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REVIEW

Tryptophan metabolism in inter-organ communication and its potential applications for disease prevention and control

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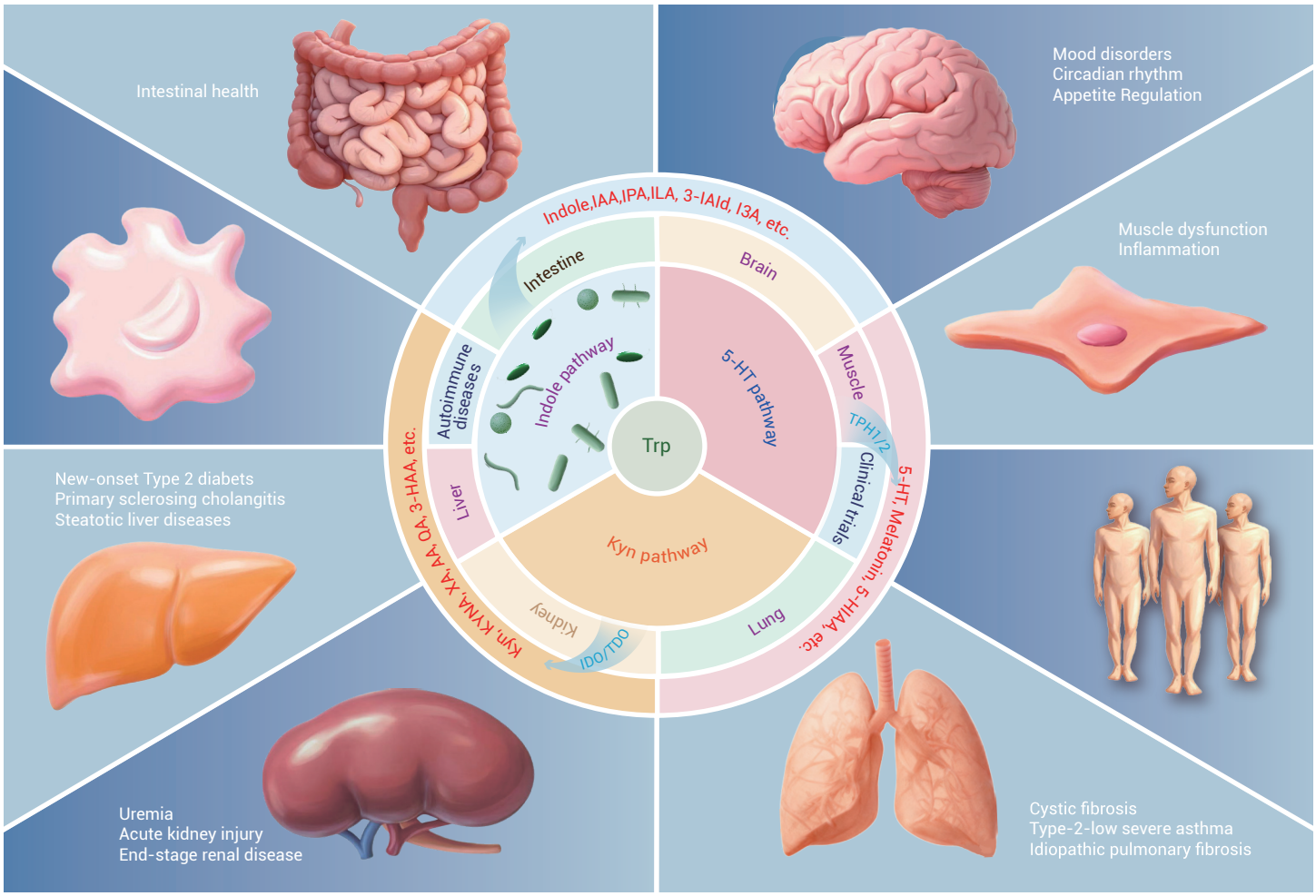
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Tryptophan (Trp) metabolism consists of the kynurenine, the 5-hydroxytryptamine, and the indole pathways.
- Trp metabolites modulate various physiological and pathological processes in many organs in the human body.
- The inter-organ communications mediated by Trp metabolites account for diseases prevention and control.

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Tryptophan (Trp) is an indispensable amino acid which, in addition to being incorporated into proteins, is involved in energy metabolism and gives rise to metabolites with pivotal functions in modulating a variety of physiological processes in mammals. These metabolites are generated in the body through two major metabolic pathways, namely the kynurenine and the 5-hydroxytryptamine pathways. Within the intestinal microbiota, Trp is a precursor for the synthesis of indole and indole-related compounds that have been shown to be active on several host's tissues and organs. Increasing experimental and clinical studies demonstrated the versatile functions of Trp metabolites in various aspects of physiological and pathophysiological processes involved in energy and nutrient metabolism, as well as organ development and inter-organ communication through both peripheral and local regulatory networks. Recent research highlights the importance of such inter-organ communication in the maintenance of the host health. In this context, this review comprehensively summarizes the function of Trp metabolites and their physiological implications in communication between different organs and tissues, and between the intestinal microbiota and the lodging host's cells. The metabolic connection between the intestine and other organs such as brain, liver, lung, kidney, and muscle are presented. The potential therapeutic applications of the regulation of Trp metabolism in different pathophysiological situations are discussed.

LIST OF ABBREVIATIONS

Trp: Tryptophan
Kyn: Kynurenine:
5-HT: 5-Hydroxytryptamine
NAD^+: Nicotinamide adenine dinucleotide
5-HTP: 5-Hydroxytryptophan
NFK: *N*-Formyl-kynurenine
IDO: Indoleamine 2,3-dioxygenase
TDO: Tryptophan 2,3-dioxygenase
KYNA: Kynurenic acid
KYNU: Kynureninase
AFMID: Arylformamidase
AADC: Aromatic l-amino acid decarboxylase
AANAT: Arylalkylamine N-acetyltransferase
KMO: Kynurenine-3-monooxygenase
KAT: Kynurenine aminotransferase
HAAO: 3-Hydroxyanthranilate 3,4-Dioxygenase
ACMSD: Aminocarboxymuconate Semialdehyde Decarboxylase
AA: Anthranilic acid
MAO: Monoamine oxidase
ASMT: Acetylserotonin O-methyltransferase
NAD^+: Nicotinamide adenine dinucleotide
3-HKyn: 3-Hydroxy-kynurenine
3-HAA: 3-Hydroxyanthranilic acid
3-IAld: Indole-3-aldehyde
QUIN: Quinolinic acid
NMDA: N-methyl-D-aspartate
TPH: Tryptophan hydroxylase
5-HIAL: 5-Hydroxyindoleacetate
5-HNFK: 5-Hydroxy-N-Formylkynurenine
5-HKYN: 5-Hydroxy-kynurenine
5-MIAA: 5-Methoxyindoleacetic acid
IPYA: Indole-3-pyruvate
IAA: Indole-3-acetic acid
ILA: Indole-3-lactic acid
IA: Indole acrylic acid
IPA: Indole-3-propionic acid
IAM: Indole-3-acetamide
IAN: Indole-3-acetonitrile
DDC: Aaromatic-L-amino-acid
AHR: Aryl hydrocarbon receptor
DSS: Dextran sulfate sodium
ROS: Reactive oxygen species
CNS: Central nervous system
LNAA: Large neutral amino acids
BBB: Blood-brain barrier
SCFAs: Short-chain fatty acids
GLP-1: Glucagon-like peptide-1
PYY: Peptide YY
MASLD: Metabolic dysfunction-associated steatotic liver disease
MAFLD: Metabolic-associated fatty liver disease
NAFLD: Non-alcoholic fatty liver disease
PSC: Primary sclerosing cholangitis
T2DM: New-onset type 2 diabetes mellitus
KTR: Kyn/Trp ratio
CFTR: Cystic fibrosis transmembrane conductance regulator
PTEN: Phosphatase and tensin homolog

ESRD: End-stage renal disease
AKI: Acute kidney injury
Tregs: Regulatory T cells

INTRODUCTION

In mammals, tryptophan (Trp) must be obtained from the diet since no endogenous synthesis is operative.[1] Trp and its metabolites are deeply involved in various physiological and pathological processes of the human body through a variety of complex metabolic pathways. In addition to its role as building brick for protein synthesis, Trp is used for the synthesis of numerous compounds with biological activities including kynurenine (Kyn) and 5-hydroxytryptamine (5-HT, also known as serotonin). In addition, Trp utilization in mammalian cells can lead to the synthesis of the non-indispensable amino acid alanine, and to pyruvate and NAD^+ (nicotinamide adenine dinucleotide).[2,3] Pyruvate can enter the tricarboxylic acid cycle after conversion to acetyl-CoA, while NAD^+ is an important coenzyme for energy metabolism.[2] Trp metabolism is related to neurotransmitter synthesis, sleep regulation, cognitive function, appetite control, immune regulation, energy metabolism, intestinal homeostasis, cardiovascular health, growth and development, and many other aspects. Currently, two main metabolic pathways of Trp are known in human body, which are Kyn pathway, and 5-HT pathway. In addition, indole and indole-related compounds can be synthesized from Trp by the bacteria of the intestinal microbiota. Most of the metabolites produced in these pathways act as signal transduction molecules playing key regulatory roles in the body.[4,5]

The Kyn pathway is the main pathway in Trp metabolism and play a critical role in immune regulation, neurotransmission, emotion regulation, sleep, and circadian rhythm. Dysregulation of Kyn pathway is often linked to the occurrence and development of a variety of diseases, including neurodegenerative diseases, inflammatory bowel disease and tumor growth.[6-7] In central neurons and enterochromaffin cells, Trp can be converted to 5-hydroxytryptophan (5-HTP) which further generates 5-HT.[8] As a key neurotransmitter, 5-HT modulates numerous neurological processes such as mood, sleep, appetite, stress control, and pain perception.[9,10] Similarly, impaired 5-HT pathway has also been reported to be associated with irritable bowel syndrome, sleep disorders, depression and anxiety disorders.[11-14] In addition, some bacterial species among the intestinal microbiota can convert Trp into indole and its derivatives, a process known as the indole pathway. This pathway is largely involved in regulating intestinal immune response, energy metabolism, intestinal development, and intestinal barrier function. Abnormality of indole pathway disrupts the intestinal homeostasis, causing diseases both in the digestive tract and peripheral systems.[15]

The function of Trp metabolism, and its regulatory network within different organs have been summarized systematically. Moreover, the potential clinical application of Trp-derived metabolites in disease control has also been included in this review.

