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Review

Tryptophan degradation in autoimmune diseases

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Abstract. Recent evidence points to tryptophan (Trp) degradation as a potent immunosuppressive mechanism involved in the maintenance of immunological tolerance. Both Trp depletion and downstream Trp catabolites (TCs) appear to synergistically confer protection against excessive inflammation. In this review, we give an overview of the immunosuppressive properties of Trp degradation with special focus on TCs. Constitutive and inducible Trp degradation in different cell types and tissues of human and murine origin is summarized. We address the influence of Trp degradation on different aspects of autoimmune disorders such as multiple sclerosis. Possible therapeutic approaches for autoimmune disorders targeting Trp degradation are presented, and key issues relevant for the development of such therapeutic strategies are discussed.

Keywords. Autoimmunity, IDO, immunosuppression, kynurenine, multiple sclerosis, tolerance, tryptophan.

Introduction

The essential amino acid L-tryptophan (L-Trp) serves not only as a building block for proteins and neurotransmitters such as serotonin but is also intricately involved in the regulation of immune responses. In the early 80s, Pfefferkorn (1984) observed that interferon-γ (IFN-γ), a pro-inflammatory cytokine that induces Trp degradation, blocks the growth of *Toxoplasma gondii* [1]. Subsequently it was suggested that the induction of Trp degradation by inflammatory agents inhibits the growth of pathogens and cancer cells by depriving them of Trp [2]. In the following years, research focused on biostatic Trp depletion as a means of aiding the immune system in fighting infection and neoplasia. A paradigm shift occurred when Munn and Mellor discovered that the activity of the rate-limiting Trp-degrading enzyme, indoleamine 2,3-dioxygenase (IDO), prevented T cell-mediated rejection of allogenic fetuses in pregnant mice [3]. The authors proposed that IDO-induced local Trp depletion limits the free Trp supply for proliferating T cells, thus preventing a T cell response against the developing fetus. Emerging evidence now points to a synergistic role of both Trp depletion and downstream Trp catabolites (TCs) in regulating adaptive immunity [4, 5].

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Immune modulation by Trp depletion

Local depletion of Trp is one of the proposed mechanisms of action of IDO. A large body of evidence has been published supporting this concept: IDO-induced Trp deficiency inhibits immune cells, and some of these effects are reversible by addition of Trp. Munn and colleagues identified the general control non-derepressible-2 (GCN2) kinase as a downstream mediator for several key effects of IDO-mediated Trp depletion [6]. GCN2 is a stress-response kinase that is activated by accumulation of uncharged transfer RNA (tRNA) in response to insufficient amino acid supply [7]. Activation of GCN2 kinase initiates a stress-response program, referred to as the integrated stress response (ISR), that can trigger cell-cycle arrest, differentiation, adaptation or apoptosis, depending on the cell type and the initiating stress [8]. GCN2 kinase is required for $CD8^+$ T cells to sense and respond to Trp depletion created by IDO. T cells lacking GCN2 proliferate normally in the presence of IDO^+ dendritic cells (DCs) and are not susceptible to IDO-induced anergy [6].

However, the question of whether Trp depletion is responsible for the immunosuppressive effects of IDO *in vivo* is a matter of current debate. Most of the results suggesting Trp depletion as the mechanism of IDO-induced immunosuppression were obtained *in vitro*, where Trp depletion from the culture medium is easily possible. In contrast, *in vivo* Trp is continually supplied *via* the circulation, with plasma levels in the range of 50–100 μM [9]; Trp depletion would require concentrations of <0.5–1 μM to be maintained in the local microenvironment for a critical time period. Plasma levels do not reach such low concentrations, and the diffusion of Trp into tissues is estimated to be faster than the local degradation rate [9]. Consequently, the Trp depletion hypothesis may not be the sole explanation for the immunomodulatory properties elicited by IDO.

Trp is degraded via the kynurenine pathway

Two rate-limiting enzymes initiate the first step of Trp catabolism: Trp 2,3-dioxygenase (TDO), which is expressed in the liver, and IDO, which is almost ubiquitously expressed at low levels and is induced by various pro-inflammatory stimuli. These two enzymes mediate the conversion of Trp to N-formylkynurenine, which leads to the common downstream kynurenine pathway (Fig. 1). N-formylkynurenine is further degraded to L-kynurenine by formamidase. L-kynurenine subsequently serves as a substrate for a distinct set of enzymes: kynureninase gives rise to anthranilic acid, kynurenine monooxygenase yields 3-hydroxykynurenine and kynurenine aminotransferases produce kynurenic acid by the irreversible transamination of L-kynurenine.

3-hydroxykynurenine is converted to 3-hydroxyanthranilic acid by kynureninase. The 3-hydroxyanthranilic acid oxygenase catalyzes the conversion of 3-hydroxyanthranilic acid to 2-amino-3-carboxymuconic acid semialdehyde, which either rearranges non-enzymatically to form quinolinic acid or serves as a substrate of 2-amino-3-carboxymuconic acid semialdehyde decarboxylase, which leads to the production of picolinic acid. Quinolinic acid phosphoribosyltransferase catalyses the conversion of quinolinic acid to nicotinic acid mononucleotide, which is further degraded to NAD^+.

Immune modulation by TCs

As shown in Table 1, TCs differentially regulate immune responses. Most studies have focused on the effect of TCs on T cell proliferation. L-kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid, picolinic acid as well as 3,4-dimethoxycinnamoyl anthranilic acid (3, 4-DAA) suppress T cell proliferation. 3,4-DAA is considered to be a synthetic tryptophan metabolite [10]; however, a possible contribution of its cinnamonyl group to its immunosuppressive properties remains to be elucidated. TCs inhibit proliferation of $CD4^+$ and $CD8^+$ T cells stimulated by a variety of stimuli such as myelin antigens [10], allogeneic cells [11, 12], anti-CD3 antibody [12], phytohemagglutinin (PHA) [11] and common receptor-γ chain cytokines [13]. Suppression of T cells by TCs appears to be specific for activated T cells, as kynurenine-suppressed T cells cannot be restimulated by the same stimulus, but resting T cells respond normally to a different stimulus [11, 12]. Induction of T cell death [4, 12, 14] as well as cell cycle arrest [10, 11] has been proposed as the cause for T cell suppression. Th1-polarized cells appear to be more susceptible to kynurenine-mediated suppressive effects than Th2 cells [14]. T cell suppressive effects can be enhanced by combining different TCs, indicating that different TCs share common signalling pathways to suppress T cells [11, 12]. Interestingly, reduced Trp concentrations augment the suppression of T cell proliferation by TCs [11]. It is tempting to speculate that TCs may mediate their immunosuppressive effects by competing with Trp to modulate known or as-yet-unidentified signalling pathways. TCs also suppress natural killer (NK) cells [11, 12], whereas B cells are not affected by L-kynurenine or quinolinic

