Cytokine 122 (2019) 154148

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

The interplay between cytokines and the Kynurenine pathway in inflammation and atherosclerosis

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ARTICLE INFO

Keywords:
Atherosclerosis
Inflammation
Cytokine
Kynurenine
Tryptophan

ABSTRACT

The kynurenine pathway (KP) is the major metabolic route of tryptophan (Trp) metabolism. Indoleamine 2,3-dioxygenase (IDO1), the enzyme responsible for the first and rate-limiting step in the pathway, as well as other enzymes in the pathway, have been shown to be highly regulated by cytokines. Hence, the KP has been implicated in several pathologic conditions, including infectious diseases, psychiatric disorders, malignancies, and autoimmune and chronic inflammatory diseases. Additionally, recent studies have linked the KP with atherosclerosis, suggesting that Trp metabolism could play an essential role in the maintenance of immune homeostasis in the vascular wall. This review summarizes experimental and clinical evidence of the interplay between cytokines and the KP and the potential role of the KP in cardiovascular diseases.

1. Introduction

The kynurenine pathway (KP) is the major metabolic route of degradation of the essential amino acid tryptophan (Trp). The majority of Trp metabolism occurs in the liver, intestine, kidney, spleen, and epididymis, where one of the two rate-limiting enzymes of the KP is constitutively expressed, either Tryptophan 2,3-Deoxygenase (TDO2) or Indoleamine 2,3-Dioxygenase 1 (IDO1). Seminal studies suggest the KP enzyme genes to be conserved across some species, including chicken, turkeys, mice, rats, pigs, and humans, while the pathway could be altered in others such as rabbits, hamsters, and gerbils [1]. Hence, evidence from mice and humans suggests that TDO2 governs Trp breakdown under basal conditions, while IDO is induced and regulated by inflammation [2,3]. Recent studies have linked the KP with atherosclerosis, suggesting that Trp metabolism in the vessel wall, via this pathway, is essential for the maintenance of vascular immune homeostasis. This review summarizes the experimental and clinical evidence of the interplay between cytokines and the KP, as well as support for a potential role in the peripheral metabolism of Trp in cardiovascular disease (CVD).

2. The atherosclerotic process

CVDs, which are largely due to atherosclerosis, are the major causes of death in the Western world and are increasingly becoming so in developing countries [4]. Atherosclerosis is a diffuse process that occurs in the large- and medium-sized arteries and is characterized by lipid deposition, inflammation and fibrosis. It starts during childhood and usually progresses asymptomatically through most of adult life. Most likely later in life, it manifests clinical symptoms.

The role of inflammation in atherosclerosis is well recognized [5]. The disease is initiated by ApoB-containing lipoproteins, particularly low-density lipoproteins (LDL), that accumulate in the intimal layer of the artery, triggering the recruitment of monocytes and T cells, which drive a local inflammatory response [6]. Smooth muscle cells (SMCs) also migrate to the intima, where they proliferate, secrete extracellular matrix (ECM) proteins, and create a plaque-stabilizing fibrous cap [7]. Orchestrated by cytokines, persistent inflammation can cause thinning of the fibrous cap, plaque destabilization and rupture. A superimposed thrombosis, triggered by exposure of the lesion's core molecules to coagulation factors and platelets in the blood, promotes the lethal

Abbreviations: 3-HAA, 3-Hydroxyanthranilic acid; 3-HK, 3-Hydroxykynurenine; ACMSD, Aminocarboxymuconate Semialdehyde Decarboxylase; AhR, aryl hydrocarbon receptor; APC, antigen presenting cell; CA, cinnabrinic acid; CVD, cardiovascular disease; CNS, central nervous system; DC, dendritic cell; ECM, extracellular matrix; GM−CSF, granulocyte-macrophage colony stimulating factor; HAAO, 3-Hydroxyanthranilate 3,4-Dioxygenase; IDO1, Indoleamine 2,3-Dioxygenase 1; IMT, intima-media thickness; KMO, Kynurenine monooxygenase; KP, kynurenine pathway; KYAT, Kynurenine-aminotransferases; Kyn, kynurenine; KynA, kynurenic acid; LDL, low-density lipoprotein; LPS, lipopolysaccharide; M−CSF, macrophage colony-stimulating factor; MSC, mesenchymal stem cell; NAD, nicotinamide adenine dinucleotide; NK, natural killer cells; NMDA, N-methyl-D-aspartate; PA, picolinic acid; PBMCs, peripheral blood mononuclear cells; pDC, plasmacytoid DCs; QA, quinolinic acid; QPRT, Quinolinate Phosphoribosyltransferase; SMC, Smooth muscle cells; TDO2, Tryptophan 2,3-Deoxygenase; Th, T helper cell; Treg, Regulatory T cell; Trp, Tryptophan; XA, Xanthurenic acid

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http://dx.doi.org/10.1016/j.cyto.2017.09.004
Received 5 May 2017; Received in revised form 1 September 2017; Accepted 2 September 2017
Available online 11 September 2017

effects of atherosclerosis, including myocardial infarction and stroke [8].

3. Innate and adaptive immune cytokines in atherosclerosis: brief overview

Both innate and adaptive immune responses in atherosclerosis are orchestrated by cytokines, which can influence all stages of the disease [9]. Attracted by chemokines in the inflammatory milieu of the plaque, monocytes can infiltrate the arterial intima and differentiate into macrophages or dendritic-like cells. In the plaque, macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma (IFNγ), Interleukin-4 (IL-4) and Interleukin-13 (IL-13) play key roles in the differentiation and polarization of these immune cells [10].

M1 polarization of macrophages can be triggered by IFNγ and/or Toll-like receptor 4 (TLR4) ligation. These cells are the predominant population of cells in the progressing plaque and are regarded as major pro-atherogenic players–they secrete pro-inflammatory cytokines such as interleukin 1 beta (IL-1β), interleukin 12 (IL-12), and TNF. Moreover, they express high levels of the co-stimulatory molecules CD80 and CD86 and major histocompatibility complex class II (MHC-II), which help trigger T helper 1 (Th1)-type T cell responses [5,6,11]. M2 polarization of macrophages can be induced by IL-4 and IL-13. M2 macrophages characteristically produce anti-inflammatory cytokines such as IL-10, TGFβ, interleukin 1 receptor agonist (IL-1 RA) and have a high endocytic activity. M2 macrophages are key for the resolution of inflammation and are regarded as anti-atherogenic [11].

Cytokines also play a key role in the differentiation and polarization of T and B cells. The adaptive immune response of T and B cells has also been implicated in the inflammatory processes of atherosclerosis [5]. IL-12 and IFNγ are promoters of Th1 cells, which, in turn, secrete IFNγ and TNF, two major pro-atherogenic and plaque-destabilizing cytokines [12]. IL-4 and IL-13 promote the polarization of naïve T cells into Th2 cells, which secrete IL-4, IL-5 and IL-13, while TGFβ in synergy with IL-6 or IL-1β promotes Th17 cells, which secrete IL-17A/F and IL22 [12]. While the role of Th2 and Th17 cells in atherogenesis remains controversial, another T helper subtype, regulatory T cells (Treg), has been shown to be anti-atherogenic, through their release of anti-inflammatory cytokines such as IL-10 and TGFβ and their regulation of lipoprotein metabolism [13].

4. Tryptophan degradation via the Kynurenine pathway

The KP has been extensively studied in the context of neuropsychiatric disorders (reviewed in [14,15]). Kynurenic acid (KynA), which is generated upon action of Kynurenine-aminotransferases (KYATs 1-4), is an endpoint-stable metabolite that has been implicated in neuroprotection [16]. By contrast, other metabolites, such as 3-Hydroxykynurenine (3-HK), 3-Hydroxyanthranilic acid (3-HAA) and quinolinic acid (QA), have been proposed to mediate excitotoxic and neurodegenerating effects [16–20], partly due to agonistically signaling through N-methyl-D-aspartate (NMDA) receptors [21]. KynA, which has also been shown to interact with the aryl hydrocarbon receptor (AhR) [22], G protein-coupled receptor 35 (GPR35) [23], and potentially alpha-7 nicotinic receptor [24], can antagonize the effects of 3-HK, 3-HAA, and QA in the central nervous system (CNS) [25].

Breakthrough discoveries boosted the field of Trp research in the 1990s. Notably, work from Munn and Mellor 1998 showed that IDO is required for maternal immune tolerance during pregnancy and that pharmacological inhibition of IDO leads to abortion [26]. This discovery and the notion that the KP can be induced by inflammation expanded the research in the field beyond neurological disorders. For example, since the 1950s it has been known that the KP is activated in certain types of cancer [27,28]. However, not until the 2000s was it confirmed that tumors themselves can express IDO, which has been regarded as an important immune-escape mechanism of these cells [29]. Nowadays, immune-regulatory properties of the KP are described outside the CNS and in several autoimmune and chronic inflammatory diseases, including atherosclerosis.

Among the mechanisms by which the KP regulates immunity, it has been proposed that increased IDO expression and activity lead to microenvironmental depletion of Trp and increased intracellular pool of uncharged $tRNA^{Trp}$. Uncharged tRNAs are sensed by the General control nonderepressible 2 (GCN2) that, via the phosphorylation of Eukaryotic initiation factor 2α kinase (eIF2α), leads to decreased ribosomal mRNA translation, protein synthesis, and immune cell division [30]. However, the fact that, IFNγ stimulation induces not only IDO but also tryptophanyl-tRNA synthetase [31] (which refuels the pool of uncharged $tRNA^{Trp}$) and that Trp depletion-mediated responses may occur only upon the "non-physiological" and almost complete absence of this amino acid [32] indicates that mechanisms other than Trp depletion could be triggered upon the induction of the KP. In this scenario, several Trp metabolites have been found to be bioactive and to affect both immune and non-immune cells.

