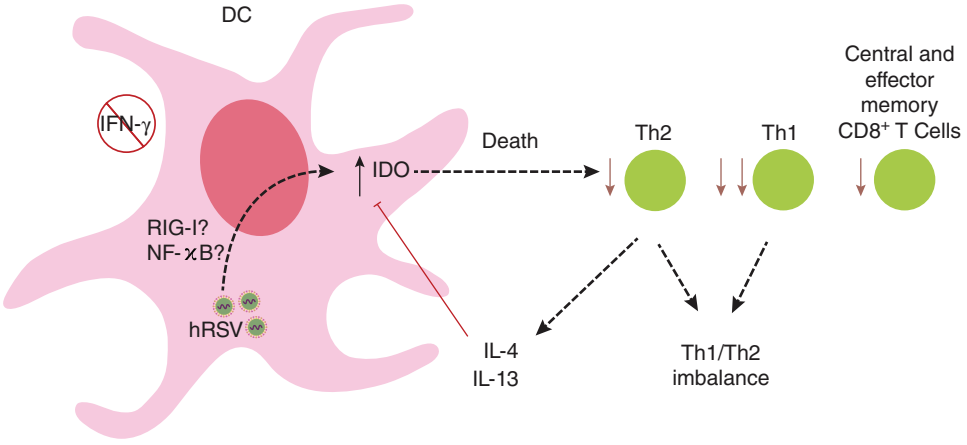

FIGURE 3 **hRSV-induced IDO activity contributes to Th1/Th2 imbalance**. During the acute phase of hRSV-infection, the activity of IDO increases independent of the presence of IFN-γ, but in a hRSV-replication-dependent manner (probably through RIG-I and NF-κB signaling). The activity of IDO induces the death of T cells, contributing to an imbalance in the proportion of Th1 and Th2 cells. IL-4 and IL-13 cytokines are characteristic from a Th2 response and inhibit the expression of IDO, which would probably be part of a regulatory mechanism of IDO

RIG-I pathway via NF-κB and p38 MAPK (Fig. 3).[26] Further, the authors showed that the induction of IDO activity was dependent on virus infection and replication.[26] Interestingly, T cell activation was partially recovered when TLR signaling was activated in epithelial cells after the addition of LPS and poly I:C, mimicking bacterial and viral infections, respectively.[114] To date, the immunosuppressive effect of IDO induced by hRSV has only been demonstrated in vitro. Thus, it would be necessary to corroborate this effect in an in vivo model of infection in order to propose this enzyme as a target for therapy.

The increase in the expression of IDO can be up to 70-fold in mesenchymal stem cells at 72 h after infection with hRSV, as compared to uninfected cells and the use of anti-IFN-β reduced the expression of IDO.[86] Importantly, the overexpression of IDO in hRSV-infected mesenchymal stem cells negatively affects the proliferation of lymphocytes, which could be related to the lack of immune protection against subsequent hRSV infections.[86]

Because IDO up-regulation occurs immediately after infection (24 h p.i.), as determined in an in vivo model of infection with influenza virus,[89] it is likely that this enzyme is similarly induced shortly after hRSV infection and that it may be able to promptly shift the immune response toward a Th2 response (IL-4, IL-13), altogether down-regulating IDO expression (Fig. 3).

It is known that hRSV can promote IDO expression during viral infections[26] and that this virus promotes Th2 polarization that causes significant secretion of IL-4, IL-5, and IL-13 that contributes to airway inflammation.[115] Additionally, type 2 Innate Lymphoid Cells (ILC-2), have been associated with triggering an exacerbated inflammatory response in the airways contributing to pathology after the hRSV infection.[116] This effect promotes a higher cytokine amount and eosinophils recruitment in the lungs associated with respiratory diseases such as asthma.[117–119] In a study with patients with asthma, it was found that eosinophils from these individuals displayed high levels of IDO expression, which sustained the polarization of a Th2 response.[120] Also, this Th2 polarization could be modulated by DCs.[121] In this context, it was possible to suggest that hRSV-infection through IDO expression could contribute to ILC-2 activation and promote allergy-like pulmonary responses and diseases that are typically associated with hRSV.