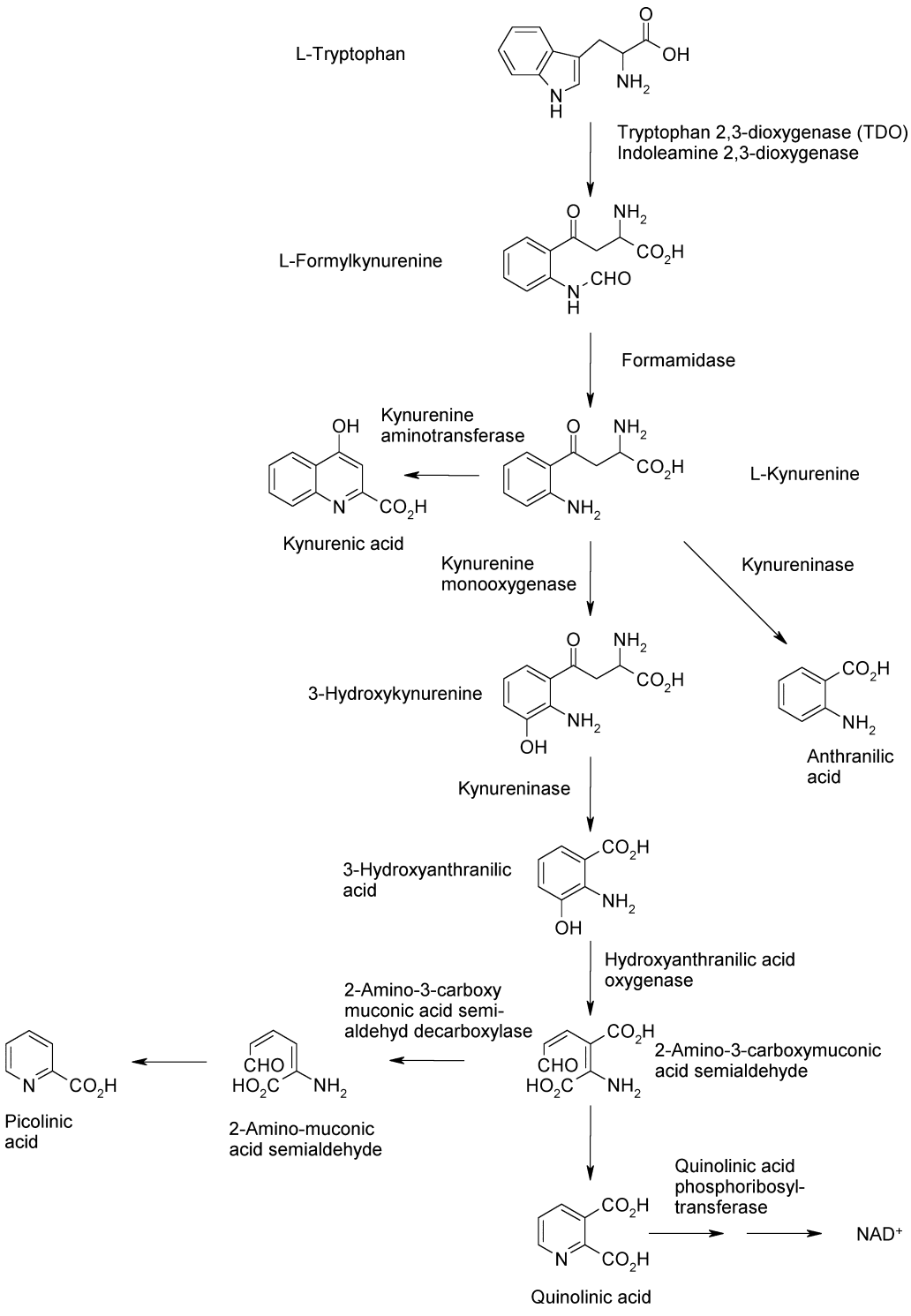

Figure 1. The kynurenine catabolic pathway.

acid alone [11]. A mixture of TCs, on the other hand, induces B cell death [12]. Direct suppression of antigen-presenting cells (APCs) may represent another putative mechanism underlying the immunosuppressive effects of TCs. DCs do not respond to a mixture of TCs [12], whereas other monocyte-derived cells seem to be killed by 3-hydroxyanthranilic acid [15, 16]. In mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS), the synthetic TC 3,4-DAA significantly reduces the expression of major histocompatibility complex (MHC) class II, CD40, CD80, CD86 and

inducible nitric oxide synthase (iNOS) in microglial cells [10].

Apart from their direct immunosuppressive properties, TCs may play a role in the protection of immune cells against oxidative stress. In particular 3-hydroxykynurenine and 3-hydroxyanthranilic acid, but not their non-hydroxylated metabolic precursors, are potent radical scavengers [17]. In response to infection [18] and kynurenine loading [19], large concentrations of quinolinate accumulate intracellularly in leukocytes. This observation prompted Moffett and Namboodiri to hypothesize that quinolinate could be stored as a substrate for extrahepatic NAD^+ synthesis in order to prevent NAD^+ depletion caused by the poly (ADP-ribose) polymerisation (PARP) reaction in response to oxidative DNA damage during immune reactions [20].

IDO itself also possesses strong antioxidant properties, as it utilizes O_2^- and even has a lower Km for O_2^- than superoxide dismutase [21]. The activation of IDO and Trp catabolism during inflammation may therefore also protect tissues against damage by inflammation-induced oxidative stress.

TCs – mechanism of action

The mechanism of action of TCs is largely unknown. Fallarino and coworkers recently reported an early down-regulation of the T cell receptor (TCR) ξ-chain in $CD8^+$ cells and a longer-term transforming growth factor-β (TGF-β)-mediated induction of a regulatory phenotype in naive $CD4^+$ T cells as a result of the combined effects of Trp starvation and TCs [5]. The $CD8^+$ T cells with suppressed TCR ξ-chain expression display impaired cytotoxic activity *ex vivo*, whereas $CD4^+$ regulatory T cells (Tregs) treated with TCs and Trp starvation were shown to effectively control diabetogenic T cells when transferred *in vivo* [5]. Both down-regulation of the TCR ξ-chain and the induction of a regulatory phenotype in $CD4^+$ T cells require activation of the GCN2 kinase [5].

L-kynurenine was recently shown to interfere with the activity of NK cells by selectively inhibiting the cytokine-induced up-regulation of NKp46- and NKG2D-activating receptors [22]. Following L-kynurenine treatment, NK cells are less efficient in killing via NKp46 and/or NKG2D receptors but still maintain the ability to kill via NKp30 [22].

The kynurenine pathway intermediate kynurenic acid was identified as a ligand for GPR35, a previously orphan G protein-coupled receptor expressed in immune cells and the gastrointestinal tract [23]. Binding of kynurenic acid to GPR35 inhibits LPS-induced tumour necrosis factor-α (TNF-α) secretion in peripheral blood mononuclear cells, suggesting that this receptor-ligand pair may play important roles in regulating immune responses [23]. On excitatory amino acid receptors in the central nervous system, kynurenic acid acts as an antagonist [24], whereas quinolinic acid functions as an agonist [25].