TRYPTOPHAN METABOLIC PATHWAYS IN THE BODY

Kynurenine pathway

The Kyn pathway accounts for approximately 95% of Trp catabolism in mammals. Initially, Trp is converted into *N*-Formyl-kynurenine (NFK) by the rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). TDO is predominantly synthesized in hepatocytes, while IDO1/2 is a monomeric enzyme that is widely distributed across various tissues and expression of this enzyme can be induced by inflammatory stimuli.[16,17] Additionally, IDO1 also modulates immune responses, particularly in cancer and infectious diseases.[18,19] Then, arylformamidase initiates the degradation of NFK into Kyn, which further generates four different components namely formyl-anthranilate, kynurenic acid (KYNA), anthranilic acid and 3-hydroxy-kynurenine (3-HKyn). Next, 3-HKyn can be converted into xanthurenic acid and 3-hydroxyanthranilic acid (3-HAA). Finally, a variety of enzymes further catalyze the 3-HAA into quinolinic acid (QUIN), picolinic acid and the acetyl-CoA, respectively (Figure 1).

5-Hydroxytryptophan pathway

The 5-HT pathway generates neurotransmitters involving in the regulation of neural activities. Firstly, Trp is hydroxylated to 5-HTP by tryptophan hydroxylase (TPH) which are mostly found in 5-HT-producing cells (TPH1 in enterochromaffin cells and TPH2 in brain stem).[20] Then, 5-HTP acts as a precursor for 5-HT synthesis by the action of aromatic l-amino acid decarboxylase (AADC). 5-HT can be further converted into 5-hydroxyindoleacetate (5-HIAL) by monoamine oxidase, and N-Acetylserotonin by arylalkylamine N-acetyltransferase (AANAT). Next, 5-HIAL and N-Acetylserotonin can be metabolized into 5-hydroxyindoleacetic acid and melatonin, respectively (Figure 1). Both 5-HT and melatonin are capable of modulating neural activities, such as sleep, pain, appetite, depression and behaviors.[21] Approximately 5% of 5-HT can be found in the mature brain of mammals, and the rest (95% of 5-HT) is synthesized in the gastrointestinal tract.[22,23] Recent studies have shown that 5-HT is involved in diverse pathophysiological processes such as carcinogenesis, obesity, and kidney diseases.[24-26]

Of note, a subset of microorganisms including *Cordyceps militaris*, *Ganoderma lucidum*, *Streptomyces albus J1074* strain and *Actinomadura luzonensis DSM 43766* have been found to express bacterial Tph (bTpH) which convert Trp into 5-HTP.[27-29] However, 5-HTP in these bacteria is sequentially metabolized into 5-Hydroxy-N-Formylkynurenine (5-HNFK) and 5-Hydroxykynurenine (5-HKyn) by IDO and arylformamidase, respectively.

Indole pathway

The indole pathway is operative in numerous Gram-positive and Gram-negative bacterial species.[30-32] Bacteria among the intestinal microbiota generate indole and various indole derivatives including indole-3-pyruvate (IPYA), indole-3-acetic acid (IAA), indole-3-lactic acid (ILA), indole acrylic acid (IA) and indole-3-propionic acid (IPA) which are found within the intestinal luminal fluid.[33] There are three metabolic branches for bacteria-mediated indole pathway (Figure 1). Firstly, the *Escherichia coli* and *Vibrio cholerae* are two well-known bacteria species reported to metabolize Trp into indole since 1897.[34,35] Bacteria-generated tryptophanase cleaves the carbon-carbon bond of Trp to release indole and an unstable enamine product that tautomerizes to an imine form, which in turn undergoes hydrolytic deamination to form pyruvate and ammonia.[36,37] Indole has been reported to modulate intestinal hormone release in enteroendocrine L-cells by regulating the level of glucagon-like peptide 1, and can be further metabolized into indoxyl, acetylindocyl and N-Acetylisatin.[38] Secondly, Trp can be metabolized into tryptamine by *Ruminococcus gnavus* and *Clostridium sporogenes* under the activation of aromatic-L-amino-acid (DDC). Tryptamine promotes gastrointestinal motility by modulating the secretion of 5-HT.[39,40] Tryptamine can be further metabolized into indole-3-acetamide (IAM) though the intermediate indole-3-acetonitrile (IAN). Next, IAM is converted to IAA by IAM hydrolase encoded by *IaaH* gene. Interestingly, Trp also can be directly catalyzed into IAA in immune cells by enzymatic activation of interleukin-4-induced gene 1.[41] Thirdly, aromatic amino acid aminotransferases produced by *Lactobacilli* and *Clostridium sporogenes* catalyze Trp into IPYA, which is further converted into ILA through the activation of aromatic 2-oxoacid reductase. IPYA acts as the precursor of IA which is further converted into IPA by activating acyl-CoA-dehydrogenase (Figure 1).[42] Of note, many of these intestinal microbiota-derived Trp metabolites are often acting as aryl hydrocarbon receptor (AHR) ligands to participate in various aspects of physiological and pathophysiological processes involved in host metabolism and metabolic diseases (Table 1).

TRYPTOPHAN METABOLISM IN INTESTINAL HEALTH

Recent studies have revealed that microbiota-derived Trp metabolites play a pivotal role in enhancing mucus secretion by upregulating Mucin 2 expression in goblet cells, thereby strengthening the first physical barrier of the small intestine.[43,50] This effect is partially mediated through the activation of AHR, which regulates transcription of genes involved in mucin biosynthesis independent of IL-22.[52,94] In addition to indole-3-aldehyde (3-IAld) and IPA, ILA, a metabolite produced by *Lactobacillus spp.*, has been shown to suppress intestinal inflammation by inhibiting the phosphorylation of NF-κB and STAT3 signaling in macrophages and epithelial cells.[43] Tryptamine modulates ion secretion in intestinal epithelial cells by acting on 5-hydroxytryptamine receptor 4, promoting water movement and intestinal motility.[57,95] This neuroepithelial signaling contributes to the maintenance of luminal fluid balance and may influence the microbial colonization niche.[57]

