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Tryptophan-kynurenine pathway is dysregulated in inflammation, and immune activation

Qiongxin Wang[1], Danxia Liu[2], Ping Song[1], Ming-Hui Zou[1]

[1]Division of Molecular Medicine, Department of Medicine, and Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA, [2]Division of Cardiology and Endocrinology, Department of Internal Medicine, Hubei Provincial Corps Hospital, Chinese People's Armed Police Forces, Wuhan, Hubei 430061, China

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1. ABSTRACT

The kynurenine (Kyn) pathway is the major route for tryptophan (Trp) metabolism, and it contributes to several fundamental biological processes. Trp is constitutively oxidized by tryptophan 2, 3-dioxygenase in liver cells. In other cell types, it is catalyzed by an alternative inducible indoleamine-pyrrole 2, 3-dioxygenase (IDO) under certain pathophysiological conditions, which consequently increases the formation of Kyn metabolites. IDO is up-regulated in response to inflammatory conditions as a novel marker of immune activation in early atherosclerosis. Besides, IDO and the IDO-related pathway are important mediators of the immunoinflammatory responses in advanced atherosclerosis. In particular, Kyn, 3-hydroxykynurenine, and quinolinic acid are positively associated with

inflammation, oxidative stress (SOX), endothelial dysfunction, and carotid artery intima-media thickness values in end-stage renal disease patients. Moreover, IDO is a potential novel contributor to vessel relaxation and metabolism in systemic infections, which is also activated in acute severe heart attacks. The Kyn pathway plays a key role in the increased prevalence of cardiovascular disease by regulating inflammation, SOX, and immune activation.

2. INTRODUCTION

Tryptophan (Trp) is the least abundant of all essential amino acids, and it is necessary for protein synthesis. The liver metabolizes Trp to maintain serum concentrations of 50–100 μM. In addition to being one of the building blocks for protein synthesis in humans and animals, Trp is the only source of substrate for the production of several important molecules.

The major catabolic route of Trp in mammals is the kynurenine (Kyn) pathway, which ultimately leads to the biosynthesis of the essential cofactor, nicotinamide adenine dinucleotide (NAD^+) (1, 2). This pathway accounts for >90% of peripheral Trp metabolism in mammals (3). The Kyn pathway plays an important role in several fundamental biological processes, including central nervous system (CNS) disorders (4-8), peripheral disorders (9, 10), infections (11, 12), immunoregulation (10, 13, 14), and ultraviolet protection and cataract formation in the lens (15, 16). Recently, the Kyn pathway has drawn considerable attention as an important factor in the pathogenesis of cardiovascular disease (CVD). As inflammation, oxidative stress (SOX), and immune activation have been postulated to be crucially involved in the pathogenesis of atherosclerosis and CVD, it is important to study the possible role of the Kyn pathway in CVD in relation to these contributing factors.

3. KYNURENINE PATHWAY

The metabolic fate of Trp is dependent on various factors, including Trp availability and enzyme activities, which modulate the synthesis of Trp-derived Kynurenines.

The initial and rate-limiting reaction of the Kyn pathway is the oxidation of Trp to N-formyl-Kynurenine (Nfk) (1, 17). In liver cells, Trp is constitutively oxidized by tryptophan 2, 3-dioxygenase (TDO, also known as tryptophan oxygenase and L-tryptophan pyrrolase) to Nfk. In other types of cells, Trp can be metabolized to Nfk by an alternative inducible enzyme, indoleamine-pyrrole 2,3-dioxygenase (IDO, also known as tryptophan pyrrolase), which is transcribed under certain pathophysiological conditions (1, 17-21)_ENREF_16. Both TDO and IDO contain one noncovalently bound iron–protoporphyrin IX per monomer. In addition, they belong to the family of oxidoreductases, specifically those acting on single donors with O_2 as the oxidant and the incorporation of two atoms of oxygen into the substrate (oxygenases) (1, 19, 22)_ENREF_18. The incorporated oxygen does not need to be derived from O_2 (23). Nfk then decomposes spontaneously to formic acid and Kyn. The expression of TDO is induced by Trp itself and by steroids, whereas IDO is powerfully induced by proinflammatory stimuli and T-helper cell-derived cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 (7, 8, 24), and interferon (IFN)-γ, in several cell types (7, 11, 15, 16, 25-31).

Following its synthesis by IDO, Kyn can be further metabolized by various enzymes (Figure1) (1, 32-34). Kynureninase produces anthranilic acid (AA) from Kyn (35, 36). Kynurenine-3-monooxygenase (KMO) converts Kyn into the neurotoxic free-radical generator, 3-hydroxykynurenine (3-OHkyn) (37), which can be taken by kynurenine aminotransferase (KAT) to produce xanthurenic acid (XA) or by the kynureninase to form 3-hydroxyanthranilic acid (3-HAA). 3-HAA is further metabolized to the excitotoxin, quinolinic acid (QA), which is a powerful excitant and convulsant (38, 39). In addition, KAT metabolizes Kyn into kynurenic acid (KYNA) (40), which is a neuroprotective compound due to its N-methyl-D-aspartate (NMDA) receptor antagonist properties (39). KYNA production can be catalyzed by three aminotransferases: KAT I, KAT II, and mitochondrial aspartate aminotransferase (mitAAT). KAT II is expressed predominantly in the rat and human brain (33). In human macrophages and microglia cells, IFN-γ enhances the expression and activity of KMO (27, 28). A robust increase in KMO expression is associated with high levels of TNF-α and IL-6 in the rat brain following a systemic inflammatory challenge, although no changes in KAT II expression are observed (24). However, the constitutive expression of KAT II is much higher than KMO in the rat brain (approximately 8-fold higher in cortex, and 20-fold higher in the hippocampus) (24).

AS Trp, Kyn, AA, 3-OHkyn and XA readily cross the blood-brain barrier (41-44), the effects of systemic Trp on the brain Kyn pathway are in part driven by its peripheral conversion to Kyn and 3-OHkyn, and the subsequent entry of these metabolites into the brain. In contrast to several other kynurenine pathway metabolites, and because of the polar nature and the apparent lack of efficacious transport processes, KYNA, 3-HAA and QA penetrate the blood-brain barrier poorly and must be formed locally within the brain (41, 42).

3.1. Major enzymes

3.1.1. Indoleamine-pyrrole 2, 3-dioxygenase

IDO is a heme-containing dioxygenase that catalyzes the first and rate-limiting step in the major pathway of L-Trp catabolism in mammals. The heme of

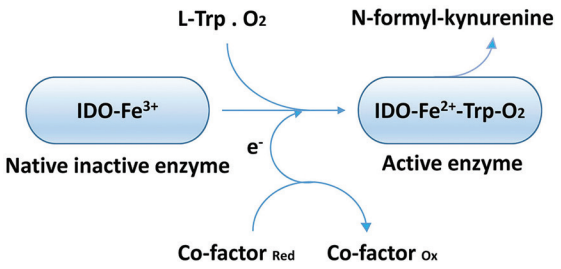

Figure 1. The catalytic properties of IDO. IDO activation involves the single electron reduction of heme-iron from the ferric to ferrous form that facilitates the subsequent binding of L-Trp and O2 to the enzyme active site and oxidation of pyrrole ring of the amino acid to form Nfk.

IDO is essential for enzyme activity, and IDO is purified in an inactive state with the heme present as ferric-iron. Its activation requires the single-electron reduction of ferric- to ferrous-iron, which facilitates the binding of L-Trp and O_2 to the active site of the enzyme (Figure 1) (1, 19, 45). The synthesized IDO holoenzyme catalyzes the oxidative cleavage of the pyrrole ring of L-Trp to generate Nfk, which is metabolized to formic acid and the stable end product, kyn (Figure 2).