The regulation of Trp-degrading enzymes during inflammation

The immunomodulatory role of the Trp degradation pathway is further supported by its tight regulation through important immunological mediators. The initial and rate-limiting enzyme of Trp degradation, IDO, is constitutively expressed in immune privileged environments, *e.g.* the lower gut [26] and placenta [3]. In these environments, a constitutive shift of immune responses towards the induction of tolerance limits potentially harmful inflammatory responses. On the other hand, in cell types with pro-inflammatory potential, such as monocyte-derived macrophages, DCs, fibroblasts and endothelial cells, Trp-metabolising enzymes are rapidly induced by inflammatory mediators, suggesting that Trp degradation may limit collateral damage to infected tissues. The inflammatory mediators that induce IDO activity include interferons, most potently IFN-γ [27, 28], interleukin-1 (IL-1) and TNF-α [29], cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) [30], prostaglandin E2 (PGE2) [31, 32] and the Toll-like receptor (TLR) ligands polyinosinic:polycytidylic acid (pI:C) [33], lipopolysaccharide (LPS) [34] and unmethylated cytosine phosphatidyl guanosine (CpG) motifs [35, 36]. Similar to the induction of IDO, albeit to a lesser extent, expression of the downstream enzymes kynureninase, kynurenine monooxygenase and hydroxyanthranilic acid oxygenase is also increased by IFN-γ and pI:C [4, 33].

Pointing to the importance of Trp catabolism for the immune system, IDO expression is precisely regulated both positively and negatively by crosstalk between costimulatory receptors and ligands on immune cells. Among others, the interaction between CTLA-4 on $CD4^+$ T cells or GITR with DC CD80/86 molecules or soluble GITR, respectively, strongly induces IDO [37–43], whereas interference with CD40-CD40L interactions results in the induction of $CD8^+$ Tregs that promote local immune privilege via the induction of IDO [44].

Interestingly, IDO was recently identified as an essential triggering mechanism to induce IFN-α production by murine $CD19^+$ DCs following B7 ligation [45]. A detailed overview of the induction of IDO in different cells types in humans and in other

Table 1. Immune modulation by Trp catabolites.

TC	Target cells	Alteration	Concentration	References
L-Kyn	human NK cells	suppression of NKp46 and NKG2D expression reversible suppression of killing	0.3–0.6 mM	[22]
	human T cells stimulated with allogeneic DCs	induction of T cell death, restimulation only with 3rd party DCs	I_{50}: 157 μM	[12]
	human CD3-activated T cells	induction of T cell death	I_{50}: 53 μM	
	human PHA-stimulated PBL	block of cell cycle in mid-G1 phase; synergistic effect of L-kynurenine + picolinic acid (250 μM each) block specific to cells responding to activating stimulus	50–1000 μM with 26 μM trp in medium; 8–1000 μM in Trp-free medium	[11]
	human $CD4^+$ T cells > $CD8^+$ T cells > NK cells, not B cells	inhibition (enhanced in the absence of Trp)	1 mM	
KA	human PBLs	inhibition of LPS-induced TNF-α secretion possibly mediated by GPR35 activation	0.1–1 mM	[23]
3-HK	human CD3-activated T cells	induction of T cell death	I_{50} :187 μM	[12]
	murine MBP Ac1–11 TCR transgenic $CD4^+$ T cells	suppression of antigen-specific proliferation associated with G1/S-phase arrest; reduced release of IL-2, IFN-γ and TNF-α; increased release of IL-4 and IL-10	200 μM	[10]
3-HAA	human CD3-activated T cells	induction of T cell death	I_{50}: 96 μM	[12]
	human T cells	induction of apoptosis of Th1 but not Th2 cells	10 μM	[14]
	$CD8^+$ T cells	inhibition of proliferation induced by cytokines	50 μM	[13]
	monocyte-derived cells	induction of apoptosis (enhanced by the presence of ferrous or manganese ions)	200 μM	[15, 16]
	murine MBP Ac1–11 TCR transgenic $CD4^+$ T cells	suppression of antigen-specific proliferation associated with G1/S-phase arrest; reduced release of IL-2, IFN-γ and TNF-α; increased release of IL-4 and IL-10		[10]
	HUVECs stimulated with TNF-α	inhibition of MCP-1 secretion, VCAM-1 expression and NF-κB	25–50 μM	[129]
	activated murine macrophages	down-regulation of iNOS expression by enhancing heme oxygenase-1 expression	25–75 μM	[50, 55, 130]
		is a co-antioxidant for alpha-tocopherol, inhibiting human low density lipoprotein and plasma lipid peroxidation	1.25–10 μM	[131]
QA	murine thymocytes and T cells	induction of apoptosis of thymocytes and Th1 cells but not Th2 cells	10 μM	[14]
	murine Ag-specific $CD4^+$ T cells	induction of apoptosis	induced by 200 U/mL INF-γ + 10 μM Kyn	[4]
	human PHA-stimulated PBL	block of cell cycle of in mid-G1 phase	8–1000 μM only in Trp-free medium	[11]
	$CD4^+$ and NK cells, $CD8^+$ only in the absence of Trp, not B-cells	inhibition enhanced in the absence of Trp	1 mM	
PA	human PHA-stimulated PBL	block of cell cycle in mid-G1 phase; synergistic effect of L-Kyn + PA (250 μM each)	100–1000 μM 26 μM Trp in medium; 8–1000 μM in Trp-free medium	[11]
	$CD4^+$ T cells, > $CD8^+$ T cells and NK cells, not B cells	inhibition (enhanced in the absence of Trp)	1 mM	
	human macrophages	induction of macrophage inflammatory protein MIP-1α/β by transcriptional activation and mRNA stabilization	4 mM	[132]
		enhances inhibition of Candida albicans growth by murine neutrophils	> 4 mM or 2 mM in combination with IFN-γ	[133]
	human neuroblastoma cell lines	induction of VEGF production and secretion	4 mM	[134]

Table 1 *(Continued)*

TC	Target cells	Alteration	Concentration	References
3, 4-DAA	MBP Ac1–11 TCR-transgenic $CD4^+$ T cells	suppression of antigen-specific proliferation		[10]
	microglial cells treated with IFN-γ and LPS	suppression of iNOS expression and NO release		[10, 135]
	murine spinal cord microglial cells	reduction of expression of MHC class II, CD40, CD80, CD86, and iNOS after treatment of mice with EAE		[10]
Kyn + 3-HK + AA + 3-HAA + QA	human CD3-activated T cells	suppression by preferentially killing activated T-cells; additive effect of Trp metabolites	$I_{50} = 15$ μM	[12]
	human T, B and NK cells, but not DC	induction of cell death		

AA, anthranilic acid; 3,4-DAA, 3,4-dimethoxy-cinnamonyl-anthranilic acid; 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; KA, kynurenic acid; Kyn, kynurenine; PA, picolinic acid; QA, quinolinic acid; Trp, tryptophan.

species is given in Tables 2 and 3. Table 4 shows the expression of downstream kynurenine pathway enzymes.

