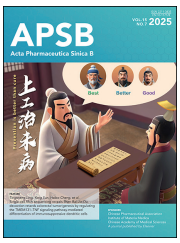
Acta Pharmaceutica Sinica B 2025;15(7):3404−3418

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Indoleamine-2,3-dioxygenase: An important controller in maintaining mesenchymal stem cell-mediated immunomodulatory homeostasis

Yufei Hui[a,†], Xue Jiao[a,†], Li Yang[a], Dejin Lu[a,c], Yanbo Han[a], Wen Yang[a], Yanli Cao[d], Yuxi Miao[a,*], Shiqiang Gong[a,*], Minjie Wei[a,b,*]

[a]*Department of Pharmacology, School of Pharmacy, China Medical University, Shenyang 110122, China*
[b]*Liaoning Medical Diagnosis and Treatment Center, Shenyang 110000, China*
[c]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*
[d]*The First Affiliated Hospital of China Medical University, Shenyang 110001, China*

Received 3 January 2025; received in revised form 9 March 2025; accepted 12 March 2025

KEY WORDS

Mesenchymal stem cells (MSCs);
Indoleamine-2,3-dioxygenase (IDO);
Immunomodulatory;
Plasticity;
Inflammation;
Tryptophan (Trp);
Immune cells;
Clinical therapeutics;
Autoimmune diseases

Abstract Mesenchymal stem cells (MSCs) have been widely used in the treatment of various autoimmune and inflammation-related diseases due to their potent immunomodulatory properties. Several studies have demonstrated that MSC-mediated immunomodulation is complex and bidirectional, with the *in vivo* microenvironment influencing the direction of this modulation. Indoleamine-2,3-dioxygenase (IDO), an immunosuppressive factor, has been identified as a key "switch" in the immunomodulatory role of MSCs. In this review, we explore how IDO functions as a critical regulator of MSC immunoregulatory plasticity. We delve into the mechanisms by which changes in IDO expression affect the function of various immune cells, summarize relevant research and clinical advances regarding the role of IDO expression in MSC-based therapies for various diseases, and discuss potential therapeutic strategies that target IDO to enhance the stability of MSC therapeutic effects. This provides a theoretical foundation for optimizing MSCs as safer and more effective clinical therapeutic agents.

*Corresponding authors.
E-mail addresses: mjwei@cmu.edu.cn (Minjie Wei), 20161013@cmu.edu.cn (Shiqiang Gong), yxmiao@cmu.edu.cn (Yuxi Miao).
[†]The authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2025.04.022

1. Introduction

Mesenchymal stem cells (MSCs) are among the most extensively studied pluripotent stem cells, known for their self-renewal potential, multilineage differentiation capacity, and immunomodulatory properties[1]. MSCs can be isolated from various tissues, including the umbilical cord, bone marrow, adipose tissue, and dental pulp. Compared with embryonic stem cells and induced pluripotent stem cells[2], MSCs have almost no tumorigenicity and ethical issues and have the advantages of low immunogenicity and clear efficacy, which make them the most widely used stem cells in clinical treatment[3−5].

Regarding the mechanism of action of MSCs, one of the most frequently addressed questions concerns their ability to home to, colonize and differentiate at sites of injury. Researchers have focused on leveraging MSCs homing ability to enable their migration to the damaged tissue, where they can colonize and differentiate, and then replace the damaged cells to produce therapeutic effects on the relevant diseases[6]. However, recent studies suggest that the differentiation capacity of MSCs may not be the primary means by which they exert their powerful therapeutic effects, with their immunomodulatory properties playing a more significant role[7−10]. Several studies have shown that MSCs are capable of affecting a wide range of innate immune cells by direct contact and inhibiting the proliferation and activation of T and B cells. In addition, MSCs can also exert immunomodulatory functions through their secretion of chemokines, cytokines, and extracellular vesicles, which contain transcription factors, mRNAs, microRNAs, and even mitochondrial regeneration compounds[11−13]. The complexity and bidirectionality of the MSC-mediated immunomodulation[14], which is largely influenced by the *in vivo* microenvironment and can result in either immunosuppressive or immunostimulatory effects, have prompted further investigation into the immunoregulatory plasticity of MSCs. Researchers are particularly interested in identifying the "switch" that determines the direction of MSC-mediated immunomodulation. It has been widely reported that indoleamine-2,3-dioxygenase (IDO) plays a key role in MSC immunomodulation and determines the direction of MSCs immune regulation, whether it is inhibition or promotion[15]. Therefore, we believe that IDO is an important 'switch' molecule that mediates the immune regulation of MSCs.

The potent immunomodulatory capacity of MSCs has led to their application in the treatment of a variety of diseases. Their immunomodulatory function is mainly achieved through a series of immunomodulatory factors, such as interferon-gamma (IFN-γ), IDO, inducible nitric oxide synthase (iNOS), programmed cell death ligand (PD-L) and prostaglandin E2 (PGE2), among others. IDO and iNOS are key factors in mediating the immunosuppressive effects of MSCs in different species. J Su et al. found that in animals such as mice, rats, hamsters and rabbits, the immunosuppression of MSCs is mainly mediated by iNOS, whereas in humans, monkeys and pigs, the immunosuppressive effects of MSCs mainly depends on IDO[16,17]. This article focuses on IDO's role in maintaining MSC-mediated immunomodulatory homeostasis.

The direction of immunoregulation in MSCs depends on the local inflammatory microenvironment[18]. Inflammatory factors such as IFN-γ, tumor necrosis factor α (TNF-α), interleukin-1α (IL-1α) and interleukin-1β (IL-1β), released at sites of tissue damage, trigger the inflammatory licensing of MSCs, leading to the expression of chemokines and adhesion factors. These factors facilitate the aggregation and adhesion of T cells to MSCs[19]. At the same time, MSCs after inflammatory licensing suppressed T cell reactivity through an IDO-mediated process. However, when IDO production is insufficient to trigger immunosuppression, the excessive aggregation of T cells can exacerbate inflammation, attenuating or even reversing MSC-mediated immunosuppression. Thus, IDO plays a critical role in determining the direction of immunoregulation[15]. The immunoregulatory plasticity of MSCs highlights the need for an in-depth understanding of the specific mechanisms governing IDO production and its mode of action. Such knowledge will enhance our understanding of the immunomodulatory mechanisms of MSCs. In addition, MSCs can induce IDO production in immune cells, leading to a cascade of subsequent immunosuppressive responses.

This review discusses the way in which IDO acts as an immunomodulatory "switch", from the mechanism of IDO immunosuppression in MSCs, the effect of IDO expression on immune cells, the important role and clinical application of IDO in the treatment of various diseases by MSCs, and the modification of MSCs targeting IDO to enrich our understanding of the mechanism of the immunomodulatory effects of MSCs. Enrich our understanding of the immunomodulatory mechanism of MSCs. In addition, the study of the IDO switching factor will help us adjust the expression level or activity of IDO according to the specific immune regulation needs in clinical applications, so as to optimize the immune regulation function of MSCs, and thus obtain better results in the treatment of inflammatory diseases and autoimmune diseases.

2. Physiological functions of IDO

IDO is a heme-containing cytoplasmic monomeric enzyme that plays a key role in the tryptophan (Trp) metabolic pathway[20]. It has a molecular mass of around 45 kDa and consists of two structural domains, the large and small domains, and the internal heme. The large domain is a full helical domain composed of 13 α-helices and two 3_{10}-helices, while the small domain is composed of six α-helices, two β-helices and three 3_{10}-helices[21]. IDO is expressed in a variety of cells, including antigen-presenting cells, epithelial cells and tumor cells. Its immunomodulatory capacity was first discovered in the placenta, where it mainly functions to prevent allogeneic fetuses from being rejected by maternal T cells[22]. Subsequent studies on IDO have mostly focused on its immunosuppressive effects. It is well known that an uncontrolled immune response can be fatal, and IDO, as an immunosuppressive factor, plays a crucial role in controlling excessive immune activation[23,24]. Furthermore, IDO is implicated in the pathogenesis of various diseases such as inflammation[25], cancer[26,27], autoimmune diseases[28], graft-*versus*-host disease

(GVHD) [29] and infections[30]. Beyond that IDO also affects the vascular[31] and nervous systems[32].

The basal expression level of IDO in cells is usually low and is generally induced by IFN-γ. As a pro-inflammatory cytokine, IFN-γ is usually produced by various cell types, including T cells, natural killer (NK) cells and macrophages. It has been demonstrated that IFN-γ treatment activates the mTOR signaling pathway, which enhances the expression of IDO and PGE2[33,34]. The upstream signal of IFN-γ-induced IDO expression is mainly mediated by the STAT1 pathway. Under the premise of sufficient PI3Kα signal, STAT1 overexpression can enhance the upregulation of IDO expression by IFN-γ on the one hand, and induce an inhibitory environment for T cells on the other hand. It is an essential upstream signal for IDO expression[35,36].

The most important physiological function of IDO is to catalyze Trp metabolism. Trp is an essential amino acid for all animals, and its metabolic pathway occurs through three main pathways, namely the kynurenine (KYN) pathway, 5-hydroxytryptophan pathway and indole pathway (Fig. 1). The KYN pathway is the principal route of Trp metabolism, accounting for 95% of total Trp metabolism[37,38]. As the first rate-limiting enzyme in the KYN pathway, IDO catalyzes the conversion of Trp to KYN, which ultimately leads to the production of nicotinamide adenine dinucleotide (NAD^+), a key cofactor involved in energy metabolism. Furthermore, intermediate metabolites of the KYN pathway such as KYN, Kynurenic acid (KYNA), and 3-hydroxyanthranilic acid (3-HK) have been shown to possess immunomodulatory and anti-inflammatory properties[39,40]. Therefore, the Trp metabolic pathway may play a pivotal role in the regulation of both immune function and inflammatory responses. In particular, for immune cells, Trp is also an essential amino acid for cell proliferation, and IDO can also inhibit the proliferation of immune cells or other cells through local Trp depletion[41].

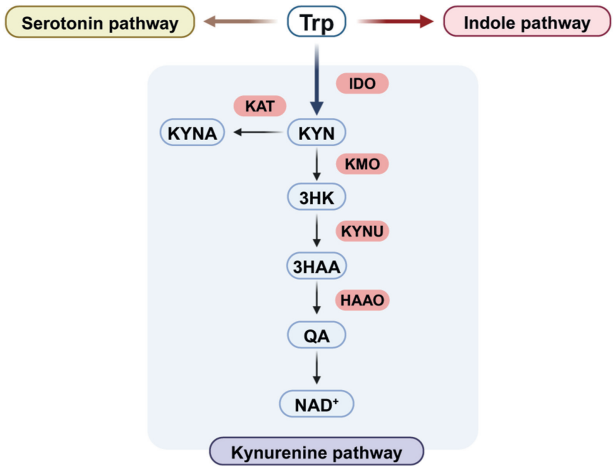


Figure 1 Schematic diagram of Trp metabolism. There are three main Trp metabolic pathways: the 5-HT pathway, the KYN pathway (95% of total Trp metabolism) and the indole pathway. Trp: tryptophan; KYN: kynurenine; KYNA: kynurenine acid; 3-HAA: 3-hydroxyanthranilic acid; 3-HK: 3-hydroxykynurenine; QA: quinolinic acid; NAD^+: nicotinamide adenine dinucleotide; KAT: lysine acetyltransferase; KMO: Kynurenine-3-monooxygenase; KYNU: Kynureninase; HAAO: 3-hydroxy-o-cyanobenzoic acid 3,4-dioxygenase. Figure created with BioRender.

IDO not only plays an enzymatic role but also acts as a signal transduction molecule to participate in immunomodulation. Maria et al. found that in plasmacytoid DC (pDC), TGF-β was able to induce phosphorylation of immunoreceptor tyrosine-based inhibitory motifs in the non-catalytic domain of IDO, recruit and activate tyrosine phosphatases SHP-1 and SHP-2, and then activate the non-classical nuclear factor-κB (NF-κB) pathway, leading to upregulation of TGF-β expression and IDO's own expression, and ultimately conferring on pDC an immunosuppressive phenotype, promoting the generation of Tregs, and leading to long-term immune tolerance of the organism[22,42–44]. In summary, IDO has a dual role as a catalyst and a signal transduction molecule in immune regulation.