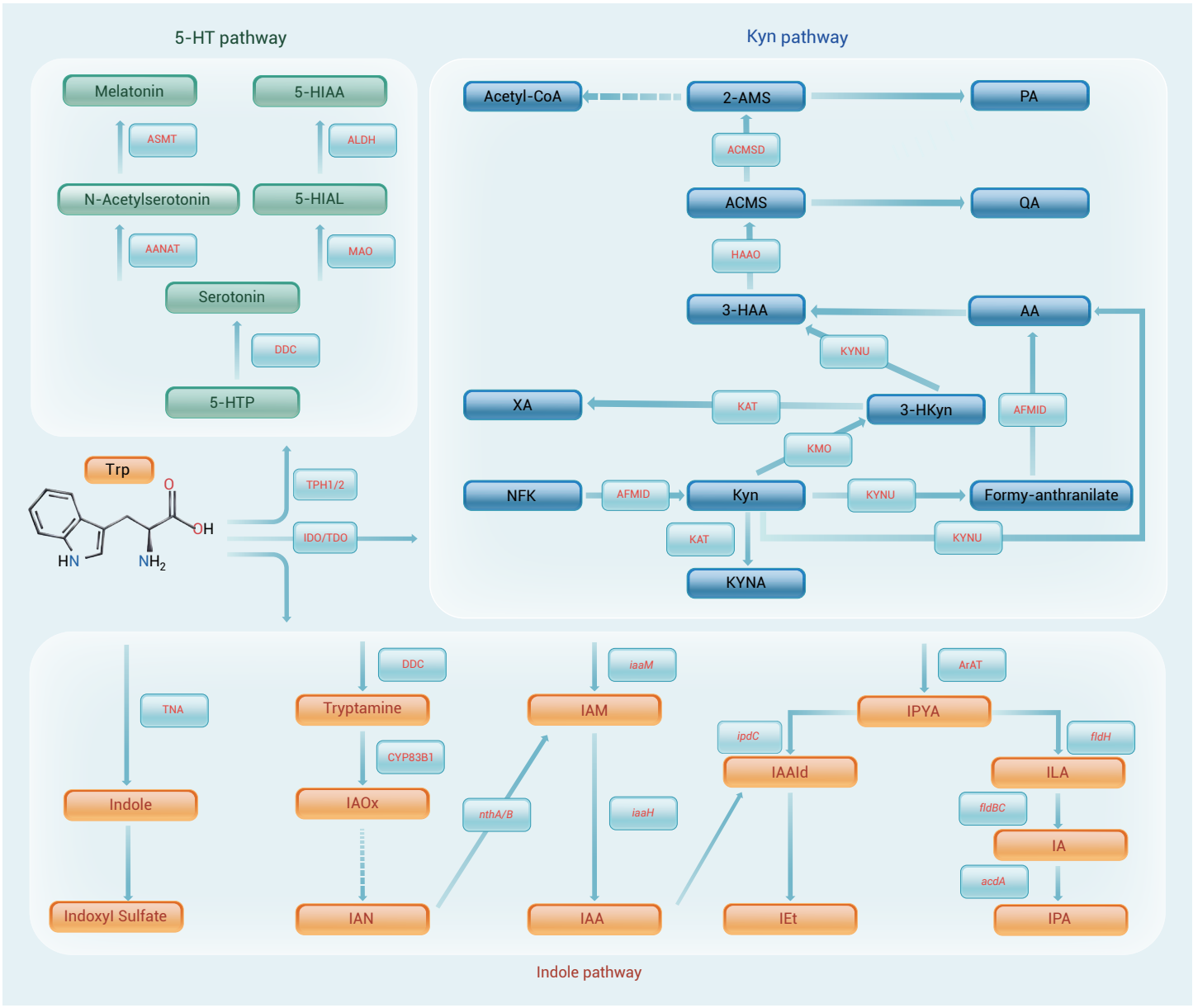

Figure 1. The metabolic pathways of Trp Trp metabolism consists of three major metabolic outcomes termed the kynurenine (Kyn), 5-hydroxytryptamine (5-HT) and indole pathways, notably operative in bacterial species belonging to the intestinal microbiota, all of which generate various bioactive metabolites that participate in regulating multiple physiological processes in the host body. Trp: tryptophan; IDO: Indoleamine 2,3-Dioxygenase; TDO: tryptophan 2,3-dioxygenase; AFMID: arylformamidase; KYNU: kynureninase; KMO: kynurenine 3-monooxygenase; KAT: kynurenine aminotransferase; KAT-II: kynurenine aminotransferase II; HAAO: 3-Hydroxyanthranilate 3,4-Dioxygenase; ACMSD: Aminocarboxymuconate Semialdehyde Decarboxylase; NFK: N-Formylkynurenine; Kyn: Kynurenine; AA: anthranilic acid; KYNA: Kynurenic acid; 3-HKyn: 5-Hydroxy- Kynurenine; 3-HAA: 3-hydroxyanthranilic acid; TPH1/2: tryptophan 5-monooxygenase; DDC: aromatic-L-amino-acid; MAO: monoamine oxidase; ALDH: aldehyde dehydrogenase (NAD+); AANAT: arylalkylamine N-acetyltransferase; ASMT: acetylserotonin O-methyltransferase; 5-HTTP: 5-Hydroxy-tryptophan; 5-HIAA: 5-hydroxyindole acetic acid; 5-HIAL: 5-hydroxy-indolelactic acid; tnaA: tryptophanase; iaaM: Tryptophan 2-monooxygenase; iaaH: indoleacetamide hydrolase; nthA/B: nitrile hydratase subunit alpha; CYP83B1: aromatic aldoxime N-monooxygenase; ArAT: Aromatic amino acid aminotransferases; ipdC: indolepyruvate decarboxylase; fldH: aromatic 2-oxoacid reductase; fldBC: phenyllactyl-CoA dehydratase; acdA: acyl-CoA dehydrogenase; IAOx: Indole-3-acetaldoxime; IAN: Indole-3-acetonitrile; IAM: Indole-3-acetamide; IAA: Indoleacetate; IAAld: Indole-3-acetaldehyde; IPYA: Indolepyruvate; ILA: Indolelactic acid; IA: 3-Indoleacrylic acid; IPA: 3-Indolepropionic acid.

Tryptophan metabolites also influence innate immune sensors in intestine. Reduced indole production increases the expression of TLR4 and NOD2 in epithelial cells, strengthening their responsiveness to LPS and muramyl dipeptide, which lead to exaggerated NF-κB signaling and upregulation of proinflammatory cytokines.[96,97] Under stress or inflammatory conditions, the host upregulates IDO1, depleting local Trp pools and suppressing microbial production of presumably beneficial metabolites such as IPA and 3-IAId, thereby shifting the immunometabolic landscape toward a pro-inflammatory state.[32,33] Furthermore, gut bacteria regulate Trp availability by expressing distinct metabolic enzymes. For instance, *E. coli* express tryptophanase that converts free Trp into indole, while *Lactobacillus reuteri* expresses aromatic amino acid aminotransferases that facilitate indole pyruvate conversion into 3-IAId and IPA.[32,43] These findings highlight novel mechanisms by which microbial Trp metabolism modulates mucosal integrity, immune activation, and neuro-regulation in the gut.[32]

Beyond its anti-inflammatory effects, microbial Trp metabolites also exhibit potent antioxidant capacity in intestinal tissues. For instance, IPA significantly scavenges hydroxyl radicals and superoxide anions, and its antioxidant capacity is comparable to that of vitamin C.[53,98] In dextran sulfate sodium (DSS)-induced colitis models, IPA supplementation decreased ROS levels, malondialdehyde concentration, and restored glutathione in the colonic epithelium.[53] In terms of immune regulation, indole derivatives-mediated AHR activation leads to activation of antimicrobial peptides such as Reg IIIγ and β-defensins in Paneth and epithelial cells, thereby enhancing the intestinal defense system.[43] This antimicrobial response not only suppresses potential pathogens but also shapes the commensal microbial ecosystem by favoring

Table 1. The actions of tryptophan metabolites in different organs.

Trp metabolites	Function/Mechanism	Interaction Sites	Diseases	Refs
IAld	AhR activation; ↑IL-22; ↓NF-κB; JNK; IL-6; IL-1β; TNF-α; MCLK/p-MLC; Antifungal/mucosal protection	Stomach; Peyer's patches; Vagina; Colon mucosa; Epithelium; Lamina propria;Macrophages; Brain	Mucosal candidiasis (*Candida albicans*); Ameliorated colitis, Neuroinflammation,LPS-induced epithelial dysfunction	33,43,44
I3A/3-IAld	AhR activation; ↓ROS; NF-κB/NLRP3; Preserves mitochondrial membrane potential; ↑ZO-1/occludin; Barrier protection; Inhibits fat accumulation in the liver; ↓Fungal infection	Colon mucosa; Kidney; Liver; Gut and lung	LPS-induced intestinal inflammation; NLRP3-driven mucosal inflammation; IBD; NAFLD;	45,46,47-49
IAA	Microbial AHR agonist; ↑IL-22 (ILCs/TH22), Reg3g/Reg3b; Anti-inflammatory; Enhances neutrophilic invasion; Mitigates pulmonary fibrosis	Colon (lamina propria/epithelium); Mesenteric lymph nodes; Lung;	Ameliorated IBD, Severe asthma (type2-low), Pulmonary fibrosis	50,51
IPA	Potent hydroxyl radical scavenger; Prevents lipid peroxidation; AHR/PXR; Neuroprotection; Post-stroke recovery; Barrier integrity; insulin sensitivity; ↓Astrocyte Ccl2/Nos2; Inhibits NF-κB signaling and reduces the levels of proinflammatory cytokines (TNFα, IL-1β, and IL-6); Represses hepatic inflammation and liver injury; Inhibits the expression of fibrogenic and collagen genes; Inhibits the activation of hepatic stellate cells	Brain; Hippocampal neurons; Astrocytes; CNS; Macrophages; Liver; Hepatic stellate cells	Alzheimer's disease(Aβ toxicity model); Oxidative stress-related neurodegeneration;Neuroprotection; NASH; T2DM	52,53,54,55,56
Tryptamine	Epithelial 5-HT4R agonist; ↑cAMP, Cl−/HCO3−secretion; Accelerates transit	Proximal colon epithelium; Colonoids	Functional constipation; IBS-C; Slow GI transit	57
5-HTP	AhR ligand; ↑ILC3; Antibody-independent partial effect	Maternal gut → milk/placenta → neonatal small intestine	Protection from bacterial translocation	58
5-HT	5-HT2C (hypothalamus) → satiety control; Mood modulation;↑5-HT2A; Induces hepatic steatosis; EEC–vagal signaling; Synergy with GLP-1/PYY;	Gut (EC cells); CNS neurons; Skeletal muscle	Insulin sensitivity; NAFLD; Muscle development	59-63,64,65
Melatonin	Circadian time signal; Immunomodulation (Mel1a/Mel1b/Mel1c/RORs); ↑B/T lymphocyte activity; ↑Phagocyte function; Antioxidant (↑SOD, ↑GSH-Px); Improves circadian disorders and controls weight	Pineal gland; Retina; Bursa of Fabricius; Thymus; Spleen; Brain	Circadian/sleep disorders; Seasonal physiology; Mood/behavior; Skeletal muscle growth	66,67
Kyn	AHR; BBB transport; Neuroinflammatory bias; Inhibits ROS in neutrophils; Promotes survival; Attenuates airway inflammation and pulmonary fibrosis	Systemic; microbiota-kynurenine-liver Axis; Lung	Immune/metabolic effects; Neuroinflammation; Nonalcoholic hepatic steatosis; Airway inflammation, Pulmonary fibrosis;	68-70,71,72,73,74
KYNA	NMDA Glycine-site antagonism; Anti-excitotoxic, Neuroprotection; ↓TNFα	CNS; Skeletal muscle	Muscle injury	75-77,78
QA	NMDA receptor agonism; excitotoxicity; neurotoxicity; ↑ROS	Brain (microglia/astrocytes)	Alzheimer's disease model; neuronal damage; Sarcopenia	52,79,80,81
Indole	Modulates microglial/AHR anti-inflammatory tone; EEC activation (GLP-1/PYY); restoring liver, macrophage M2 polarization; ↑Treg	Gut, Liver, Arthrosis; Microglial cell	Autoimmune diseases, Arthritis	44,63,82
ILA	AHR activation; Anti-inflammatory tone	Gut and Kidney; Muscle stem cells	Uremia, Sarcopenia(ameliorated)	83,84,85,86,87
5-methoxytryptophan	Inhibit IκB/NF-κB signaling and enhance Keap1/Nrf2 signaling	Lung and Kidney	Idiopathic pulmonary fibrosis, Renal interstitial fibrosis (ESRD)	88
Indoxyl sulfate	Aggravates chronic kidney diseases, exerting its deleterious effects on kidney cells, involving in the inflammatory process in proximal renal tubular cells, reducing the superoxide scavenging activity in the kidney	Gut and kidney; Renal tubular	CKD aggravation; inflammation; Oxidative stress	89-91
5-MIAA	Activates Nrf2 → oxidative stress protection	Gut and Kidney	Acute kidney injury, Oxidative stress	92
I3A	Activating the AHR-mediated immune pathway	Gut and Skin	Atopic dermatitis	93

beneficial bacterial strains. Trp metabolites also act on dendritic cells to modulate immune responses. AHR activation in intestinal dendritic cells induces the secretion of IL-10 and promotes the expression of retinoic acid-producing enzymes, which facilitate regulatory T cells (Tregs) differentiation and immune tolerance in gut-associated lymphoid tissue.[52,99] Similarly, Trp metabolites can directly promote the expansion of Foxp3$^+$ Tregs. Studies