The mere induction of IDO expression does not imply the initiation of Trp catabolism, as IDO protein can be expressed without functional enzymatic activity. Mouse splenic DCs express IDO protein; however, only $CD8^+$ DCs (not $CD8^-$ DCs) catabolise Trp [31, 46]. The $CD8^+$ IDO-competent DC phenotype was found to be associated with down-modulation of the *Tyrop* gene encoding the signalling adaptor DAP12 [47, 48]. Also, human DCs were found to express IDO protein but required activation by IFN-γ and CD80/CD86 for enzymatic activity [43]. The post-translational regulation of IDO is not fully understood, but some important factors have been elucidated. IDO enzymatic activity requires a heme prosthetic group in its active site, and the inhibition of heme biosynthesis inhibits the functional activity of IDO without influencing protein expression [49]. Antioxidants were reported to inhibit IDO activity in human IFN-γ-activated macrophages [49]. Nitric oxide (NO) appears to be an important regulator of IDO by (i) interfering with transcriptional activation [50], (ii) directly inhibiting IDO enzymatic activity [49, 51, 52] and (iii) promoting its degradation through the proteasome pathway [51, 52]. Similar to IDO, NO is induced by IFN-γ and LPS during inflammation through iNOS [53]. Several regulatory interactions have also been delineated between iNOS and the kynurenine pathway. The Trp metabolite 3-hydroxyanthranilic acid and the synthetic TC 3,4-DAA inhibit iNOS at both the expression and catalytic levels [10, 54, 55], whereas picolinic acid functions synergistically with IFN-γ to induce iNOS expression [54]. In macrophages, NO can react with superoxide, a product of the respiratory burst, to form peroxynitrite. Peroxynitrite was shown to nitrate and inactivate IDO [34]. In addition, peroxynitrite formation was found to block IFN-γ signalling through Stat-1, leading to impaired transcriptional induction of the IDO gene [56].

Trp degradation and autoimmunity

The loss of tolerance against "self" leads to an ongoing and overwhelming activation of the immune system, causing the destruction of cells and tissues and often resulting in chronic and debilitating diseases. Most human autoimmune disorders involve the activation of $CD4^+$ T cells by autoantigens as a common critical pathway. In light of the immunosuppressive properties of Trp degradation and its activation by inflammatory mediators, this mechanism is likely to be involved in the maintenance of immunological self-tolerance [57]. The following section will consider the involvement of Trp degradation in different aspects of autoimmune disorders (Table 5).

Impaired Trp degradation may be involved in the loss of tolerance in autoimmune disease

Type 1 diabetes is a T cell-mediated autoimmune disease leading to the destruction of insulin-producing beta cells in the pancreatic islets of Langerhans [58]. The nonobese diabetic (NOD) mouse strain is a widely used animal model for type 1 diabetes [59, 60]. APCs, such as DCs and macrophages, are critically involved in the pathogenesis of type 1 diabetes by generating self-reactive effector T cells and Tregs. The transfer of IFN-γ-stimulated DCs into NOD mice provides long-lasting protection against insulin-dependant diabetes in recipient mice [61]. IFN-γ potentiates the tolerogenic potential of a subset of splenic DCs via activation of IDO and the production of T cell-suppressive TCs [46, 62], indicating that IDO

Table 2. IDO expression and induction in human cells and tissues.

Tissue/cell types	Constitutive	Induced by	Inhibited by	References
human A-22 arachnoidea	No	IFN-γ		[136]
human A-431 epidermoid carcinoma	No	IFN-γ		[137, 138]
human A431 vulva carcinoma cell line	No	IFN-γ		[139]
human A498 kidney carcinoma cell line	No	IFN-γ		[138]
human A549 lung carcinoma	No	IFN-γ		[138]
human aortic smooth muscle cells	No	IFN-γ		[140]
human bone marrow stromal cells	No	IFN-γ		[141]
human brain	Yes			[142]
human brain microvascular endothelial cells	No	IFN-γ		[143, 144]
human bronchial epithelium	No	IFN-γ		[145]
human C41 cervical carcinoma cell line	No	IFN-γ		[139]
human CAOV-3 ovarian carcinoma cell line	No	IFN-γ		[139]
human $CD4^+$ T cells	No	IFN-β		[146]
human $CD4^+$ T cells	No	CTLA-4-Ig		[38]
human DC	No	IFN-γ		[62]
	No	CTLA-4-Ig		[38]
	No	CTLA-4 on $CD4^+$ T cells		[43]
	No	thymosin-α1		[147]
	No	PGE2 (2^{nd} signal through TNF-α or TLR necessary for functional IDO)		[31]
human DCs associated with tumours	Yes	PGE2		[32, 71, 148]
human endometrium during decidualization	Yes	IFN-γ		[149]
human endothelium (SVEC)	No	IFN-γ		[150]
human eosinophils	No	IFN-γ		[151]
human epidermal Langerhans cells	No	IFN-γ		[152]
human uroepithelial cell line RT4	No	IFN-γ	IL-1, NO	[51, 153]
human fibroblasts	No	IFN-γ	IL-4, IL-10, TGF-β	[1, 27, 136–138, 154–159]
human fibrosarcoma cell line 2C4	No		IL-4, IL-13	[160]
human FL amnion cells	No	IFN-γ		[137]
human glioblastoma cell line	No		IL-4, IL-10	[157]
human glioblastoma cell line 86HG39	No	IFN-γ		[161]
human glioblastoma cells	No		TGF-β	[157]
human HeLa cervical carcinoma cells	No	IFN-γ		[136, 137]
Hep-2 human epithelial type 2 cells	No	IFN-γ		[156]
human HK-2351 scalp	No	IFN-γ		[136]
human HS578T breast cancer cell line	No	IFN-γ		[139]
human HTB-138 astroglioma cell line	No	IFN-γ		[162, 163]
human I407 epithelial cell line	No	IFN-γ		[156]
human intestine	Yes			[164]
human J82 bladder carcinoma cell line	No	IFN-γ		[138]
human KATO-111 stomach cancer cells	No	IFN-γ		[137]
human KB oral carcinoma	No	IFN-γ		[156]
human keratinocytes	No	IFN-γ		[165]
human LB1156-SCCHN pharyngeal squamous cell carcinoma cell line	Yes			[72]
human LB1263-SCCHN laryngeal carcinoma cell line	Yes			[72]
human LB1610-MEL melanoma cell line	Yes			[72]