IDO is expressed intracellularly in a constitutive manner in the placenta, epididymis, prostate, esophagus, intestine, colon, cecum, spleen, thymus, lung, brain, and skin (46-49). Notably, the morphological features of many IDO-expressing cells closely resemble those of antigen-presenting cells and epithelial cells (46). The tissue distribution and cellular localization characteristics of IDO serve two main functions: (1) to deplete Trp in an enclosed microenvironment, such as in the epididymal duct lumen, to prevent bacterial or viral infection, and (2) to produce bioactive Trp catabolites that suppress T-cell-mediated immune responses against self-antigens, fetal antigens, or allogeneic antigens (46, 49).

In most cell types, IDO is induced at the transcriptional level in response to specific inflammatory stimuli. IFN-γ is the principal IDO inducer *in vitro* and *in vivo*. Exposure to IFN-γ increases IDO transcription in myeloid cells (monocyte/macrophages (26-28, 50) and dendritic cells (DCs) (25, 29)), fibroblasts (15), endothelial cells (30), epithelial cells (16), smooth muscle cells (31), and many tumor cell lines (19, 51, 52). Other inflammatory stimuli, such as IFN-α, IFN-β, lipopolysaccharide (LPS), and cytotoxic T lymphocyte-associated antigen (CTLA)-4, also induce IDO to a lesser degree than that of IFN-γ (1, 8, 29, 50, 53, 54). Depending on the cell type and cytokine milieu, the IDO expression can be modulated by molecules, such as IL-4, IL-6, IL-10, TGF-α, prostaglandin (PG) E_2, CD40, suppressor of cytokine signaling 3, Bin1/amphiphysin/Rvs167 adaptor-encoding protein, and DNAX activation protein of 12 kDa (1, 7, 8, 11, 24, 29, 55). Finally, cellular infection with microbial agents (e.g., some viruses and other intracellular pathogens) (7, 11, 20, 21, 56, 57) can induce IDO in certain cell types. Vascular endothelial cells are the primary site of IDO expression in models of malaria infection, and this response is systemic, with the vascular endothelium of brain, heart, lung, spleen, and uterus staining positive for IDO (56, 57).

Once expressed, active IDO depletes L-Trp from local tissue microenvironments and promotes the formation of metabolites of the Kyn pathway. The ability of IDO to deprive cells of an essential amino acid and to promote the formation of bioactive Kynurenines underscores its biological role in many human diseases, including cancer (58-61), chronic infectious diseases (11, 51)_ENREF_44, allergy, autoimmune diseases (29, 51, 54, 62-64), neurodegeneration, psychiatric disorders (34, 65-67), and other immunosuppressive disorders (9, 10, 40).

Trp catabolism by IDO has been suggested to mediate antiproliferative effects during infection (51), especially on infectious microorganisms that may rely on Trp for growth (51). Trp-deprived T cells arrest at a mid-G1 phase of the cell cycle (52). In addition, Vassiliou *et al.* have demonstrated that the eicosapentanoic acid (EPA) metabolite-induced increase in IDO expression in DCs inhibits T-cell proliferation (68). Then, IDO increases p53 levels, and both IDO and p53 inhibit cell proliferation, glucose consumption and glycolysis in alloreactive T cells. Besides, lactate production and glutaminolysis are also suppressed by IDO (69).

Many studies have shown that IDO overexpression can blunt immune responses to neoantigens (29, 62). Cell lines overexpressing IDO limit antigen-specific T-cell responses *in vitro* (51). In murine tumor cell lines, IDO overexpression renders tumor allografts resistant to immune rejection *in vivo* (62). The ectopic expression of IDO protects allogeneic lung transplants from rejection (70). Similarly, adenoviral-mediated IDO gene transfer into pancreatic islet cells prolongs survival in allogeneic hosts (71). CTLA-4 signaling induces IDO, and pre-treatment of mice with the CTLA-4-immunoglobulin to induce IDO expression suppressed the rejection of pancreatic isl*et al*lografts (53). Then, IDO may suppress overactive immune response in the α-GalCer-induced hepatitis model (72). Deficiency of IDO exacerbated liver injury in α-GalCer-induced hepatitis. IDO induced by proinflammatory cytokines may decrease the number of TNF-α-producing immune cells including NK cells and macrophages in the liver. Moreover, recent encouraging results from phase II clinical trials of recombinant CTLA-4-immunoglobulin fusion protein in autoimmune rheumatoid arthritis (RA) (54) imply that it may be possible to induce IDO expression in settings where immunosuppression would

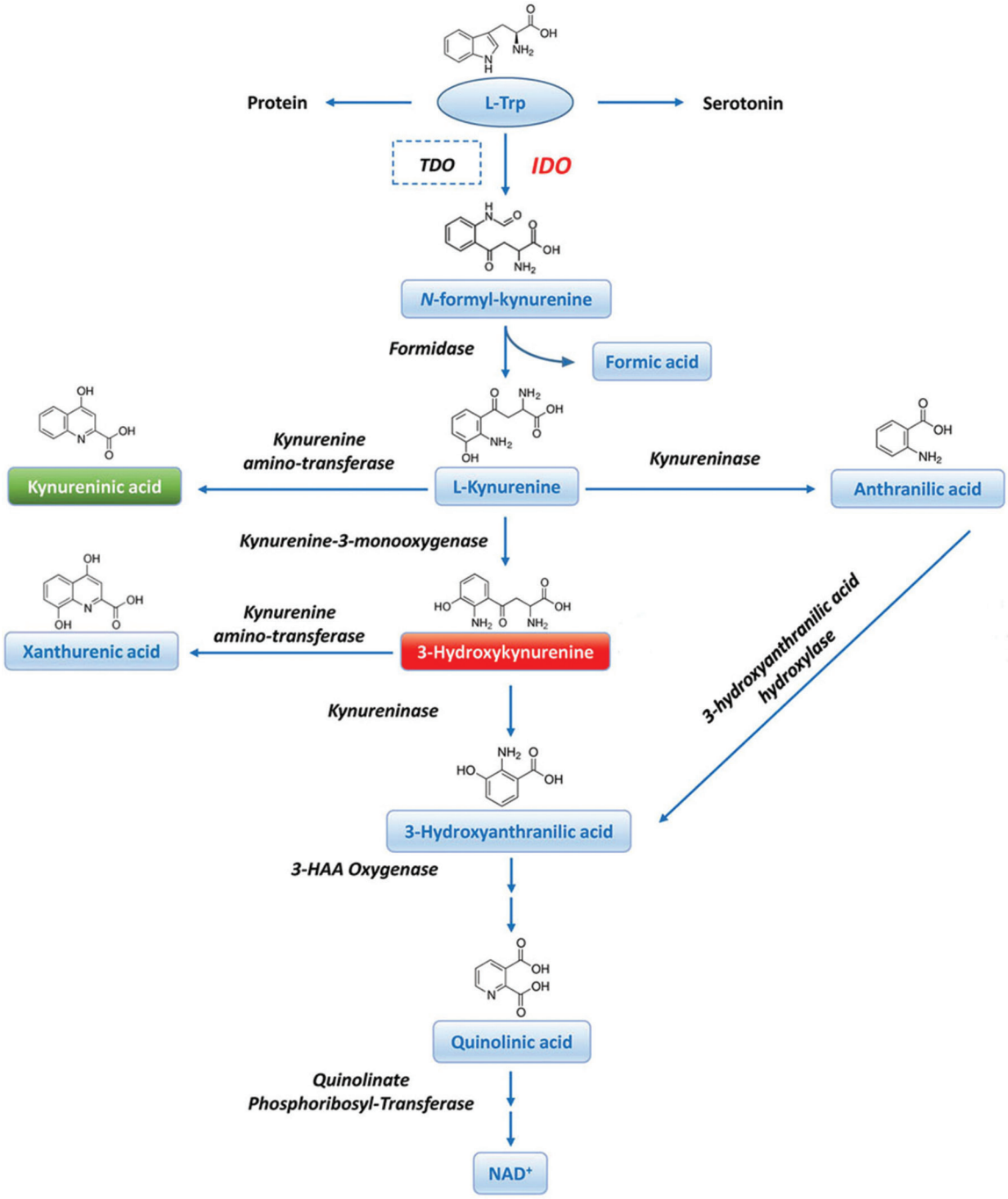

Figure 2. Schematic representation of Trp catabolism along the kyn pathway in mammals. The initial and rate-limiting step is catalyzed in the liver by TDO or in extra-hepatic tissue by IDO. Nfk is then converted to Kyn and formic acid. Depending on the cell-type, Kyn can then be catalyzed to form various metabolites, which can exhibit immunological, prooxidant, antioxidant or neurological activities. Trp, tryptophan; Nfk, N-formyl-Kynurenine; TDO, tryptophan 2, 3-dioxygenase; IDO, indoleamine- pyrrole 2,3-dioxygenase; Kyn, kynurenine; 3-OHkyn, 3-hydroxykynurenine; KYNA, kynurenic acid; XA, xanthurenic acid; 3-HAA, 3-hydroxyanthranilic acid; QUIN, quinolinic acid.