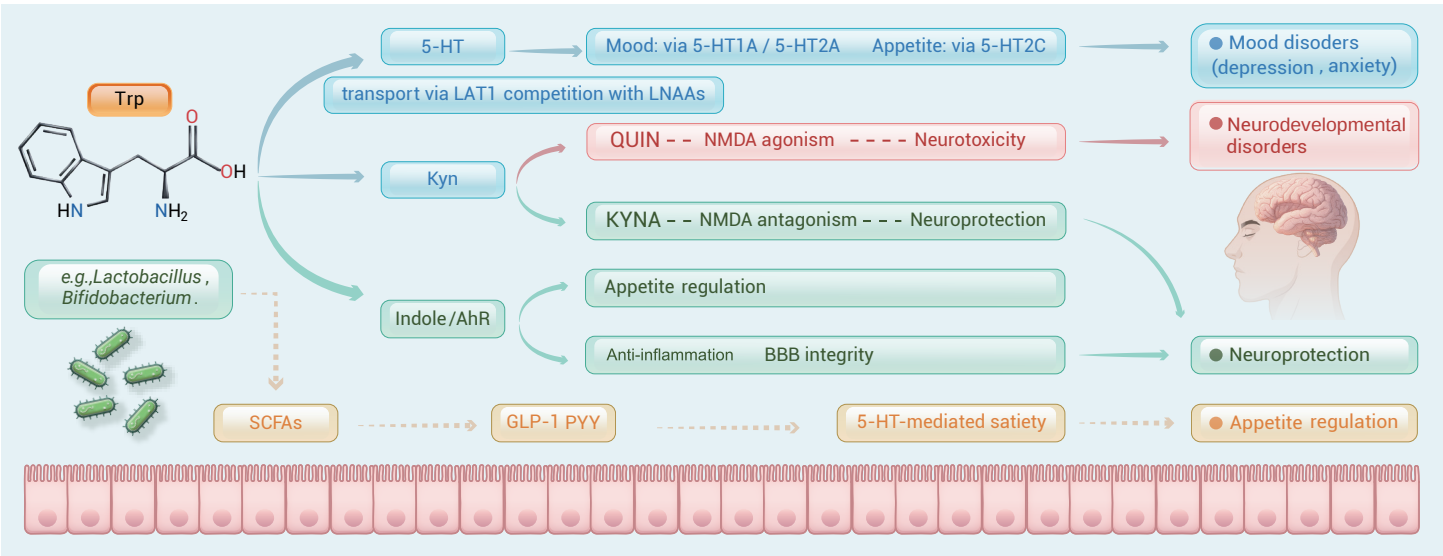

Figure 2. Trp metabolism in neurological activity in the brain Dietary Trp enters the circulation system and crosses the blood–brain barrier (BBB) via the large neutral amino-acid transporter to either support cerebral 5-HT synthesis, or promote Kyn production. Kyn can be further metabolized into neuroprotective kynurenic acid (KYNA) or into neurotoxic quinolinic acid (QUIN), both of which disrupts the BBB integrity and promotes neurodegeneration. Concurrently, gut commensal flora such as *Lactobacillus* and *Bifidobacterium* degrade Trp into aryl-hydrocarbon receptor (AHR)-activating indole metabolites that reinforce BBB integrity and decrease neuroinflammation. In addition, these bacteria also produce short-chain fatty acids (SCFAs) that stimulate enteroendocrine GLP-1 and peptide YY (PYY) secretion, conveying satiety cues via the vagus and systemic circulation to the brain. The balanced Trp-Kyn/KYNA-QUIN axis together with SCFA-GLP-1/PYY signaling maintains neuroprotection and appetite, regulation whereas skewing toward QUIN amplifies neuroinflammation.

show that 3-IAld and ILA enhance Treg frequency via the AHR-IL-10 axis and inhibit Th17 polarization in lamina propria.[58,100] Additionally, gut-resident macrophages respond to indole signals, with reduced production of the inducible form of nitric oxide synthase and proinflammatory cytokines (IL-1β, TNF-α), and increased phagocytic and tissue-repair capacity.[52,101] Trp metabolism also modulates intestinal epithelial-immune interaction through regulation of inflammasomes. Indole derivatives inhibit NLRP3 inflammasome activation by blocking mitochondrial ROS production and ATP-dependent caspase-1 cleavage, reducing IL-1β release and pyroptosis in colonic epithelium.[45,102] Finally, maternal microbial Trp metabolism has been shown to influence neonatal immune development. For example, 3-IAld produced by maternal gut flora can cross the placenta or reach neonatal gut via breast milk, activating AHR in neonatal innate lymphoid cells and supporting postnatal gut immune education.[99]

TRYPTOPHAN METABOLISM IN NEUROLOGICAL ACTIVITY IN THE BRAIN

Tryptophan metabolism is a critical interface where dietary, microbial, and neural signals converge to sustain central nervous system (CNS) homeostasis.[33,103] Kyn pathway yield neuroactive metabolites in the CNS with opposing actions: QUIN acts as an endogenous N-methyl-D-aspartate (NMDA) receptor agonist that promotes excitotoxicity, whereas KYNA confers neuroprotection primarily via NMDA receptor antagonism.[68-70,79,80] Perturbations of this network initiates mood pathology.[75-77] Central 5-HT drives satiety through hypothalamic 5-HT2C receptors, whereas peripheral cues including enterochromaffin-cell serotonin and microbial indoles act via vagal and enteroendocrine system to modulate GLP-1 and PYY secretion and improve insulin sensitivity.[102,104,105] Beyond mood and energy homeostasis, increasing evidence supports the importance of the microbiota-Trp-AHR axis in acute brain injury.[71] After ischemic stroke, the AHR-ligand pool shifts from microbiota-derived indoles toward host-derived Kyn, with sustained depletion of indoles in the subacute phase.[72] Restoring this balance by supplementing indole metabolites reduces microglial activation, dampens neuroinflammation, and improves functional recovery in preclinical models.[44,106]Collectively, these observations position Trp metabolism as a tractable node to influence psychiatric and neurological outcomes in the brain (Figure 2).[44,59,60]

Mood disorders

Mood disorders like depression and anxiety are closely linked to impaired Trp metabolism, particularly by changing the 5-HT level.[61-63] Within the CNS, 5-HT binds to its receptors 5-HT1A and 5-HT2A on mood state.[107-109] Reduced 5-HT levels caused by either impaired Trp metabolism or reduced Trp transportation have been observed in patients with depression and anxiety.[54,110,111] Emerging research highlights the regulatory role of bacteria involved in Trp metabolism on CNS function.[55,112] For example, *Lactobacillus reuteri* and *Bifidobacterium longum* have been shown to enhance 5-HT production to reduce depressive symptoms.[82,113,114] Intestinal microbiota dysbiosis skews Trp metabolism toward neurotoxic Kyn metabolites to increase the risk of mood disturbances.[115-117] Preclinical studies showed that impaired Trp metabolism is associated with anxiety- and depressive-like behaviors.[118-120] For instance, reduced 5-HT levels or increased Kyn lead to social withdrawal and stress reactivity.[121-123] Clinically, patients with depression and anxiety frequently exhibit a lower level of plasma Trp and 5-HT. Adequate Trp intake enhances the synthesis of 5-HT and stabilizes mood state.[124-126] Moreover, inhibition of IDO activity is able to mitigate the excessive production of neurotoxic Kyn metabolites in the brain.[127-129]

Appetite regulation

Appetite regulation is a multifaceted complex physiological process orchestrated by intricate interactions between neurotransmitters, hormones, and metabolic pathways.[130,131] Trp metabolites, particularly 5-HT, play a pivotal role in modulating appetite and energy homeostasis.[132-134] The hypothalamus serves as the central hub that integrates serotonergic signals to regulate satiety and food intake.[134-136] 5-HT exerts direct inhibitory effects on feeding behavior through activation of various receptors including 5-HT2C whose activation reduced appetite and calorie intake.[137-139] Pharmacological agents targeting 5-HT receptors promotes weight loss by enhancing satiety and suppressing hunger signals in both animal models and human clinical trials.[105] A high Trp diet potentially augments central 5-HT synthesis to promote satiety.[140,141] However, this effect is modulated by the competitive transport of large neutral amino acids (LNAAs) crossing the blood-brain barrier (BBB), which influences Trp availability for 5-HT synthesis.[142-144] Elevated levels of LNAAs limit Trp entrance into the CNS to attenuate the 5-HT-mediated satiety response.[145-147] Notably, the intestinal microbiota impact appetite by generating various bioactive metabolites.[148,149] Short-chain fatty acids (SCFAs), produced through microbial fermentation of dietary fibers and some specific amino acids,[150] act on enteroendocrine cells to stimulate the secretion of appetite-regulating hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY).[151-154] These hormones synergize with 5-HT to suppress appetite and regulate glucose metabolism, thereby contributing to

energy homeostasis.[131,155-157] Furthermore, indole derivatives ILA and 3-IAld regulate energy metabolism and appetite by activating AHR signaling.[158-161] Additionally, indole and its derivatives also regulate appetite via modulating neural circuits involved in energy balance and feeding behavior.[162-164] Impairment of the Trp/5-HT levels and intestinal microbial composition are closely associated with obesity and eating disorders.[165,166] Obesity is often accompanied by intestinal microbiota dysbiosis, a lower Trp/5-HT ratio and elevated Kyn activity.[167-169] Obesity-induced chronic inflammation exacerbates the activation of Kyn pathway, leading to increased production of neurotoxic metabolites such as QA.[83,170,171]

The microbiota-Trp-5-HT axis play a significant role in regulating eating disorders, such as anorexia and binge eating disorder.[84,85] Altered gut microbial composition and Trp metabolism contribute to heightened anxiety and rigid food intake pattern in anorexia patient.[172-174] Elevated inflammatory responses and disrupted 5-HT signaling have been observed in individuals with anorexia, suggesting a link between immune dysregulation and impaired appetite control.[175-177] Conversely, altered Trp metabolism leads to impaired satiety signaling and increased caloric intake in the context of binge eating disorder.[84,173] Therapeutic strategies targeting Trp metabolism offer promising avenues for treating appetite-related disorders.[178-180] Probiotics supplementation has been shown to improve appetite by increasing Trp availability for 5-HT synthesis.[59,181] *Bifidobacterium longum* supplementation enhances GLP-1 secretion and promotes weight loss in obese individuals.[182-184] Administration of the agonists of 5-HT2C receptor has been approved for inducing weight loss due to their ability to enhance satiety.[185,186]