In the late 80s, Trp supplementation was linked to an increased incidence of eosinophilia myalgia syndrome (EMS) [33], which led to a ban on its use by the United States Food and Drug Administration (FDA). However later, epidemiologic tracing studies linked EMS to an impurity, 3-(phenylamino)-L-alanine (PAA), of L-Trp manufacturing from a single source [34]. In 2005, the FDA lifted the ban on L-Trp dietary supplements. Interestingly, Trp was recently identified as an endogenous ligand for GPR139 and GPR142 [35,36]. GPR142 ligation has been shown to regulate glucose homeostasis, as well as the immune system [37]. Intriguingly, treatment of mice with a GPR142 agonist and GPR142 deficiency have been linked to reduced severity of collagen antibody-induced arthritis (CAIA) in mice [37], warranting further investigation.

3-HK, 3-HAA and QA can induce apoptosis of activated T cells, monocytes and epithelial cells [38–40]. KynA and Kynurenine (Kyn) have been shown to modulate endothelial cell responses, e.g., adhesion of monocytes under flow conditions [41] and nitric oxide (NO) production [42], respectively. Through the interaction with AhR, Kyn has also been implicated in the generation of Tregs in the thymus [43] and the downregulation of IFNγ production by T cells [44,45]. Notably, an autocrine IDO-Kynurenine/AhR-IDO loop has been identified as an inhibitory feedback mechanism in dendritic and cancer cells [46,47].

Under basal conditions, Trp degradation occurs mainly in the liver, where TDO2 and the enzymes necessary for nicotinamide adenine dinucleotide (NAD+) synthesis are present. On the other hand, extrahepatic degradation of Trp becomes significant only when IDO expression is increased, e.g., in response to inflammation. Recent studies have shown that NAD+, similar to the KP, can regulate T cell immunity [48,49]. Whether NAD+ levels due to increased IDO activity can influence immunity remains unclear. Nevertheless, most tissues and/or cell types seem to lack QPRT, the KP enzyme required for the synthesis of QA and the *de novo* synthesis of NAD+ [13]. This suggests that NAD-independent mechanisms may be more predominant, at least extrahepatically, upon the activation of the KP.

5. The interplay between cytokines and the KP

The KP is tightly regulated by cytokines. Cytokines can affect the expression of various KP enzymes, thus orchestrating metabolic changes that can influence immune cell responses. Tables 1 and 2, and Fig. 1 summarize the relevant findings that support the influence of cytokines on the peripheral expression of the KP and vice versa.

5.1. Cytokines fine-tune Trp metabolism along the KP

Cytokines regulate Trp degradation along the KP in many cell types, including non-immune cells, e.g., fibroblasts, keratinocytes, epithelial

Table 1
Overview of the regulation of the KP by cytokines.

Cytokine	Effect	Cells involved	Species	Ref.
IL-1β	[↑] KYNU	Fibroblasts	human	[53]
	[−] KMO, KAT1-4			
	[↑] IDO1, KMO	Pancreatic island cells	rat	[52]
	[−] KYNU, QPRT, KYAT2, KYAT 4			
	[↓] TDO2, KYAT1, KYAT3			
	[−] IDO1	Pancreatic island cells	human	[74]
IL-4 (IFNγ)	[↓] IDO1	Monocytes	human	[73]
		Pancreatic island cells		[74]
IL-6	[↑] IDO1	Tumor cells	human	[47]
	[↑] IDO1	MDSC	human	[62]
	[−] KYNU, KMO, KYAT 1-4	Fibroblasts	human	[53]
IL-10 (+LPS)	[↓] IDO1	DC	mouse	[54]
(+IFNγ)	[↑] IDO	DC	mouse	[75]
(+IFNγ)	[↑] IDO	MSC	human	[76]
	[−] IDO1, KYNU	PBMC, Endothelial cells	human	[83]
IL-12(+LPS)	[↑] IDO1	DC	mouse	[54]
	[↑] IDO1	Osteosarcoma cell line	human	[55]
IL-13	[−] IDO1, KYNU	PBMC, Endothelial cells	human	[83]
IL-17	[−] IDO1, KYNU	PBMC, Endothelial cells, Keratinocytes	human	[83]
IL-18	[↑] IDO1	Osteosarcoma cell line	human	[55]
IL-22	[↑] KYNU	Keratinocytes	human	[138]
IL-23	[↑] IDO1, KYNU	Whole skin	mouse	[56]
	[−] TDO2, IDO2			
IL-27	[↑] IDO1	Intestinal epithelial cells	mouse	[57]
IFNα	[↑] IDO1	Splenocytes	mouse	[58]
	[↑] IDO1	DC	human	[139]
IFNβ	[↑] IDO1, IDO2, KMO, KYNU	MSC	human	[60]
	[−] IDO2, TDO2, KYAT1, KYAT2, HAAO, ACDMS, QPRT			
	[↑] IDO1	Macrophages	human	[59]
	[−] HAAO, QPRT,			
IFNγ	[↑] IDO1, IDO2; KMO, KYNU HAAO	MSC	mouse human	[60]
	[−] TDO2			
	[↓] KYAT1, KYAT2, QPRT, ACDMS			
	[↑] IDO1, IDO2, (KMO), KYNU, HAAO, (TDO2)	Macrophages	human	[60,80]
	[↓] KYAT1, KYAT2, KYAT3, ACDMS, (QPRT)			
	[↑] IDO1; KYNU	PBMCs	human	[83,140]
	[↑] IDO1, TDO2, KMO, KYNU, HAAO	DC	human	[69][80]
	[↓] QPRT, KYAT1, KYAT2, KYAT3, ACMSD			
	[↑] IDO1, KYNU, HAAO, ACMSD[−]TDO2; IDO2, KMO, KYAT2 KYAT4, QPRT,	Fibroblast	human	[53,81,82]
	[↓] KYAT1, KYAT3			
	[↑] IDO1, KMO, KYNU, HAAO, ACMSD	Keratinocytes	human	[81,83]
	[−] TDO2, IDO2, QPRT, KYAT1-4,			
	[↑] IDO1, KAT3	Prim. pancreatic island cells	rat	[52]
	[−] TDO2, KMO, QPRT, KYAT1, KYAT2, KYAT4			
	[↑] IDO1, KAT3, QPRT	INS-1 cells	rat	[52]
	[−] TDO2, KMO, KYAT1, KYAT2, KYAT4			
	[↑] IDO1, KYNU, HAAO, KYAT2, KYAT3	Preadipocytes	human	[50]
	[−] KYAT1, QPRT			
	[↑] IDO1, KYNU, HAAO, KYAT3	Adipocytes	human	[50]
	[−] KYAT1, KYAT2, QPRT			
	[↑] IDO1	Endothelial cells	human	[83]
	[−] KYNU			
IFNλ	[↑] IDO1	Respiratory epithelial cell line	human	[61]
TNF	[↑] KYNU	Fibroblasts	human	[53,82]
	[−] IDO1, TDO2, KAT1-4, KMO, HAAO, QPRT			
	[↑] IDO1, KYNU	Endothelial cells	human	[83]
TNF(+IFNγ)	[↑] IDO1, KYNU, HAAO	Fibroblasts	human	[53,82]
	[−] KYAT2, KMO			
	[↓] TDO2, KYAT1, KYAT3, KYAT4, QPRT			
TGFβ	[↑] IDO1	pDCs	mouse	[43,77]

() additional stimuli are shown between brackets; [↑] or [↓] indicates expressional up- or downregulation, [−] when not influenced; enzymes in round brackets () are differently regulated dependent on the investigated cell type; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; TDO2, Tryptophan 2,3-Deoxygenase; IDO1, Indoleamine 2,3-Dioxygenase1; IDO2, Indoleamine 2,3-Dioxygenase 2; KMO, Kynurenine monooxygenase; KYNU, Kynureninase; KYATs, Kynurenine-aminotransferases; HAAO, 3-Hydroxyanthranilate 3,4-Dioxygenase; QPRT, Quinolinate Phosphoribosyltransferase, ACMSD, Aminocarboxymuconate Semialdehyde Decarboxylase.

cells, endothelial cells, SMCs, and tumor cells. IDO mRNA is often found to be low or undetectable under physiological or non-inflammatory conditions [50]. On the other hand, IFNγ stimulation can increase IDO mRNA by thousands of fold [51]. IFNγ triggers Jak/Stat1 and PKCδ signaling, and a gamma interferon activation site (GAS) and internal ribosome entry site (IRES) can be found in the promoter region of the *IDO1* gene [51]. Similar to the effects of IFNγ, other cytokines, such as TNF, IL-1β, IL-6, IL-12, IL-18, IL-23, and type I interferons have been reported to induce IDO expression [52–62]. Hence, the canonical and non-canonical NF-κB [63] and c-Jun [64] signaling pathways have been implicated in transducing the signal from cytokines.

Although several cytokines may act alone in the modulation of IDO expression, recently, the synergistic effects of IFNγ and TLR ligation, CD40-CD40L, and CD80/86-CTLA-4 [65–67] have been identified.

Table 2
Overview of the regulation of inflammation and cytokine release by KP metabolites.