be clinically beneficial. Conversely, it has shown that IDO inhibitor 1-Methyl-DL-tryptophan (1-MT) alone or in combination of methotrexate (MTX) delays the onset and alleviates the severity of joint inflammation in a RA mouse model by blocking folate metabolism (64).

IDO is part of the molecular mechanism that contributes to tumor-induced tolerance (58, 59) and promotes cancer metastasis by inducing immunosuppressive environment (60). Host DCs expressing immunosuppressive IDO are found in

tumor-draining lymph nodes, and IDO can also be expressed by tumor cells themselves (59). IDO creates a tolerogenic milieu in the tumor and tumor-draining lymph nodes by directly suppressing T cells and enhancing local regulatory T cell-mediated immunosuppression. It can also function as an antagonist to other activators of antitumor immunity (58). Furthermore, in IDO knockout ($IDO^{-/-}$) mice treated with anti-CTLA-4 antibody, a striking delay in B16 melanoma tumor growth and increased overall survival have been observed compared to wild-type mice, as well as treated with antibodies targeting Programmed death (PD)-1/PD-Ligand 1 and glucocorticoid-induced TNFR family related gene (GITR) (61). This effect is T cell dependent, leading to enhanced infiltration of tumor-specific effector T cells and a marked increase in the effector-to-regulatory T cell ratios in the tumors.

There is evidence of a link between IDO activity and certain psychiatric disorders. Increased Trp degradation can induce serotonin depletion and depressive moods (73). Also, the downstream metabolites from this pathway, such as 3-OHkyn, QA, and KYNA (43), are neuroactive components that can modulate several neurotransmissions, such as glutamatergic, GABAergic, dopaminergic, and noradrenergic neurotransmissions. In turn, these neurotransmissions can induce changes in the neuronal-glial network and result in neuropsychiatric consequences (65). Hyangin *et al.* (74) have shown that upregulation of IDO results in the increased Kyn/Trp ratio and decreased serotonin/Trp ratio in the bilateral hippocampus of the brain. Either IDO gene knockout or pharmacological inhibition of hippocampal IDO activity attenuates both nociceptive and depressive behavior. In accord with this, it has shown (67) the IDO inhibitor Coptisine ameliorates cognitive impairment in a mouse model of Alzheimer's disease.

3.1.2. Tryptophan 2, 3-dioxygenase

TDO is a heme-containing cytosolic enzyme that is encoded by TDO2 (75). It is ubiquitously found in both eukaryotes (human, rat, and rabbit) (17, 19) and prokaryotes (*Xanthomonas campestris* and *Pseudomonas fluorescens*) (76, 77). With the exception of mouse early concepti (78) and rat skin (79), TDO expression in mammals is restricted to the liver, where it is degrades L-Trp to ultimately synthesize NAD^+ and nicotinamide adenine dinucleotide phosphate ($NADP^+$).

TDO catalyzes the first and rate-limiting step of Trp degradation in the Kyn pathway to regulate systemic Trp levels (1, 17, 18, 75)_ENREF_31. It plays a central role in the physiological regulation of Trp flux in the human body. TDO is expressed in a significant proportion of human tumors (75), and its expression prevents their rejection by immunized mice. In line with this, a TDO inhibitor was shown to restore the ability of these mice to reject TDO-expressed tumors, thus demonstrating its potential in cancer therapy. In addition, TDO is potentially involved in the metabolic pathway that is responsible for anxiety-related behavior (80). Compared to wild-type mice, TDO-deficient mice showed increased plasma levels of Trp, serotonin, and 5-Hydroxyindoleacetic acid in the hippocampus and midbrain. A variety of tests, such as the elevated-plus maze and open-field tests, showed anxiolytic modulation in TDO-deficient mice. These findings reveal a direct link between TDO and Trp metabolism or anxiety-related behavior under physiological conditions.

3.1.3. Kynurenine-3-monooxygenase

KMO is a therapeutically important target on the eukaryotic Trp catabolic pathway, where it converts L-Kyn to 3-OHkyn. KMO is a β-nicotinamide adenine dinucleotide 2′-phosphate (NADPH)-dependent flavin monooxygenase, which is localized in the outer mitochondrial membrane in the CNS and is predominantly expressed in microglia (81, 82). It exists as an apoenzyme and interacts with flavin-adenine dinucleotide to form a holoenzyme, whereas the flavin moiety of the protein acts as an electron donor (83). KMO specifically catalyzes the incorporation of one atom of oxygen into Kyn in the presence of NADPH as an electron donor.

Under both physiological and pathological conditions, KMO possesses a high affinity for the substrate, with the Km in the low micromolar range (84), suggesting that it metabolizes most of the available Kyn to produce 3-OHkyn. Notably, KMO expression increases in inflammatory conditions or after immune stimulation (24). The position of KMO at this branch point in the pathway makes it a potential therapeutic target for treating neurodegenerative disorders, such as Alzheimer's disease (85) and Huntington's disease (86). Many studies have demonstrated the positive effects of KMO inhibitors in brain injury models (87), although poor penetration of the blood-brain barrier is a problem (85).

3.1.4. Kynurenine aminotransferase

The KAT are essential in the Kyn pathway, because they produce irreversibly the only endogenous antagonist of the NMDA receptor, KYNA, from L-Kyn. In humans, rats, and mice, three proteins (KAT I, II, and III) are involved in KYNA synthesis in the CNS (88-90). Most recently, mitAAT from rat and human brains has been reported to catalyze the transamination of Kyn to KYNA; this was referred to as KAT IV (91). Moreover, KAT I, which is also known as kynurenine-pyruvate transaminase, recognizes 3-OHkyn as a substrate to produce XA (92).

These enzymes are distinguished by substrate specificity and other discrete biochemical and biophysical characteristics. KAT I and KAT III share similar genomic structures and show high sequence identity (90), whereas

KAT II has a completely different genomic structure (93). KAT I was previously found in glia and neurons, especially in areas for blood pressure and heart rate regulation (94). This supports its neuromodulatory role for KYNA in NMDA-mediated autonomic function. KAT III and KAT I are both expressed in multiple tissues, including the kidney, liver, heart, lung, and neuroendocrine organs, and their biological functions overlap (89, 90). KAT II is composed of 13 exons and is most abundant in the rat and human brain, whereas mitAAT plays a major role in the mouse brain (91). Biochemical and pharmacological data and studies in lesioned brain tissues indicated that KAT II, rather than KAT I, is the major biosynthetic enzyme of KYNA in the rat brain (88). MitAAT may be involved in a range of physiological and pathological processes that are associated with glutamatergic and nicotinergic function. A number of neurobiologically relevant issues have unveiled the realization that mitAAT accounts for a quantitatively significant proportion of total brain KAT activity (91).

3.1.5. Kynureninase

Kynureninase is a pyridoxal phosphate-dependent enzyme, which catalyzes the transformation of 3-OHkyn and Kyn into 3-HAA and AA, respectively (35, 36). Humans express one kynureninase enzyme that is encoded by the L-Kyn hydrolase gene http://en.wikipedia.org/wiki/Gene located on chromosome 2 (36). In rats, the enzyme is predominantly located in the cytoplasm (34, 95), and it displays higher affinity and maximal velocity towards L-3-OHkyn than L-Kyn (34, 36).