IDO1 and IDO2 are two closely related tryptophan catabolizing enzymes encoded by linked genes. It is generally accepted that IDO2 is less active than IDO1 in catalyzing Trp metabolism. Knocking out *Ido1* will lead to a decrease in serum Kyn levels, whereas knocking out *Ido2* will not cause this phenomenon[22]. Furthermore, it has been shown that IDO2 plays a pro-inflammatory role in B-cell mediated autoimmune diseases[45]. In addition to IDO, tryptophan dioxygenase (TDO) is also a key enzyme in the catabolism of Trp, but TDO is mainly expressed in the liver and brain[22] and is less effective than IDO1 in regulating peripheral inflammation and immune cells. In summary, since IDO1 plays a dominant role in peripheral immunomodulation and there are currently a large number of reports on its mediation of MSCs immunoregulation, this article focuses on IDO1. Unless otherwise specified, the IDO mentioned below refers to IDO1.

3. Mechanisms of IDO-mediated immunosuppression

It is generally accepted that IDO exerts its immunosuppressive functions through two main mechanisms: (1) Trp depletion, which inhibits T cell proliferation and, (2) the accumulation of Trp metabolites, which further contribute to immunosuppression[46,47]. In addition, IDO can produce immunosuppressive effects by affecting cellular energy metabolism, acting as a signal transduction molecule. These immunosuppressive pathways of IDO are also important mechanisms for MSCs to exert immunomodulatory effects.

3.1. IDO-induced Trp depletion impairs T cell proliferation

Some studies have suggested that Trp depletion caused by IDO expressed by antigen-presenting cells (APCs) leads to the accumulation of uncharged tRNA, which in turn activates the general regulatory inhibitory protein kinase (GCN2) signal in responding T cells. GCN2 is a stress response kinase that acts as a molecular sensor of intracellular Trp. It can receive uncharged tRNA signals and inhibit translation initiation factor 2α (eIF2α), blocking protein production and cell growth, thereby inhibiting T cell proliferation and promoting Treg differentiation, producing immunosuppressive effects. This process is induced by APCs through IDO and synergistic with T cell receptor signaling[48,49].

Other studies have shown that Trp depletion caused by high expression of IDO in tumor cells leads to immunosuppression by inhibiting the mTOR pathway and causing cell autophagy[50,51]. Trp depletion inhibits mTORC1 activity, leading to increased autophagy activating kinase 1/2 (ULK1/2) kinase activity, and then ULK1/2 phosphorylates key subunits such as autophagy-related gene 13 (ATG13) and focal adhesion kinase family interacting protein of 200 kD, making the ULK complex active. The

active ULK complex is transferred to the endoplasmic reticulum, initiating cell autophagy and producing an immunosuppressive effect[51]. Böttcher et al.[52] found that tryptophan depletion caused by IDO expressed in MSCs leads to mTOR inactivation and thus suppression of T cell responses. However, the role of the mTOR pathway in IDO-mediated effects remains controversial. Some studies have shown that mTOR inhibitors, such as rapamycin, do not significantly affect IDO-induced proliferative suppression[48]. The result may suggest that IDO's immunosuppressive mechanisms are not mTOR-dependent. While both GCN2 and mTOR pathways detect amino acid deprivation, they may respond to different types of amino acids. GCN2 is able to sense the absence of multiple amino acids (such as tryptophan), whereas the mTOR pathway can sense the presence of specific amino acids, especially leucine[53]. This distinction could explain why mTOR inhibitors do not block the IDO-induced suppression of T cell proliferation (Fig. 2).

3.2. *IDO leads to accumulation of Trp metabolites producing immunosuppression*

It has been proposed that the accumulation of Trp metabolites is the primary mechanism through by which IDO exerts an immunosuppressive effect. These metabolites include KYN, KYNA, 3-hydroxyanthranilic acid (3-HAA), 3-HK and quinolinic acid (QA). KYN, the first product of Trp metabolism, has been identified as an aryl hydrocarbon receptor (AhR) agonist. Studies have shown that the AhR regulates the differentiation of Treg and TH17 cells in a ligand-specific manner, and it plays a crucial role in inflammation control[49,54–56]. Under normal tryptophan metabolism, intermediate metabolites such as KYN are weak AhR agonists, but in conditions of tryptophan depletion, they strongly induce AhR[49].

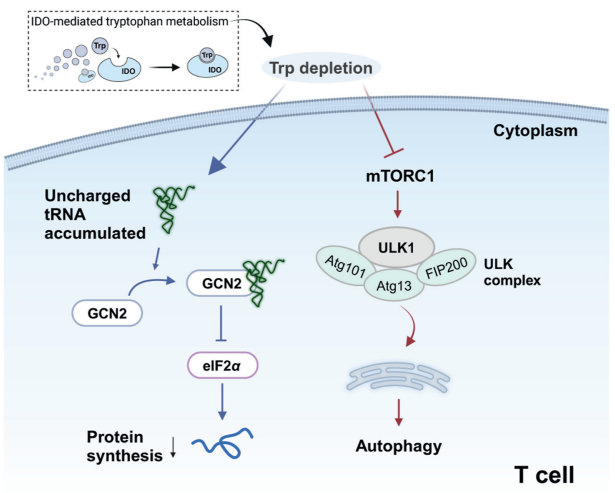


Figure 2 Schematic representation of the mechanism by which Trp depletion produces immunosuppressive effects. Under Trp-deficient conditions, uncharged tRNA accumulates, responding to GCN2 signaling and inhibiting downstream eIF2α, thereby blocking proteogenesis and cell growth; Trp depletion inhibits mTORC1 activity, leading to activation of the ULK complex, which is transferred to the endoplasmic reticulum, triggering cell autophagy and producing an immunosuppressive effect. ULK1: UNC- 51-like kinase 1; Atg101: autophagy-related gene 101; Atg13: autophagy-related gene 13; FIP200: focal adhesion kinase family interacting protein of 200 kD. Figure created with BioRender.

Liu et al.[57] found that IFN-γ induces dormancy in tumor-repopulating cells through the IDO−Kyn−AhR−P27 pathway, leading to immunosuppression and immune evasion by tumour cells, suggesting that inhibitors of IDO or AhR may target TRCs to enhance antitumour effects. KYN also induces AhR-mediated differentiation of Treg, resulting in immunosuppression[58,59]. Kuca-Warnawin et al.[60] found that adipose-derived stem cells tumor-repopulating cells exert inhibitory effects on the proliferation of CD4 and CD8 T cells mainly through soluble factors such as KYN and PGE. Li et al.[61] reported that IDO-catalyzed KYN in adipose-derived mesenchymal stem cells (ASCs) production promotes the expression of nuclear factor erythroid 2-related factor 2 (NRF2) *via* AhR activation, switching macrophages to anti-inflammatory phenotype. Additionally, KYN has been shown to enter NK cells *via* AhR on the cell surface, inhibiting NK cell function through the STAT1 and STAT3 pathways[62,63].

KYNA, a downstream metabolite of KYN, is also an important immunosuppressive agent. Like KYN, KYNA induces Treg differentiation *via* AhR activation. Sanam et al. demonstrated that KYNA inhibits the differentiation of Th17 cells and reduces the expression of inflammatory factors by activating the G-protein-coupled receptor 35[64,65]. Gao et al.[66] found that KYNA inhibits lipopolysaccharide-induced macrophage pyroptosis through NRF2 activation, thereby exerting anti-inflammatory effects. Furthermore, Wang et al.[67] suggested that KYNA activates AhR signaling and mediates immunosuppression by increasing tumor necrosis factor-α-stimulated gene/protein-6 (TSG-6) expression mediates the anti-inflammatory effects of human mesenchymal stem cells (hMSCs). Ye et al.[68] found that IFN-γ and KYNA pre-treated human ASCs can promote the polarisation of intestinal macrophages towards M2, exert an anti-inflammatory effect, induce the expression of IDO1, and enhance the signal transduction of IDO1.

KYN is metabolized by kynurenine-3-monooxygenase and Kynureninase to produce 3-HK and 3-HAA. These metabolites can inhibit the activation and proliferation of $CD4^+$ T cells *in vitro*, preventing graft rejection[69,70]. Iken et al.[71] found that intraperitoneal injection of 3-HAA prevented lung allograft injury in mice. They assessed the protective effects of IDO and the Trp metabolite 3-HAA against lung allograft injury, finding that the protective effect was achieved through increased IDO activity or its metabolite, with no significant difference between the treatments. This suggests that 3-HAA has the potential as a therapeutic agent. Finally, the Trp metabolite QA has been shown to mediate the formation of an immunosuppressive microenvironment, inducing a highly immunosuppressive M2 macrophage state *via* the NMDAR/PPARγ signaling axis[72] (Fig. 3).

3.3. *Other mechanisms of immunosuppression by IDO*

The immunosuppressive effects of IDO can also be understood in the context of energy metabolism. Theodoros et al. used the IDO inhibitor Indoximod (1-MT) and the P53 inhibitor pifithrin-α in a mixed lymphoid reaction to investigate IDO's impact on cellular metabolism. Their findings demonstrated that IDO, by activating GCN2, reduced glucose flux into T cells, altering key metabolic enzymes and thereby reducing aerobic glycolysis and glutaminolysis, and is unable to satisfy the energy demands of a large number of activated T cells. Simultaneously, IDO elevated P53 levels, which plays a role in inhibiting cell proliferation, glucose consumption and glycolysis[73,74]. However, there is currently

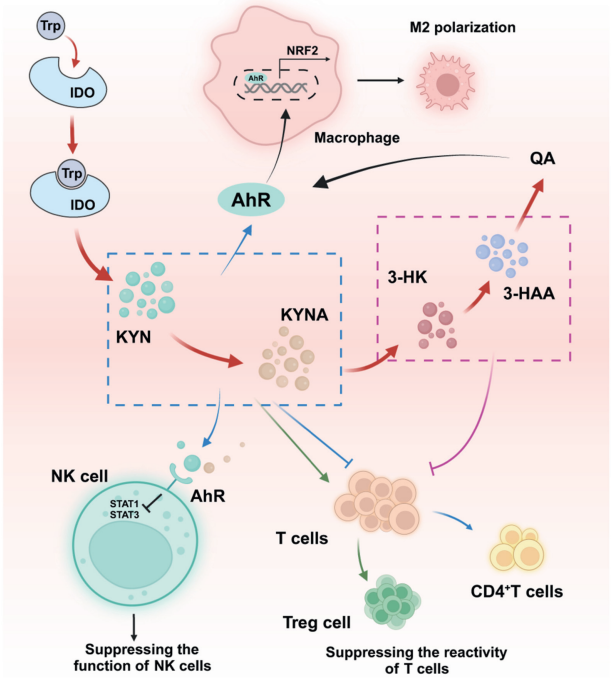


Figure 3 Schematic diagram of the mechanism by which accumulation of Trp metabolites produces immunosuppressive effects. IDO acts as a key Trp-catalysing enzyme, producing the metabolites KYN, KYNA and QA, which inhibit NK cell function and induce M2 macrophage polarisation *via* the AhR aromatic receptor; the metabolites KYN, KYNA, 3-HK and 3-HAA inhibit T cell reactivity, thereby mediating immunosuppression. KYN: kynurenine; KYNA: kynurenine acid; 3-HAA: 3-hydroxyanthranilic acid; 3-HK: 3-hydroxykynurenine; QA: quinolinic acid; NRF2: nuclear factor erythroid 2-related factor 2; AhR: aryl hydrocarbon receptor; STAT 1: signal transducer and activator of transcription 1; STAT 3: signal transducer and activator of transcription 3. Figure created with BioRender.

insufficient evidence to conclusively demonstrate that IDO regulates immune cell activity through metabolism, warranting further research in this area. Understanding IDO's effects on energy metabolism could provide novel insights with far-reaching implications. In addition, as previously described, in addition to its catalytic role, IDO also acts as a signal transduction molecule in pDCs to mediate the TGF-β-triggered immunosuppressive effects resulting in long-term immune tolerance in the organism[22,42–44].

Recently studies have shown that the immunomodulatory properties of MSCs are not only solely derived from living cells, but the apoptotic MSCs can also exert immunomodulatory effect[75,76]. Galleu et al.[76] found that cytotoxic cells induced the apoptosis of MSCs, and that phagocytosis of apoptotic MSCs led to the production of IDO, triggering immunosuppression. Interestingly, direct injection of apoptotic MSCs did not induce the same immunosuppressive response, suggesting that MSCs can initiate immunosuppression only by apoptosis at specific sites or processes *in vivo*, and that phagocytosis-expressed IDO is a major mediator in this process. This indicates that IDO continues to play a critical role in the immunosuppressive capacity of MSCs, whether they are alive or apoptotic.