Metabolite	Cell-type	Effect directly or indirectly influencing cytokine production	Species/Cell line	Reference
Trp	T cells	Restores T cell proliferation in IDO induced T cell anergy	mouse	[141]
Kyn	T cells	Th1 apoptosis	human	[40,69]
		Treg induction (via AhR*)	mouse	[43]
	Neutrophils	Apoptosis	mouse	[142]
	Mast cells	[↑] IL-6 (via AhR*)	RBL2H3	[112]
	Mast cells	[↑] IL-13 (via AhR)	mouse human	[113]
	iNKT	[↓] IL-13 and IFNγ, and at higher concentrations also IL-4	mouse	[44]
	Whole blood	[↓] IFNγ upon in LPS/PHA	human	[45]
3-HK	Epithelial cells	Apoptosis	HLE-B3	[39]
	T cells	[↑] IL-22 when activated with CD3/CD28 (via downstream metabolite)	human	[95]
3-HAA	iNKT	[↓] IL-13 and IFNγ, and at higher concentrations also IL-4	mouse	[44]
	T cells	[↑] IL-22 when activated with CD3/CD28 (via downstream metabolite)	human	[95]
	T cells	Apoptosis of Th1 but not Th2	mouse	[40]
	T cells	Apoptosis of activated Th2 cells (via PDK1/NF-κB inhibition)	mouse	[38]
	Th17 cells	[↓] IL-17	mouse	[143]
	T cells	Inhibits differentiation of Th1 but not Th17, and induces Treg differentiation.	mouse	[98]
	T cells	Apoptosis when activated with SEA (via GSH depletion)	mouse	[144]
	T cells	[↓] IL-2 in ApoB100 directed T cell hybridoma, upon ApoB100 or ConA	mouse	[135]
	Macrophages	Apoptosis	mouse	[40]
	DC	[↓] of IL-12, IL-6 and TNF upon LPS (via c-Jun/p38)	mouse	[100]
	DC	[↑] TGFβ and induction of Tregs	mouse	[98]
	DC	Promotes maturation of LPS treated DC	human	[145]
	Keratinocytes	[↑] IL-20	human	
AA	iNKT	[-] IL-4, IL-13 and IFNγ	mouse	[44]
	Whole blood	[↓] IL-10 upon LPS/PHA	human	[45]
	Thymocytes	Apoptosis	mouse	[40]
	Keratinocytes	[↑] IL-20	human	[83]
KynA	Mast cells	[-] IL-6 or IL-13 (via AhR)	RBL2H3 mouse human	[112] [113]
	Macrophages	[↓] IL-10 upon LPS (via ERK2 and Mrp4)	mouse	[107]
	PBMC/Monocytes	[↓] TNF upon LPS	human	[23]
	Whole blood	Reduction in LPS/PHA induced TNF	human	[45]
	Splenocytes	[↑] IL-1β, IL-6, IL-10 and TNF[↓] IL-6 and TNF upon LPS	mouse	[105]
	Breast tumor	[↑] IL-6 release upon IL-1β (via AhR)	MCF-7	[22]
	iNKT	[↓] IL-4 release upon αGalCer (via GPR35)	human	[106]
Pico	Macrophages	Augments IFNγ signaling	mouse	[146]
CA	T cells	[↑] IL-22 upon CD3/CD28 (via AhR)	human	[95]
XA	Whole blood	[↓] IL-10 in LPS/PHA induced	human	[45]

Only non-neuronal cells were included in the table; metabolites increase [↑] or reduce [↓] cytokine levels alone or upon stimulation. Trp, Tryptophan; Kyn, Kynurenine; 3-HK, 3-Hydroxykynurenine; 3-Hydroxyanthralinic acid; QA, Quinolinic acid; KynA, Kynurenic acid; AA, Anthranilic; Pico, Picolinic acid; CA, Cinnabarinic acid; XA, Xanthurenic acid; AhR* indicates that Kyn has a distinct effect on the AhR, while other agonists have a different effect. SAE, staphylococcal enterotoxin A.

CD80/86-CTLA-4 signaling on dendritic cells (DCs) has been shown to promote Treg formation and tolerance [68]. IDO expression and activity can be regulated at the transcriptional and post-translational levels [69]. IL-6-dependent induction of Suppressor of cytokine signaling 3 (SOCS3) has been shown to drive IDO protein degradation in the proteasome [70]. Notably, IL-6 has been shown to inhibit IDO activity in mature DCs, even in the presence of IFNγ [71,72].

Released by Th2 cells, IL-4 has been shown to downregulate IDO expression by opposing the effects of IFNγ [73]. Also released by Th2 as well as by Tregs, IL-10-mediated effects on IDO remain unclear. It has been proposed that by opposing the effects of IFNγ, IL-10 can downregulate IDO expression [54,73,74]. However, it has also been suggested that IL-10 can act synergistically with IFNγ or IFNβ to promote IDO expression in DCs [75] and mesenchymal stem cells (MSCs) [76], respectively.

TGFβ, which can be released by fibroblasts, eosinophils, platelets, and Tregs, has emerged as a key anti-inflammatory cytokine inducing IDO expression in plasmacytoid DCs [43,77,78]. However, inhibition of IDO expression by TGFβ that can inhibit IFNγ-mediated responses has also been reported [79].

Other enzymes besides IDO in the KP can also be regulated by cytokines (summarized in Table 1). Notably, KYATs, which are responsible for catalyzing the synthesis of KynA, seem to be downregulated upon pro-inflammatory cytokine challenge, e.g., IFNγ reduces KYAT expression by macrophages [60,80], MSCs [60], and fibroblasts [53,81,82]. Similarly, the combination of pro-inflammatory cytokines, such as TNF and IL-1β, has been shown to substantially reduce KYAT expression by pancreatic cells and fibroblasts [52,53,82].

L-Kyn is a substrate for Kynurenine monooxygenase (KMO), which is the rate-limiting enzyme within the pathway branch leading to QA (Fig. 1). Similar to IDO, the promoter region of *KMO* gene contains sites for Stat1 and IRF1 binding. Thus, KMO can be induced by IFNβ and IFNγ in MSCs, keratinocytes, macrophages and DCs [60,69,80,81,83]. In line with this, increased IFNγ expression in mice results in high levels of circulating 3-HK, the product of the breakdown of L-Kyn by KMO [84]. IL-1β has also been shown to increase KMO expression in pancreatic cells and in hippocampal progenitor cells [85], while in macrophages, M2s rather than M1s have been show to express high levels of KMO [50].

Kynureninase (KYNU), which catalyzes the conversion of 3-HK into 3-HAA, has been found upregulated in the skin of patients with psoriasis disease. In these patients, KYNU is usually found co-expressed with IDO. Endothelial cells, keratinocytes, and PBMCs exposed to IFNγ and TNF express high levels of IDO and KYNU [83]. The combination of IFNγ and TNF can also induce 3-Hydroxyanthranilate 3,4-Dioxygenase (HAAO) [82], which catalyzes the synthesis of QA. There are fewer and

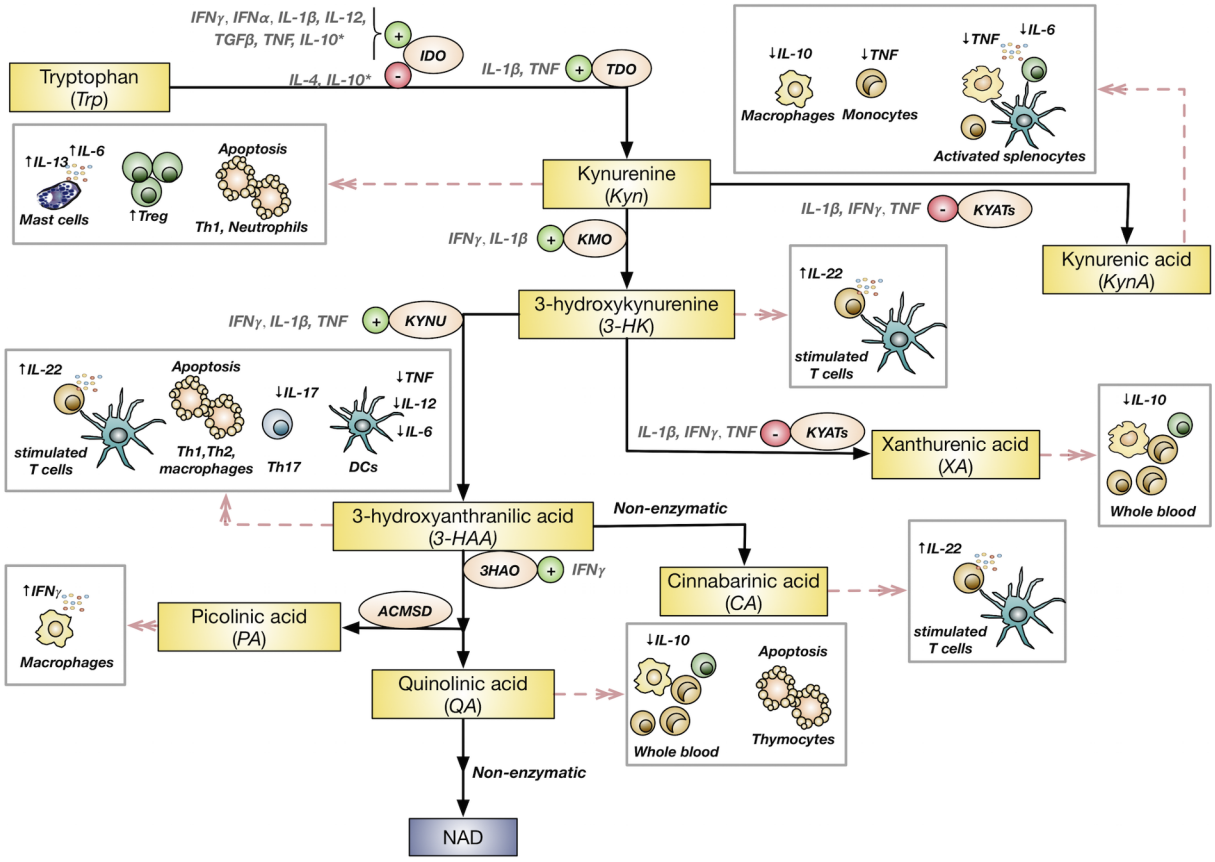

Fig. 1. Diagram of the regulation of the Kynurenine pathway (KP) and its effects on inflammation. Yellow rectangles denote metabolites; light-pink ellipses denote KP-enzymes; green circled pluses indicate induction by given cytokines; red circled minuses signify expression reduction; black solid lines show the metabolic routes of the pathway; red dashed lines indicate the effect of metabolites on immune cells; gray boxes denote cytokines; TDO2, Tryptophan 2,3-Deoxygenase; IDO1, Indoleamine 2,3-Dioxygenase1; IDO2, Indoleamine 2,3-Dioxygenase 2; KMO, Kynurenine monooxygenase; KYNU, Kynureninase; KYATs, Kynurenine-aminotransferases; HAAO, 3-Hydroxyanthranilate 3,4-Dioxygenase; QPRT, Quinolinate Phosphoribosyltransferase, ACMSD, Aminocarboxymuconate Semialdehyde Decarboxylase; NAD, Nicotinamide adenine dinucleotide; Th, T helper cell; Treg, regulatory T cell, DC, dendritic cell.

sometimes conflicting data about the regulation of TDO2, QPRT, ACMSD by cytokines [50,53,60,80,86]. While it is well known that hormones [87–89] and Trp itself [90] can regulate TDO2 expression, IL-1β has been implicated in its downregulation [52] and TNF in combination with IFNγ in its upregulation [80].