Table 2 *(Continued)*

Tissue/cell types	Constitutive	Induced by	Inhibited by	References
human lung slices	No	IFN-α, IFN-γ		[166]
human macrophages	No	IFN-γ, CpG-ODN, IFN-β, HIV-1 proteins Nef, Tat, PAF	NO, antioxidants	[49, 114, 136, 167–173]
human MDA-MB-231 breast cancer cells	No	IFN-γ		[174]
human melanoma cells	No	IFN-γ		[175]
human monocytes	No		IL-4	[176]
human monocytes (Fc(epsilon)RI = main receptor for specific IgE in type I-mediated allergies)	No	cross-linking of FcεRI		[177]
human MonoMac6 monocytic cell line	No			[182]
human MZ-PC-1 pancreatic carcinoma cell line	Yes			[72]
human NCI-H292 airway epithelial-like cells	No	IFN-γ		[178]
human NCI-H596 NSCL carcinoma cell line	Yes			
human NY osteosarcoma	No	IFN-γ		[137]
human OKK maxillary gland cells	No	IFN-γ		[137]
human osteosarcoma cell lines	No	IL-12 and IL-18		[179]
human OVCAR-3 ovarian carcinoma cell line	No	IFN-γ		[139]
human PBMC	No	IFN-γ, IFN-α, IFN-β. CTLA-4-Ig, IL-2, CpG-ODN	atorvastatin, NO, peroxynitrite, IL-4, IL-10	[38, 113, 156, 168, 170, 180–183]
human placenta	Yes			[184]
human placental chorionic villi (cultured)	Yes	IFN-γ	IL-4	[185]
human placental explant cultures	Yes	LPS		[186]
human primary conjunctival epithelial cells	No	IFN-γ		[187]
human primary fetal astrocytes	No	IFN-γ		[188]
human primary fetal microglia	No	IFN-γ		[188]
human primary fetal neurons	No	IFN-γ		[188]
human RT4 uroepithelial cells	No	IFN-γ	IL-1 (IFN-γ-induced IDO expression)	[153]
human SK-HEP-1, hepatoma	No	IFN-γ		[138]
human SK-N-SH, neuroblastoma	No	IFN-γ		[138]
human synovial cells	No	IFN-γ		[189]
human T 24 bladder carcinoma cell line	No	IFN-γ		[138, 167, 190]
human T-2346 meningeoma	No	IFN-γ		[136]
human THP-1 myelomonocytic cell line	No	IFN-γ CpG-ODN TNF-α + IL-6 TNF-α + IL-1β IL-1β + IL-6 low micromolar NO concentrations	IL-4 IL-10 atorvastatin peroxynitrite high micromolar NO concentrations	[138, 156, 183] [180, 183] [180, 182] [180, 181] [180] [111]
human U 138 MG, glioblastoma cell line	No	IFN-γ		[138]
human U937 leukemic monocyte lymphoma cell line	No	CpG-ODN low micromolar NO concentrations	 high micromolar NO concentrations	[180] [111]
human vascular smooth muscle SVSMC and ASMC	No	IFN-γ		[150]
human WiDr colon adenocarcinoma	No	IFN-γ		[156]
hepatitis C patients	No	IFN		[191]

Table 3. IDO expression and induction in non-human cells and tissues.

Tissue/cell type	Constitutive	Induced by	Inhibited by	References
mouse EC	No	CD40-Ig on $CD8^+$ Treg		[44]
mouse GITRL+ pDCs	No	Dexamethasone (induction of GITR in $CD4^+$ T cells)		[40]
mouse (systemic)	No	LPS		[34]
mouse spleen	No	IFN-α		[36, 192]
murine epididymis (caput)	Yes			[37, 193, 194]
Mouse (systemic)	No	BCG (via IFN-γ)		[195]
murine astrocytes	No	IFN-γ		[196]
murine brain	No	LPS		[197]
murine cancer cell lines: mastocytoma P815, sublines P1HTR and P511	Yes			[72]
murine $CD11c^+$ cells	No	CpG-ODN (via IFN-γ and IL-12)		[35]
murine concepti	Yes			[198]
murine DC	No	thymosin-α1 (via TLR9 and IFN type I)		[147]
murine DCs ($CD8\alpha^+$)	No	IFN-γ		[46]
murine DC subsets	No	CTLA-4-Ig		[109, 199]
murine DCs	No	CTLA-4 on $CD4^+$ T cells		[43]
murine DCs ($CD8\alpha^-$)	No		DAP12	[48, 200]
murine DCs via IFN-γ and STAT1	No	CTLA-4-Ig		[30]
murine DCs plasmacytoid splenic	No	CD200-Ig fusion protein		[147]
murine plasmacytoid DC	No	GITR-Ig		[40]
murine heart	Yes			[193]
murine hippocampus, including the dentate gyrus, the CA regions, and the entorhinal cortex	Yes	IFN-γ		[201]
murine lung	Yes	LPS (i.p.)		[193, 202]
murine macrophages	No	CpG-ODN	NO	[50, 170, 171, 203]
murine macrophages of the BAC1.2F5 cell line	No	IFN-γ		[204]
murine microglia	No	IFN-γ		[196]
murine placenta	Yes			[3, 198]
murine prostate	Yes			[193]
murine smooth muscle	Yes			[193]
murine spleen if applied systemically	No	CpG-ODN		[36]
murine thyroid	Yes			[193]
murine vascular endothelium of malaria-infected mice	No	IFN-γ		[205]
NOD mice	No		peroxynitrite	[56]
rabbit duodenum	Yes			[206]
rabbit thyroid gland	Yes			[206]
splenic DC from Lewis rats EAE model	No	estrogen		[207]
cultured bovine luteal cells	No	IFN-γ		[208]

mediates the tolerogenic effects of IFN-γ. This notion is supported by the finding that DCs from NOD mice, which are generally prone to autoimmune diseases, are unresponsive to the tolerogenic effects of IFN-γ as a result of impaired transcriptional activation of IDO [56]. Hence, defective self-tolerance and subsequent development of autoimmune disease in NOD mice appears to be a result of impaired Trp catabolism. Interestingly, mice deficient in IFN-γ or the IFN-γ receptor develop progressive and fatal EAE, suggest-

Table 4. Expression and induction of downstream enzymes of the kynurenine pathway.

Enzyme	Tissue/cell	Induced by	References
KMO / KH	human placenta		[184]
	human brain		[142]
	human liver		[209]
	human THP-1 myelomonocytic cell line	IFN- γ	[210]
	human DC	pI:C	[33]
	human monocytes	IFN-γ, TNF-α, LPS, cross-linking of FcεRI	[88, 177]
	murine DC	IFN-γ	[4]
	rat neurons		[88]
	rat astrocytes		[88]
	pig liver		[211]
	rabbit ciliary body/ iris		[212]
	rabbit liver		[212, 213]
	liver of rat, mouse, gerbil		[213]
	lung of rabbit, rat, mouse, gerbil		[213]
	brain of rabbit, mouse, gerbil		[213]
	rat brain		[213, 214]
	immortalized murine macrophages MT2	IFN-γ	[215]
	immortalized murine microglial cells N11		[215]
Kynureninase	human placenta		[184]
	human brain		[142]
	human DC	pI:C	[33]
	murine DC	IFN-γ	[4]
	rabbit liver		[212, 213]
	rabbit lung		[212, 213]
	liver of rat, mouse, gerbil		[213]
	lung of rat, mouse, gerbil		[213]
	brain of rabbit, rat, mouse, gerbil		[213]
	human brain		[142]
	rabbit iris/ciliary body		[212]
KAT1	immortalized murine macrophages MT2		[215]
	immortalized murine microglial cells N11		[215]
	human placenta		[184]
	murine DC	IFN-γ	[4]
HAO	beef liver		[216]
	rat brain		[217]
	rat liver		[217]
	immortalized murine macrophages MT2		[215]
	immortalized murine microglial cells N11		[215]
	rabbit liver		[218]