In summary, IDO can produce immunosuppressive effects through a variety of mechanisms. Whether there are corresponding dominant mechanisms in different kinds of cells and whether there will be crosstalk between the mechanisms need to be confirmed by further studies. The clarification of the above issues will help to develop novel therapeutic tools and treatments for diseases caused by excessive immune activation, such as GVHD, and autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), especially the further improvement of MSCs-based treatments.

4. Role of IDO in MSCs on immune cells

The local inflammatory microenvironment at the site of injury is crucial for initiating immunomodulation in MSCs. During the acute inflammatory phase, MSCs are first attracted to the damaged site and then recruited to the inflamed tissue in response to inflammatory factors released at the site. MSCs subsequently exert specific immunoregulatory effects based on the type and concentration of these factors. Previous studies have shown that MSC immunoregulation is highly plastic, producing different effects depending on the local microenvironment. The key factor that determines the bidirectional nature of this immunoregulation is IDO, which is recognized as an important immunosuppressive factor expressed by MSCs and is considered central to their immunosuppressive function. However, some studies have shown that when IDO is underexpressed, it can paradoxically induce immune activation and exacerbate the inflammatory response[77,78]. MSCs are activated by local inflammation at the site of damage, producing chemokines that induce the aggregation of nearby T cells. When IDO is underexpressed, it fails to initiate immune suppression, leading to a more intense immune response and increased secretion of inflammatory factors due to the large number of T cells. As a bidirectional "switch" in MSC immunomodulation, IDO not only influences the immune response *via* T cells but also affects the immunomodulatory role of MSCs by acting on multiple immune cells, thereby influencing the disease progression.

4.1. T cell

T cells originate from lymphoid stem cells in the bone marrow and primarily mediate cellular immune responses, representing the most numerous and functionally diverse class of lymphocytes[79]. MSCs suppress T cell reactivity *via* high expression of IDO, thereby modulating immune responses, which is a crucial aspect of MSC-mediated immunoregulation. The inflammatory activation of MSCs induces the expression of the immune regulatory factor IDO, a crucially important step. Sudres et al.[80] found that transplantation of MSCs prior to the onset of inflammation did not achieve the desired therapeutic effect, likely due to insufficient inflammation, resulting in low levels of IDO expression in MSCs. Additionally, the expression of IDO in MSCs was found to significantly reduce Treg cell proliferation, thereby eliminating the immunosuppressive effect of cocultured MSCs[81]. Li et al.[78] reported that when IDO expression was insufficient to activate immunosuppression, T cell proliferation was no longer inhibited and the immunosuppressive effects exerted by MSCs were completely reversed. Hence, the level of IDO expression critically influences the direction of MSC-mediated immunoregulation (Fig. 4).

Numerous studies have demonstrated that IFN-γ plays an important role in inducing IDO production in MSCs and thus in mediating immunosuppression[82–84]. It is widely recognized as a

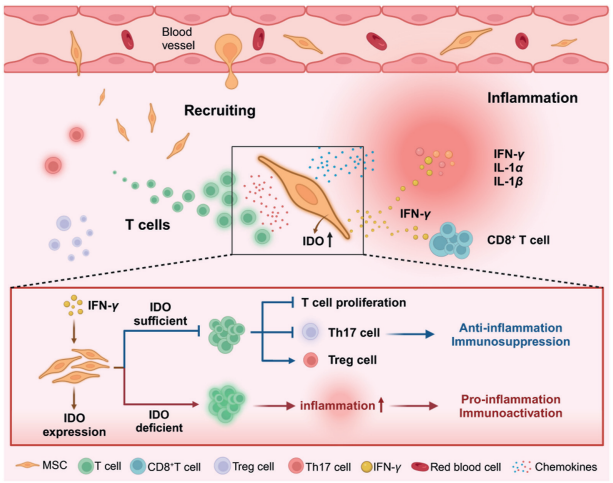


Figure 4 Schematic representation of the bi-directionality of immunoregulation in MSCs. Inflammatory factors initiated inflammatory clearance of MSCs, leading to aggregation of MSCs at the site of inflammation and expression of chemokines and adhesion factors, which induced T cells to aggregate near and adhere to MSCs. At the same time, high IDO expression by MSCs after inflammatory authorization suppressed T cell reactivity and produced immunosuppression. When IDO production was not sufficient to trigger immunosuppression, massive T cell aggregation led to an exacerbation of inflammation, at which point the immunosuppressive capacity of MSCs was attenuated or even reversed. Figure created with BioRender.

primary inducer of IDO in MSCs. Not only do damaged sites release inflammatory factors such as IFN-γ, but T cells also spontaneously release IFN-γ, which activates MSCs to produce high levels of IDO[85,86]. Wang et al.[86] found that elevated levels of IFN-γ produced by $CD8^+$ T cells in lupus patients were a key factor stimulating allogeneic human umbilical cord mesenchymal stem cells (hUCMSCs) to produce IDO, which subsequently inhibited T cell proliferation in these patients. High levels of inflammatory factors, such as IFN-γ, induce high expression of IDO in MSCs, leading to the suppression of T-cell activity through multiple mechanisms. Li et al.[85] compared MSCs derived from bone marrow, adipose tissue, placenta and human umbilical cord, and found that hUCMSCs had the strongest ability to inhibit T cell proliferation. They observed that hUCMSCs induced T cell apoptosis and cell cycle arrest through IDO high expression, thereby inhibiting T cell proliferation. When treated with the IDO inhibitor 1-MT, this inhibitory effect was completely reversed, highlighting the essential role of IDO in MSC-mediated T cell regulation. Lee et al.[87] demonstrated that Tonsil-derived MSCs expressing IDO and CD40 after induction by inflammatory factors (IFN-γ and TNF-α) were able to inhibit $CD4^+$ T cell activation and mediate immunosuppression of MSCs. Tatara et al.[88] showed that MSCs inhibit Th17 cell differentiation at least partially through IDO, and by using the IDO inhibitor 1-MT, they found that PGE2 and IDO act independently in the mechanisms by which MSCs inhibit Th17 cell differentiation. In addition, IDO regulates excessive immune response by promoting Treg cell proliferation. IDO secreted by MSCs has been found to induce graft tolerance, in part, by promoting the generation of Treg production[89,90]. Similarly, Kadle et al.[81] found that IDO is an important mediator of Treg cell stimulation by MSCs, particularly those initiated under hypoxic conditions. Inhibition of IDO significantly reduced Treg cell proliferation, suggesting that MSCs exert immunosuppressive effects through IDO high expression, mediated in part by Treg cells.

In summary, MSCs inhibit T cell proliferation[91], induce apoptosis, and cause cell cycle arrest through high expression of IDO. Additionally, they suppress the differentiation of Th17 cells and promote the generation of Treg cells, thereby regulating the local environment at the site of injury.

4.2. *Macrophages*

Macrophages are a key component of the innate immune system, playing a pivotal role in the immunomodulation of MSCs[92,93], with IDO mediating MSC-driven regulation of macrophages (Fig. 5). The enzymatic activity of IDO is necessary for MSCs to induce the transformation of monocytes into IL-10-secreting M2-type macrophages[94]. The Trp metabolite KYN plays a role in the IDO-mediated regulation of macrophages. Li et al.[61] found, in their study on the treatment of experimental periodontitis with ASC, that the KYN metabolite, catalyzed by IDO, activates AhR and enhances its binding to the NRF2 promoter in macrophages, stimulating their polarization to the M2 phenotype. Xie et al.[95] found that overexpression of IDO in bone marrow mesenchymal stem cells (BMSCs)-derived exosomes promoted macrophage polarization from M1 to M2 and increased the production of anti-inflammatory factors, thereby improving renal repair in IRI-AKI mice. Furthermore, high expression of IDO also induces cellular autophagy through the accumulation of Trp metabolites, thereby activating phagocytosis by macrophages. Yang et al.[96] discovered that IFN-IDO axis-mediated KYN accumulation enhances macrophage phagocytosis, contributing to the inhibition of

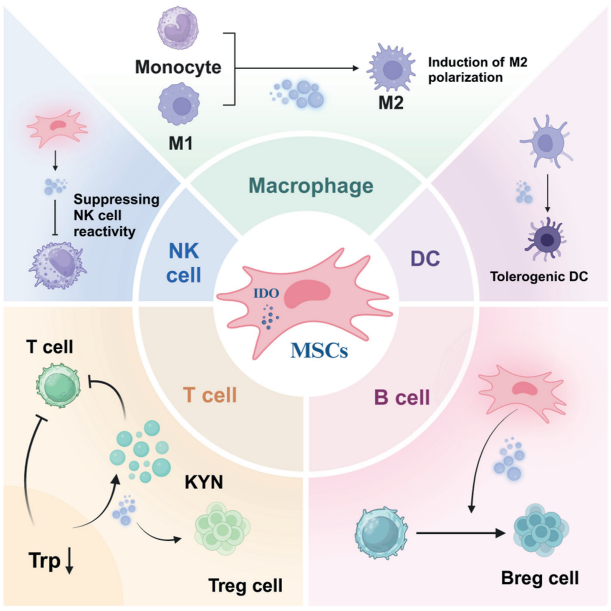


Figure 5 Schematic representation of the relationship between MSCs expressing IDO and the role of immune cells. MSCs expressing IDO were able to induce polarization of M1 monocytes and macrophages towards the M2 phenotype; inhibit NK cell function, induce tolerogenic DCs; inhibit T cell proliferation and induce Treg and Breg proliferation to exert immunosuppressive effects. Figure created with BioRender.

cervical cancer progression. The macrophage-dominated innate immune response plays an important role in the immunomodulatory process of MSCs, which induces macrophage polarization towards the M2 type, increases the production of anti-inflammatory factors and chemokines, alleviates inflammation, and modulates the immune response[68]. Among them, IDO is a critical mediator in the MSC-driven modulation of macrophages, inducing an immunosuppressive phenotype in macrophages.

4.3. NK cell

NK cells, derived from hemopoietic stem cells, are cytotoxic lymphocytes that secrete a variety of cytokines and exhibit potent anti-tumour and anti-viral effects[97]. A previous study has shown that IDO expression inhibits NK cell activation, thereby attenuating their anti-tumour responses, although IDO is not the only factor that affects NK cell function[98−100]. Similar to macrophages, NK cell activity is modulated by Trp metabolites. Della Chiesa et al.[101] found that the IDO-induced Trp metabolite KYN inhibited IL-2-induced NK cell proliferation, by selectively interfering with upregulation of NKp46 and NKG2D activation receptors. This, in turn, impaired the NK cells' killing capacity. This suggests that IDO-expressing cells within the focal tissue microenvironment can influence the function of NK cells there *via* Trp metabolites, thereby affecting the progression of disease. In addition, it has been found that IDO is also an important mediator in the inhibition of NK cell activity in MSCs, and high expression of IDO in MSCs can inhibit the proliferative activity of NK cells[102].

4.4. Dendritic cell

Dendritic cell (DC) are important antigen-presenting cells and crucial mediators between the innate and adaptive immune responses[103]. IDO is typically expressed at low levels in DCs but can be rapidly induced by IFN-γ under pathological conditions. The IFN-γ−IDO axis is highly sensitive to innate or hyper-inflammatory responses, helping to maintain homeostasis within the *in vivo* environment. In addition, IDO serves as a bridge between DCs and Tregs, facilitating Treg activation and proliferation through reverse signaling and the activation of the non-classical transcription factor NF-κB[104].

MSCs can inhibit DC maturation and function *via* IDO, converting mature DCs into tolerant DCs[89]. This process is dependent on IFN-γ induction in the *in vivo* microenvironment. Hemn et al. observed a significant increase in IDO expression in MSC-induced tolerant DCs following IFN-γ treatment[105]. Similarly, He et al.[90] reported a decrease in DC and an increase in Treg numbers after co-culturing *Ido*-transfected BMSCs with DCs in a heart transplant mouse model. These findings suggest that the IDO-mediated, IFN-γ-responsive immunoregulatory function of MSCs is, in part, mediated by DCs, which represents a critical pathway for MSC involvement in innate immunoregulation.