5.2. KP metabolites regulate inflammation and cytokine production

The concentrations of KP-metabolites range from low nanomoles to micromoles [91]. However, these levels can increase substantially in tissues, especially upon inflammation. Therefore, inflammation has been associated with increased QA levels in the CNS by more than 100-fold [92]. Site-specific differences in the concentrations of Trp metabolites can be seen in different organ compartments; for example, KynA can be found at the approximate concentrations of 65 nM in plasma, 129 nM in the spleen, and 16 μM at the lumen of the small intestine [93].

Several Trp metabolites, including Kyn, 3-HK, 3-HAA, and QA, have been shown to induce the apoptosis of T, B, and Natural Killer (NK) cells, as well as neutrophils [38,40,44,94], particularly at high micromolar concentrations levels. At lower concentrations, both 3-HK and 3-HAA have been implicated in the modulation of Th17 cells, influencing the release of IL-22 and IL-17 [95,96]. Kyn has also been suggested to influence Th17 cells, however, by shifting T cell responses towards the generation of anti-inflammatory Tregs [97].

The metabolite 3-HAA is one of the most studied Trp-derived molecules in the context of inflammation. In general, 3-HAA is referred to as an anti-inflammatory metabolite able to influence the release of IL-2, IL-6, IL-12, IL-13, IL-17, IL-20, TNF and IFNγ by different immune cells (illustrated in Table 2 and Fig. 1). On the other hand, 3-HAA has been implicated in the induction of TGFβ on DCs and increased Treg differentiation [98,99]. It has been proposed that 3-HAA's anti-inflammatory effects may involve the inhibition of the 3-phosphoinositide-dependent protein kinase-1 (PDK1), NF-κB, and the p38/c-Jun pathways [38,100]. Hence, 3-HAA has shown protective effects in several pre-clinical models of disease, including experimental autoimmune encephalomyelitis [98], asthma [38], and organ rejection [40].

Similar to 3-HAA, a synthetic analogue of this Trp metabolite, N-[3,4-dimethoxycinnamoyl]-anthranilic acid (3,4-DAA), which is commercially known as Tranilast or Rizaben, has also shown promising anti-inflammatory effects. Tranilast can modulate the release of pro-inflammatory cytokines [101] and reduce disease burden in pre-clinical models of graft versus host disease [102], experimental colitis [103], and rheumatoid arthritis [104].

Another important bioactive Trp metabolite, KynA, has been implicated in the modulation of inflammatory responses. KynA can inhibit the release of IL-6 and TNF by mouse splenocytes and human monocytes [23,45,105], as well as the release of IL-4 by α-galactosylceramide (αGalCer)-activated iNKT cells [106]. While these studies suggest an anti-inflammatory role for KynA, some studies suggest this metabolite could have pro-inflammatory effects by inhibiting IL-10 production or inducing the release of IL-6, IL-1β, TNF [22,105,107].

Cinnabarinic acid (CA), which is generated through the oxidative dimerization of 3-HAA, is a potent inducer of T cell apoptosis [108]. CA, and not 3-HAA or 3-HK, activates the AhR and influences the release of IL-22 and the balance between Th17 and Tregs [95,109,110].

Xanthurenic acid (XA) and Kyn have also been identified as potential AhR ligands [111]. Interestingly, it has been shown that Kyn can increase IL-6 and IL-13 by mast cells [112,113] while reducing the release of IL-13 by iNKT cells [44]. Such discrepancies involving the signaling of Trp metabolites via AhR suggest this interaction could be ligand-dependent. Notably, it has been suggested that AhR-mediated effects on inflammation are very distinct and depend on the nature of the ligands [114,115].

6. The KP in atherosclerosis and CVD

Alterations in the Trp metabolism through the KP have been linked to CVDs either through associations with the modulation of classic risk factors of disease, e.g., blood pressure, plasma lipoprotein and glucose levels, and obesity, or cardiovascular clinical outcomes [116]. High Kyn/Trp ratio, used as a surrogate for IDO activity, has been reported in patients with coronary heart disease [117–119] and angina pectoris [120]. In this context, Kyn/Trp ratio has been proposed as a predictive marker of acute coronary events, including unstable angina, acute myocardial infarction, and sudden death [121,122].

Whether the Kyn/Trp ratio can be used as an independent marker for atherosclerosis progression remains unclear. Positive associations between the Kyn/Trp ratio and intima-media thickness (IMT) have been shown to lose their significance after adjusting for classical disease risk factors [123,124]. Downstream of IDO in the KP, the levels of 3-HK and 3-HAA and the QA/Kyn ratio have been associated with inflammation and CVD in patients with severe renal dysfunctions [125–127]. Recently, increased KynA levels in plasma have also been associated with CVD [107].

Experimentally, the KP has been implicated in the modulation of inflammatory responses in vascular and immune cells. In the plaque, IDO expression was confirmed among macrophages, endothelial cells, and SMCs [107,128]. Interestingly, IFNγ stimulation of SMCs induces higher IDO levels and increased Trp degradation compared to that in macrophages or endothelial cells [129]. Thus, IDO expression on SMCs has been regarded to confer medial immune privilege [130].

Recently, direct evidence for the role of IDO in atherosclerosis has been obtained in hyperlipidemic animal models of disease. Pharmacological inhibition with 1-Methyl tryptophan (1-MT) [131], as well genetic ablation [101] of IDO results in a substantial increase in vascular inflammation and accelerated atherosclerosis. In these studies, IDO ablation led to increased vascular inflammation, especially influencing macrophages and other innate immune markers in the plaque [101,131]. Confirming previous evidence that the KP plays an important role in the response of SMCs, Apoe-/- mice treated with 1-MT had increased medial inflammation [131], and Apoe-/-Ido-/- mice had fewer SMCs in the plaque [101].

Regardless of whether the ablation has been shown to be deleterious to disease, increased IDO expression among DCs, particularly pDCs, has been shown to modulate T cell responses and protect against atherosclerosis [132–134]. Notably, the induction of IDO on pDCs has been linked to reduced infiltration of macrophages and T cells, as well as a substantial increase in SMCs and collagen-positive areas in the plaque [132]. On the other hand, loss of IDO^+pDCs resulted in decreased numbers of Tregs and reduced IL-10 levels in the aorta [134], corroborating the findings of Cole et al., 2015, showing that IDO deficiency leads to reduced IL-10 expression by immune cells and in serum [101]. Nevertheless, one study, using *LDLr-/-* mice, suggested a deleterious role of IDO in inflammation and atherosclerosis, and also reported contradictory data on the role of IDO in inducing IL-10 [107]. Although this raises the question of whether as-yet-unknown conditions may alter the role of the KP in the regulation of inflammation and atherosclerosis, further investigations are needed. However, given that the notion of IDO playing a deleterious role in atherosclerosis has not yet been reproduced by other studies, a cautious interpretation is warranted.

Additional evidence supporting an atheroprotective role of the KP has been raised by *in vivo* studies using Trp metabolites. Treatment of *Ldlr-/-* with 3-HAA substantially reduced vascular inflammation and decreased atherosclerosis [135]. Interestingly, 3-HAA treatment has been shown to reverse the deleterious effects of the pharmacological inhibition of IDO in atherosclerosis in *Apoe-/-* mice [131]. Surprisingly, for a metabolite first thought to be anti-inflammatory, 3-HAA showed potent lipid-lowering effects, which could have a direct impact on atherogenesis [135].

In line with the atheroprotective role of 3-HAA, its synthetic analogue Tranilast has been shown to reduce atherosclerotic lesion size in rabbits and mice [101,136]. In these studies, it was shown that Tranilast inhibited the pro-inflammatory response of T cells and promoted the anti-inflammatory response of B cells [101,136]. Tranilast has been tested in the context of CVD in humans in the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. Despite no clear benefits for restenosis, a significant reduction in myocardial infarction was observed upon its use [137].

7. Conclusions and future perspectives

Inflammation and its associated cytokine milieu play a pivotal role in the process of atherogenesis. The KP is regulated by cytokines, and recent evidence supports a key role for the KP in the regulation of inflammation and tolerance mechanisms. Not surprisingly, the KP has been linked to atherosclerosis and CVD. Thus, IDO, which can be expressed by macrophages, endothelial cells and SMCs in the vascular wall, emerges as a key atheroprotective enzyme promoting immune homeostasis. Whether other KP enzymes and their downstream Trp metabolites play a role in atherosclerosis remains largely unknown. Data obtained in pre-clinical work using 3-HAA or its synthetic analogue 3,4-DAA suggest that targeting the KP could be a very efficient way of combating atherosclerotic plaque formation. Notably, specific targeting of the KP could lead to beneficial effects on lipoprotein metabolism and other classic risk factors for CVD in addition to influencing inflammation. Despite this knowledge, the detailed mechanisms of action of several Trp metabolites and their molecular targets remain unidentified. A better understanding of the role of the KP in CVD warrants further investigation, which could lead to the discovery of novel therapeutic targets to prevent and treat CVD.