HAO, hydroxyanthranilic acid oxygenase; KAT1, kynurenine amino transferase 1; KH, kynurenine hydroxylase; KMO, kynurenine monooxygenase.

ing that IFN-γ may limit the extent of EAE by suppressing the expansion of activated $CD4^+$ T cells [63]. However, despite the importance of IFN-γ signalling, a role of aberrant Trp degradation in the etiology of autoimmune conditions other than insulin-dependant diabetes in NOD mice has not yet been elucidated. A concept of how Trp catabolism mediates T cell-mediated autoimmunity is depicted in Fig. 2.

Trp degradation as a therapeutic mechanism in autoimmune inflammation

Increased Trp degradation has been observed in various autoimmune disorders (Table 5). While it is tempting to speculate that Trp catabolism serves as an endogenous counter-regulatory mechanism to limit inflammation, evidence of its role in autoimmune diseases is limited. For instance, inhibition of IDO activity in an animal model of MS results in exacerbated disease [64, 65]. Conversely, genetic ablation of IDO in mice does not result in overt, immediate autoimmune disease [41], indicating that the absence of IDO-mediated Trp catabolism *per se* is not sufficient to unleash autoimmunity. These considerations regarding the physiological role of Trp catabolism set aside, there is a clear notion that immunomodulation through interference with Trp catabolism may be used as a treatment to suppress or enhance altered antigen-specific immunity, *i.e.* to treat autoimmune diseases [10] or transplant rejection [66–68] or to augment anti-tumour immune responses [69–73]. In this light, the development of synthetic TCs [10] or pharmacologic inhibitors of IDO [74–79] represent promising immu-

Table 5. Trp degradation in autoimmune disease.

Trp degradation involved in pathogenesis of autoimmune disease			
Disease/disease model	**Tissue/cell type**	**Alteration**	**References**
Type 1 diabetes (NOD mice)	DCs	↓ transcriptional activation of the IDO gene	[56]
Trp degradation activated to limit autoimmune inflammation			
Disease/disease model	**Tissue/cell types**	**Alteration**	**References**
murine EAE		IDO inhibitor caused exacerbation	[91]
relapsing-remitting mouse EAE	T cells, antigen-presenting cells, microglia	3, 4-DAA: ↓ autoreactive T cells ↓ release of inflammatory mediators ↓ inflammatory foci in the CNS tissue ↓ activation of APCs 3-HK and 3, 4-DAA: ↑ Treg	[10]
rat EAE	spinal cord	↑ activity of kynurenine monooxygenase ↑ 3-HK ↑ QA	[88]
rat EAE	splenic dendritic cells	suppression of EAE by estrogen was partly abrogated by inhibiting IDO	[207]
rat EAE	spinal cord	↑ QA	[89]
relapsing-remitting MS	cerebrospinal fluid	↓ L-Trp	[219]
relapsing MS	cerebrospinal fluid	↓ KA	[90]
MS	plasma	↑ KA	[220]
inflammatory bowel disease	colon	↑ IDO mRNA	[164]
Crohn′s disease	perifollicular regions of lymphoid follicles	↑ IDO	
Crohn′s disease	supernatants from colonic explant cultures	↑ Kyn ↓ L-Trp	
rheumatoid arthritis	blood	↓ L-Trp	[81, 82]
rheumatoid arthritis	blood	↓ L-Trp ↓ 3-HK ↓ 3-HAA ↑ Kyn ↔ KA	[80]
rheumatoid arthritis	synovial fluids	↓ L-Trp ↑ IDO activity	[221]
systemic lupus erythematosus	blood	↑ Kyn ↓ L-Trp	[83, 84]
primary Sjögren′s Syndrom	blood	↑ Kyn ↓ L-Trp	[84, 85]
Trp degradation involved in therapeutic approaches for autoimmune diseases			
Disease model	**Tissue/cell types**	**Therapeutic molecules/cells**	**References**
RA (DBA/1 mice)	$CD4^+$ T cells, B cells	Agonistic anti-4–1BB monoclonal antibody	[86]
rat EAMG	plasma cells	IFN-γ-treated dendritic cells	[122]
mouse diabetes (islet cell transplant model)	B7-positive murine DCs	CTLA-4–IgG	[30]
mouse EAU	murine $CD11c^+$ DCs	Agonistic anti-4–1BB monoclonal antibody	[222]
mouse EAE	T cells and spinal cord mircroglial cells	Trytophan metabolites	[10]

IDO, indoleamine-2,3-dioxygenase; 3,4-DAA, 3,4-dimethoxy-cinnamoyl-anthranilic acid; 3-HAA, 3-hydroxyanthranilic acid; 3-HK, 3-hydroxykynurenine; KA, kynurenic acid; Kyn, kynurenine; QA, quinolinic acid; L-Trp, L-tryptophan; EAE, experimental autoimmune encephalitis; EAMG, experimental autoimmune myasthenia gravis; EAU, experimental autoimmune uveitis; MS, multiple sclerosis; RA, rheumatoid arthritis.