This enzyme is crucial in the biosynthesis of nicotinamide nucleotides (34-36) and also gives rise to other pathophysiologically important compounds, such as picolinic acid, an enhancer of nitric oxide synthase expression (36, 96). Recent evidence suggested that the stimulation of kynureninase activity may also represent a relevant response in inflammation. In fact, a substantial increase in the activity of kynureninase is observed in several cerebral and systemic inflammatory conditions (97). In addition, IFN-γ has been shown to induce kynureninase activity in murine macrophages (28).

3.2. Major metabolites

Most of the kynurenines induce alterations in cellular metabolism that lead to damage and cell death (Table 1).

3.2.1. Tryptophan

Trp is one of several amino acids that are essential in mammals and cannot be synthesized *de novo*. It is the rarest and accounts for ~1% of total amino acids in cellular proteins. The incorporation of Trp into protein is initiated by tryptophanyl-transfer RNA synthetase (TrpRS). TrpRS is the only aminoacyl synthetase that responds to inflammatory mediators, such as IFN-γ (98), and the overexpression of TrpRS has been postulated to help IDO-expressing cells compensate for the reduction in intracellular Trp.

The structure of which contains a ring that can stabilize radicals through resonance or delocalization, thus enabling it to break radical chain reactions and exert antioxidant properties (99). The administration of Trp has been shown to decrease experimental endotoxic shock-induced lipid peroxidation in rats (100). Of all amino acids, Trp exhibits the highest antiradical activity (101). In addition, it is a potent scavenger of radicals that are induced by chloramine T or hydrogen peroxide (H_2O_2) (102).

3.2.2. Kynurenine

Kyn is the first product in the pathway of Trp degradation. It exhibits prooxidant effects, and the aerobic irradiation of Kyn produces superoxide radicals and leads to cytochrome C reduction (103). Additionally, Kyn is able to photooxidize cysteine, NADH, and ascorbic acid *in vitro*, and this capacity may be directly relevant to photobiological processes that occur in the lens *in vivo*. In particular, these photooxidation processes are responsible for the age-related depletion of reduced glutathione and/or formation of H_2O_2 in the lens (104). Several recent studies have shown that Kyn is prone to deamination and oxidation, which can result in the formation of α, β-unsaturated ketones that chemically react and modify len proteins (15, 16). Such reactions occur mostly at cysteinyl, histidinyl, and lysyl residues and contribute to cataract formation (105).

Increased levels of Kyn have been shown to cause cell death through the reactive oxygen species (ROS) pathway in nature killer (NK) cells (13) and lower blood pressure in systemic inflammation (20, 21). On the other hand, Kyn itself can stimulate the production of nerve growth factor in astroglial cells (106) and contribute to early neuronal growth and development. Approximately 60% of brain Kyn comes from the periphery, because it can readily cross the blood-brain barrier (41-43). In the brain, Kyn is metabolized to KYNA by astrocytes (42, 107) and to 3-OHkyn in microglia (108) and macrophages (42, 43).

3.2.3. Anthranilic acid

Although AA is generally accepted to be biologically inactive, it can interact with copper to form an anti-inflammatory complex. This complex acts as a hydroxyl radical-inactivating ligand able to remove the highly injurious hydroxyl radicals at inflammatory sites (109, 110). Nevertheless, an *in vitro* study using organotypic cultures of rat hippocampus has shown that AA (at high mM concentration) may cause neurodegeneration. Additionally, the anthranilate has elicited more pronounced effects on active than on resting rate of respiration. These contradictory effects found for AA may be due to its capability as a substrate to produce hydroxyl radicals to the 3-HAA metabolite (34).

Table 1. Kyn pathway metabolites and their biological behaviors

Metabolite	Properties	Functions and related diseases
Trp	Antioxidant Antiradical	Inhibition of lipid peroxidation
Kyn	Prooxidant Superoxide radical generation Photooxidation Lens protein modification Deamination and oxidation Nerve growth factor generation	Cataract formation Cell death Early neuronal growth and development Hypotension
AA	hydroxyl radical-inactivating ligand hydroxyl radicals producer	Anti-inflammation Neurodegeneration Active rate of respiration
KYNA	Competitive NMDA receptor blocker Noncompetitive α-7 nicotinic acetylcholine receptor inhibitor Orphan G protein-coupled receptor 35 ligand Inhibition of the release of inflammatory mediators and exitatoty amino acid Ligand-activated transcription factor (aryl hydrocarbon) activation Hydroxyl radicals and peroxynitrite scavenger Inhibition of Hcy-induced inhibition of cell proliferation and migration	Neuromodulator Anti-inflammation Immunosuppression Prevention of lipid peroxidation and ROS generation Protection against Hcy-induced cytotoxicity
3-OHkyn	Prooxidant Endogenous generator of SOX Modifications of proteins Respiratory parameters modification Antioxidant Peroxyl radicals and superoxide scavenger	Cytotoxicity Apoptosis Cataract formation Bladder cancer Respiratory control index inhibition
XA	Neurotransmission/neuromodulator Metal-chelating activities Antioxidant Peroxyl radicals and superoxide scavenger Prooxidant Superoxide and singlet oxygen generator Photosensitizer Photooxidation and polymerization of lens proteins	Inhibition of lipid peroxidation Apoptosis Cytotoxicity Cataractogenesis
3-HAA	Autooxidation Superoxide anions formation Mitochondrial pattern: Oxygen uptake inhibition, uncoupling of the respiratory chain and oxidative phosphorylation Inhibition of nuclear factor-κB activation Depletion of intracellular glutathione Antioxidant Suppression of inducible nitric oxide synthase and VCAM-1 expressions CCL2 secretion inhibition α-Tocopheroxyl radical reduction Prevention of spontaneous oxidation of glutathione and the peroxyl radicals	Apoptosis Prevention of lipid peroxidation Protection of the cerebral cortex against SOX
QA	Agonist of the NMDA receptor Excitotoxin SOX induction Free-radical generation Dysregulation in oxidant/antioxidant ratio Toxicity DNA-chain breakage	Mitochondrial dysfunction Cell death Apoptosis Inflammation Energetic deficit Behavioral and morphological alternations lipid peroxidation Protection of the cerebral cortex against SOX

3.2.4. Kynurenic acid

KYNA, an intermediate in the Trp metabolic pathway, is an endogenous competitive blocker of the strychnine-insensitive glycine co-agonist site of the NMDA receptor (111) and a noncompetitive inhibitor of the α-7 nicotinic acetylcholine receptor (112). Accordingly, dysregulation of endogenous KYNA may contribute to the physiopathology of several disorders (113-115). Kyn is the substrate for KYNA synthesis, which is mediated by KAT. However, levels of KYNA have been documented not only in brain tissue (116) and cerebrospinal fluid (117), but also in the periphery (43, 118-122). Activation of the PGC-1α1-PPARα/δ pathway increases skeletal muscle expression of KAT, thus enhancing the conversion of Kyn into KYNA (43). As opposed to Kyn, KYNA is unable to cross the blood-brain barrier and must be formed locally within the brain (41, 42). Reducing plasma Kyn protects the brain from stress-induced changes associated with depression and renders skeletal muscle-specific PGC-1a1 transgenic mice resistant to depression induced by chronic mild stress or direct Kyn administration (43).

Recent work has shown that KYNA is a ligand for the orphan G protein-coupled receptor 35 (GPR35) (123). The activation of this receptor inhibits the release of TNF-α by macrophages under LPS-induced inflammatory conditions. In this context, KYNA may exert an anti-inflammatory effect (123). Additionally, GPR35 decreases intracellular Ca^{2+} by inhibiting its entrance (124). Therefore, KYNA most likely exerts an effect on the release of inflammatory mediators and excitatory amino acids from glial cells. KYNA also activates the ligand-activated transcription factor, aryl hydrocarbon, which is a nuclear protein that is involved in the regulation of gene transcription and can cause immunosuppression (120).