Acknowledgments

The authors' research is supported by grants from the Swedish Heart-Lung Foundation, the Novo Nordisk Foundation (NNF15CC0018346), the Karolinska Institute Cardiovascular Program Career Development Grant, Stiftelsen för Gamla Tjänarinnor, Stiftelsen för Ålderssjukdomar vid Karolinska Institutet, and Stiftelsen Professor Nanna Svartz fond.

Conflict of interest

DFJK holds patents on the use of 3-hydroxyanthranilic acid for the prevention and treatment of hyperlipidemia and its complications.

References

[1] A.A. Badawy, M. Evans, Animal liver tryptophan pyrrolases: Absence of apoenzyme and of hormonal induction mechanism from species sensitive to tryptophan toxicity, Biochem. J. 158 (1976) 79–88.
[2] P.B. Larkin, K.V. Sathyasaikumar, F.M. Notarangelo, H. Funakoshi, T. Nakamura, R. Schwarcz, et al., Tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase 1 make separate, tissue-specific contributions to basal and inflammation-induced kynurenine pathway metabolism in mice, Biochem. Biophys. Acta 1860 (2016) 2345–2354.
[3] A.A. Badawy, Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects, Int. J. Tryptophan Res.: IJTR. 10 (2017) 517487138.
[4] World Health Organization, World Health Statistics 2017: Monitoring Health for the SDGs, Sustainable Development Goals, World Health Organization, Geneva,

2017.
[5] D.F. Ketelhuth, G.K. Hansson, Adaptive response of T and B cells in atherosclerosis, Circ. Res. 118 (2016) 668–678.
[6] G.K. Hansson, A. Hermansson, The immune system in atherosclerosis, Nat. Immunol. 12 (2011) 204–212.
[7] D.F. Ketelhuth, G.K. Hansson, Modulation of autoimmunity and atherosclerosis - common targets and promising translational approaches against disease, Circ. J. 79 (2015) 924–933.
[8] E. Falk, P.K. Shah, V. Fuster, Coronary plaque disruption, Circulation 92 (1995) 657–671.
[9] H. Ait-Oufella, S. Taleb, Z. Mallat, A. Tedgui, Recent advances on the role of cytokines in atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 969–979.
[10] G.J. Randolph, S. Beaulieu, S. Lebecque, R.M. Steinman, W.A. Muller, Differentiation of monocytes into dendritic cells in a model of transendothelial trafficking, Science 282 (1998) 480–483.
[11] K.J. Moore, F.J. Sheedy, E.A. Fisher, Macrophages in atherosclerosis: a dynamic balance, Nat. Rev. Immunol. 13 (2013) 709–721.
[12] A. Gisterå, G.K. Hansson, The immunology of atherosclerosis, Nat. Rev. Nephrol. 13 (2017) 368–380.
[13] R. Klingenberg, N. Gerdes, R.M. Badeau, A. Gistera, D. Strodthoff, D.F. Ketelhuth, et al., Depletion of FOXP3+regulatory T cells promotes hypercholesterolemia and atherosclerosis, J. Clin. Invest. 123 (2013) 1323–1334.
[14] B.M. Campbell, E. Charych, A.W. Lee, T. Möller, Kynurenines in CNS disease: regulation by inflammatory cytokines, Front. Neurosci. 8 (2014) 12.
[15] R. Schwarcz, T.W. Stone, The kynurenine pathway and the brain: Challenges, controversies and promises, Neuropharmacology 112 (2017) 237–247.
[16] Z. Bohár, J. Toldi, F. Fülöp, L. Vécsei, Changing the face of kynurenines and neurotoxicity: therapeutic considerations, Int. J. Mol. Sci. 16 (2015) 9772–9793.
[17] G.J. Guillemin, Quinolinic acid, the inescapable neurotoxin, FEBS J. 279 (2012) 1356–1365.
[18] V. Pérez-De La Cruz, P. Carrillo-Mora, A. Santamaría, Quinolinic acid, an endogenous molecule combining excitotoxicity, oxidative stress and other toxic mechanisms. Int. J. Tryptophan. Res. 2012; 5: pp. 1–8.
[19] Z.T. Kincses, J. Toldi, L. Vécsei, Kynurenines, neurodegeneration and Alzheimer's disease, J. Cell Mol. Med. 14 (2010) 2045–2054.
[20] F. Fazio, L. Lionetto, M. Curto, L. Iacovelli, C.S. Copeland, S.A. Neale, et al., Cinnabarinic acid and xanthurenic acid: Two kynurenine metabolites that interact with metabotropic glutamate receptors, Neuropharmacology 112 (2017) 365–372.
[21] F. Moroni, A. Cozzi, M. Sili, G. Mannaioni, Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery, J. Neural. Transm. (Vienna). 119 (2012) 133–139.
[22] B.C. DiNatale, I.A. Murray, J.C. Schroeder, C.A. Flaveny, T.S. Lahoti, E.M. Laurenzana, et al., Kynurenic acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling, Toxicol. Sci. 115 (2010) 89–97.
[23] J. Wang, N. Simonavicius, X. Wu, G. Swaminath, J. Reagan, H. Tian, et al., Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35, J. Biol. Chem. 281 (2006) 22021–22028.
[24] D. Cooper, P. Dobelis, A. Varnell, K. Staley, D. Cooper, Nicotinic α7 acetylcholine receptor-mediated currents are not modulated by the tryptophan metabolite kynurenic acid in adult hippocampal interneurons, Nat. Precedings, 2011.
[25] S. Erhardt, C.K. Lim, K.R. Linderholm, S. Janelidze, D. Lindqvist, M. Samuelsson, et al., Connecting inflammation with glutamate agonism in suicidality, Neuropsychopharmacology 38 (2013) 743–752.
[26] D.H. Munn, M. Zhou, J.T. Attwood, I. Bondarev, S.J. Conway, B. Marshall, et al., Prevention of allogeneic fetal rejection by tryptophan catabolism, Science 281 (1998) 1191–1193.
[27] M. Spacek, Kynurenine in disease, with particular reference to cancer, Can. Med. Assoc. J. 73 (1955) 198–201.
[28] L. Musajo, C.A. Benassi, A. Parpajola, Excretion and isolation of kynurenine and 3-hydroxykynurenine from human pathological urine, Clin. Chim. Acta 1 (1956) 229–235.
[29] S. Löb, A. Königsrainer, D. Zieker, B.L.L. Brücher, H.-G.G. Rammensee, G. Opelz, et al., IDO1 and IDO2 are expressed in human tumors: levo- but not dextro-1-methyl tryptophan inhibits tryptophan catabolism, Cancer Immunol. Immunother. 58 (2009) 153–157.
[30] D.H. Munn, M.D. Sharma, B. Baban, H.P. Harding, Y. Zhang, D. Ron, et al., GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase, Immunity 22 (2005) 633–642.
[31] A. Reano, M.-H. Richard, L. Denoroy, J. Viac, J.-P. Benedetto, D. Schmitt, Gamma interferon potently induces tryptophanyl-tRNA synthetase expression in human keratinocytes, J. Invest. Dermatol. 100 (1993) 775–779.
[32] A.A. Badawy, A.M. Namboodiri, J.R. Moffett, The end of the road for the tryptophan depletion concept in pregnancy and infection, Clin. Sci. 130 (2016) 1327–1333.
[33] J.A. Allen, A. Peterson, R. Sufit, M.E. Hinchcliff, J.M. Mahoney, T.A. Wood, et al., Post-epidemic eosinophilia-myalgia syndrome associated with L-tryptophan, Arthritis Rheum. 63 (2011) 3633–3639.