4.5. B cell

Other studies have mainly focused on the immunomodulatory effects of IDO on T cell proliferative, but there is considerable evidence regarding the regulation of B cells by MSCs, a process that also involves IDO[106−108]. It has been suggested that IDO in B cells plays a crucial role in autoimmunity, allergic response and protective immunity[45]. Recently, Li et al.[109] found that MSCs promoted the proliferation and function of $CD5^+$ B cells in MS patients through the IDO mechanisms. Peng et al.[110] also showed that the IDO pathway was partially responsible for MSCs promoting the survival and proliferation of $CD5^+$ regulatory B cells (Breg), thereby alleviating recalcitrant chronic graft-*versus*-host disease (cGVHD). However, direct evidence for the IDO-mediated regulation of B cells by MSCs remains limited and warrants further investigation.

5. The key role of IDO in the treatment of autoimmune diseases by MSCs

MSCs are regarded as a powerful therapeutic tool for immune-related diseases due to their potent paracrine and immunomodulatory properties. Numerous clinical trials have been conducted in recent years exploring the use of MSCs for the treatment of autoimmune diseases. According to data reported by the US National Institutes of Health, as of January 2025, 1734 MSC-based clinical trials have been completed or are still ongoing worldwide, of which a total of 354 have been conducted in China. Most clinical trials have focused on treating autoimmune diseases, GVHD, osteoarthritis, diabetes, and other diseases. We listed the clinical trials of MSCs for autoimmune diseases that have been conducted in recent years, particularly in common conditions such as SLE, GVHD and inflammatory bowel disease (IBD) (Table 1[111−120]). A growing number of clinical trials have shown that MSCs are safe and effective for the treatment of autoimmune diseases. Some researchers have suggested that human autoimmune diseases are caused by the inability of immune cells and/or stromal cells to upregulate IDO1 in response to inflammatory stimuli[41], and IDO also plays a key role in the treatment of multiple autoimmune diseases by MSCs.

5.1. GVHD

GVHD is triggered by a cascade of immune responses following T-cell activation by the graft host, and IDO has long been recognized as a key regulator of this condition, with IDO deficiency accelerating GVHD lethality[121,122]. IFN-γ induced MSCs to express IDO, thereby suppressing excessive autoimmune responses and maintaining immune homeostasis, which in turn ameliorates GVHD. Kim et al.[36] demonstrated that co-culture with IFN-γ-induced MSCs suppressed T-cell proliferation, significantly improving the survival rate in GVHD mouse models. He et al.[123] further found that Wharton jelly-derived MSCs treated GVHD by directly interacting with activated T cells, exerting immunosuppressive effects partially *via* IDO. In the same year, Peng et al.[110] reported that IDO expressed by MSCs helped treat GVHD by promoting the survival and proliferation of Breg cells. These findings suggest that IDO plays a key role in the treatment of GVHD by MSCs.

5.2. IBD

A substantial body of experimental evidence and clinical trials has demonstrated that MSCs are a safe and effective treatment for IBD[124,125]. Recent studies have suggested that IDO expression in MSCs may play an important role in their therapeutic effects on IBD. Qi et al.[126] reported that hUCMSCs increased the proportion of Tr1 cells in the spleen and mesenteric lymph nodes at various stages of colitis, with Tr1 cells playing a key role in the amelioration of IBD. In contrast, the knockdown of IDO expression in

Table 1 Examples of some recent clinical trials of MSCs for autoimmune diseases.

Diseases	MSC source	Mode of intervention	Phase	First posted	NCT NO.	Ref.
SLE	Bone marrow	Intravenous injection	Phase 2	2022	NCT03673748	111
	Bone marrow	Intravenous injection	Phase 1	2017	NCT03174587	112,113
	Umbilical cord	Intravenous injection	Phase 1	2017	NCT03171194	114
GVHD	Umbilical cord	Oral dressing	Phase 4	2023	NCT06149832	Not provided
	Placenta	Intravenous injection	Phase 3	2023	NCT06469411	Not provided
	Umbilical cord	Intravenous injection	Phase 3	2021	NCT04738981	Not provided
	Bone marrow	Intravenous injection	Phase 1/2	2015	NCT02379442	115
IBD	Adipose	Local injection	Phase 1/2	2022	NCT05521672	Not provided
	Umbilical cord	Local injection	Phase 1	2022	NCT05039411	Not provided
	Umbilical cord	Intravenous injection	Phase 1/2	2015	NCT02445547	Not provided
	Adipose	Local injection	Phase 3	2012	NCT01541579	116
RA	Umbilical cord	Intravenous injection	Phase 1	2021	NCT05003934	117
	Umbilical cord	Intravenous injection	Phase 1/2	2021	NCT04971980	Not provided
	Adipose	Intravenous injection	Phase 1/2	2012	NCT01663116	118
MS	Umbilical cord	Intravenous injection and intrathecal injection	Phase 1/2	2023	NCT05532943	Not provided
	Adipose	Intravenous injection	Phase 2	2021	NCT05116540	Not provided
	Umbilical cord	Intrathecal injection	Phase 1/2	2017	NCT03326505	119
IgA Nephropathy	Adipose	Intravenous injection	Phase 1	2020	NCT04342325	120
SS	Adipose	Local injection	Phase 2	2020	NCT04615455	Not provided

The above data are from Clinical Trials (https://clinicaltrials.gov).

hUCMSCs reversed this effect on Tr1 cells. Additionally, several studies have demonstrated that pre-treatment with IFN-γ and poly (I:C) enhances the therapeutic efficacy of MSCs in Dextran Sulfate Sodium Salt (DSS)-induced colitis, with IDO identified as a key mediator of IBD inhibition by IFN-γ and poly (I:C)-primed MSCs[127,128]. These findings indicate the crucial role of IDO in the treatment of IBD. Therefore, preconditioning or combining MSCs with IDO-targeting strategies may further improve their efficacy in treating IBD.

5.3. SLE

SLE is a multi-organ autoimmune disease with an unclear pathogenesis. However, reports on the treatment of SLE with MSCs have increased significantly in recent years[129−131]. It has also been reported that allogeneic hUCMSCs secrete large amounts of IDO, which inhibits the excessive T-cell expansion in lupus patients through the $CD8^+$ T-cell/IFNγ/IDO axis[86]. This suggests that IFN-γ-primed MSCs can modulate T cell activity *via* IDO, potentially slowing the progression of lupus.

5.4. Other autoimmune diseases

There are other autoimmune diseases, such as multiple sclerosis (MS), RA and desiccation syndrome. Although there is insufficient evidence to prove that these diseases are associated with IDO expression, many reports indicate that they have been treated with MSCs[117,132−135]. MSCs treat these autoimmune diseases by secreting anti-inflammatory and immunomodulatory factors. While we assume that IDO also plays a role, it does not necessarily dominate the therapeutic effect[109,136]. Consequently, further research in this area is greatly needed.

5.5. Cirrhosis

MSCs are proving to be an effective treatment for liver damage[6,137,138]. Milosavljevic et al.[139] found that MSCs inhibit hepatic Th17 cells in an IDO-dependent manner, thereby attenuating hepatic fibrosis. Zheng et al.[140] reported that MSCs inhibit the progression of liver fibrosis *via* follicle suppressor-like 1, which promotes MSC immunosuppression by activating the downstream JAK/STAT1/IDO pathway. We can therefore speculate that IDO is an important mediator of liver fibrosis in MSCs.

Other diseases have demonstrated a certain therapeutic effect from MSC transplantation, such as acute lung injury[67], occlusive bronchiolitis[141], and severe acute pancreatitis[142]. This therapeutic role is associated with IDO. These findings suggest that IDO not only plays an important role in the treatment of autoimmune diseases by MSCs but is also involved in the treatment of other diseases by MSCs.

6. IDO-specific modification enhances immunomodulatory function and therapeutic efficacy of MSCs

MSCs are capable of secreting a variety of immunomodulatory factors such as IDO, PGE2, TGF-β, IL-6, PD-L1, and IFN-γ to facilitate the treatment of autoimmune diseases. The local microenvironment determines the direction and function of immunomodulation in MSCs, with IDO being an important immunomodulatory factor. Many studies have shown that cellular modifications targeting IDO (usually upregulation of IDO expression in cells) can significantly enhance the immunomodulatory function and disease therapeutic effect of MSCs.

6.1. Drug/cytokine induction

Since IFN-γ induces the production of various immunomodulatory factors, including IDO, MSCs pretreated with IFN-γ have been shown to enhance their immunomodulatory capacity[36,143−145]. hMSCs treated with the inflammatory factors IFN-γ and TNF-α strongly increased IDO secretion and thus TSG-6 expression, which had a significant attenuating effect on DSS-induced colitis[146]. Conversely, MSCs inactivated for IDO were found to have a reduced ability to treat colitis[68]. This

suggests that IDO is a key factor in controlling abnormal inflammatory responses in MSCs and may be a target for treating inflammation-related diseases[147]. Phipps et al.[148] hypothesized that targeted delivery of IFN-γ to hMSCs *via* metal−organic scaffolds could enhance the immunomodulatory capacity of MSCs. They synthesized the IFN-γ-containing MOF PCN-333(Fe), which was delivered in a targeted manner to the local extracellular zone. The results showed that it was able to induce IDO formation at a lower concentration, enhancing the immunosuppressive capacity of MSCs. Park et al.[149] found that the combination of low doses of IFN-γ and the proteasome inhibitor bortezomib increased the immunosuppressive activity of MSCs by upregulating IDO. Other researchers pre-treated MSCs by increasing IDO expression *via* the TLR3 ligand polyinosinic-polycytidylic acid [poly(I:C)], which increased Treg frequency, reduced inflammation and stimulated epithelial regeneration, thereby ameliorating IBD[127]. Li et al.[150] found that the long non-coding RNA *Malat1* can mediate M2 macrophage polarization by inducing high expression of IDO and enhancing the immunosuppressive properties of MSCs. In addition, Chen et al.[151] found that upregulation of IDO expression by pretreatment of MSCs with Jujuboside A enhanced the immunomodulatory capacity.

6.2. *Genetic modification*

In addition to induction using drugs and cytokines, research on overexpressing IDO through genetic modification to enhance the therapeutic effect of MSCs is also ongoing. Gong et al.[147] found that inducing IDO overexpression in hUCMSCs increased anti-inflammatory Treg and Th2 responses while inhibiting pro-inflammatory Th1 and Th17 responses in dilated cardiomyopathy rats. The therapeutic effect was significantly reduced or even reversed after silencing *IDO* in hUCMSCs, indicating that the therapeutic effect of hUCMSCs on dilated cardiomyopathy depends on the expression level of IDO. Similarly, several studies have found that transfection of *Ido* into MSCs to overexpress it can inhibit allogeneic transplant rejection, including allogeneic heart, kidney and cornea transplants[90,91,152]. Xie et al.[95] studied the therapeutic effect of IDO-overexpressing MSCs exosomes on acute kidney injury. The results showed that IDO overexpression can amplify the therapeutic effect of MSCs exosomes and promote renal self-repair in acute kidney injury mice. He et al.[153] found that exosomes secreted by IDO-overexpressing BMSCs can reduce inflammation, promote immune tolerance, and improve the survival time of transplanted hearts.

In recent years, more studies on improving IDO expression by modifying MSCs have been reported. The upregulation of IDO expression by these different MSC pretreatment methods has consistently achieved the goal of improving the immunomodulatory capacity of MSCs. This suggests that we can look for safer and more effective ways to focus on IDO to carry out cellular modification, thereby enhancing the function and therapeutic effect of MSCs and providing more potent MSCs drugs for clinical use.

7. Discussion

Early research on MSCs primarily focused on their homing and differentiation abilities. Researchers anticipated that MSCs would be home to the injury site and differentiate in a directed manner to replace the damaged cells. However, the number of MSCs that are home to the site of injury following systemic administration is usually limited, and even fewer cells are capable of directed differentiation. Therefore, the replacement of damaged cells through directed differentiation is not the primary mechanism by which MSCs exert their therapeutic effects[154−156]. It has been found that MSCs can exert immunomodulatory effects through direct contact with immune cells or paracrine effects. This immune-modulatory mechanism is an important reason why MSCs are effective in treating a variety of diseases[157], including autoimmune disorders Consequently, a series of immunomodulatory factors, such as IDO, have become the focus of research.