On the other hand, KYNA is a reducing agent that has been shown to scavenge hydroxyl radicals (125) and peroxynitrite. It prevents $FeSO_4$-induced lipid peroxidation and ROS production in rat forebrain homogenates and in NMDA receptor-lacking *Xenopus laevis* oocytes, suggesting that the protective effect of KYNA is independent of its activity over receptors. In addition, KYNA decreases the formation of hydroxyl radicals that is induced by the acute infusion of $FeSO_4$ in the rat striatum (126).

According to Stazka *et al.*, the vascular endothelium is responsible for the production and liberation of KYNA (127). Most importantly, KYNA elicits a protective effect against the homocysteine (Hcy)-induced inhibition of endothelial cell proliferation and migration. Moreover, KYNA protects these cells against Hcy-induced cytotoxicity (128).

Overall, KYNA is an important neuromodulator and an endogenous antioxidant, and its protective effect in diverse toxic models may be due to its redox characteristics, in addition to its activity on receptors.

3.2.5. 3-Hydroxykynurenine

KMO converts Kyn to 3-OHKyn, which is a controversial Kyn that has both prooxidant and antioxidant properties. The o-aminophenol structure, which is common to 3-OHkyn, is required for it to exert its toxicity. O-aminophenol compounds are subject to several steps of oxidation reactions that are initiated by their oxidative conversion to quinoneimines, which are then accompanied by the concomitant production of ROS. The main ROS are superoxide anion and H_2O_2 (129).

As an endogenous generator of SOX, 3-OHkyn causes neuronal cell death with apoptotic features and region selectivity (37, 130). The generation of H_2O_2 is involved in the neurotoxicity of 3-OHkyn, which also counts on the role of iron (131). Endogenous xanthine oxidase activity is involved in 3-OHkyn-induced H_2O_2 generation, and it exacerbates cell damage. Furthermore, 3-OHkyn and 3-HAA have been shown to reduce copper (Cu) II to generate superoxide and H_2O_2 in a Cu-dependent manner (132).

The incubation of bovine α-crystallins with low concentrations of 3-OHkyn causes protein cross-linking and the oxidation of methionine and Trp residues (133), which indicates that the protein damage results from the generation of ROS. In the human lens, these reactions have been associated with aging and cataractous processes (134). Such modifications of proteins account for fiber cell apoptosis (15), epithelial cell apoptosis (16), and cataract formation in the mouse lens (15, 16). Also, both 3-OHkyn and 3-HAA can provoke protein oxidative damage and induce apoptosis, which is characterized by chromatin condensation and internucleosomal DNA cleavage in PC12, GT1-7, SK-N-SH (130, 132, 135), and T cells (14). *In vivo* experiments have demonstrated that the injection of 3-OHkyn into the striatum causes tissue damage (136). In support of this, 3-OHkyn has been shown to accelerate endothelial cell apoptosis and cause endothelial dysfunction by promoting the generation of NADPH oxidase–mediated superoxide anions *in vivo* and *in vitro* (30).

In addition to its cytotoxic effects, 3-OHkyn can cause bladder cancer (137). Moreover, it modifies the respiratory parameters, decreases the respiratory control index, and lowers the adenosine diphosphate/oxygen ratio of glutamate/malate-respiring heart mitochondria (129).

Conversely, 3-OHkyn has been proposed to be an antioxidant that scavenges peroxyl radicals in inflammatory diseases (138) and scavenges superoxide in the Malpighian tubes of insects (139). Because 3-OHkyn is an o-aminophenol, it might be expected

to undergo complex oxidative processes. Similar to vitamin C and trolox, 3-OHkyn and 3-HAA belong to the class of small molecules that react very rapidly with peroxyl radicals and are potentially important biological antioxidants. In particular, they protect B-phycoerythrin from peroxyl radical-mediated oxidative damage more effectively than equimolar amounts of either ascorbate or Trolox (138). The antioxidative efficiency of 3-OHkyn appears to be better than that of glutathione, as it was more reactive with the ferryl complex.

The redox behavior of 3-OHkyn has been proposed, such that it can initially act as two-electron donors (antioxidant) to oxidatively form ortho-quinoneimine, which produces ROS in the process (prooxidant) (140). Therefore, the behavior of 3-OHkyn depends on the redox status of the cell.

3.2.6. Xanthurenic acid

XA is a metabolite that is synthesized through 3-OHkyn transamination, and it is closely related structurally to KYNA but possesses different biological roles. The formation of XA is thought to be the main route to prevent the accumulation of the potentially toxic 3-hydroxykynurenine excess (44). XA plays a role in the neurotransmission/neuromodulation effect that is inhibited in the absence of adenosine triphosphate (44), because it is actively taken up by synaptic vesicles from the rat brain. Peripheral administration of XA in rats induced a large increase in the concentration of XA in numerous regions of the brain, indicating exogenous XA can penetrate the brain blood barrier easily (44).

Some groups have shown that XA has metal-chelating activities and antioxidant properties (138, 141, 142). In the 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) system, XA is an efficient scavenger of hydroxyl radicals and $ABTS^{\cdot+}$. It can inhibit iron- and copper oxidation-induced lipid peroxidation in low-density lipoproteins (LDL) in a pH-dependent manner (141, 142). Moreover, XA prevents the inactivation of $NADP^{+}$-isocitrate dehydrogenase that is induced by the oxidation of these metals (141). XA scavenges superoxide in a hematoxylin autooxidation system (34) and acts as a peroxyl radical scavenger *in vitro* (138). The antioxidant properties of XA could be related to the fact that all phenolic metabolites show antioxidant activities, thus implicating the importance of the phenolic moiety as the active entity (138).

On the contrary, XA sometimes acts as a prooxidant due to its chelating effect (143). Furthermore, it induces apoptosis in vascular smooth muscle and lens epithelial cells (144, 145). Additionally, XA acts as a photosensitizer and generates superoxide and singlet oxygen upon irradiation (146). The photooxidation and polymerization by XA of lens proteins are related to age-dependent cataractogenesis (147). All of these studies suggest that the cytotoxic action of XA may be explained by the prooxidant properties of chelate complexes with metals.

3.2.7. 3-Hydroxyanthranilic acid

As a product of 3-OHkyn, 3-HAA is prone to autooxidation in a process that favors the formation of superoxide anions (83). This autooxidation of 3-HAA involves the generation of quinoneimine, followed by condensation and oxidation reactions to yield cinnabarinic acid. This process requires molecular oxygen and generates superoxide radicals and H_2O_2. In experimental models, the pattern of 3-HAA in mitochondrial processes involves the inhibition of oxygen uptake by mitochondrial respiring with NAD-dependent substrates, uncoupling of the respiratory chain, and oxidative phosphorylation (129, 148).

Furthermore, 3-HAA induces apoptosis in monocyte/macrophage cell lines (149) and activated T cells (150-152). It has been suggested that 3-HAA inhibits nuclear factor-κB activation upon T-cell antigen receptor engagement by specifically targeting phosphoinositide-dependent kinase-1 (152). Additionally, it was demonstrated that 3-HAA induces the depletion of intracellular glutathione in activated T cells without increasing ROS formation (151).

On the contrary, 3-HAA has been shown to be a potent antioxidant (153). It suppresses inducible nitric oxide synthase expression in macrophages (154, 155) and inhibits monocyte chemoattractant protein-1 (CCL2) secretion and vascular cell adhesion molecule (VCAM)-1 expression in endothelial cells (156) via inducing the nuclear translocation of nuclear factor-erythroid 2-related factor-dependent heme oxygenase-1 expression. Additionally, 3-HAA reduces the α-tocopheroxyl radical, thus restoring the levels of α-tocopherol and preventing LDL lipid peroxidation (153). Furthermore, 3-HAA and 3-OHkyn have been shown to inhibit spontaneous lipid peroxidation in the brain, and this inhibitory property remained even in the presence of Fe^{3+} and protected the cerebral cortex against SOX (157). The spontaneous oxidation of glutathione and the peroxyl radicals were significantly prevented by 3-HAA (158).