[34] E.M. Kilbourne, R.M. Philen, M.L. Kamb, H. Falk, Tryptophan produced by Showa Denko and epidemic eosinophilia-myalgia syndrome. J. Rheumatol. Suppl. 1996; 46: pp. 81–88; discussion 9-91.
[35] M.A. Shehata, A.C. Nohr, D. Lissa, C. Bisig, V. Isberg, K.B. Andersen, et al., Novel agonist bioisosteres and common structure-activity relationships for the orphan G protein-coupled receptor GPR139, Sci. Rep. 6 (2016) 36681.
[36] M. Yu, M. Lizarzaburu, A. Motani, Z. Fu, X. Du, J.J. Liu, et al., Aminopyrazole-phenylalanine based GPR142 agonists: discovery of tool compound and in vivo efficacy studies, ACS Med. Chem. Lett. 4 (2013) 829–834.
[37] M. Murakoshi, H. Kuwabara, M. Nagasaki, Y.M. Xiong, J.D. Reagan, H. Maeda, et al., Discovery and pharmacological effects of a novel GPR142 antagonist, J. Recept. Signal Transduct. Res. 37 (2017) 290–296.
[38] T. Hayashi, J.-H. Mo, X. Gong, C. Rossetto, A. Jang, L. Beck, et al., 3-Hydroxyanthranilic acid inhibits PDK1 activation and suppresses experimental asthma by inducing T cell apoptosis, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 18619–18624.
[39] M. Mailankot, R.H. Nagaraj, Induction of indoleamine 2,3-dioxygenase by interferon-gamma in human lens epithelial cells: apoptosis through the formation of 3-hydroxykynurenine, Int. J. Biochem. Cell Biol. 42 (2010) 1446–1454.
[40] F. Fallarino, U. Grohmann, C. Vacca, R. Bianchi, C. Orabona, A. Spreca, et al., T cell apoptosis by tryptophan catabolism, Cell Death Diff. 9 (2002) 1069–1077.
[41] M.C. Barth, N. Ahluwalia, T.J. Anderson, G.J. Hardy, S. Sinha, J.A. Alvarez-Cardona, et al., Kynurenic acid triggers firm arrest of leukocytes to vascular endothelium under flow conditions, J. Biol. Chem. 284 (2009) 19189–19195.
[42] Y. Wang, H. Liu, G. McKenzie, P.K. Witting, J.-P.P. Stasch, M. Hahn, et al., Kynurenine is an endothelium-derived relaxing factor produced during inflammation, Nat. Med. 16 (2010) 279–285.
[43] J.D. Mezrich, J.H. Fechner, X. Zhang, B.P. Johnson, W.J. Burlingham, C.A. Bradfield, An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells, J. Immunol. 185 (2010) 3190–3198.
[44] A. Molano, P.A. Illarionov, G.S. Besra, C. Putterman, S.A. Porcelli, Modulation of invariant natural killer T cell cytokine responses by indoleamine 2,3-dioxygenase, Immunol. Lett. 117 (2008) 81–90.
[45] M. Maes, I. Mihaylova, M.D. Ruyter, M. Kubera, E. Bosmans, The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation, Neuro Endocrinol Lett. 28 (2007) 826–831.
[46] Q. Li, J.L. Harden, C.D. Anderson, N.K. Egilmez, Tolerogenic phenotype of IFN-γ-induced IDO+dendritic cells is maintained via an autocrine IDO-kynurenine/AhR-IDO loop, J. Immunol. 197 (2016) 962–970.
[47] U.M. Litzenburger, C.A. Opitz, F. Sahm, K.J. Rauschenbach, S. Trump, M. Winter, et al., Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR, Oncotarget. 5 (2014) 1038–1051.
[48] S.G. Tullius, H.R. Biefer, S. Li, A.J. Trachtenberg, K. Edtinger, M. Quante, et al., NAD+protects against EAE by regulating CD4+T-cell differentiation, Nat. Commun. 5 (2014) 5101.
[49] A. Elkhal, H. Rodriguez Cetina Biefer, T. Heinbokel, H. Uehara, M. Quante, M. Seyda, et al., NAD(+) regulates Treg cell fate and promotes allograft survival via a systemic IL-10 production that is CD4(+) CD25(+) Foxp3(+) T cells independent, Sci. Rep. 6 (2016) 22325.
[50] M. Favennec, B. Hennart, R. Caiazzo, A. Leloire, L. Yengo, M. Verbanck, et al., The kynurenine pathway is activated in human obesity and shifted toward kynurenine monooxygenase activation, Obesity. 23 (2015) 2066–2074.
[51] A.W.S. Yeung, A.C. Terentis, N.J.C. King, S.R. Thomas, Role of indoleamine 2,3-dioxygenase in health and disease, Clin. Sci. 129 (2015) 601–672.
[52] J.J. Liu, S. Raynal, D. Bailbé, B. Gausseres, C. Carbonne, V. Autier, et al., Expression of the kynurenine pathway enzymes in the pancreatic islet cells. Activation by cytokines and glucolipotoxicity, Biochem. Biophys. Acta 1852 (2015) 980–991.
[53] A.-S.S. Johansson, B. Owe-Larsson, L. Asp, T. Kocki, M. Adler, J. Hetta, et al., Activation of kynurenine pathway in ex vivo fibroblasts from patients with bipolar disorder or schizophrenia: cytokine challenge increases production of 3-hydroxykynurenine, J. Psychiatr. Res. 2013; 47: pp. 1815–1823.
[54] I. Jung, M.-G. Lee, J. Chang, J. Lee, Y.-I. Jeong, C.-M. Lee, et al., Blockade of indoleamine 2,3-dioxygenase protects mice against lipopolysaccharide-induced endotoxin shock, J. Immunol. 182 (2009) 3146–3154.
[55] C. Liebau, A.W. Baltzer, S. Schmidt, C. Roesel, C. Karreman, J.B. Prisack, et al., Interleukin-12 and interleukin-18 induce indoleamine 2,3-dioxygenase (IDO) activity in human osteosarcoma cell lines independently from interferon-gamma, Anticancer Res. 22 (2002) 931–936.
[56] D. Cibrian, M.L.L. Saiz, H. de la Fuente, R. Sánchez-Díaz, O. Moreno-Gonzalo, I. Jorge, et al., CD69 controls the uptake of L-tryptophan through LAT1-CD98 and AhR-dependent secretion of IL-22 in psoriasis, Nat. Immunol. 17 (2016) 985–996.
[57] J. Diegelmann, T. Olszak, B. Göke, R.S. Blumberg, S. Brand, A novel role for interleukin-27 (IL-27) as mediator of intestinal epithelial barrier protection mediated via differential signal transducer and activator of transcription (STAT) protein signaling and induction of antibacterial and anti-inflammatory proteins, J. Biol. Chem. 287 (2012) 286–298.
[58] J. Chalise, M. Pallotta, S. Narendra, B. Carlsson, A. Iacono, J. Namale, et al., IDO1 and TGF-β mediate protective effects of IFN-α in antigen-induced arthritis, J. Immunol. 197 (2016) 3142–3151.
[59] G.J. Guillemin, S.J. Kerr, L.A. Pemberton, D.G. Smith, G.A. Smythe, P.J. Armati, et al., IFN-β1bInduces kynurenine pathway metabolism in human macrophages: potential implications for multiple sclerosis treatment, J. Interferon Cytokine Res. 21 (2001) 1097–1101.
[60] J. Croitoru-Lamoury, F.M. Lamoury, M. Caristo, K. Suzuki, D. Walker, O. Takikawa, et al., Interferon-γ regulates the proliferation and differentiation of mesenchymal stem cells via activation of indoleamine 2,3 dioxygenase (IDO), PLoS One 6 (2011) e14698.
[61] J.M. Fox, J.M. Crabtree, L.K. Sage, S.M. Tompkins, R.A. Tripp, Interferon lambda upregulates IDO1 expression in respiratory epithelial cells after influenza virus infection, J. Interferon Cytokine Res. 35 (2015) 554–562.
[62] J. Yu, Y. Wang, F. Yan, P. Zhang, H. Li, H. Zhao, et al., Noncanonical NF-kappaB