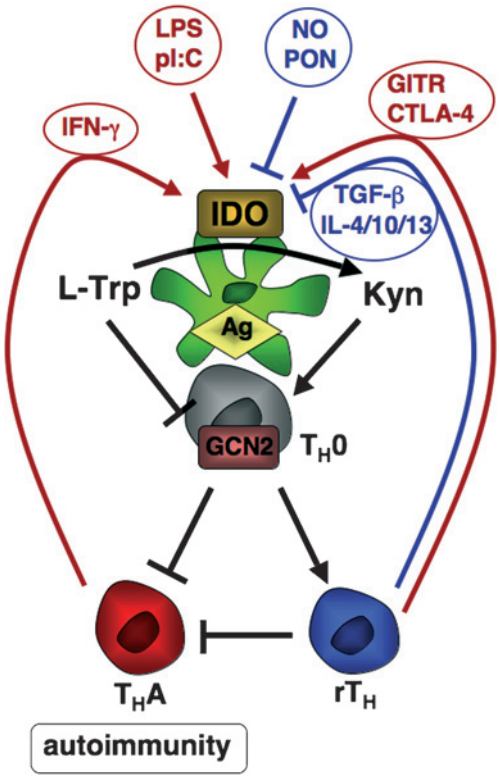

Figure 2. Modulation of T cell-mediated autoimmunity by Trp catabolism. Indoleamine-2,3-dioxygenase (IDO) is up-regulated in dendritic cells by pro-inflammatory mediators such as interferon-γ (IFN-γ), lipopolysaccharide (LPS) and synthetic double-stranded RNA (pI:C), whereas nitric oxide (NO) and peroxynitrite (PON) are strong suppressors of IDO. IDO activity results in the depletion of L-tryptophan (L-Trp) and in the accumulation of kynurenine (Kyn). Depletion of L-Trp results in the disinhibition of general control non-derepressable 2 (GCN2) kinase in naive T_H0, promoting their differentiation into regulatory T_H cells (rT_H) upon antigen-mediated activation. Kyn equally suppress the generation of autoaggressive T_H cells (T_HA), promoting autoimmunity and inducing differentiation into rT_H cells by an as-yet-unidentified mechanism. rT_H cells are capable of suppressing T_HA cells. T_HA cells release pro-inflammatory IFN-γ, thus providing a feedback inhibitory signal to suppress excess autoimmunity. rT_H cells can suppress IDO induction via the release of interleukins (IL)-4, -10 and -13 and transforming growth factor-β (TGF-β) as well as induce IDO induction via cell contact-dependent signalling through cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR) expressed on their surface.

nomodulatory strategies. In the following paragraphs, Trp degradation as both an endogenous feedback inhibitory mechanism in autoimmune diseases and a therapeutic target will be discussed using rheumatoid diseases and MS as examples.

Trp degradation in rheumatoid disease

Patients with rheumatoid arthritis (RA) [80–82], systemic lupus erythematosus (SLE) [83, 84] and primary Sjögren's Syndrome (pSS) [85] display significantly decreased blood levels of Trp as well as increased levels of kynurenine in comparison with healthy controls. In addition, decreased 3-hydroxykynurenine and 3-hydroxyanthranilic acid as well as increased xanthurenic acid were detected in patients with RA in comparison to healthy controls, while kynurenic acid concentrations remained normal [80]. The induction of Trp degradation may be associated with the progression or additional symptoms of disease. For instance, in RA increased Trp degradation correlates with the progression of disease (RA stages 1–4 according to Steinbrocker) [82]. In patients with SLE, enhanced Trp degradation was found when serositis or decreased complement and blood counts (anaemia, leukopaenia, lymphopaenia) were present, but only a weak association between Trp degradation and the SLE disease activity index (SLEDAI) was observed [84]. No differences in clinical manifestations of pSS were noted between patients with high or low Trp degradation [85]; however, Trp degradation appeared to be related to the severity and activity of pSS, reflected by a higher number of American-European consensus criteria fulfilled in the high-IDO activity group [85]. Collectively, these data solely indicate the fact that increased Trp metabolism is associated with autoimmunity. The functional relevance of Trp metabolism for the clinical course of human autoimmune diseases remains unknown.

Further insight into the function of Trp degradation in autoimmune disease may lead not only to a better understanding of the pathophysiology of autoimmune diseases but also to the development of novel therapeutic strategies. Evidence from animal models, for instance, indicates that Trp degradation is critically involved in suppression of RA by agonistic antibodies directed against the costimulatory molecule CD137 (4-1BB) [86]. Similarly, Trp degradation appears to be involved in the immunosuppressive effects of a fusion protein consisting of immunoglobulin and CD152/CTLA-4, a costimulatory molecule on T cells that binds to CD80/B7-1 and CD86/B7-2 on APCs [30]. The CTLA-4-Ig fusion protein Abatacept™ was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of RA [87]. However, the contribution of Trp degradation *versus* costimulatory blockade to the clinical efficacy of this compound remains to be determined.

Trp degradation in MS

Similar to RA, Trp catabolism is activated in MS, possibly as a feedback inhibitory mechanism to help counteract the loss of immunological tolerance and to

limit neuroinflammation. In EAE, Trp degradation is increased in the brain and the spinal cord during the acute phase of disease [64, 88–91]. This observation suggests that IFN-γ from encephalitogenic Th1 cells may provoke local IDO expression, which in turn may be involved in the resolution of inflammation during the remitting phases of EAE and MS [64]. Treatment with 1-methyl-Trp, a pharmacological inhibitor of IDO, resulted in a exacerbation of EAE [64, 91], reinforcing the notion that Trp degradation represents an endogenous inhibitory mechanism to limit neuroinflammation. These data collectively suggest that Trp catabolism may serve as an attractive novel target to treat autoimmune diseases [92]. However, one has to keep in mind that systemic activation of Trp catabolism may also have unfavourable effects. For instance, in neuroinflammatory diseases such as MS, certain TCs such as quinolinic acid may contribute to neurodegeneration and permanent loss of function. Quinolinic acid elicits neurotoxic effects by acting as an agonist on excitatory NMDA receptors [25]. The source of excitotoxic quinolinic acid in the CNS is microglia [93] and infiltrating macrophages [94]. Indeed, quinolinic acid was found to be elevated selectively in the spinal cords of rats with EAE [88, 89]. Whether quinolinic acid accumulation in the CNS during autoimmune neuroinflammation is sufficient to provoke functional or structural neuron defects, however, remains to be proven.

In contrast to quinolinic acid, kynurenic acid, another Trp metabolite, is an endogenous antagonist of excitatory amino acid receptors and was shown to exert neuroprotective functions. In patients with stable relapsing-remitting MS, decreased levels of kynurenic acid were detected in the cerebrospinal fluid (CSF) [90], whereas during acute relapses the levels of kynurenic acid in the CSF were increased [95]. This increase in kynurenic acid during acute MS relapses may protect against the toxic effects of glutamate on neurons and oligodendrocytes by antagonizing NMDA receptors.