Results from electrochemical studies suggested that 3-HAA can initially act as an antioxidant and then as a prooxidant (140), because its product, ortho-quinone-imine, possesses oxidant properties. The dual effect of 3-HAA *in vitro* is most likely concentration dependent. Recent clinical data show marked changes in the levels of 3-HAA, associated with changes in AA levels, in patients with a range of neurological and other disorders including osteoporosis, chronic brain injury, Huntington's disease, coronary heart disease, thoracic disease, stroke and depression. In most cases, there is a decrease in 3-HAA levels and an increase in AA levels, which could

possibly be a protective response to limit primary and secondary damage (159).

3.2.8. Quinolinic acid

QA, a neuroactive metabolite of 3-HAA, is an established intermediate in the synthesis of nicotinic acid and NAD^+. It is an agonist of the NMDA receptor and has a high potency as an excitotoxin *in vivo* (160). QA induces SOX by activating NMDA receptors, producing mitochondrial dysfunction (161, 162), or increasing free-radical generation (163, 164).

QA can generate a dysregulation in the oxidant/antioxidant ratio by several ways: (1) affecting the reduced glutathione: oxidized glutathione ratio (165), (2) depleting the activity of copper- and zinc-dependent superoxide dismutase activity (Cu, Zn-SOD) (166, 167), (3) recruiting the early and time-dependent formation of peroxynitrite as a key reactive nitrogen species (168, 169), and (4) contributing to lipid peroxidation (170, 171). All of these processes can result in cell death (172, 173).

Other toxic effects of QA through NMDA receptors have been observed, such as inflammatory events, energetic deficits, and behavioral and morphological alterations (42, 160, 174). The activity and toxicity of QA can change, depending on its levels. It has also been shown to participate in the apoptosis of oligodendrocytes, neurons, and astrocytes via NMDA-dependent ROS formation (172, 173).

Furthermore, QA can form complexes with Fe^{2+} and modulate lipid peroxidation (175). The QA-Fe^{2+} complex is relatively stable at physiological pH. Although this complex initiates the generation of hydroxyl radicals, it forms a QA derivative that enables the redox cycling of Fe^{2+} and Fe^{3+} ions, thus maintaining hydroxyl radical formation (176). The QA-Fe^{2+} complex has been shown to be responsible for *in vitro* DNA-chain breakage and lipid peroxidation that are mediated by hydroxyl radicals (177) .

4. THE ABNORMAL KYNURENINE PATHWAY LINKS OXIDATIVE STRESS, INFLAMMATION, AND IMMUNE DISORDER IN CARDIOVASCULAR DISEASES

4.1. Immune regulatory role of the kynurenine pathway in atherosclerosis

4.1.1. Modulation of immunoinflammatory responses by IDO

The relationship between IDO activity and coronary heart disease (CHD) has been demonstrated in a few multi-center prospective studies. In a large cohort study of the general population (n=921, 46–76 years old), IDO activity, as indicated by Kyn/Trp ratio (KTR), was positively correlated with early atherosclerosis and increased carotid artery intima-media thickness (CA-IMT) in both sexes, suggesting that IDO is a sensitive marker of atherosclerosis (178). Consistently, in a cohort of 3224 patients who were followed for 55 months, urine KTR, which is a novel urinary marker of inflammation marker, was strongly associated with adverse prognosis in patients with suspected stable coronary artery disease (179) .

In another study, an oral load of L-Trp caused patients with myocardial infarction or angina pectoris to have higher KTR as compared to controls, indicating higher Trp degradation in these patients (180). The positive correlation between IDO activity and age was to be expected, as IDO activity is known to increase with age (181, 182). There was also a significant correlation between IDO and body mass index (BMI), waist circumference, and waist-to-hip ratio in both sexes. In parallel with this finding, Trp depletion and increased IDO activity were observed in morbidly obese patients, and this persisted even after weight reduction and led to chronic immune activation (183).

A prospective multi-center study of 986 young adults has identified that IDO activity (reflected by KTR) correlates significantly with CA-IMT in female subjects. IDO activity correlated significantly with several risk factors for atherosclerosis in females, such as age, low-density lipoprotein cholesterol (LDL-C), and BMI. In addition, it correlated weakly with C-reactive protein (CRP) and inversely with high-density lipoprotein cholesterol (HDL-C) and triglyceride. In males, IDO activity correlated significantly with CRP and inversely with HDL-C. These results suggested that the IDO enzyme is a novel marker of immune activation in early atherosclerosis in young females (184). The Tampere vascular study has revealed that the up-regulation of IDO and its related genes are pronounced in atherosclerotic plaques. Immunohistochemical analyses demonstrated the expression of IDO protein in the atheromatous core and its co-distribution with monocyte-macrophages. In a gene-set enrichment analysis, the IDO pathway revealed a significant regulatory T cell, fork-head box protein 3-initiated CD28-CTLA-4-inducible T-cell co-stimulator-driven pathway that leads to the activation of IDO expression in antigen-presenting cells. It has been concluded that IDO and the IDO-related pathway are important mediators of the immunoinflammatory responses in advanced atherosclerosis (185).

Moreover, increased IDO activity, as indicated by KTR, was found in subjects with angiographically verified CHD compared with healthy controls (186). The increase in IDO activity coincided with decreased Trp concentration and increased neopterin concentration, thus indicating an active cellular immune response. A close association between KTR and markers of immune activation, such as neopterin, has been established (187). In line with this, the Hordaland health study has shown

that plasma neopterin and KTR levels can predict acute coronary events in older adults without previous CHD (188).

In addition to IDO, the possible role of TDO in the enhancement of Trp degradation in the preclinical stages of atherosclerosis cannot be excluded, although IDO seems to be a more probable activator. TDO regulates basal serum Trp concentrations, and IDO is up-regulated in response to inflammatory conditions that are characteristics of early atherosclerosis (29).

4.1.2. Protective role of the kynurenine pathway

The protective role of IDO has been reported. The blockage of IDO expression in lymphoid tissue plasmacytoid dendritic cells (PDCs) from atherosclerotic mice abrogates the suppressive effect of PDCs on T-cell proliferation, suggesting that PDCs exert their protective role in atherosclerosis extravascularly by dampening T-cell proliferation and function in an IDO-dependent manner (189). Simultaneously, in the presence of the IDO inhibitor, 1-MT, the beneficial effects of EPA on atherosclerosis regression were inhibited, which suggested that IDO mediates EPA (190). The administration of 1-MT significantly increased macrophage contents in atherosclerotic lesions and $CD4^+$ T-cell contents in the EPA-treated group compared with the solvent-treated EPA group. In particular, IDO expression in DCs is indispensable for atherosclerotic plaque regression, because the administration of the IDO inhibitor blocked the beneficial effects of EPA and increased inflammatory cell infiltration and plaque formation to the extent of control with the IDO inhibitor (190). Besides, it has been indicated that (191) the protective effects of stem cell therapy in ischemia-reperfusion (IR) injury of hind limb are critically dependent on the expression of IDO to induce its anti-inflammatory effects. In $IDO^{-/-}$ mice, inflammation induced by the IR injury is more pronounced and so is necrosis and apoptosis of the tissues, which leads to a longer recovery time seen clinically.

Moreover, 3-HAA has been identified to inhibit atherosclerosis by regulating lipid metabolism and inflammation, which are two major components of this disease (192). Treatment of mice with 3-HAA for eight weeks significantly reduced the size of lesions in the aorta and modulated local and systemic inflammatory responses. A major cellular component of atherosclerotic lesions is the foam cells, which are initially formed by the uptake of oxidized LDL by macrophages. Importantly, 3-HAA has been reported to inhibit this uptake of oxidized LDL, and it can significantly affect plasma cholesterol and triglyceride levels in LDL $receptor^{-/-}$ mice, likely due to the modulation of signaling through peroxisome proliferator-activated receptors.