As mentioned above, IDO inhibits T cell reactivity and mediates immunosuppression in MSCs by inflammatory cues initiated by cytokines such as IFN-γ, TNF and IL-1β. However, a certain concentration of these inflammatory factors is necessary for this process to occur. It has been found that when inflammatory factors are insufficient, the presence of MSCs can actually promote inflammation[78]. This is related to the inability of low concentrations of inflammatory factors to induce MSCs to produce sufficient amounts of IDO to switch on the immunosuppressive response. In addition, the expression of IDO in immune cells in response to inflammatory factors is also critical for the direction of immunoregulation in MSCs. Thus, IDO plays a pivotal "switch-like" role in the immunoregulatory balance of MSCs, where the concentration of IDO can drive the immune regulation mediated by MSCs in different directions. However, the exact threshold or critical point of this "switch" effect remains unclear. If this critical point could be identified, it would allow for more precise control over the therapeutic effects of MSCs. In this review, we have described in detail the mechanisms and ways in which IDO exerts immunosuppression, but the immunomodulatory role of MSCs is an extremely complex process, and the study of a single immunomodulatory factor cannot fully capture the underlying mechanisms of MSCs' *in vivo* actions. Apart from IDO, several other factors, such as PGE2, HGF, galectin-1, and IL-10, also contribute to the immunomodulatory functions of MSCs[158]. However, the important role of IDO as a key 'switch' molecule is well-established. Therefore, cell engineering strategies targeting IDO to enhance the immunomodulatory function and therapeutic efficacy of MSCs represent a promising and innovative approach in the development of MSC-based therapies.

The studies of pre-treatment or overexpression of IDO in MSCs by using the IDO inducer IFN-γ have been detailed above, and the modified MSCs were not only able to reduce T-cell proliferation as well as induce Treg proliferation to attenuate the immune response, but also able to produce more IDO-rich exosomes. This enhances the tissue repair capacity of MSCs and helps control abnormal inflammatory reactions[68,95]. However, as an immunosuppressive factor, IDO can also mediate immune escape from tumour tissue[159−161]. Ling et al.[162] demonstrated that in the tumour microenvironment, MSCs respond to inflammatory factors and then mediate immune escape *via* IDO thereby promoting tumour cell proliferation and migration. Additionally, Heidari et al.[163] found that silencing the expression of IDO in ASCs attenuated their immunosuppressive effects as well as their pro-tumour proliferation and metastasis. These findings highlight the need for caution during the modification of MSCs, considering the potential tumor-promoting effects induced by IDO. A more comprehensive evaluation of the safety of MSC-modified therapies is essential to assess the risks associated with such modifications.

Given the critical role of IDO in immune regulation and the immunomodulatory functions of MSC-based therapies, it is essential to conduct in-depth research into the mechanisms

governing its expression. For example, in DCs, IDO transcription is promoted by factors such as IRF-8 and repressed by DAP12[164]. At the post-translational level, SOCS3 binds IDO and targets the IDO/SOCS3 complex for ubiquitination and subsequent proteasomal degradation[165]. In the human epithelial cell line RT4, nitric oxide directly inactivates the heme active site and promotes proteasome-mediated degradation of IDO proteins[166]. In addition, although inflammatory factors are usually considered to be inducers of IDO expression, it has been found that inflammatory signals do not always stimulate IDO expression in APCs. In fact, certain inflammatory factors can even downregulate IDO expression in APCs[167]. The expression of IDO is tightly regulated, but our understanding of this regulatory process remains incomplete. More follow-up research is needed to comprehensively understand the processes of IDO production, activation, inhibition, and degradation. Such research will contribute to a deeper understanding of the pathological mechanisms underlying immune-related diseases and the mechanisms of novel immunemodulatory drugs, such as MSC-based therapies, thus facilitating the development of safer and more effective MSC-based therapeutics.

It is important to note that the key factors mediating the immunosuppression of MSCs vary between species. In humans, monkeys, and pigs, IDO serves as the central "switch" factor for MSC-mediated immunomodulation, whereas in rats/mice, rabbits, and hamsters, the corresponding factor is iNOS[16]. Recognizing this species-specific difference is crucial for research on the immunomodulatory mechanisms of MSCs and drug development. This is particularly relevant given that rodent models are commonly used in both physiological and pharmacological studies. On the one hand, it is important to consider that the immunomodulatory mechanisms of MSCs derived from rodents may differ from those of human-derived MSCs. On the other hand, in the non-clinical research phase of MSC drug development, the choice of animal species can significantly influence the evaluation of the therapeutic effects and mechanistic studies of human-derived MSC drugs.

In the development of immunomodulatory drugs based on MSCs, a deeper understanding of IDO will help to formulate more effective administration strategies. While most research has focused on the effects of IDO-mediated MSCs on immune cells, it is crucial to recognize that the interaction between MSCs and immune cells is bidirectional, with immune cells also influencing MSCs. In a study by Deng et al.[168], which investigated the use of human amniotic mesenchymal stem cells (hAMSCs) for treating liver fibrosis, it was found that Tregs could enhance the secretion of hepatocyte growth factor HGF and the differentiation potential of hAMSCs by modulating the TGF-β−IDO signaling pathway. Additionally, the combined infusion of hAMSCs and Tregs demonstrated superior therapeutic outcomes compared to the infusion of either cell type alone[168]. Moreover, exosomes derived from MSCs have increasingly been utilized in the treatment of various diseases in recent years, with IDO playing a critical role in exosome-based therapies. Xie et al.[95] discovered that exosomes derived from IDO-overexpressing MSCs could promote the polarization of M1 macrophages to M2 macrophages in a mouse model of ischemia−reperfusion-induced acute kidney injury, resulting in the production of more anti-inflammatory factors and significant recovery of kidney function. These effects were superior to those observed with exosomes from MSCs that did not overexpress IDO. Furthermore, exosomes from IDO-overexpressing MSCs accelerated renal tubular cell proliferation, and inhibited apoptosis, fibrosis, and the secretion of inflammatory cytokines[95]. Therefore, exosomes from IDO-overexpressing MSCs hold potential as a novel class of therapeutics, offering an alternative to MSCs for treating immune-mediated diseases in the future.

8. Conclusions

MSCs possess robust immunomodulatory capabilities and have demonstrated promising therapeutic effects in clinical trials for autoimmune diseases and other conditions as cell-based therapies. Indoleamine 2,3-dioxygenase serves as a key "switch" factor mediating the immunosuppressive functions of MSCs and plays a pivotal role in determining the direction of MSC-mediated immune regulation. In this review, we elucidate the physiological functions of IDO and the mechanisms through which it mediates immune suppression. We explore the effects of IDO in MSCs on various immune cells, including T cells and macrophages, and summarize its critical role in the therapeutic potential of MSCs in autoimmune diseases. Based on these discussions, we propose that targeting IDO for cellular modification may serve as an effective strategy to enhance the immunomodulatory functions and therapeutic efficacy of MSCs. This review aims to provide a comprehensive understanding of the mechanisms underlying MSC therapy, offering insights into the improvement of MSC-based drugs for the treatment of immune-mediated diseases. Further, a more thorough and in-depth investigation of IDO-mediated immune suppression is required to better understand the pathogenesis of immune diseases, thereby optimizing the therapeutic effects of MSC-based drugs, minimizing treatment risks, and ultimately developing safer and more effective cell-based therapies for autoimmune diseases.

Acknowledgments

This study was supported by the Scientific research funds of colleges and universities in Liaoning province (No. JYTMS20230131, China), National Key R&D Program of China (No. 2023ZD0508203).

Author contributions

Yufei Hui: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization, Software. Xue Jiao: Conceptualization, Writing - Original Draft, Visualization. Li Yang: Writing - Review & Editing. Dejin Lu: Conceptualization, Investigation. Yanbo Han: Investigation. Wen Yang: Investigation. Yanli Cao: Investigation. Yuxi Miao: Writing - Review & Editing, Supervision. Shiqiang Gong: Writing - Review & Editing, Supervision. Minjie Wei: Supervision, Project administration.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N, Suganuma N. Biological functions of mesenchymal stem cells and clinical implications. *Cell Mol Life Sci* 2019;**76**:3323−48.