Circadian rhythm

Tryptophan metabolism contributes to circadian rhythm regulation primarily through its conversion into 5-HT and subsequently melatonin, a neurohormone exhibiting pronounced circadian oscillations.[187] This biosynthetic cascade occurs via TPH, AADC, AANAT, and acetylserotonin O-methyltransferase (ASMT) in a stepwise manner.[187] Among these enzymes, AANAT functions as the rate-limiting enzyme in melatonin synthesis and exhibits strong circadian rhythmicity.[187] Its transcription is positively regulated by CLOCK–BMAL1 heterodimers binding to E-box motifs within its promoter. Experimental evidence indicate that the expression of AANAT peaks during the dark phase, consistent with nocturnal melatonin secretion, and declines during the light phase, ensuring synchronization with environmental photoperiod cycles.[188] Interestingly, the expression and activity of AANAT and ASMT are also influenced by rhythmic epigenetic modifications and post-translational phosphorylation, suggesting a multi-layered regulation of the Trp-melatonin axis by the circadian clock.[187] In the pineal gland, norepinephrine released in response to photic signals further regulates AANAT activity via the cAMP/PKA pathway, thereby linking environmental cues to melatonin biosynthesis.[189] Additionally, melatonin provides feedback signals to the central circadian pacemaker in the suprachiasmatic nucleus occurring through MT1 and MT2 receptors, contributing to the entrainment of the circadian system. In peripheral tissues such as the intestine and liver, local melatonin production follows its own rhythmic patterns and may help coordinate tissue-specific oscillators.[189,190].Recent findings also suggest that circadian genes may, in turn, influence Trp metabolic flux. For example, core clock components such as PER2 and REV-ERBα have been shown to affect the transcription of TPH1 and IDO1, two key enzymes in serotonin and kynurenine pathways, respectively.[191-193] This bidirectional interaction further supports the role of Trp metabolism as both a regulator and a target of circadian control.[193] Moreover, microbiota-derived Trp metabolites such as indole and IAA have been implicated in modulating host circadian gene expression in peripheral tissues, although detailed molecular mechanisms remain to be fully elucidated.[194]

TRYPTOPHAN METABOLISM IN LIVER DISEASES

The physiological interaction between the liver and the gut, both anatomically and functionally, is known as the intestine-liver axis.[195] The intestinal epithelial barrier serves as both a physical and functional shield between the gut and the liver. Indole produced by the gut microbiota can be absorbed in the portal vein and exerts beneficial effects on liver cells. For instance, Indole reduces the production of pro-inflammatory mediators in the liver.[196] In obese mice, indole appears hepatoprotective by reducing low grade hepatic damage and its associated inflammatory response.[197] Indole derivatives indole-3-acetate alleviates hepatotoxicity induced by high-fat diet in a mice model.[198] Indole-3-acetate also reduces the expression of fatty acid synthase to regulate fatty acid production in hepatocytes.[199,66] Indoxyl sulfate is produced in the liver by several enzymes belonging to the cytochrome P450 (CYP) family.[67] It interferes with the transport processes in liver by affecting the efflux transporter P-gp,[200] and by decreasing the uptake of the conjugated taurocholate.[201] Furthermore, excessive indoxyl sulfate reduces hepatocyte viability and cause a decreased mitochondrial membrane potential and ATP content, thus causing dysfunction of energy metabolism in hepatocytes.[201]

Metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), an updated nomenclature of metabolic-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD), has been accurately used to define fatty liver diseases associated with metabolic dysfunction.[202,203] The onset of MASLD is mainly characterized by a disorder of lipid metabolism and insulin resistance (Figure 3). TDO is mainly expressed in the liver and exhibits a higher binding affinity with Trp than that of IDO.[204] Elevated TDO2 expression and triglyceride levels have been reported in patients with MASLD.[205] TDO2 drives macrophages toward the pro-inflammatory M1 phenotype by activating the Kyn/AHR/NF-κB signaling pathway, thereby accelerating hepatic steatosis in MASLD patients.[205,206] Moreover, both the increased Kyn level and the relative abundance of *Collinsella*, *Acinetobacter*, and *Actinobacter* have been found in the feces of MASLD patients, highlighting the potential crosstalk between intestinal microbiota and the Kyn pathway in the pathogenesis of MASLD.[207] Inhibition of IDO activity decreased the expression of pro-inflammatory genes (TNF-α and IL-1β) as well as fibrosis responsive genes (TGF-β and α-SMA) to reduce liver fibrosis.[208] In addition, peripheral 5-HT acts as an endocrine regulator of lipid metabolism in the liver. Overexpression of 5-HT and HTR2A in the liver has been considered as a risk factor for hepatic steatosis.[209] High fat diet-fed mice exhibited enhanced serotonin catabolism and concomitant oxidative stress in the liver.[46] Fecal transplantation with *Akkermansia*, *Bacteroides*, and *Parabacteroides* significantly ameliorated metabolic dysregulation in NAFLD mice by preventing hepatic steatosis, body fat accumulation, and dyslipidemia.[46] Indole derivatives also participate in the progression of NAFLD. Decreased level of IPA and IAA have been reported in the feces of patients with hepatic steatosis.[210] Serum IPA induces IL-6 secretion and activates the AMPK pathway, which in turn reduces hepatic TG synthesis and enhance fatty acid oxidation to attenuate intrahepatic lipid accumulation.[211] Indole-3-carboxaldehyde (I3A) inhibits fat accumulation in the liver by promoting the AHR pathway to suppress hepatic inflammatory responses and slow down the progression of NAFLD.[199]

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, idiopathic inflammatory disease characterized by progressive cholestasis and bile duct fibrosis. PSC induces epithelial inflammation, fibrosis and segmental stenosis in the intrahepatic or extrahepatic bile ducts, ultimately leading to biliary cirrhosis and eventual liver failure. The mechanism of pathogenesis of PSC remains poorly understood, but emerging evidence suggest that dysregulation of Trp metabolism may be linked to PSC. The Kyn/Trp ratio is significantly increased in PSC patients, implying its regulatory connection with PSC.[212] Impaired Kyn pathway compromised mitochondrial energy production in PSC by disrupting the NAD^+ biosynthesis.[213] Additionally, bile and serum TPH2 levels appears to be a latent indicator of prognosis for PSC patients.[214]

New-onset type 2 diabetes

New-onset type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive impairment of pancreatic β-cell function.[215] Elevated plasma Trp level has been reported in T2DM patients. The Kyn-NAD^+ metabolic pathway participates in the regulation of insulin resistance by affecting blood glucose level.[216,217] Notably, the Kyn/Trp ratio (KTR) is positively correlated with blood glucose levels and serves as an indicator of IDO activity. Elevated serum KTR in T2DM patients

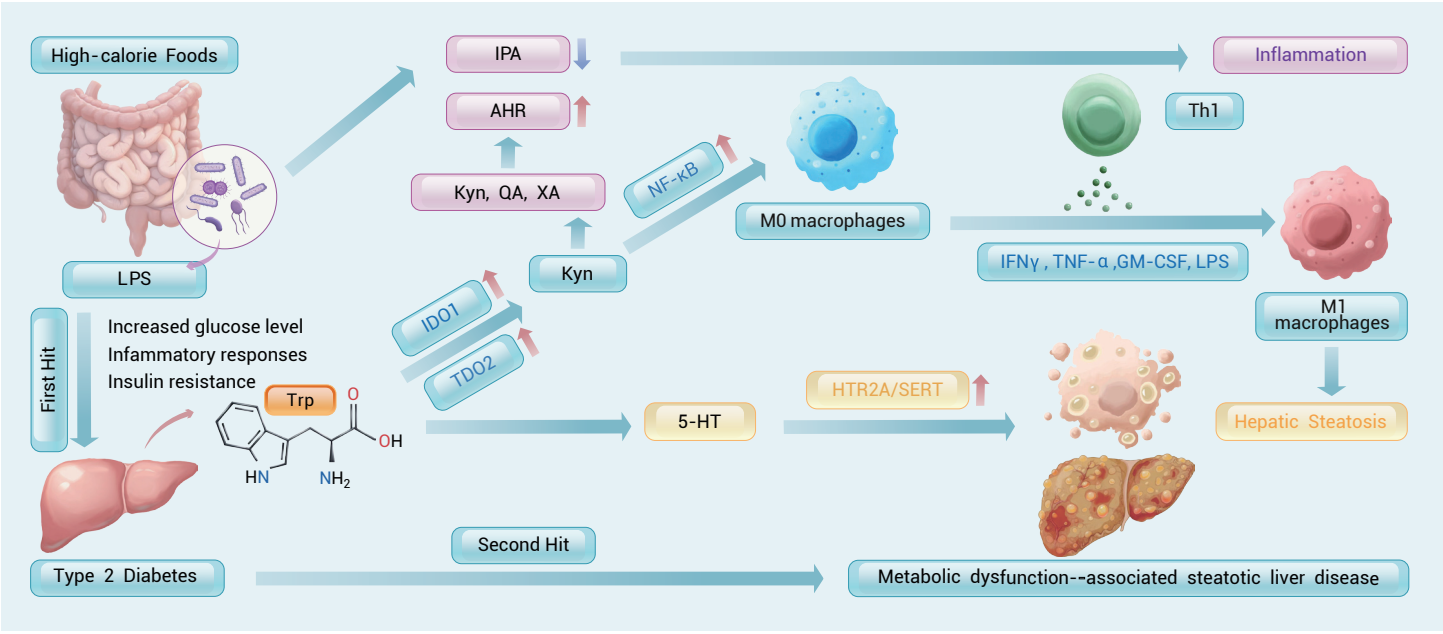

Figure 3. Trp metabolism in liver diseases Excessive ingestion of high-calorie foods alters intestinal epithelium permeability and accumulates abnormal gut bacteria. Then, bacteria-derived lipopolysaccharide (LPS) enters the portal vein and reach the liver, triggering the secretion of inflammatory cytokines, insulin resistance, and hyperglycemia, a phenomenon termed the "first hit". Subsequently, insulin resistance-mediated lipid accumulation in hepatocytes contributes to the onset and progression of type 2 diabetes, which exacerbates hepatocellular injury and forms the "second hit", ultimately causing hepatic metabolic dysfunction. The liver injury is often associated with impaired Trp metabolism and enhanced inflammatory responses. Firstly, activation of 5-HT upregulates the expression of HTR2A and SERT to induce hepatic steatosis. Secondly, elevated TDO2 expression promotes the Kyn pathway and activates the expression of NF-κB factors and their downstream inflammatory cytokines (IFN-γ, TNF-α, GM-CSF) and LPS, driving the polarization of immature M0 macrophages into M1 macrophages which in turn exacerbates inflammation and hepatic steatosis. Concurrently, activated IDO1 also increases the production of Kyn, quinolinic acid (QA), and xanthurenic acid (XA), all of which activate the AHR pathway. Overactivation of AHR alters gut microbial diversity to decrease indole-3-propionic acid (IPA) production which lead to development of inflammation, disrupting the intestinal barrier between gut and liver.