activation mediates STAT3-stimulated IDO upregulation in myeloid-derived suppressor cells in breast cancer, J. Immunol. 193 (2014) 2574–2586.
[63] S.W. Tas, M.J. Vervoordeldonk, N. Hajji, J.H.N. Schuitemaker, K.F. van der Sluijs, M.J. May, et al., Noncanonical NF-κB signaling in dendritic cells is required for indoleamine 2,3-dioxygenase (IDO) induction and immune regulation, Blood 110 (2007) 1540–1549.
[64] Y. Wang, M.A. Lawson, R. Dantzer, K.W. Kelley, LPS-induced indoleamine 2,3-dioxygenase is regulated in an interferon-γ-independent manner by a JNK signaling pathway in primary murine microglia, Brain Behav. Immun. 24 (2010) 201–209.
[65] P. Hwu, M.X. Du, R. Lapointe, M. Do, M.W. Taylor, H.A. Young, Indoleamine 2,3-dioxygenase production by human dendritic cells results in the inhibition of T cell proliferation, J. Immunol. 164 (2000) 3596–3599.
[66] F. Orhan, M. Bhat, K. Sandberg, S. Ståhl, F. Piehl, consortium K, et al., Tryptophan metabolism along the kynurenine pathway downstream of toll-like receptor stimulation in peripheral monocytes, Scand. J. Immunol. 84 (2016) 262–271.
[67] U. Grohmann, R. Bianchi, C. Orabona, F. Fallarino, C. Vacca, A. Micheletti, et al., Functional plasticity of dendritic cell subsets as mediated by CD40 versus B7 activation, J. Immunol. 171 (2003) 2581–2587.
[68] P. Puccetti, U. Grohmann, IDO and regulatory T cells: a role for reverse signalling and non-canonical NF-κB activation, Nat. Rev. Immunol. 7 (2007) 817–823.
[69] M.L. Belladonna, U. Grohmann, P. Guidetti, C. Volpi, R. Bianchi, M.C. Fioretti, et al., Kynurenine pathway enzymes in dendritic cells initiate tolerogenesis in the absence of functional IDO, J. Immunol. 177 (2006) 130–137.
[70] C. Orabona, M.T. Pallotta, C. Volpi, F. Fallarino, C. Vacca, R. Bianchi, et al., SOCS3 drives proteasomal degradation of indoleamine 2,3-dioxygenase (IDO) and antagonizes IDO-dependent tolerogenesis, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 20828–20833.
[71] U. Grohmann, F. Fallarino, R. Bianchi, M.L. Belladonna, C. Vacca, C. Orabona, et al., IL-6 inhibits the tolerogenic function of CD8 alpha + dendritic cells expressing indoleamine 2,3-dioxygenase, J. Immunol. 167 (2001) 708–714.
[72] C. Orabona, U. Grohmann, M. Belladonna, F. Fallarino, C. Vacca, R. Bianchi, et al., CD28 induces immunostimulatory signals in dendritic cells via CD80 and CD86, Nat. Immunol. 5 (2004) 1134–1142.
[73] T. Musso, G.L. Gusella, A. Brooks, D.L. Longo, L. Varesio, Interleukin-4 inhibits indoleamine 2,3-dioxygenase expression in human monocytes, Blood 83 (1994) 1408–1411.
[74] S.A. Sarkar, R. Wong, S.I. Hackl, O. Moua, R.G. Gill, A. Wiseman, et al., Induction of indoleamine 2,3-dioxygenase by interferon-gamma in human islets, Diabetes 56 (2007) 72–79.
[75] Y. Yanagawa, K. Iwabuchi, K. Onoe, Co-operative action of interleukin-10 and interferon-gamma to regulate dendritic cell functions, Immunology 127 (2009) 345–353.
[76] J.Y. Lim, K.I. Im, E.S. Lee, N. Kim, Y.S. Nam, Y.W. Jeon, et al., Enhanced immunoregulation of mesenchymal stem cells by IL-10-producing type 1 regulatory T cells in collagen-induced arthritis, Sci. Rep. 6 (2016) 26851.
[77] M. Pallotta, C. Orabona, R. Bianchi, C. Vacca, F. Fallarino, M. Belladonna, et al., Forced IDO1 expression in dendritic cells restores immunoregulatory signalling in autoimmune diabetes, J. Cell Mol. Med. 18 (2014) 2082–2091.
[78] M.T. Pallotta, C. Orabona, C. Volpi, C. Vacca, M.L. Belladonna, R. Bianchi, et al., Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells, Nat. Immunol. 12 (2011) 870–878.
[79] W. Yuan, A. Collado-Hidalgo, T. Yufit, M. Taylor, J. Varga, Modulation of cellular tryptophan metabolism in human fibroblasts by transforming growth factor-beta: selective inhibition of indoleamine 2,3-dioxygenase and tryptophanyl-tRNA synthetase gene expression, J. Cell. Physiol. 177 (1998) 174–186.
[80] N. Braidy, H. Rossez, C.K. Lim, B.-E. Jugder, B.J. Brew, G.J. Guillemin, Characterization of the kynurenine pathway in CD8 + human primary monocyte-derived dendritic cells, Neurotox. Res. 30 (2016) 620–632.
[81] D. Sheipouri, R. Grant, S. Bustamante, D. Lovejoy, G.J. Guillemin, N. Braidy, Characterisation of the kynurenine pathway in skin-derived fibroblasts and keratinocytes, J. Cell. Biochem. 116 (2015) 903–922.
[82] L. Asp, A.-S. Johansson, A. Mann, B. Owe-Larsson, E.M. Urbanska, T. Kocki, et al., Effects of pro-inflammatory cytokines on expression of kynurenine pathway enzymes in human dermal fibroblasts, J. Inflamm. (Lond.) 8 (2011) 1–7.
[83] J.L. Harden, S.M. Lewis, S.R. Lish, M. Suárez-Fariñas, D. Gareau, T. Lentini, et al., The tryptophan metabolism enzyme L-kynureninase is a novel inflammatory factor in psoriasis and other inflammatory diseases, J. Allergy Clin. Immunol. 137 (2016) 1830–1840.
[84] Y. Murakami, T. Ishibashi, E. Tomita, Y. Imamura, T. Tashiro, K. Watcharanurak, et al., Depressive symptoms as a side effect of Interferon-α therapy induced by induction of indoleamine 2,3-dioxygenase 1, Sci. Rep. 6 (2016) 29920.
[85] P.A. Zunszain, C. Anacker, A. Cattaneo, S. Choudhury, K. Musaelyan, A.M. Myint, et al., Interleukin-1β: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis, Neuropsychopharmacology 37 (2012) 939–949.
[86] F.O. Martinez, S. Gordon, M. Locati, A. Mantovani, Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression, J. Immunol. 177 (2006) 7303–7311.
[87] D.E. Comings, D. Muhleman, G. Dietz, M. Sherman, G.L. Forest, Sequence of human tryptophan 2,3-dioxygenase (TDO2): presence of a glucocorticoid response-like element composed of a GTT repeat and an intronic CCCCT repeat, Genomics 29 (1995) 390–396.
[88] I.P. Braidman, D.P. Rose, Effects of sex hormones on three glucocorticoid-inducible enzymes concerned with amino acid metabolism in rat liver, Endocrinology 89 (1971) 1250–1255.
[89] T. Nakamura, H. Shinno, A. Ichihara, Insulin and glucagon as a new regulator system for tryptophan oxygenase activity demonstrated in primary cultured rat hepatocytes, J. Biol. Chem. 255 (1980) 7533–7535.
[90] W.E. Knox, A.H. Mehler, The adaptive increase of the tryptophan peroxidase-oxidase system of liver, Science 113 (1951) 237–238.
[91] A. Badawy, C.J. Morgan, Rapid isocratic liquid chromatographic separation and quantification of tryptophan and six kynurenine metabolites in biological samples with ultraviolet and fluorimetric detection, Int. J. Tryptophan. Res. 3 (2010) 175–186.
[92] T.P. Obrenovitch, Quinolinic acid accumulation during neuroinflammation. Does it imply excitotoxicity? Ann. NY Acad. Sci. 939 (2001) 1–10.
[93] G. Oxenkrug, M. Turski, M. Turska, P. Paluszkiewicz, J. Parada-Turska, G. Oxenkrug, Kynurenic acid in the digestive system—new facts, new challenges, Int. J. Tryptophan. Res. 6 (2013) 47–55.
[94] P. Terness, T.M. Bauer, L. Röse, C. Dufter, A. Watzlik, H. Simon, et al., Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase–expressing dendritic cells mediation of suppression by tryptophan metabolites, J. Exp. Med. 196 (2002) 447–457.
[95] M.M. Lowe, J.E. Mold, B. Kanwar, Y. Huang, A. Louie, M.P. Pollastri, et al., Identification of cinnabarinic acid as a novel endogenous aryl hydrocarbon receptor ligand that drives IL-22 production, PLoS One 9 (2014) e87877.
[96] D. Favre, J. Mold, P.W. Hunt, B. Kanwar, P. Loke, L. Seu, et al. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Sci. Transl. Med. 2010; 2: 32ra6.
[97] L. Romani, F. Fallarino, A. Luca, C. Montagnoli, C. D'Angelo, T. Zelante, et al., Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease, Nature 451 (2008) 211–215.
[98] Y. Yan, G.-X. Zhang, B. Gran, F. Fallarino, S. Yu, H. Li, et al., IDO upregulates regulatory T cells via tryptophan catabolite and suppresses encephalitogenic T cell responses in experimental autoimmune encephalomyelitis, J. Immunol. 185 (2010) 5953–5961.
[99] M.D. Sharma, L. Huang, J.-H. Choi, E.-J. Lee, J.M. Wilson, H. Lemos, et al., An inherently bifunctional subset of Foxp3 + T helper cells is controlled by the transcription factor Eos, Immunity 38 (2013) 998–1012.
[100] W.-S. Lee, S.-M. Lee, M.-K. Kim, S.-G. Park, I.-W. Choi, I. Choi, et al., The tryptophan metabolite 3-hydroxyanthranilic acid suppresses T cell responses by inhibiting dendritic cell activation, Int. Immunopharmacol. 17 (2013) 721–726.
[101] J.E. Cole, N. Astola, A.P. Cribbs, M.E. Goddard, I. Park, P. Green, et al., Indoleamine 2,3-dioxygenase-1 is protective in atherosclerosis and its metabolites provide new opportunities for drug development, Proc. Natl. Acad. Sci. U.S.A. 112 (2015) 13033–13038.
[102] J. Xu, J. Wei, M. Huang, X. Zhu, J. Guan, J. Yin, et al., Tryptophan metabolite analog, N-(3,4-dimethoxycinnamonyl) anthranilic acid, ameliorates acute graft-versus-host disease through regulating T cell proliferation and polarization, Int. Immunopharmacol. 17 (2013) 601–607.
[103] Q. Wen, L. Zhou, H. Chen, Y. Zhang, N-(3', 4'-dimethoxycinnamonyl) anthranilic acid alleviated experimental colitis by inhibiting autoimmune response and inducing CD4 + CD25 + regulatory T cells production, J. Gastroenterol. Hepatol. 28 (2013) 1330–1338.
[104] J.J. Inglis, G. Criado, M. Andrews, M. Feldmann, R.O. Williams, M.L. Selley, The anti-allergic drug, N-(3',4'-dimethoxycinnamonyl) anthranilic acid, exhibits potent anti-inflammatory and analgesic properties in arthritis, Rheumatology (Oxf). 46 (2007) 1428–1432.
[105] J. Małaczewska, A.K. Siwicki, R.M. Wójcik, W.A. Turski, E. Kaczorek, The effect of kynurenic acid on the synthesis of selected cytokines by murine splenocytes – in vitro and ex vivo studies, Cent. Eur. J. Immunol. 1 (2016) 39–46.
[106] S. Fallarini, L. Magliulo, T. Paoletti, C. de Lalla, G. Lombardi, Expression of functional GPR35 in human iNKT cells, Biochem. Biophys. Res. Commun. 398 (2010) 420–425.
[107] S. Metghalchi, P. Ponnuswamy, T. Simon, Y. Haddad, L. Laurans, M. Clément, et al., Indoleamine 2,3-dioxygenase fine-tunes immune homeostasis in atherosclerosis and colitis through repression of interleukin-10 production, Cell Metab. 22 (2015) 460–471.
[108] R. Hiramatsu, T. Hara, H. Akimoto, O. Takikawa, T. Kawabe, K.-I. Isobe, et al., Cinnabarinic acid generated from 3-hydroxyanthranilic acid strongly induces apoptosis in thymocytes through the generation of reactive oxygen species and the induction of caspase, J. Cell. Biochem. 103 (2008) 42–53.
[109] I. Monteleone, A. Rizzo, M. Sarra, G. Sica, P. Sileri, L. Biancone, et al., Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract, Gastroenterology 141 (2011) 237–2480.
[110] P. Wei, Hu. G-h, Kang H-y, Yao H-b, W. Kou, H. Liu, et al., An aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress the Th17 response in allergic rhinitis patients, Lab. Invest. 94 (2014) 528–535.
[111] F.J. Quintana, D.H. Sherr, Aryl hydrocarbon receptor control of adaptive immunity, Pharmacol. Rev. 65 (2013) 1148–1161.
[112] K. Maaetoft-Udsen, L.M. Shimoda, H. Frøkiær, H. Turner, Aryl hydrocarbon receptor ligand effects in RBL2H3 cells, J. Immunol. 9 (2012) 327–337.
[113] H. Kawasaki, H.W. Chang, H.C. Tseng, S.C. Hsu, S.J. Yang, C.H. Hung, et al., A tryptophan metabolite, kynurenine, promotes mast cell activation through aryl hydrocarbon receptor, Allergy 69 (2014) 445–452.
[114] M.S. Denison, A.A. Soshilov, G. He, D.E. DeGroot, B. Zhao, Exactly the same but different: promiscuity and diversity in the molecular mechanisms of action of the aryl hydrocarbon (dioxin) receptor, Toxicol. Sci. 124 (2011) 1–22.
[115] R. Nuti, M. Gargaro, D. Matino, D. Dolciami, U. Grohmann, P. Puccetti, et al., Ligand binding and functional selectivity of L-tryptophan metabolites at the mouse aryl hydrocarbon receptor (mAhR), J. Chem. Inf. Model 54 (2014) 3373–3383.
[116] K.A. Polyzos, D.F. Ketelhuth, The role of the kynurenine pathway of tryptophan