2. Gopalarethinam J, Nair AP, Iyer M, Vellingiri B, Subramaniam MD. Advantages of mesenchymal stem cell over the other stem cells. *Acta Histochem* 2023;**125**:152041.
3. Zeng L, Yu G, Yang K, Xiang W, Li J, Chen H. Efficacy and safety of mesenchymal stem cell transplantation in the treatment of autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and ankylosing spondylitis): a systematic review and meta-analysis of randomized controlled trial. *Stem Cells Int* 2022;**2022**:9463314.
4. Weng Z, Zhang B, Wu C, Yu F, Han B, Li B, et al. Therapeutic roles of mesenchymal stem cell-derived extracellular vesicles in cancer. *J Hematol Oncol* 2021;**14**:136.
5. Shi L, Wang L, Xu R, Zhang C, Xie Y, Liu K, et al. Mesenchymal stem cell therapy for severe COVID-19. *Signal Transduct Target Ther* 2021;**6**:339.
6. Yuan M, Hu X, Yao L, Jiang Y, Li L. Mesenchymal stem cell homing to improve therapeutic efficacy in liver disease. *Stem Cell Res Ther* 2022;**13**:179.
7. Yang G, Fan X, Liu Y, Jie P, Mazhar M, Liu Y, et al. Immunomodulatory mechanisms and therapeutic potential of mesenchymal stem cells. *Stem Cell Rev Rep* 2023;**19**:1214−31.
8. Li H, Dai H, Li J. Immunomodulatory properties of mesenchymal stromal/stem cells: the link with metabolism. *J Adv Res* 2023;**45**: 15−29.
9. Song N, Scholtemeijer M, Shah K. Mesenchymal stem cell immunomodulation: mechanisms and therapeutic potential. *Trends Pharmacol Sci* 2020;**41**:653−64.
10. Weiss ARR, Dahlke MH. Immunomodulation by mesenchymal stem cells (MSCs): mechanisms of action of living, apoptotic, and dead MSCs. *Front Immunol* 2019;**10**:1191.
11. Huang Y, Wu Q, Tam PKH. Immunomodulatory mechanisms of mesenchymal stem cells and their potential clinical applications. *Int J Mol Sci* 2022;**23**:10023.
12. Zhou Y, Yamamoto Y, Xiao Z, Ochiya T. The immunomodulatory functions of mesenchymal stromal/stem cells mediated *via* paracrine activity. *J Clin Med* 2019;**8**:1025.
13. Velarde F, Ezquerra S, Delbruyere X, Caicedo A, Hidalgo Y, Khoury M. Mesenchymal stem cell-mediated transfer of mitochondria: mechanisms and functional impact. *Cell Mol Life Sci* 2022;**79**:177.
14. Wang Y, Fang J, Liu B, Shao C, Shi Y. Reciprocal regulation of mesenchymal stem cells and immune responses. *Cell Stem Cell* 2022; **29**:1515−30.
15. Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. *Nat Immunol* 2014;**15**:1009−16.
16. Su J, Chen X, Huang Y, Li W, Li J, Cao K, et al. Phylogenetic distinction of iNOS and IDO function in mesenchymal stem cell-mediated immunosuppression in mammalian species. *Cell Death Differ* 2014;**21**:388−96.
17. Ren G, Su J, Zhang L, Zhao X, Ling W, L'Huillie A, et al. Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression. *Stem Cells* 2009;**27**:1954−62.
18. Shi Y, Wang Y, Li Q, Liu K, Hou J, Shao C, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat Rev Nephrol* 2018;**14**:493−507.
19. Majumdar MK, Keane-Moore M, Buyaner D, Hardy WB, Moorman MA, McIntosh KR, et al. Characterization and functionality of cell surface molecules on human mesenchymal stem cells. *J Biomed Sci* 2003;**10**:228−41.
20. Oxenkrug GF. Metabolic syndrome, age-associated neuroendocrine disorders, and dysregulation of tryptophan−kynurenine metabolism. *Ann N Y Acad Sci* 2010;**1199**:1−14.
21. Sugimoto H, Oda S, Otsuki T, Hino T, Yoshida T, Shiro Y. Crystal structure of human indoleamine 2,3-dioxygenase: catalytic mechanism of O_2 incorporation by a heme-containing dioxygenase. *Proc Natl Acad Sci U S A* 2006;**103**:2611−6.
22. Pallotta MT, Rossini S, Suvieri C, Coletti A, Orabona C, Macchiarulo A, et al. Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme. *FEBS J* 2022;**289**:6099−118.
23. Munn DH, Mellor AL. Indoleamine 2,3 dioxygenase and metabolic control of immune responses. *Trends Immunol* 2013;**34**:137−43.
24. Heidari F, Ramezani A, Erfani N, Razmkhah M. Indoleamine 2, 3-dioxygenase: a professional immunomodulator and its potential functions in immune related diseases. *Int Rev Immunol* 2022;**41**: 346−63.
25. Chen LM, Bao CH, Wu Y, Liang SH, Wang D, Wu LY, et al. Tryptophan-kynurenine metabolism: a link between the gut and brain for depression in inflammatory bowel disease. *J Neuroinflammation* 2021;**18**:135.
26. Guo Y, Liu Y, Wu W, Ling D, Zhang Q, Zhao P, et al. Indoleamine 2,3-dioxygenase (Ido) inhibitors and their nanomedicines for cancer immunotherapy. *Biomaterials* 2021;**276**:121018.
27. Zhai L, Bell A, Ladomersky E, Lauing KL, Bollu L, Sosman JA, et al. Immunosuppressive IDO in cancer: mechanisms of action, animal models, and targeting strategies. *Front Immunol* 2020;**11**: 1185.
28. Nguyen NT, Nakahama T, Le DH, Van Son L, Chu HH, Kishimoto T. Aryl hydrocarbon receptor and kynurenine: recent advances in autoimmune disease research. *Front Immunol* 2014;**5**:551.
29. Ju JM, Nam G, Lee YK, Jung M, Chang H, Kim W, et al. IDO1 scavenges reactive oxygen species in myeloid-derived suppressor cells to prevent graft-*versus*-host disease. *Proc Natl Acad Sci U S A* 2021;**118**:e2011170118.
30. Li Q, Li X, Quan H, Wang Y, Qu G, Shen Z, et al. IL-$10^{-/-}$ enhances DCs immunity against *Chlamydia psittaci* infection *via* OX40L/NLRP3 and IDO/Treg pathways. *Front Immunol* 2021;**12**: 645653.
31. Wang Y, Liu H, McKenzie G, Witting PK, Stasch JP, Hahn M, et al. Kynurenine is an endothelium-derived relaxing factor produced during inflammation. *Nat Med* 2010;**16**:279−85.
32. Zhou W, Dantzer R, Budac DP, Walker AK, Mao-Ying QL, Lee AW, et al. Peripheral indoleamine 2,3-dioxygenase 1 is required for comorbid depression-like behavior but does not contribute to neuropathic pain in mice. *Brain Behav Immun* 2015;**46**:147−53.
33. Liu Y, Yuan X, Munoz N, Logan TM, Ma T. Commitment to aerobic glycolysis sustains immunosuppression of human mesenchymal stem cells. *Stem Cells Transl Med* 2019;**8**:93−106.
34. Jitschin R, Bottcher M, Saul D, Lukassen S, Bruns H, Loschinski R, et al. Inflammation-induced glycolytic switch controls suppressivity of mesenchymal stem cells *via* STAT1 glycosylation. *Leukemia* 2019;**33**:1783−96.
35. Mounayar M, Kefaloyianni E, Smith B, Solhjou Z, Maarouf OH, Azzi J, et al. PI3kalpha and STAT1 interplay regulates human mesenchymal stem cell immune polarization. *Stem Cells* 2015;**33**: 1892−901.
36. Kim DS, Jang IK, Lee MW, Ko YJ, Lee DH, Lee JW, et al. Enhanced immunosuppressive properties of human mesenchymal stem cells primed by interferon-γ. *EBioMedicine* 2018;**28**:261−73.
37. Höglund E, Øverli Ø, Winberg S. Tryptophan metabolic pathways and brain serotonergic activity: a comparative review. *Front Endocrinol (Lausanne)* 2019;**10**:158.
38. Badawy AA. Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects. *Int J Tryptophan Res* 2017;**10**: 1178646917691938.
39. Savitz J. The kynurenine pathway: a finger in every pie. *Mol Psychiatr* 2020;**25**:131−47.
40. Xue C, Li G, Zheng Q, Gu X, Shi Q, Su Y, et al. Tryptophan metabolism in health and disease. *Cell Metab* 2023;**35**:1304−26.
41. Platten M, Nollen EAA, Röhrig UF, Fallarino F, Opitz CA. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. *Nat Rev Drug Discov* 2019;**18**:379−401.
42. Pantouris G, Serys M, Yuasa HJ, Ball HJ, Mowat CG. Human indoleamine 2,3-dioxygenase-2 has substrate specificity and inhibition characteristics distinct from those of indoleamine 2,3-dioxygenase-1. *Amino Acids* 2014;**46**:2155−63.

43. Merlo LMF, DuHadaway JB, Montgomery JD, Peng WD, Murray PJ, Prendergast GC, et al. Differential roles of IDO1 and IDO2 in T and B cell inflammatory immune responses. *Front Immunol* 2020;**11**: 1861.
44. Chen W. IDO: more than an enzyme. *Nat Immunol* 2011;**12**:809−11.
45. Merlo LMF, Peng W, Mandik-Nayak L. Impact of IDO1 and IDO2 on the B Cell immune response. *Front Immunol* 2022;**13**:886225.
46. Mbongue JC, Nicholas DA, Torrez TW, Kim NS, Firek AF, Langridge WH. The role of indoleamine 2, 3-dioxygenase in immune suppression and autoimmunity. *Vaccines (Basel)* 2015;**3**:703−29.
47. Platten M, Wick W, Van den Eynde BJ. Tryptophan catabolism in cancer: beyond IDO and tryptophan depletion. *Cancer Res* 2012;**72**: 5435−40.
48. Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, Ron D, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. *Immunity* 2005;**22**:633−42.
49. Solvay M, Holfelder P, Klaessens S, Pilotte L, Stroobant V, Lamy J, et al. Tryptophan depletion sensitizes the AHR pathway by increasing AHR expression and GCN2/LAT1-mediated kynurenine uptake, and potentiates induction of regulatory T lymphocytes. *J Immunother Cancer* 2023;**11**:e006728.
50. Metz R, Rust S, Duhadaway JB, Mautino MR, Munn DH, Vahanian NN, et al. IDO inhibits a tryptophan sufficiency signal that stimulates mTOR: a novel IDO effector pathway targeted by D-1-methyl-tryptophan. *Oncoimmunology* 2012;**1**:1460−8.
51. Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. *J Clin Invest* 2015;**125**:25−32.
52. Böttcher M, Hofmann AD, Bruns H, Haibach M, Loschinski R, Saul D, et al. Mesenchymal stromal cells disrupt mTOR-signaling and aerobic glycolysis during T-cell activation. *Stem Cells* 2016;**34**: 516−21.
53. Gallinetti J, Harputlugil E, Mitchell JR. Amino acid sensing in dietary-restriction-mediated longevity: roles of signal-transducing kinases GCN2 and TOR. *Biochem J* 2013;**449**:1−10.
54. Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, et al. Control of T_{reg} and T_H17 cell differentiation by the aryl hydrocarbon receptor. *Nature* 2008;**453**:65−71.
55. Stockinger B, Di Meglio P, Gialitakis M, Duarte JH. The aryl hydrocarbon receptor: multitasking in the immune system. *Annu Rev Immunol* 2014;**32**:403−32.
56. Piper CJM, Rosser EC, Oleinika K, Nistala K, Krausgruber T, Rendeiro AF, et al. Aryl hydrocarbon receptor contributes to the transcriptional program of IL-10-producing regulatory B cells. *Cell Rep* 2019;**29**:1878−92.e7.
57. Liu Y, Liang X, Yin X, Lv J, Tang K, Ma J, et al. Blockade of IDO-kynurenine-AhR metabolic circuitry abrogates IFN-gamma-induced immunologic dormancy of tumor-repopulating cells. *Nat Commun* 2017;**8**:15207.
58. Fong W, Li Q, Ji F, Liang W, Lau HCH, Kang X, et al. Lactobacillus gallinarum-derived metabolites boost anti-PD1 efficacy in colorectal cancer by inhibiting regulatory T cells through modulating IDO1/Kyn/AHR axis. *Gut* 2023;**72**:2272−85.
59. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol* 2010; **185**:3190−8.
60. Kuca-Warnawin E, Plebanczyk M, Bonek K, Kontny E. Inhibition of allogeneic and autologous T cell proliferation by adipose-derived mesenchymal stem cells of ankylosing spondylitis patients. *Stem Cells Int* 2021;**2021**:6637328.
61. Li H, Yuan Y, Chen H, Dai H, Li J. Indoleamine 2,3-dioxygenase mediates the therapeutic effects of adipose-derived stromal/stem cells in experimental periodontitis by modulating macrophages through the kynurenine−AhR−NRF2 pathway. *Mol Metab* 2022;**66**: 101617.
62. Park A, Yang Y, Lee Y, Kim MS, Park YJ, Jung H, et al. Indoleamine-2,3-dioxygenase in thyroid cancer cells suppresses natural killer cell function by inhibiting NKG2D and NKP46 expression *via* STAT signaling pathways. *J Clin Med* 2019;**8**:842.
63. Trikha P, Moseman JE, Thakkar A, Campbell AR, Elmas E, Foltz JA, et al. Defining the AhR-regulated transcriptome in NK cells reveals gene expression programs relevant to development and function. *Blood Adv* 2021;**5**:4605−18.
64. Salimi Elizei S, Poormasjedi-Meibod MS, Wang X, Kheirandish M, Ghahary A. Kynurenic acid downregulates IL-17/1L-23 axis *in vitro*. *Mol Cell Biochem* 2017;**431**:55−65.
65. Wirthgen E, Hoeflich A, Rebl A, Günther J. Kynurenic acid: The janus-faced role of an immunomodulatory tryptophan metabolite and its link to pathological conditions. *Front Immunol* 2017;**8**:1957.
66. Gao Y, Guo X, Zhou Y, Du J, Lu C, Zhang L, et al. Kynurenic acid inhibits macrophage pyroptosis by suppressing ROS production *via* activation of the NRF2 pathway. *Mol Med Rep* 2023;**28**:13098.
67. Wang G, Cao K, Liu K, Xue Y, Roberts AI, Li F, et al. Kynurenic acid, an IDO metabolite, controls TSG-6-mediated immunosuppression of human mesenchymal stem cells. *Cell Death Differ* 2018; **25**:1209−23.
68. Ye Y, Zhang X, Su D, Ren Y, Cheng F, Yao Y, et al. Therapeutic efficacy of human adipose mesenchymal stem cells in Crohn's colon fibrosis is improved by IFN-γ and kynurenic acid priming through indoleamine 2,3-dioxygenase-1 signaling. *Stem Cell Res Ther* 2022;**13**:465.
69. Piscianz E, Cuzzoni E, De Iudicibus S, Valencic E, Decorti G, Tommasini A. Differential action of 3-hydroxyanthranilic acid on viability and activation of stimulated lymphocytes. *Int Immunopharmacol* 2011;**11**:2242−5.
70. Zaher SS, Germain C, Fu H, Larkin DF, George AJ. 3-hydroxykynurenine suppresses $CD4^+$ T-cell proliferation, induces T-regulatory-cell development, and prolongs corneal allograft survival. *Invest Ophthalmol Vis Sci* 2011;**52**:2640−8.
71. Iken K, Liu K, Liu H, Bizargity P, Wang L, Hancock WW, et al. Indoleamine 2,3-dioxygenase and metabolites protect murine lung allografts and impair the calcium mobilization of T cells. *Am J Respir Cell Mol Biol* 2012;**47**:405−16.
72. Kesarwani P, Kant S, Zhao Y, Prabhu A, Buelow KL, Miller CR, et al. Quinolinate promotes macrophage-induced immune tolerance in glioblastoma through the NMDAR/PPARgamma signaling axis. *Nat Commun* 2023;**14**:1459.
73. Eleftheriadis T, Pissas G, Yiannaki E, Markala D, Arampatzis S, Antoniadi G, et al. Inhibition of indoleamine 2,3-dioxygenase in mixed lymphocyte reaction affects glucose influx and enzymes involved in aerobic glycolysis and glutaminolysis in alloreactive T-cells. *Hum Immunol* 2013;**74**:1501−9.
74. Eleftheriadis T, Pissas G, Antoniadi G, Spanoulis A, Liakopoulos V, Stefanidis I. Indoleamine 2,3-dioxygenase increases p53 levels in alloreactive human T cells, and both indoleamine 2,3-dioxygenase and p53 suppress glucose uptake, glycolysis and proliferation. *Int Immunol* 2014;**26**:673−84.
75. Fu Y, Sui B, Xiang L, Yan X, Wu D, Shi S, et al. Emerging understanding of apoptosis in mediating mesenchymal stem cell therapy. *Cell Death Dis* 2021;**12**:596.
76. Galleu A, Riffo-Vasquez Y, Trento C, Lomas C, Dolcetti L, Cheung TS, et al. Apoptosis in mesenchymal stromal cells induces *in vivo* recipient-mediated immunomodulation. *Sci Transl Med* 2017; **9**:eaam7828.
77. Chen X, Gan Y, Li W, Su J, Zhang Y, Huang Y, et al. The interaction between mesenchymal stem cells and steroids during inflammation. *Cell Death Dis* 2014;**5**:e1009.
78. Li W, Ren G, Huang Y, Su J, Han Y, Li J, et al. Mesenchymal stem cells: a double-edged sword in regulating immune responses. *Cell Death Differ* 2012;**19**:1505−13.
79. Schumacher TN, Gerlach C, van Heijst JW. Mapping the life histories of T cells. *Nat Rev Immunol* 2010;**10**:621−31.
80. Sudres M, Norol F, Trenado A, Grégoire S, Charlotte F, Levacher B, et al. Bone marrow mesenchymal stem cells suppress lymphocyte proliferation *in vitro* but fail to prevent graft-*versus*-host disease in mice. *J Immunol* 2006;**176**:7761−7.