are often accompanied by enhanced IDO activity.[218] It is evident that oxidative stress and inflammatory responses in T2DM patients activate the Kyn pathway, leading to increased conversion of Trp into Kyn and impaired lipid metabolism.[73,219] The interaction between 5-HT and HTR2A contributes to hepatic steatosis and liver oxidative stress.[64,209] Genetic deletion of 5-HT2C results in hyperphagia-induced obesity.[220] Recently, the decreased level of IPA has been found in patients with T2DM.[221] IPA inhibits the activation of hepatic stellate cells, thereby reducing fibrosis, and decreasing hepatic fat accumulation.[56] Under specific physiological conditions, IPA exhibits antioxidant and anti-inflammatory activities in response to T2DM pathogenesis.[222]

TRYPTOPHAN METABOLISM IN LUNG DISEASES

Human respiratory tract and digestive tract tissues are derived from the endoderm of the original digestive tube.[223] Certain immune cells, such as type 2 innate lymphoid cells can migrate form the gut to the lungs via the systemic circulation.[224] The AHR is abundantly expressed in the gut and lung, and serves as a key endogenous ligands-binding receptor for Trp metabolites to exert their function in intestinal and pulmonary immunity. Besides respiratory tract infections and pulmonary inflammation, multiple other types of lung diseases including cystic fibrosis, type-2 severe asthma, and idiopathic pulmonary fibrosis, have been found to be closely associated with Trp metabolism in the gut and lung (Figure 4).

Cystic fibrosis

Cystic fibrosis is an autosomal recessive genetic disease caused by a single gene mutation on the long arm of chromosome 7, resulting in abnormal function of the cystic fibrosis transmembrane conductance regulator (CFTR).[225] As a multisystem disease, cystic fibrosis primarily affects the lungs, pancreas, gastrointestinal tract, and liver. In recent years, the gut-lung axis has been found to be closely associated with the phenotype and disease progression of patients with cystic fibrosis.

Recently, multiple evidences have found that Trp metabolism can influence the course of cystic fibrosis and clinical outcomes through the gut-lung axis via AHR.[226] Firstly, CFTR promoter region owns the AHR binding sites, by which the AHR ligands can correct the cystic fibrosis defects.[227-230] AHR agonism antagonizes hypoxia-driven inflammation and restore immune homeostasis in cystic fibrosis patients and mice model.[228] Meanwhile, *Lactobacillus reuteri* exhibits its beneficial effects on infection and on pulmonary functions in cystic fibrosis patients by producing 3-IAld.[231,232] Delivery of 3-IAld into gut or lung in a murine model of cystic fibrosis enhances the recovery of immune homeostasis and mitigates inflammatory pathologies during fungal infection.[233] In addition to its clinical improvement in airway immunity, *Lactobacillus* supplementation also changes the intestinal microbiota in children with cystic fibrosis, in which the relative abudance of *Bifidobacteria* are significantly enriched.[234] *Bifidobacterium* species have the capacity to metabolize Trp into indole metabolites, such as ILA , hydroxyphenyllactic acid, indole-3-ethanol, and indole-3-carboxaldehyde.[235,236] However, most *P. aeruginosa* strains in cystic fibrosis patients synthesize a high level of Kyn, resulting in the inhibition of reactive oxygen species (ROS) production in neutrophils to promote cell survival.[237]

Type-2-low severe asthma

Type-2-low severe asthma, also called non-type-2 severe asthma, is different from the type-2-high severe asthma which is often accompanied by high level of eosinophilia, but exhibits non-allergic and non-eosinophilic characteristics. While some studies found that the type-2-low severe asthma also manifests neutrophilic inflammation, mixed granulocytic inflammation, or Th1/Th17-driven inflammatory responses.[238-240] Type-2-low severe asthma accounts for about 30-50% in patients with severe asthma, and antibodies and drugs that are effective for severe allergies and eosinophilic asthma are not appropriate for these patients.[238] Currently, the connection between Trp metabolism and type-2-low severe asthma has been recognized.

Trp metabolism regulation alleviate the asthma or type-2-high asthma by activating the AHR pathway.[241-243] In the mouse asthma model, Trp metabolites Kyn regulates Treg responses to attenuate airway inflammation.[47] Increased Trp metabolites shifts the maturation of precursor T cells toward Treg but not the Th17, and then improves the balance of Th17/Treg differentiation to control asthma.[47,48] The anti-IL-22 therapy has been utilized to improve the clinical effect on the type 2-low severe neutrophilic asthma.[238] Abnormal AHR activation can induce Th17 immune responses to produce IL-22 cytokine, which is in line with the neutrophilic invasion characteristic observed in type 2-low severe asthma.[49] However, some researchers also

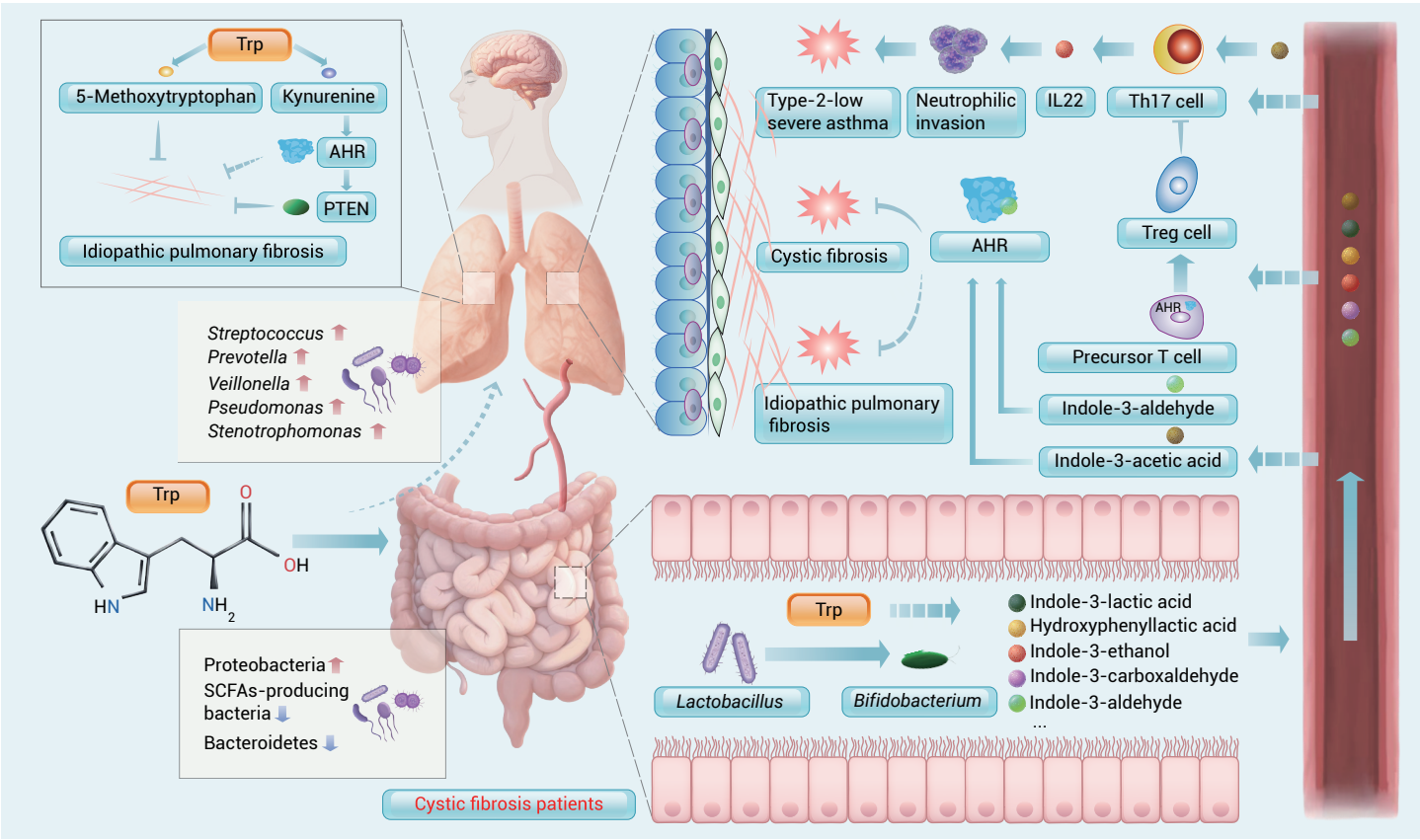

Figure 4. Trp metabolism in lung diseases The relative abundance of *Streptococcus*, *Prevotella*, and *Veillonella*, *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas* are enriched in the lung of the cystic fibrosis patients. Meanwhile, these patients also exhibit the increased abundance of Proteobacteria and decreased levels of short-chain fatty acids (SCFAs)-producing bacteria and Bacteroidetes in the gut. Supplementation of *Lactobacillus* increases the relative abundance of *Bifidobacteria* which metabolize Trp into indole metabolites, such as indole-3-lactic acid, hydroxyphenyllactic acid, indole-3-ethanol, and indole-3-carboxaldehyde, to improve the progression of cystic fibrosis. Additionally, indole metabolites reach the lung by circulation system can shift the maturation of precursor T cells toward regulatory T cells (Tregs) to improve the balance of Th17/Treg, in which Th17 cells produce IL-22 to enhance the neutrophilic pathogenic activity to modulate the type 2-low severe asthma. Moreover, 5-Methoxytryptophan and kynurenine in the lung attenuate idiopathic pulmonary fibrosis through the activation of AHR pathway and Phosphatase and tensin homolog (PTEN).

found that the reduced level of IAA generated from Lactobacilli was linked to the reduced IL-22 activity in pulmonary disease.[244] It is likely that the IAA level in the gut or airway may contribute to the occurrence and progression of type 2-low severe asthma. Therefore, Trp metabolism may play a double-edged role in type 2-low severe asthma by generating different metabolites.