4.2. The kynurenine pathway is associated with the prevalence of cardiovascular disease in chronic renal disease patients

Many recent studies have postulated that the activation of the Kyn pathway is associated with increased SOX, inflammation, and atherosclerotic CVD prevalence in renal dysfunction patients (193-196).

4.2.1. Relationship to the severity of chronic kidney disease

In a prospective blinded endpoint analysis of patients with chronic kidney disease (CKD) (193), the serum levels of Kyn, KYNA, and QA increased with CHK severity (stages 4 and 5), although Trp levels were unchanged. IDO activity, which may be estimated via the KTR, was significantly induced in patients with CKD (197), and it correlated with disease severity (stages 3-5) and key inflammatory markers (hypersensitive C reactive protein (hsCRP) and soluble tumor necrosis factor receptor-1 (sTNFR-1)) independent of serum creatinine, age, and body weight. IDO products (Kyn, KYNA, and QA) also correlated with hsCRP and sTNFR-1. Overall, the induction of IDO and serum Kyns may primarily be a consequence of chronic inflammation, which is a well-known feature in CKD.

4.2.2. Association with the markers of inflammation and oxidative status

Other clinical trials (194-196) have also shown that serum levels of Trp catabolites of the Kyn pathway increase with CHK severity and associate with markers of inflammation and SOX, which are in agreement with the previous report.

In a cohort of patients with CKD (194), Kyn, AA, and cellular adhesion molecule (soluble intercellular adhesion molecule-1 (sICAM-1) and soluble VCAM-1 (sVCAM-1)) concentrations were significantly higher in undialyzed patients with CKD compared with healthy subjects. In addition to these increases, significantly elevated levels of KYNA and the SOX marker, Cu/Zn SOD, were observed in two groups of dialyzed patients. Kyn, KYNA, and AA were positively associated with elevated sICAM-1 and sVCAM-1 in the whole CKD group, and a strong positive relationship was observed between Kyn and hsCRP, a surrogate of inflammation. Multivariable analysis showed that Kyn was a strong independent correlate of sICAM-1. Simultaneously, another study (195) has reported that CKD patients show a significant increase in plasma concentrations of 3-HAA, AA, CCL2, inflammatory protein-1β (CCL4), Cu/Zn SOD, and hsCRP, compared with controls. Multiple stepwise regression analysis has identified 3-HAA as the independent variable that was significantly associated with increased CCL2 and CCL4, which are correlated with increased SOX and carotid atherosclerosis (198).

Furthermore, a cross-sectional study on CKD patients (196) has indicated that the Kyns are positively associated with various endothelial markers: von Willebrand factor (vWF), thrombomodulin (TM), sICAM 1, and sVCAM-1. CA-IMT positively correlated with Kyn, 3-OHkyn, and QA. Finally, multiple regression analysis has identified QA levels as the independent variable that was significantly associated with increased IMT in this population. This study suggested that the activation of the Kyn pathway, endothelial dysfunction, and the progression of atherosclerosis in CKD patients are related, whereas the endothelium is pivotal in the control of hemostasis and thrombosis.

Even more important, a recent clinical trial has shown that both Kyn and Kyn/Trp ratio significantly decreased after Amelioration of both oxidative and inflammation status by cholesterol lowering treatment in CKD, to values comparable with healthy controls after one year treatment (197).

4.2.3. Correlation with cardiovascular diseases

Along with the earlier studies, new evidence has provided support for the link between Kyn pathway activation and CVD prevalence or pathogenesis in patients with end-stage renal disease (ESRD) (199-205).

A clinical trial of patients with ESRD has revealed that (199) the levels of Kyn pathway metabolites, TM, and vWF were significantly elevated in ESRD patients compared with controls. However, Trp concentrations in uremics were significantly lower than in healthy people. Kyn, 3-OHkyn, and QA levels were positively associated with TM and vWF in the whole ESRD group. A positive relationship between Cu/Zn SOD and Kyn, 3-OHkyn, and QA levels was observed, whereas the SOX marker, malondialdehyde, was correlated with 3-OHkyn and QA concentrations. Multiple stepwise regression analysis has shown that Kyn metabolites and oxidative status are the independent variables that were significantly associated with increases in TM and vWF levels in uremic patients. This study has demonstrated that Kyn metabolites are independently and significantly associated with endothelial dysfunction in ESRD patients.

Pawlak *et al.* have reported that (200) both Kyn and 3-OHkyn are positively associated with Cu/Zn SOD and an index of inflammation (hsCRP) in the ESRD group. Univariate quasi-Newton and Rosenbrock's logistic regression analysis have shown that the prevalence of CVD in the population of uremic patients was significantly associated with low Trp and high Kyn and 3-OHkyn levels. Furthermore, logistic regression analysis has confirmed that 3-OHkyn levels were independently associated with the presence of CVD in uremics. In another cross-sectional study (201) on chronic renal failure patients, Kyns were associated with hyperfibrinolysis, which has been causally related to the development of atherosclerosis and cardiovascular complications (206). These results suggested a relationship between Kyn pathway activation and increased SOX, inflammation, and CVD prevalence in ESRD patients. In addition, Kyn, QA, matrix metalloproteinases (MMPs), and a tissue inhibitor of MMPs were significantly higher in continuous ambulatory peritoneal dialysis (CAPD) patients with CVD than in patients without CVD and controls (202). QA was positively correlated with MMP-2 and the tissue inhibitor of MMP-2, which are responsible for the degradation of extracellular matrix components that are involved in vascular wall remodeling (207). QA and the QA/Kyn ratio have been identified to be the factors that are independently associated with MMP-2, thus suggesting a connection between Kyn pathway activation, arterial remodeling, and CVD prevalence in uremic patients on CAPD treatment.

Pawlak *et al.* have further demonstrated that the plasma concentrations of Kyn, QA, and the QA/Kyn ratio are positively associated with the inflammation indicator (hsCRP), SOX markers (Cu/Zn SOD, total peroxide, and malondialdehyde), and CA-IMT values in uremics (203). Moreover, multiple stepwise regression analysis has identified QA and the QA/Kyn ratio as the independent variables that were significantly associated with increased CA-IMT in this population. In a clinical trial on hemodialysis (HD) patients (204), a positive association was observed between log-transformed KTR and log-transformed hsCRP. Serum Kyn was also positively correlated with log-transformed hsCRP. These results confirmed a possible relationship between the activated Kyn pathway and inflammation in HD patients. It also demonstrated that log-transformed KTR was similarly related to an increase in CA-IMT in HD patients. In addition, the diameter of maximal plaque was significantly larger in the top quartile of KTR compared with the bottom quartile, and the ankle-brachial pressure index was significantly higher in the lowest quartile of KTR. These findings suggested that the Kyn/Trp ratio was associated with carotid plaque enlargement and stenosis of peripheral arteries in the legs, as well as arterial wall thickness. Another study on HD patients has shown that IDO concentration is increased in HD patients and is further increased in HD patients with CHD (205).

Intriguingly, inverse correlations have been observed between KYNA levels and CVD prevalence in ESRD patients (121, 122). Kyn, KYNA, and QA levels were significantly higher in peritoneal dialysis (PD) patients than in controls, whereas Trp was significantly lower in PD patients (121). In addition, PD patients with CVD had lower KYNA levels compared with PD patients without CVD. Logistic regression analysis has shown that low KYNA levels are independently associated with the presence of CVD in PD patients. Similar relationships have been observed in patients undergoing CAPD (122). KYNA concentrations and the KYNA/Kyn ratio were

significantly lower in patients without CVD, and they were positively associated with Hcy in all CAPD patients and with hyperhomocysteinemia in CVD+ patients. These findings are in agreement with previous reports that KYNA may have a protective influence on the endothelium during hyperhomocysteinemia *in vitro* (128).