metabolism in cardiovascular disease, Emerg. Field Hamostaseologie 35 (2015) 128–136.
[117] W. Swardfager, N. Herrmann, Y. Dowlati, P.I. Oh, A. Kiss, S.E. Walker, et al., Indoleamine 2,3-dioxygenase activation and depressive symptoms in patients with coronary artery disease, Psychoneuroendocrinology 34 (2009) 1560–1566.
[118] B. Wirleitner, V. Rudzite, G. Neurauter, C. Murr, U. Kalnins, A. Erglis, et al., Immune activation and degradation of tryptophan in coronary heart disease, Eur. J. Clin. Invest. 33 (2003) 550–554.
[119] Y. Ozkan, M.K. Sukuroglu, M. Tulmac, U. Kisa, B. Simsek, Relation of kynurenine/tryptophan with immune and inflammatory markers in coronary artery disease, Clin Lab. 60 (2014) 391–396.
[120] E.R. Pedersen, Ø. Midttun, P.M. Ueland, H. Schartum-Hansen, R. Seifert, J. Igland, et al., Systemic markers of interferon-γ-mediated immune activation and long-term prognosis in patients with stable coronary artery disease, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 698–704.
[121] S. Eussen, P. Ueland, S.E. Vollset, O. Nygård, Ø. Midttun, G. Sulo, et al., Kynurenines as predictors of acute coronary events in the Hordaland Health Study, Int. J. Cardiol. 189 (2015) 18–24.
[122] G. Sulo, S.E. Vollset, O. Nygård, Ø. Midttun, P.M. Ueland, S.J. Eussen, et al., Neopterin and kynurenine-tryptophan ratio as predictors of coronary events in older adults, the Hordaland Health Study, Int. J. Cardiol. 168 (2013) 1435–1440.
[123] P. Niinisalo, A. Raitala, M. Pertovaara, S.S. Oja, T. Lehtimäki, M. Kähönen, et al., Indoleamine 2,3-dioxygenase activity associates with cardiovascular risk factors: The Health 2000 study, Scand. J. Clin. Lab. Invest. 68 (2009) 767–770.
[124] M. Pertovaara, A. Raitala, M. Juonala, T. Lehtimäki, H. Huhtala, S.S. Oja, et al., Indoleamine 2,3-dioxygenase enzyme activity correlates with risk factors for atherosclerosis: the Cardiovascular Risk in Young Finns Study, Clin. Exp. Immunol. 148 (2007) 106–111.
[125] K. Pawlak, T. Domaniewski, M. Mysliwiec, D. Pawlak, The kynurenines are associated with oxidative stress, inflammation and the prevalence of cardiovascular disease in patients with end-stage renal disease, Atherosclerosis 204 (2009) 309–314.
[126] K. Pawlak, A. Kowalewska, M. Mysliwiec, D. Pawlak, 3-hydroxyanthranilic acid is independently associated with monocyte chemoattractant protein-1 (CCL2) and macrophage inflammatory protein-1beta (CCL4) in patients with chronic kidney disease, Clin. Biochem. 43 (2010) 1101–1106.
[127] K. Pawlak, M. Myśliwiec, D. Pawlak, Kynurenine pathway - a new link between endothelial dysfunction and carotid atherosclerosis in chronic kidney disease patients, Adv. Med. Sci. 55 (2010) 196–203.
[128] P. Niinisalo, N. Oksala, M. Levula, M. Pelto-Huikko, O. Järvinen, J.-P. Salenius, et al., Activation of indoleamine 2,3-dioxygenase-induced tryptophan degradation in advanced atherosclerotic plaques: Tampere Vascular Study, Ann. Med. 42 (2009) 55–63.
[129] J.B. Sakash, G.I. Byrne, A. Lichtman, P. Libby, Cytokines induce indoleamine 2,3-dioxygenase expression in human atheroma-associated cells: Implications for persistent chlamydophila pneumoniae infection, Infect. Immun. 70 (2002) 3959–3961.
[130] M.C. Cuffy, A.M. Silverio, L. Qin, Y. Wang, R. Eid, G. Brandacher, et al., Induction of indoleamine 2,3-dioxygenase in vascular smooth muscle cells by interferon-gamma contributes to medial immunoprivilege, J. Immunol. 179 (2007) 5246–5254.
[131] K.A. Polyzos, O. Ovchinnikova, M. Berg, R. Baumgartner, H. Agardh, J. Pirault, et al., Inhibition of indoleamine 2,3-dioxygenase promotes vascular inflammation and increases atherosclerosis in Apoe−/− mice, Cardiovasc. Res. 106 (2015) 295–302.
[132] K. Nakajima, T. Yamashita, T. Kita, M. Takeda, N. Sasaki, K. Kasahara, et al., Orally administered eicosapentaenoic acid induces rapid regression of atherosclerosis via modulating the phenotype of dendritic cells in LDL receptor-deficient mice, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 1963–1972.
[133] I. Daissormont, A. Christ, L. Temmerman, S. Millares, T. Seijkens, M. Manca, et al., Plasmacytoid dendritic cells protect against atherosclerosis by tuning T-Cell proliferation and activity novelty and significance, Circ. Res. 109 (2011) 1387–1395.
[134] T.J. Yun, J.S. Lee, K. Machmach, D. Shim, J. Choi, Y.J. Wi, et al., Indoleamine 2,3-Dioxygenase-expressing aortic plasmacytoid dendritic cells protect against atherosclerosis by induction of regulatory T Cells, Cell Metab. 24 (2016) 886.
[135] L. Zhang, O. Ovchinnikova, A. Jonsson, A.M. Lundberg, M. Berg, G.K. Hansson, et al., The tryptophan metabolite 3-hydroxyanthranilic acid lowers plasma lipids and decreases atherosclerosis in hypercholesterolaemic mice, Eur. Heart J. 33 (2012) 2025–2034.
[136] T. Matsumura, K. Kugiyama, S. Sugiyama, Y. Ota, H. Doi, N. Ogata, et al., Suppression of atherosclerotic development in Watanabe heritable hyperlipidemic rabbits treated with an oral antiallergic drug, tranilast, Circulation 1999; 99: pp. 919–924.
[137] D.R. Holmes, M. Savage, J.M. LaBlanche, L. Grip, P.W. Serruys, P. Fitzgerald, et al., Results of prevention of REStenosis with tranilast and its outcomes (PRESTO) trial, Circulation 106 (2002) 1243–1250.
[138] S.M. Sa, P.A. Valdez, J. Wu, K. Jung, F. Zhong, L. Hall, et al., The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis, J. Immunol. 178 (2007) 2229–2240.
[139] S. Parlato, G. Romagnoli, F. Spadaro, I. Canini, P. Sirabella, P. Borghi, et al., LOX-1 as a natural IFN-α–mediated signal for apoptotic cell uptake and antigen presentation in dendritic cells, Blood 115 (2010) 1554–1563.
[140] S. Eminel, N. Jin, M. Rostami, S. Dibbert, U. Mrowietz, I. Suhrkamp, Dimethyl- and monomethylfumarate regulate indoleamine 2,3-dioxygenase (IDO) activity in human immune cells, Exp. Dermatol. 26 (2016) 685–690.
[141] K.A. Swanson, Y. Zheng, K.M. Heidler, T. Mizobuchi, D.S. Wilkes, CDllc + cells modulate pulmonary immune responses by production of indoleamine 2,3-dioxygenase, Am. J. Respir. Cell Mol. Biol. 30 (2004) 311–318.
[142] M. El-Zaatari, Y.-M.M. Chang, M. Zhang, M. Franz, A. Shreiner, A.J. McDermott, et al., Tryptophan catabolism restricts IFN-γ-expressing neutrophils and Clostridium difficile immunopathology, J. Immunol. 193 (2014) 807–816.
[143] L. Desvignes, J.D. Ernst, Interferon-γ-responsive nonhematopoietic cells regulate the immune response to mycobacterium tuberculosis, Immunity 31 (2009) 974–985.
[144] S.-M. Lee, Y.-S. Lee, J.-H. Choi, S.-G. Park, I.-W. Choi, Y.-D. Joo, et al., Tryptophan metabolite 3-hydroxyanthranilic acid selectively induces activated T cell death via intracellular GSH depletion, Immunol. Lett. 132 (2010) 53–60.
[145] M. Hill, S. Tanguy-Royer, P. Royer, C. Chauveau, K. Asghar, L. Tesson, et al., IDO expands human CD4 + CD25high regulatory T cells by promoting maturation of LPS-treated dendritic cells, Eur. J. Immunol. 37 (2007) 3054–3062.
[146] L. Varesio, M. Clayton, E. Blasi, R. Ruffman, D. Radzioch, Picolinic acid, a catabolite of tryptophan, as the second signal in the activation of IFN-gamma-primed macrophages, J. Immunol. 145 (1990) 4265–4271.