81. Kadle RL, Abdou SA, Villarreal-Ponce AP, Soares MA, Sultan DL, David JA, et al. Microenvironmental cues enhance mesenchymal stem cell-mediated immunomodulation and regulatory T-cell expansion. *PLoS One* 2018;**13**:e0193178.
82. Croitoru-Lamoury J, Lamoury FM, Caristo M, Suzuki K, Walker D, Takikawa O, et al. Interferon-γ regulates the proliferation and differentiation of mesenchymal stem cells *via* activation of indoleamine 2,3 dioxygenase (IDO). *PLoS One* 2011;**6**:e14698.
83. English K, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. *Immunol Lett* 2007;**110**:91−100.
84. Bulati M, Miceli V, Gallo A, Amico G, Carcione C, Pampalone M, et al. The immunomodulatory properties of the human amnion-derived mesenchymal stromal/stem cells are induced by INF-γ produced by activated lymphomonocytes and are mediated by cell-to-cell contact and soluble factors. *Front Immunol* 2020;**11**:54.
85. Li X, Xu Z, Bai J, Yang S, Zhao S, Zhang Y, et al. Umbilical cord tissue-derived mesenchymal stem cells induce T lymphocyte apoptosis and cell cycle arrest by expression of indoleamine 2, 3-dioxygenase. *Stem Cells Int* 2016;**2016**:7495135.
86. Wang D, Feng X, Lu L, Konkel JE, Zhang H, Chen Z, et al. A CD8 T cell/indoleamine 2,3-dioxygenase axis is required for mesenchymal stem cell suppression of human systemic lupus erythematosus. *Arthritis Rheumatol* 2014;**66**:2234−45.
87. Lee HJ, Jung H, Kim DK. IDO and CD40 may be key molecules for immunomodulatory capacity of the primed tonsil-derived mesenchymal stem cells. *Int J Mol Sci* 2021;**22**:5772.
88. Tatara R, Ozaki K, Kikuchi Y, Hatanaka K, Oh I, Meguro A, et al. Mesenchymal stromal cells inhibit Th17 but not regulatory T-cell differentiation. *Cytotherapy* 2011;**13**:686−94.
89. Ge W, Jiang J, Arp J, Liu W, Garcia B, Wang H. Regulatory T-cell generation and kidney allograft tolerance induced by mesenchymal stem cells associated with indoleamine 2,3-dioxygenase expression. *Transplantation* 2010;**90**:1312−20.
90. He JG, Li BB, Zhou L, Yan D, Xie QL, Zhao W. Indoleamine 2,3-dioxgenase-transfected mesenchymal stem cells suppress heart allograft rejection by increasing the production and activity of dendritic cells and regulatory T cells. *J Investig Med* 2020;**68**:728−37.
91. Ke H, Zhang W, Xu W, Cao Q, Li L, Liu H. Indoleamine 2, 3-dioxygenase-transfected bone marrow-derived mesenchymal stem cells promote corneal allograft survival by inhibiting T cell proliferation: a rat study. *Transpl Immunol* 2024;**82**:101960.
92. Pajarinen J, Lin T, Gibon E, Kohno Y, Maruyama M, Nathan K, et al. Mesenchymal stem cell−macrophage crosstalk and bone healing. *Biomaterials* 2019;**196**:80−9.
93. Lo Sicco C, Reverberi D, Balbi C, Ulivi V, Principi E, Pascucci L, et al. Mesenchymal stem cell-derived extracellular vesicles as mediators of anti-inflammatory effects: endorsement of macrophage polarization. *Stem Cells Transl Med* 2017;**6**:1018−28.
94. Francois M, Romieu-Mourez R, Li M, Galipeau J. Human MSC suppression correlates with cytokine induction of indoleamine 2,3-dioxygenase and bystander M2 macrophage differentiation. *Mol Ther* 2012;**20**:187−95.
95. Xie X, Yang X, Wu J, Tang S, Yang L, Fei X, et al. Exosome from indoleamine 2,3-dioxygenase-overexpressing bone marrow mesenchymal stem cells accelerates repair process of ischemia/reperfusion-induced acute kidney injury by regulating macrophages polarization. *Stem Cell Res Ther* 2022;**13**:367.
96. Yang SL, Tan HX, Niu TT, Liu YK, Gu CJ, Li DJ, et al. The IFN-γ-IDO1-kynureine pathway-induced autophagy in cervical cancer cell promotes phagocytosis of macrophage. *Int J Biol Sci* 2021;**17**:339−52.
97. Poznanski SM, Ashkar AA. What defines NK cell functional fate: phenotype or metabolism?. *Front Immunol* 2019;**10**:1414.
98. Li T, Yang Y, Hua X, Wang G, Liu W, Jia C, et al. Hepatocellular carcinoma-associated fibroblasts trigger NK cell dysfunction *via* PGE2 and IDO. *Cancer Lett* 2012;**318**:154−61.
99. Torre E, Pinton G, Lombardi G, Fallarini S. Melanoma cells inhibit iNKT cell functions *via* PGE2 and IDO1. *Cancers (Basel)* 2023;**15**:3498.
100. Peng YP, Zhang JJ, Liang WB, Tu M, Lu ZP, Wei JS, et al. Elevation of MMP-9 and IDO induced by pancreatic cancer cells mediates natural killer cell dysfunction. *BMC Cancer* 2014;**14**:738.
101. Della Chiesa M, Carlomagno S, Frumento G, Balsamo M, Cantoni C, Conte R, et al. The tryptophan catabolite L-kynurenine inhibits the surface expression of NKp46- and NKG2D-activating receptors and regulates NK-cell function. *Blood* 2006;**108**:4118−25.
102. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. *Blood* 2008;**111**:1327−33.
103. Waisman A, Lukas D, Clausen BE, Yogev N. Dendritic cells as gatekeepers of tolerance. *Semin Immunopathol* 2017;**39**:153−63.
104. Puccetti P, Grohmann U. IDO and regulatory T cells: a role for reverse signalling and non-canonical NF-kappaB activation. *Nat Rev Immunol* 2007;**7**:817−23.
105. Mohammadpour H, Pourfathollah AA, Zarif MN, Tahoori MT. TNF-alpha modulates the immunosuppressive effects of MSCs on dendritic cells and T cells. *Int Immunopharmacol* 2015;**28**:1009−17.
106. Fan L, Hu C, Chen J, Cen P, Wang J, Li L. Interaction between mesenchymal stem cells and B-cells. *Int J Mol Sci* 2016;**17**:650.
107. Chen X, Cai C, Xu D, Liu Q, Zheng S, Liu L, et al. Human mesenchymal stem cell-treated regulatory $CD23^{+}CD43^{+}$ B cells alleviate intestinal inflammation. *Theranostics* 2019;**9**:4633−47.
108. Liu J, Liu Q, Chen X. The immunomodulatory effects of mesenchymal stem cells on regulatory B cells. *Front Immunol* 2020;**11**:1843.
109. Li H, Deng Y, Liang J, Huang F, Qiu W, Zhang M, et al. Mesenchymal stromal cells attenuate multiple sclerosis *via* IDO-dependent increasing the suppressive proportion of $CD5^{+}$ IL-10^{+} B cells. *Am J Transl Res* 2019;**11**:5673−88.
110. Peng Y, Chen X, Liu Q, Zhang X, Huang K, Liu L, et al. Mesenchymal stromal cells infusions improve refractory chronic graft *versus* host disease through an increase of $CD5^{+}$ regulatory B cells producing interleukin 10. *Leukemia* 2015;**29**:636−46.
111. Barbado J, Tabera S, Sánchez A, García-Sancho J. Therapeutic potential of allogeneic mesenchymal stromal cells transplantation for lupus nephritis. *Lupus* 2018;**27**:2161−5.
112. Jang E, Jeong M, Kim S, Jang K, Kang BK, Lee DY, et al. Infusion of human bone marrow-derived mesenchymal stem cells alleviates autoimmune nephritis in a lupus model by suppressing follicular helper T-cell development. *Cell Transplant* 2016;**25**:1−15.
113. Shim JS, Sung YK, Joo YB, Lee HS, Bae SC. Prevalence and incidence of systemic lupus erythematosus in South Korea. *Rheumatol Int* 2014;**34**:909−17.
114. Kamen DL, Wallace C, Li Z, Wyatt M, Paulos C, Wei C, et al. Safety, immunological effects and clinical response in a phase I trial of umbilical cord mesenchymal stromal cells in patients with treatment refractory SLE. *Lupus Sci Med* 2022;**9**:e000704.
115. Holtan SG, Pasquini M, Weisdorf DJ. Acute graft-*versus*-host disease: a bench-to-bedside update. *Blood* 2014;**124**:363−73.
116. Garcia-Olmo D, Gilaberte I, Binek M, AJL DH, Lindner D, Selvaggi F, et al. Follow-up study to evaluate the long-term safety and efficacy of darvadstrocel (mesenchymal stem cell treatment) in patients with perianal fistulizing crohn's disease: ADMIRE-CD phase 3 randomized controlled trial. *Dis Colon Rectum* 2022;**65**:713−20.
117. Wang L, Huang S, Li S, Li M, Shi J, Bai W, et al. Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: a prospective phase I/II study. *Drug Des Devel Ther* 2019;**13**:4331−40.
118. Álvaro-Gracia JM, Jover JA, García-Vicuña R, Carreño L, Alonso A, Marsal S, et al. Intravenous administration of expanded allogeneic adipose-derived mesenchymal stem cells in refractory rheumatoid