The results of these studies suggested a relationship between the activation of the Kyn pathway and increased SOX, inflammation, and the progression of atherosclerosis in patients with CKD.

4.3. Kynurenines affect the cardiovascular system during systemic inflammation

4.3.1. Vessel relaxation

IDO activity is increased in patients with inflammatory diseases, such as severe infection (18, 20), collagen diseases (208), and sepsis (21, 209). Blood pressure is tightly regulated by various mediators that are released from nerve endings, endocrine glands, and the endothelium. A decrease in the production of vasoconstricting factors and an increase in relaxing factors can cause blood pressure to drop. Kyn is the active compound in the IDO pathway that is responsible for lowering blood pressure in mice infected with malarial parasites (18, 20)_ENREF_19. A new clinical study has shown that IDO is expressed in resistance vessels in human sepsis, and its activity correlates with hypotension in human septic shock. IDO is thus a potential novel contributor to hypotension in sepsis (21). Jung *et al.* (210) have reported that $IDO^{-/-}$ mice and 1-MT-treated, endotoxin-shocked mice have decreased levels of the cytokines, TNF-α, IL-6, and IL-12, and enhanced levels of IL-10. Blockade of IDO is thought to promote host survival in LPS-induced endotoxin shock. In addition, KYNA has been reported to attenuate NMDA-induced pial arteriolar dilation in newborn pigs (211). Co-application of KYNA dose-dependently reduces NMDA-induced vasodilation and attenuates the kainate-induced response.

4.3.2. Metabolism

In cardiovascular patients with systemic inflammation, low plasma vitamin B6 status affected the metabolism through the Kyn pathway (212). Plasma 3-OHkyn acted as a systemic vitamin B6 marker that was inversely related to plasma pyridoxal 5'-phosphate, which is a commonly used marker for vitamin B6. Furthermore, inflammation was positively related to 3-OHkyn.

4.4. Activation of the kynurenine pathway in acute severe heart attacks

A study on biochemical changes has provided data to support the monitoring of Trp degradation as a potential means of detecting immune activation in a porcine cardiac arrest model (213). The KTR may serve as a short-term measurement of immune activation and therefore permit an estimate of the extent of immune activation. Moreover, the Kyn pathway has been shown to be activated after cardiac arrest in rats, pigs, and humans (214). Decreases in Trp occurred during the post-resuscitation period and were accompanied by significant increases in its major metabolites, 3-HAA and KYNA, in each species. In rats, changes in Kyn pathway metabolites reflected changes in post-resuscitation myocardial function. In pigs, changes in Trp and increases in 3-HAA were significantly related to the severity of cerebral histopathological injuries. Similar to rats and pigs, there was a trend toward lower plasma levels of Trp and higher levels of Kyn in resuscitated patients than in healthy volunteers. The plasma levels of KYNA and 3-HAA were significantly higher at 1 h post-resuscitation. Patients who survived after resuscitation presented lower plasma levels of KYNA and 3-HAA in comparison to those who died. Interestingly, the plasma levels of 3-HAA were approximately doubled in patients who died compared to those who survived. In this fully translational investigation, the Kyn pathway was activated following resuscitation from cardiac arrest and may have contributed to post-resuscitation outcomes.

In mice with acute viral myocarditis, postinfection with the encephalomyocarditis virus increased Kyn serum levels, decreased Trp serum levels, and enhanced IDO activity in the spleen and heart (215). The survival rate of $IDO^{-/-}$ or 1-MT-treated mice was significantly greater than that of $IDO^{+/+}$ mice. Indeed, the viral load was suppressed in $IDO^{-/-}$ or 1-MT–treated mice. Furthermore, the levels of type I IFN in $IDO^{-/-}$ mice and $IDO^{-/-}$ bone marrow-transplanted $IDO^{+/+}$ mice were significantly higher than those in $IDO^{+/+}$ mice, and treatment of $IDO^{-/-}$ mice with Kyn metabolites eliminated the effects of $IDO^{-/-}$ on the improved survival rates (215). These results suggested that IDO has an important role in acute viral myocarditis. Specifically, IDO is postulated to increase the accumulation of Kyn pathway metabolites, which suppress the production of type I IFN and enhance viral replication. The inhibition of the Trp-Kyn pathway appears to ameliorate acute viral myocarditis. In line with this, upregulated type I IFN has been observed in $IDO^{-/-}$ and 1-MT-treated mice with retrovirus infection compared with those form WT mice, resulting in suppression of virus replication, suggesting that modulation of the IDO pathway may be an effective strategy for treatment of virus infection (216).

5. CONCLUSIONS

In summary, the Kyn pathway plays a key role in the pathophysiological process of CVD by regulating inflammation, SOX, and immune activation (Figure 3). It offers previously uncharacterized therapeutic targets and possibilities for the development of novel therapies that can retard the inflammatory and oxidative states, reduce immune activation, and consequently decrease the prevalence of CVD.

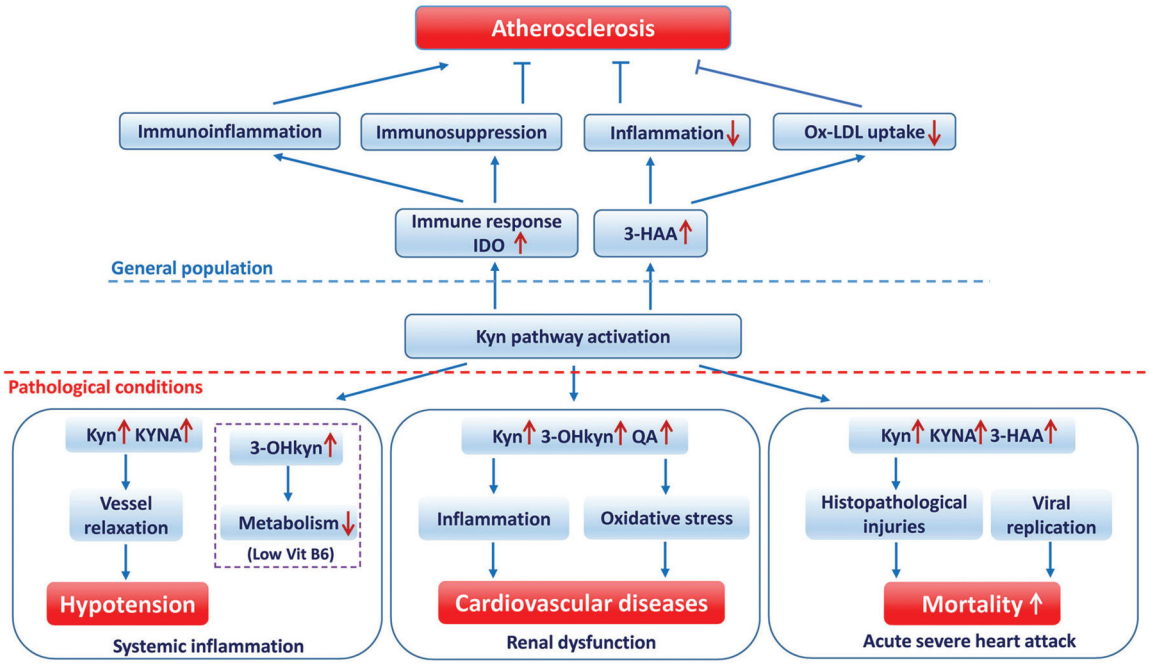

Figure 3. The activation of Kyn pathway in cardiovascular system. Kyn pathway regulates inflammation, SOX and immune responses in cardiovascular disease, especially under some pathological conditions, including chronic renal dysfunction, systemic inflammation and acute severe heart attack. Ox-LDL, oxidized low density lipoprotein; Vit, vitamin

6. ACKNOWLEDGMENTS

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Send correspondence to: Ming-Hui Zou, Division of Molecular Medicine, Department of Medicine, and Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA, Tel: 405-271-3974, Fax: 405-271-3973, E-mail: ming-hui-zou@ouhsc.edu