Idiopathic pulmonary fibrosis

Pulmonary fibrosis is a chronic lung disease, which is characterized by abnormal fibrotic responses involving the aberrant repair of lung parenchyma, proliferation of fibroblasts, and the accumulation of extracellular matrix, accompanied by inflammatory damages and tissue structure destruction. Idiopathic pulmonary fibrosis is the most common form of pulmonary fibrosis with limited clinical treatment strategies. In recent years, the pathogenesis of pulmonary fibrosis is found to be microbiota-dependent. Reshaping the gut microbiome by using fecal microbiota transplantation can alter pulmonary immunity and the progression of pulmonary fibrosis, highlighting the regulatory importance of gut-lung axis on pulmonary fibrosis.[86,245]

Through the gut-lung axis, Trp intervention is found to influence the pathological reaction of idiopathic pulmonary fibrosis. High level of Kyn is a typical clinical symptom in idiopathic pulmonary fibrosis patients.[246] By enhancing the AHR-PTEN axis, Kyn attenuates pulmonary fibrosis by acting as a signaling molecule.[246] Another study found that, upon the activation of the AHR pathway, Kyn promotes T cell dysfunction and apoptosis, proliferation of Treg and Th17, and alters Th1/Th2 response to alleviate idiopathic pulmonary fibrosis.[247] Trp metabolite 5-methoxytryptophan also inhibits the ability to control tissue fibrosis, implying its potential in developing a new anti-fibrotic drug.[248,249] 5-methoxytryptophan improves the therapeutic action in patients with idiopathic pulmonary fibrosis by downregulating the TGF-β/SMAD3 and PI3K /AKT signaling pathways.[250] Indole-derived small molecules also exhibit their potential therapeutic effects on treatment of organ fibrosis and respiratory diseases. IAA inhibits fibroblast activation and attenuates alveolar epithelial cell senescence, thereby mitigating the progression of pulmonary fibrosis.[251] By targeting angiogenesis and fibrosis pathways, indole-based non-acidic autotaxin inhibitors have been shown to ameliorate idiopathic pulmonary fibrosis.[252,253] These evidences suggest that Trp metabolites may play important roles in the development of idiopathic pulmonary fibrosis.

TRYPTOPHAN METABOLISM IN KIDNEY DISEASES

The development of kidney diseases, such as uremia and nephrolithiasis, significantly change the characteristics of intestinal microbiota.[51,254] By contrast, transplanting the altered microbes into the gut also trigger pathological progression in the kidney. Therefore, the gut and kidney are metabolically interconnected. Dietary supplementation of probiotics, such as *Lactobacillus*, significantly regulate the severity of kidney diseases by involving Trp and its bacterial metabolites.[51,254] Thus, Trp metabolism may effectively regulate kidney functions by the microbiota-gut-kidney axis, and early intervention of this axis may delay the development of kidney diseases and improve life quality (Figure 5).

Uremia

Uremic toxins accumulation in patients with chronic kidney disease and uremia aggravate renal dysfunction.[255] Indoxyl sulfate has been identified as a protein-bound uremic toxin which may accumulate in urine before excretion. The total amount of indoxyl sulfate in blood increases from micromolar concentrations in healthy individuals up to millimolar concentrations in patients with severe chronic kidney diseases.[256] High concentration of indoxyl sulfate aggravates the development of chronic kidney diseases.[74] In the blood of healthy individuals, most indoxyl sulfate is bound to albumin.[257,258] Circulating free from of indoxyl sulfate is then excreted in the urine by proximal renal tubular cells through basolateral organic anion transporters.[259] As chronic

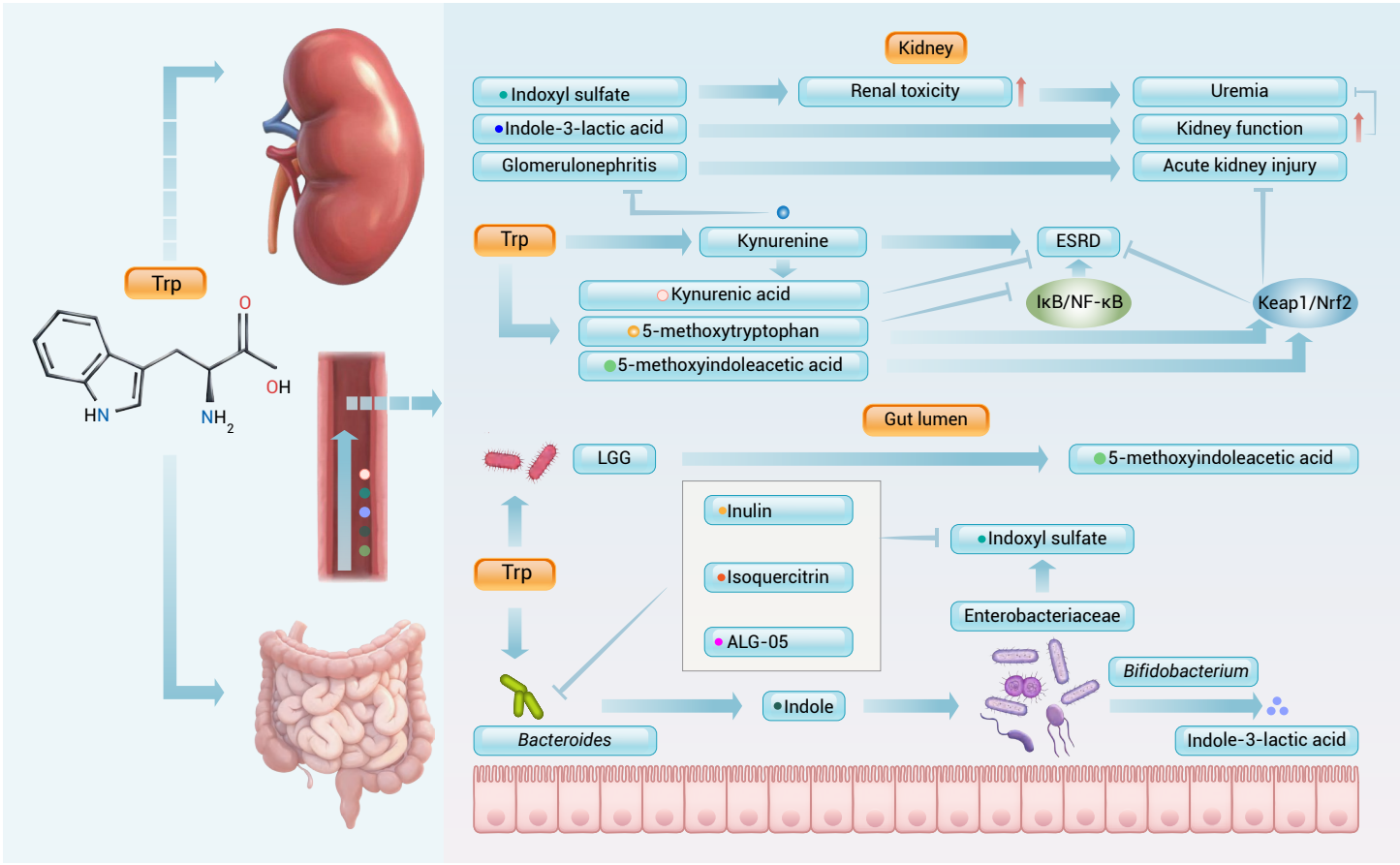

Figure 5. Trp metabolism in kidney diseases The indoxyl sulfate functions as uremic toxin to damage kidney. Inulin, isoquercitrin, and ALG-05 inhibit the production of indole sulfate to alleviate uremia symptoms. Moreover, *Bifidobacterium* transforms indole into indole-3-lactic acid to improve kidney dysfunction via blood circulation. Accumulated kynurenine accelerates the progressive loss of renal functions and contribute to progression of End-stage renal disease (ESRD). However, shunting the Kyn to kynurenic acid may inhibit this process. Additionally, the Trp metabolite 5-methoxytryptophan is able to inhibit the IκB/NF-κB signaling and enhance the Keap1/Nrf2 signaling to ameliorate renal interstitial fibrosis in ESRD. Kynurenine also prevent kidney from glomerulonephritis towards acute kidney injury. 5-methoxyindoleacetic acid produced by *Lactobacillus rhamnosus* (LGG) in the gut reaches the kidney via circulation system and activates the Keap1/Nrf2 signaling to protect against oxidative stress.

kidney disease progresses, the total concentration of indoxyl sulfate in blood increases, accordingly.[260,261]

Excessive indoxyl sulfate increases the expression of genes involved in the inflammatory process in proximal renal tubular cells, which is associated with the increased production of ROS and oxidative stress in these renal cells.[262–265] In addition, indoxyl sulfate adversely reduces the concentration of glutathione in the renal tubular cells and decreases the superoxide scavenging activity in kidney to render the kidney cells even more vulnerable to oxidative stress.[266,267] The level of reactive oxygen (and nitrogen) species are generally elevated in renal tubular cells during the progression of chronic kidney disease.[268]

Lastly, excessive indoxyl sulfate has been suggested to be involved in the progression of renal fibrosis accompanied by the accumulation of extracellular matrix components after initial renal insult.[269] Administration of indoxyl sulfate promotes the transformation of kidney fibroblasts into matrix-producing phenotype and increase the collagen deposition, leading to glomerular sclerosis and interstitial fibrosis in experimental models of chronic kidney diseases.[89,90] Additionally, indoxyl sulfate also increases the expression of genes involved in the process of kidney fibrosis.[91]

Gut dysbiosis induces the expansion of Enterobacteriaceae family to produce excessive indoxyl sulfate.[270] Bacterial tryptophanase is widely distributed in *Bacteroides* that can convert Trp into indole, which is further transformed to produce indoxyl sulfate.[271] In a dietary intervention-based clinical trial, inulin-type fructans may restrict microbiota-generated indole in the gut to alleviate the symptoms of peritoneal dislysis.[272] By inhibiting the establishment of H proton potential, isoquercitrin inhibits the biosynthesis of indole and indole sulfate, in which the deglycosylation activity of flavonoid glycosides may play a key action.[273] (3S) ALG-05, as a tryptophanase inhibitor, reduces the production of indole in cecum and indoxyl sulfate in serum, helping to control the development of chronic kidney diseases and improving their associated complications.[274] In addition, the sodium-glucose cotransporter 2 inhibitors also inhibit the Trp metabolism and reduce microbial uremic toxins formation.[275] Different from the functions of indole and indoxyl sulfate, ILA may exert beneficial effects in uremia. *Bifidobacterium* species can transform exogenous indole to synthesize ILA to improve kidney dysfunction.[236]