Interferon-β and Trp catabolism in MS

Interferon-β (IFN-β) is the mainstay of disease-modifying therapy for patients with relapsing-remitting MS [96]. The mechanism by which IFN-β exerts beneficial disease-modifying effects in MS remains unclear but, among other mechanisms, may involve suppression of T cell activation [97, 98]; inhibition of IFN-γ-induced MHC class II expression on endothelial cells [99]; a decrease in TNF-α and increase in IL-6 production [100]; an increase of B7-H1 (PD-L1) on monocytes and DCs [101]; up-regulation of monocyte-derived HLA-G [102]; an increase of the costimulatory molecules CD80, CD86 and CD40 on monocytes [103]; inhibition of matrix metalloproteinases [104, 105], leading to reduced T cell migration [106]; induction of TGF-β1 and its receptor [107]; and inhibition of iNOS expression [108]. Some of the above-mentioned mechanisms such as T cell suppression [109] and the induction of HLA-G [110] can be mediated by IDO; others, such as induction of the costimulatory molecules CD80, CD86 [30, 43] and CD40 [44] as well as inhibition of iNOS [51, 52, 111], may increase the cells' ability to induce IDO. These observations may imply that the immunosuppressive therapeutic effects of IFN-β in patients with MS may in part be mediated through tryptophan catabolism. In 1981 Yoshida and colleagues reported that murine fibroblast IFN-α/β induce IDO expression in murine lung slices [112]. Subsequently, IFN-β-mediated IDO induction in human PBMC was observed both *in vitro* [113] and *in vivo* after treatment of cancer patients with IFN-β [114]. More recently, concentrations of IFN-β1b comparable to those found in the sera of MS patients were shown to increase IDO mRNA expression and quinolinic acid production in human macrophages [115]. Plasma levels of kynurenic acid were not changed in MS patients after initial treatment with IFN-β or after long-term IFN-β treatment [116]. In contrast, after initiation of IFN-β1a/b treatment, there was an increase in the kynurenine/tryptophan (K/T) ratio, indicating an induction of IDO [116]. However, in patients receiving long-term IFN-β, the K/T ratio did not differ from the healthy control group [116]. At present the impact of IFN-β-mediated induction of Trp catabolism in patients with autoimmune diseases remains elusive. As the inhibition of Trp catabolism exacerbates EAE [91], induction of Trp catabolism by IFN-β could be beneficial in MS but does not appear to be involved in the long-term effects of IFN-β treatment [116]. On the other hand, induction of quinolinic acid production by IFN-β could also account for toxic effects on neurons or oligodendrocytes [115]. Depression was considered to be a side effect of IFN-β and has been discussed to result from the depletion of Trp by the IFN-β-mediated induction of Trp catabolism [117]; however, recent studies could not confirm induction of depression by IFN-β1a or IFN-β1b in long-term IFN-β-treated MS patients [118–120].

TCs as immune-modulating agents

Circulating L-kynurenine, 3-hydroxykynurenine and anthranilic acid are taken up into the brain by the large neutral amino acid carrier (L-system) of the blood-

brain barrier, whereas quinolinic acid, kynurenic acid and 3-hydroxyanthranilic acid cross the blood-brain barrier poorly [121]. As the global activation of Trp degradation during neuroinflammation may also be detrimental due to production of neurotoxic substances such as quinolinic acid, alternative therapeutic strategies circumventing the generation of toxic neuroactive TCs accessing the CNS hold great promise for the treatment of autoimmune neuroinflammation. Certain non-toxic TCs show potent immunemodulating activity. Kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid were shown to strongly suppress T cell proliferation *in vitro*, and a mixture of kynurenine and 3-hydroxyanthranilic acid significantly prolonged graft survival in a skin allograft model [66]. In the relapsing-remitting mouse model of EAE, the orally active synthetic Trp derivative 3,4-DAA suppressed the frequency and function of autoreactive Th1 cells, inhibited the release of inflammatory mediators such as IFN-γ, TNF-α and IL-12/23 p40 and led to a reduction of the inflammatory foci in the CNS tissue [10]. In addition, the natural Trp catabolite 3-hydroxykynurenine and the synthetic Trp metabolite 3,4-DAA induced antigen-specific IL-10-producing T cells with regulatory potential *in vitro* and *in vivo* [10]. A regulatory phenotype in naive T cells producing IL-10 and TGF-β was also induced by a mixture of 3-hydroxykynurenine, 3-hydroxyanthranilic acid and quinolinic acid in combination with low Trp concentrations [5]. The activation of APCs was also suppressed by a synthetic TC, as spinal cord microglial cells exhibited drastically reduced expression of pro-inflammatory molecules when mice with EAE were treated with 3,4-DAA [10]. Collectively, these findings suggest that TCs and their analogues may be more effective in treating autoimmune disorders than global induction of Trp degradation.

Future directions: Trp degradation as a therapeutic strategy for autoimmune diseases

The immunosuppressive properties of Trp degradation may be exploited for the treatment of autoimmune diseases using three distinct approaches:
1) treatment with compounds that induce Trp catabolism
2) cell therapy with cells expressing Trp-degrading enzymes
3) treatment with TCs or synthetic derivatives thereof

1) Treatment with compounds that induce Trp metabolism

In order to successfully employ this therapeutic approach, we need to have a better understanding of individual enzymatic steps during Trp degradation in different cell types, their regulation, and the distribution of TCs in different organ systems. For instance, for most cell types, we do not know which TCs are produced to which extent upon stimulation. The impact of various stimulants of Trp degradation is likely to vary between different cell types; this may allow for the design of compounds that specifically induce Trp metabolism in certain cell types. To employ the induction of Trp degradation as a therapeutic strategy for autoimmune diseases, however, we need to gain further insight into potential adverse effects of Trp breakdown products.

2) Cell therapy with cells expressing Trp-degrading enzymes

Cell therapy with cells expressing Trp-degrading enzymes can be achieved either by stimulating the cells with compounds inducing Trp-degrading enzymes *ex vivo* and then transferring them into the recipient [122] or by transferring cells that have been genetically modified [123, 124]. This therapeutic approach has the advantage of specifically producing TCs in the inflamed tissue of interest if cell types with a particular homing pattern are used as vehicles. Neuronal stem cells, for example, show inflammation-directed homing toward pathology [125]. DCs also respond to inflammatory stimuli that promote the recruitment of immature DCs into tissues, initiate the DC maturation process and boost the recruitment of mature DCs into lymphatic vessels [126]. Questions that need to be addressed before applying transfer of Trp-degrading cells as a therapeutic strategy for autoimmune diseases include the time period in which the manipulated cells degrade Trp, their administration, their migratory behaviour, their influence on other cells as well as their life span after transplantation.

3) Treatment with TCs or their synthetic derivatives

The approach of using TCs therapeutically may offer several benefits, as a single Trp metabolite will be more specific than globally activating the entire cascade of Trp degradation. In addition, a single metabolite is less likely to activate many different signalling pathways that could induce adverse side effects. Furthermore, treatment with TCs may be more practical than the therapeutic approaches outlined above, as orally active synthetic TCs are already available for use and could serve as models for the generation of novel compounds [92]. For instance,

quinoline derivatives such as teriflunomide [127] and laquinimod [128] suppress T cell responses similarly to structurally analogous TCs and are currently undergoing clinical evaluation for the treatment of MS. Structural similarity to Trp catabolites may be involved in the mechanism of action of some compounds that are currently being used to modulate immune responses; acetylsalicylic acid, for instance, is structurally similar to anthranilic acid.

A key question concerning the therapeutic use of Trp degradation is how TCs mediate immunosuppressive effects. To date neither the receptors of the TCs nor the signalling pathways they activate are fully understood. However, this question needs to be addressed not only to develop novel compounds capable of modelling the immunosuppressive effects of TCs but also to understand the entire concept of immunosuppression by TCs. Additional unanswered issues concerning TCs as therapeutic targets for autoimmune disease include the effect of different TCs on distinct cell types, their tolerability, their pharmacodynamics as well as their pharmacokinetics.

In summary, Trp metabolism appears to be a promising target for the development of novel therapeutic strategies to treat autoimmune disorders. However, many unresolved questions remain to be elucidated to fully understand this important immunosuppressive metabolic pathway and to translate this knowledge into designing novel therapeutic strategies for autoimmune diseases.

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