arthritis (Cx611): results of a multicentre, dose escalation, randomised, single-blind, placebo-controlled phase Ib/IIa clinical trial. *Ann Rheum Dis* 2017;**76**:196−202.
119. Alghwiri AA, Jamali F, Aldughmi M, Khalil H, Al-Sharman A, Alhattab D, et al. The effect of stem cell therapy and comprehensive physical therapy in motor and non-motor symptoms in patients with multiple sclerosis: a comparative study. *Medicine (Baltim)* 2020;**99**: e21646.
120. Tanaka A, Furuhashi K, Fujieda K, Maeda K, Saito S, Mimura T, et al. Protocol for a phase 1, open-label, multiple-center, dose-escalation study to evaluate the safety and tolerability of ADR-001 in the treatment of immunoglobulin A nephropathy. *Front Med (Lausanne)* 2022;**9**:883168.
121. Jasperson LK, Bucher C, Panoskaltsis-Mortari A, Taylor PA, Mellor AL, Munn DH, et al. Indoleamine 2,3-dioxygenase is a critical regulator of acute graft-*versus*-host disease lethality. *Blood* 2008;**111**:3257−65.
122. Lu Y, Giver CR, Sharma A, Li JM, Darlak KA, Owens LM, et al. IFN-gamma and indoleamine 2,3-dioxygenase signaling between donor dendritic cells and T cells regulates graft *versus* host and graft *versus* leukemia activity. *Blood* 2012;**119**:1075−85.
123. He H, Nagamura-Inoue T, Takahashi A, Mori Y, Yamamoto Y, Shimazu T, et al. Immunosuppressive properties of Wharton's jelly-derived mesenchymal stromal cells *in vitro*. *Int J Hematol* 2015;**102**: 368−78.
124. Huldani H, Margiana R, Ahmad F, Opulencia MJC, Ansari MJ, Bokov DO, et al. Immunotherapy of inflammatory bowel disease (IBD) through mesenchymal stem cells. *Int Immunopharmacol* 2022; **107**:108698.
125. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet* 2016;**388**:1281−90.
126. Qi L, Wu J, Zhu S, Wang X, Lv X, Liu C, et al. Mesenchymal stem cells alleviate inflammatory bowel disease *via* Tr1 cells. *Stem Cell Rev Rep* 2022;**18**:2444−57.
127. Lim JY, Kim BS, Ryu DB, Kim TW, Park G, Min CK. The therapeutic efficacy of mesenchymal stromal cells on experimental colitis was improved by the IFN-γ and poly(I:C) priming through promoting the expression of indoleamine 2,3-dioxygenase. *Stem Cell Res Ther* 2021;**12**:37.
128. Ryu DB, Lim JY, Lee SE, Park G, Min CK. Induction of indoleamine 2,3-dioxygenase by pre-treatment with poly(I:C) may enhance the efficacy of msc treatment in DSS-induced colitis. *Immune Netw* 2016;**16**:358−65.
129. Li A, Guo F, Pan Q, Chen S, Chen J, Liu HF, et al. Mesenchymal stem cell therapy: hope for patients with systemic lupus erythematosus. *Front Immunol* 2021;**12**:728190.
130. Chun W, Tian J, Zhang Y. Transplantation of mesenchymal stem cells ameliorates systemic lupus erythematosus and upregulates B10 cells through TGF-β1. *Stem Cell Res Ther* 2021;**12**:512.
131. Cheng T, Ding S, Liu S, Li Y, Sun L. Human umbilical cord-derived mesenchymal stem cell therapy ameliorates lupus through increasing $CD4^+$ T cell senescence *via* MiR-199a-5p/Sirt1/p53 axis. *Theranostics* 2021;**11**:893−905.
132. Bačenková D, Trebuňová M, Morochovič R, Dosedla E, Findrik Balogová A, Gašparová P, et al. Interaction between mesenchymal stem cells and the immune system in rheumatoid arthritis. *Pharmaceuticals (Basel)* 2022;**15**:941.
133. Andrzejewska A, Dabrowska S, Lukomska B, Janowski M. Mesenchymal stem cells for neurological disorders. *Adv Sci (Weinh)* 2021; **8**:2002944.
134. Manganeli Polonio C, Longo de Freitas C, Garcia de Oliveira M, Rossato C, Nogueira Brandão W, Ghabdan Zanluqui N, et al. Murine endometrial-derived mesenchymal stem cells suppress experimental autoimmune encephalomyelitis depending on indoleamine-2,3-dioxygenase expression. *Clin Sci (Lond)* 2021;**135**:1065−82.
135. Liu R, Su D, Zhou M, Feng X, Li X, Sun L. Umbilical cord mesenchymal stem cells inhibit the differentiation of circulating T follicular helper cells in patients with primary Sjögren's syndrome through the secretion of indoleamine 2,3-dioxygenase. *Rheumatology (Oxford)* 2015;**54**:332−42.
136. Massalska M, Ciechomska M, Kuca-Warnawin E, Burakowski T, Kornatka A, Radzikowska A, et al. Effectiveness of soluble CTLS-4-FC in the inhibition of bone marrow T-cell activation in context of indoleamine 2.3-dioxygenase (IDO) and $CD4^+Foxp3^+$ Treg induction. *J Inflamm Res* 2022;**15**:6813−29.
137. Hu C, Zhao L, Zhang L, Bao Q, Li L. Mesenchymal stem cell-based cell-free strategies: safe and effective treatments for liver injury. *Stem Cell Res Ther* 2020;**11**:377.
138. Wang H, Yao W, Wang Y, Dong H, Dong T, Zhou W, et al. Meta-analysis on last ten years of clinical injection of bone marrow-derived and umbilical cord MSC to reverse cirrhosis or rescue patients with acute-on-chronic liver failure. *Stem Cell Res Ther* 2023;**14**:267.
139. Milosavljevic N, Gazdic M, Simovic Markovic B, Arsenijevic A, Nurkovic J, Dolicanin Z, et al. Mesenchymal stem cells attenuate liver fibrosis by suppressing Th17 cells—an experimental study. *Transpl Int* 2018;**31**:102−15.
140. Zheng X, Zhou X, Ma G, Yu J, Zhang M, Yang C, et al. Endogenous Follistatin-like 1 guarantees the immunomodulatory properties of mesenchymal stem cells during liver fibrotic therapy. *Stem Cell Res Ther* 2022;**13**:403.
141. Zheng G, Qiu G, Ge M, He J, Huang L, Chen P, et al. Human adipose-derived mesenchymal stem cells alleviate obliterative bronchiolitis in a murine model *via* IDO. *Respir Res* 2017;**18**:119.
142. Liu H, Liu S, Song X, Jiang A, Zou Y, Deng Y, et al. Nanoparticle encapsulated CQ/TAM combination harmonizes with MSCs in arresting progression of severity in AP mice through iNOS (IDO) signaling. *Mater Today Bio* 2022;**14**:100226.
143. Carvalho AÉS, Sousa MRR, Alencar-Silva T, Carvalho JL, Saldanha-Araujo F. Mesenchymal stem cells immunomodulation: the road to IFN-γ licensing and the path ahead. *Cytokine Growth Factor Rev* 2019;**47**:32−42.
144. Dunn CM, Kameishi S, Cho YK, Song SU, Grainger DW, Okano T. Interferon-gamma primed human clonal mesenchymal stromal cell sheets exhibit enhanced immunosuppressive function. *Cells* 2022;**11**: 3738.
145. Ogawa T, Kajiya M, Horikoshi S, Yoshii H, Yoshino M, Motoike S, et al. Xenotransplantation of cryopreserved human clumps of mesenchymal stem cells/extracellular matrix complexes pretreated with IFN-γ induces rat calvarial bone regeneration. *Regen Ther* 2022;**20**:117−25.
146. Zhang S, Fang J, Liu Z, Hou P, Cao L, Zhang Y, et al. Inflammatory cytokines-stimulated human muscle stem cells ameliorate ulcerative colitis *via* the IDO-TSG6 axis. *Stem Cell Res Ther* 2021;**12**:50.
147. Gong C, Chang L, Sun X, Qi Y, Huang R, Chen K, et al. Infusion of two-dose mesenchymal stem cells is more effective than a single dose in a dilated cardiomyopathy rat model by upregulating indoleamine 2,3-dioxygenase expression. *Stem Cell Res Ther* 2022;**13**:409.
148. Phipps J, Haseli M, Pinzon-Herrera L, Wilson B, Corbitt J, Servoss S, et al. Delivery of immobilized IFN-γ with PCN-333 and its effect on human mesenchymal stem cells. *ACS Biomater Sci Eng* 2023;**9**:671−9.
149. Park HY, Kim CE, Lee SM, Ahn JM, Yoon EH, Yoo M, et al. Priming mesenchymal stem/stromal cells with a combination of a low dose of IFN-γ and bortezomib results in potent suppression of pathogenic Th17 immunity through the IDO1−AHR axis. *Stem Cells* 2023;**41**:64−76.
150. Li X, Song Y, Liu F, Liu D, Miao H, Ren J, et al. Long non-coding RNA MALAT1 promotes proliferation, angiogenesis, and immunosuppressive properties of mesenchymal stem cells by inducing VEGF and IDO. *J Cell Biochem* 2017;**118**:2780−91.
151. Chen JC, Xiao HH, Zhang Q, Kong L, Wang TM, Tian Y, et al. Jujuboside A inhibits oxidative stress damage and enhances immunomodulatory capacity of human umbilical cord mesenchymal stem cells through up-regulating IDO expression. *Chin J Nat Med* 2022; **20**:494−505.

152. He Y, Zhou S, Liu H, Shen B, Zhao H, Peng K, et al. Indoleamine 2, 3-dioxgenase transfected mesenchymal stem cells induce kidney allograft tolerance by increasing the production and function of regulatory T cells. *Transplantation* 2015;**99**:1829−38.
153. He JG, Xie QL, Li BB, Zhou L, Yan D. Exosomes derived from IDO1-overexpressing rat bone marrow mesenchymal stem cells promote immunotolerance of cardiac allografts. *Cell Transplant* 2018;**27**:1657−83.
154. van Hennik PB, de Koning AE, Ploemacher RE. Seeding efficiency of primitive human hematopoietic cells in nonobese diabetic/severe combined immune deficiency mice: implications for stem cell frequency assessment. *Blood* 1999;**94**:3055−61.
155. Cui J, Wahl RL, Shen T, Fisher SJ, Recker E, Ginsburg D, et al. Bone marrow cell trafficking following intravenous administration. *Br J Haematol* 1999;**107**:895−902.
156. Karp JM, Leng Teo GS. Mesenchymal stem cell homing: the devil is in the details. *Cell Stem Cell* 2009;**4**:206−16.
157. Jiang W, Xu J. Immune modulation by mesenchymal stem cells. *Cell Prolif* 2020;**53**:e12712.
158. Gonzalez-Pujana A, Igartua M, Santos-Vizcaino E, Hernandez RM. Mesenchymal stromal cell based therapies for the treatment of immune disorders: recent milestones and future challenges. *Expert Opin Drug Deliv* 2020;**17**:189−200.
159. Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. *Nat Med* 2005;**11**:312−9.
160. Lee SY, Choi HK, Lee KJ, Jung JY, Hur GY, Jung KH, et al. The immune tolerance of cancer is mediated by IDO that is inhibited by COX-2 inhibitors through regulatory T cells. *J Immunother* 2009;**32**: 22−8.
161. Muller AJ, Sharma MD, Chandler PR, Duhadaway JB, Everhart ME, Johnson 3rd BA, et al. Chronic inflammation that facilitates tumor progression creates local immune suppression by inducing indoleamine 2,3 dioxygenase. *Proc Natl Acad Sci U S A* 2008;**105**: 17073−8.
162. Ling W, Zhang J, Yuan Z, Ren G, Zhang L, Chen X, et al. Mesenchymal stem cells use IDO to regulate immunity in tumor microenvironment. *Cancer Res* 2014;**74**:1576−87.
163. Heidari F, Razmkhah M, Razban V, Erfani N. Effects of indoleamine 2, 3-dioxygenase (IDO) silencing on immunomodulatory function and cancer-promoting characteristic of adipose-derived mesenchymal stem cells (ASCs). *Cell Biol Int* 2021;**45**:2544−56.
164. Orabona C, Puccetti P, Vacca C, Bicciato S, Luchini A, Fallarino F, et al. Toward the identification of a tolerogenic signature in IDO-competent dendritic cells. *Blood* 2006;**107**:2846−54.
165. Orabona C, Pallotta MT, Volpi C, Fallarino F, Vacca C, Bianchi R, et al. SOCS3 drives proteasomal degradation of indoleamine 2,3-dioxygenase (IDO) and antagonizes IDO-dependent tolerogenesis. *Proc Natl Acad Sci U S A* 2008;**105**:20828−33.
166. Hucke C, MacKenzie CR, Adjogble KD, Takikawa O, Däubener W. Nitric oxide-mediated regulation of gamma interferon-induced bacteriostasis: inhibition and degradation of human indoleamine 2,3-dioxygenase. *Infect Immun* 2004;**72**:2723−30.
167. Grohmann U, Bianchi R, Orabona C, Fallarino F, Vacca C, Micheletti A, et al. Functional plasticity of dendritic cell subsets as mediated by CD40 *versus* B7 activation. *J Immunol* 2003;**171**: 2581−7.
168. Deng Z, Zhou J, Mu X, Gu J, Li X, Shao Q, et al. Regulatory T cells improved the anti-cirrhosis activity of human amniotic mesenchymal stem cell in the liver by regulating the TGF-β-indoleamine 2,3-dioxygenase signaling. *Front Cell Dev Biol* 2021;**9**:737825.