Regarding B cells, it was recently reported that hRSV could infect human neonatal regulatory B cells (nBreg).[122] In this study, it was found that the F-protein hRSV can bind to the B cell receptor and that G-protein hRSV interacts with the chemokine receptor CX3CR1, which allows viral entry. Importantly, nBreg cell infection promoted IL-10 secretion that inhibits Th1 polarization of T cells, thus increasing the viral loads in the infected tissue and disease severity.[122] Although no evidence suggests a role for IDO in the regulation of B cells infected with hRSV, it has been shown that IDO can regulate humoral immunity in response to T cell-independent Ags.[123] According to this study, intrinsic *ido1* in B cells controls the hypersensibility of these cells to self T cell-independent Ags and therein, prevents the development of autoimmune responses. Thus, considering these findings, we can speculate that it is possible that hRSV-infected B cells increase the secretion of IL-10, favoring the Th1/Th2 unbalanced response commonly observed during hRSV pathology. However, further research is required to demonstrate that these associations take place.

6 | CONCLUDING REMARKS

IDO is an enzyme that participates in the catabolism of Trp, which is an essential amino acid for vital cellular functions. The enzyme is activated during infections to deprive pathogens of Trp. Nonetheless, the catabolism of Trp and the metabolites it generates can also induce an immunosuppressive environment. It has been suggested that the dominant nature of the role of IDO during infections is pathogen-specific, i.e., antimicrobial or immunoregulatory. Some reports show both, antiviral and immunosuppressive effects by the activity of IDO during hRSV infection. However, currently, there is not enough information in the literature about the relationship between IDO expression and hRSV infection. Indeed, the immunoregulatory effects of IDO need to be demonstrated in vivo to generate more robust conclusions.

Two relevant characteristics of hRSV infection are a Th1/Th2 imbalance and both, effector and memory $CD8^+$ T cells impairment in the lungs. hRSV-induced IDO activity contributes to this cell proportion imbalance in favor of the survival of Th2 over Th1 cells, yet this selectivity remains unexplained. From this point of view, hRSV-induced IDO activity could be participating as a mechanism to avoid Th1 immune responses. On the other hand, the up-regulation of IDO results in a decrease in both, central and effector memory CD8+ T cells, which could explain hRSV-reinfections or infections later on in life, as older adults show a lower number of hRSV-specific memory T cells. Increased activity of IDO induced by hRSV seems to be an early event (acute phase) during infection. Likely, the virus takes advantage of the immunosuppressive effects of IDO activity in order to avoid the immune response mediated by T cells, suggesting that, after a Th2 immune response is set against the virus, both IL-4 and IL-13 regulate IDO activity, and this change could contribute to clear the virus in a later phase of infection. However, this idea needs further empirical confirmation. New therapeutic strategies, as the use of complementary anti-IDO treatment, could improve both, the immunological memory[83,88] and the cytokine profile[89] of the host during viral infection. Thus, it would be interesting to assess if 1MT can work as an "adjuvant push" for emerging vaccines, such as vaccines against hRSV and hMPV, which are currently under development.[124–126] An anti-IDO treatment or adjuvant therapy for hRSV infection would require corroborating the up-regulation of IDO and the subsequent inhibition of T cell proliferation and activation in an in vivo model as a first step. Different viruses cause acute respiratory infections; however, there is little information on the relationship between IDO activity and infection by different pathogens within that category. To date, most studies assess hRSV and influenza virus. However, the development of new prophylactic and therapeutic approaches against viral diseases requires understanding the pathogenesis of the disease to improve vaccine responses and the design of treatments to prevent and

potentially cure chronic viral infections. It may be important to focus on studying the role of IDO during respiratory infections caused by other pathogens.

AUTHORSHIP

All authors have made substantial, direct, and intellectual contribution to the work and approved it for publication. F.B. was associated with conceptualization, writing original draft, review, editing, and revision of the final version. J.S., M.P.O., K.B., P.G., and S.B. edited and revised the final version. A.K. was associated with conceptualization, revision of original draft, editing, and revision of final version.

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DISCLOSURE

The authors declare no conflict of interest.

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