End-stage renal disease (ESRD)

The ESRD refers to the end stage of various chronic kidney diseases in which the kidney function is severely impaired and has reached an irreversible state. An epidemiology study and mendelian randomization analysis reveals the association between Kyn-to-Trp ratio and chronic kidney diseases.[276,277] In the serum of patients with type 2 diabetes, Trp exhibits the negative association with the risk of ESRD, while the Kyn-to-Trp ratio is positively correlated with the risk of ESRD.[278] These evidences indicate that increased Trp catabolism in the Kyn pathway may accelerate the progressive loss of renal functions. On the other hand, shunting the Kyn pathway toward KYNA branch may brake ESRD progression. In hyperglycemia-triggered renal cell dysfunctions, Trp metabolism is involved in *Rosa laevigata Michx*-mediated antioxidative, anti-inflammatory, and renoprotective roles to alleviate ESRD symptoms.[279] Therefore, correction of Trp metabolic disturbances may delay the development of diabetic nephropathy. In addition, the level of 5-methoxytryptophan exhibits a strong correlation with some clinical markers in the patients with different stages of chronic kidney disease. 5-methoxytryptophan inhibits the IκB/NF-κB signaling and enhances the Keap1/Nrf2 signaling to ameliorate renal interstitial fibrosis in ESRD.[280]

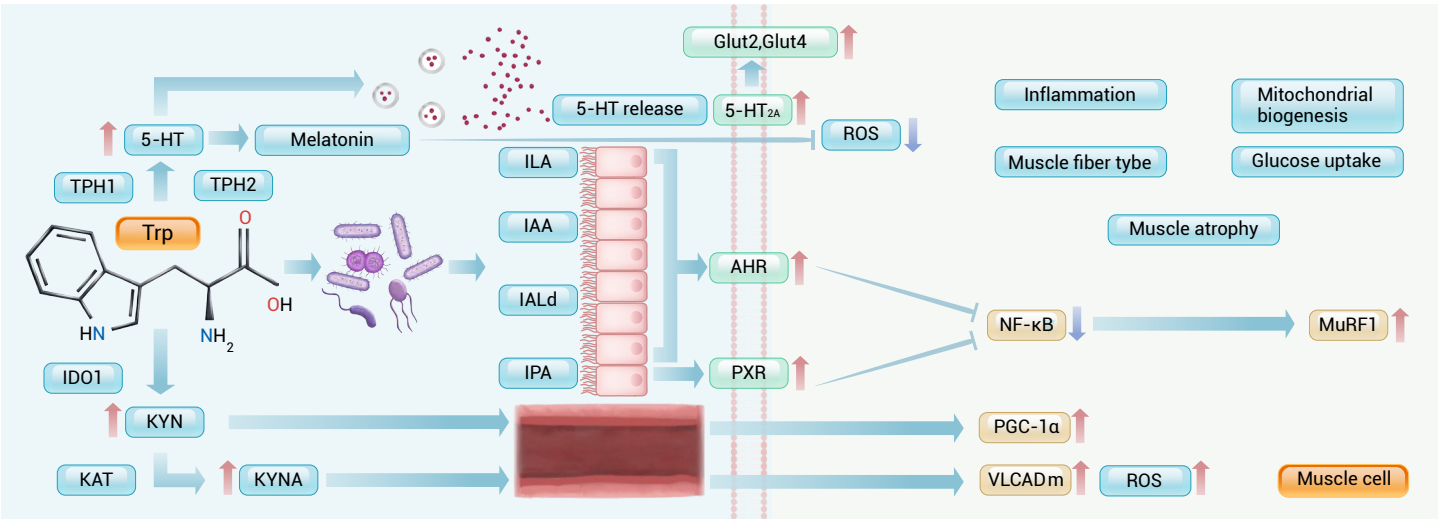

Figure 6. Trp metabolism in muscle dysfunction Kyn-derived metabolites enter the muscle through the blood circulation to enhance the expression of peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α), very long-chain acyl-CoA dehydrogenase (VLCADm), and generation of reactive oxygen species (ROS), thereby modulating mitochondrial biogenesis in the muscle. Moreover, metabolites from the 5-HT pathway can directly enter muscle cells via activating 5-HT receptors to decrease intracellular ROS production, causing muscle atrophy. 5-HT metabolites also indirectly regulate the neural signal transmission between the central nervous system and the muscle by activating 5-HT receptors and increasing the translocation of glucose transporter type 4 (GLUT4) and glucose transporter type 2 (GLUT2) transporters in muscle cells, thereby enhancing glucose uptake. Besides, ILA, IAA, and IALd produced by intestinal microbiota activate AHR, while the IPA activates regnane X receptor (PXR) to inhibit the expression of inflammatory factors and reduce muscle inflammation. Under pathological conditions, the reduction of inflammatory factors activate Muscle RING Finger 1 (MURF1) expression to regulate the types of muscle fiber.

Nephrolithiasis and acute kidney injury

In the metabolomics analysis of urine samples from nephrolithiasis patients (patients with calculi within kidneys), the Trp metabolic pathways are greatly altered.[281] In rats with nephrolithiasis, the concentrations of intestinal Trp and its metabolites are decreased.[282] High salt intake is considered to contribute to the calcium stone formation. In such situation, urinary levels of compounds related to indole and Trp metabolism are reduced.[283] These evidences indicate that abnormal Trp metabolism may be related to nephrolithiasis. However, there is no direct evidence to explain the causal relationship between Trp metabolism and nephrolithialis. Similar to the chronic kidney disease, in the condition of acute kidney injury (AKI), the level of Trp metabolites including the Kyn, 5-hydroxyindoleacetic acid, and indoxyl sulfate are increased and used as biomarkers for early identification of AKI.[270] In vancomycin-associated AKI, increased ratio of 5-hydroxyindoleacetic acid/5-hydroxytryptamine are also utilized as AKI surrogate marker to reflect acute oxidative stress and inflammation.[284] In a cisplatin-induced AKI model, the accumulation of indoxyl sulfate in blood and kidney cortex and medulla is observed. Meanwhile, the CYP2E1 inhibitor chlormethiazole decreases the production of indoxyl sulfate and attenuates renal toxicity in response to AKI.[285] However, Kyn confers protection for glomerulonephritis in AKI, in which the regulation of T cell subsets is involved in this process via increasing NAD^+ production.[286] Some AKI patients also show higher levels of indole metabolites including skatole, trans-3-indoleacrylic acid, and 5-methoxyindoleacetic acid.[287] 5-methoxyindoleacetic acid produced by *LGG* was reported to act as a small molecule activator of Nrf2 to protect against oxidative stress upon AKI.[288]

TRYPTOPHAN METABOLISM IN MUSCLE DYSFUNCTION

The concept of "gut-muscle axis" refers to the bidirectional communication and regulatory relationship between intestinal microbiota, gut, and muscle cells.[289,290] Different Trp-derived metabolites modulate protein synthesis or glycolysis in muscle cells, contributing to muscle development, growth, and function (Figure 6).[291,292,88]

Chronic Trp deprivation not only causes a reduction in muscle fiber diameter but also promotes the tricarboxylic acid cycle and inhibits glycolytic reactions.[293] Kyn supplementation decreases the diameter and cross-sectional area of muscle fibers and promotes lipid peroxidation in muscle cells.[294] Kyn pathway-derived metabolites are involved in the modulation of muscle growth and function. The Kyn level has been shown to negatively affect muscle development. Increased Kyn level induces ROS level in muscle cells, causing muscle atrophy and lipid peroxidation to inhibit muscle growth.[295,296] In addition, cachexia-related muscle atrophy is often accompanied by elevated Kyn levels and reduced mTOR activity, resulting in decreased muscle protein synthesis.[297,298] Exercise increases the expression of KAT and promotes the conversion of Kyn to KYNA in skeletal muscle. KYNA alleviates high-intensity exercise-induced microdamage and inflammatory responses in skeletal muscle by suppressing TNF production.[299] QA has been shown to induce the expression of muscle atrophy-related genes MuRF1 and Atrogin-1 by activating the NF-κB signaling pathway.[92] Additionally, NAD^+ levels contributes to muscle development and maintains its normal physiological function by improving mitochondrial function and energy metabolism.[300] KYNA is involved in repairing muscle damage by modulating energy and fat metabolism through G protein-coupled receptor 35 (Gpr35).[301]

The 5-HT pathway plays an important regulatory role in muscle energy metabolism and muscle cell proliferation. 5-HT stimulates the proliferation of smooth muscle cells.[302,303] It has been reported that 5-HT activates the expression of calcium-dependent protein kinases CaMK to promote muscle cell proliferation.[304] Additionally, 5-HT also enhances the expression of myogenic genes by interacting with 5-HT2A to activate the differentiation of muscle cells.[294,305] 5-HT promotes the conversion of myofibers to fast-condensing glycolytic myofibers through modulation of the TGF-β1/Smad2 signaling pathway.[306] In vitro studies have demonstrated that 5-HT treatment increases the activities of 5-HT2A and 6-phosphofructose-1-kinase to enhance glucose uptake in muscle tissue, and to promote glycolysis in muscle cells.[305] Melatonin is mainly synthesized in the pineal gland, but its production is also regulated by the intestinal microbiota.[307,308] Melatonin reduces oxidative stress and inflammatory response in muscle cells by reducing the production of free radicals and promoting the activity of antioxidant enzymes. It also inhibits muscle cell apoptosis and promotes muscle regeneration by improving the efficiency of the mitochondrial electron transport chain.[78,309,310] Recent studies have found that melatonin not only inhibits skeletal muscle fiber splitting, but also promotes skeletal muscle growth and muscle fiber hypertrophy by improving mitochondrial function and decreasing fat deposition in muscle.[311,312]

Indole and its derivatives also participate in muscle development, regeneration, and atrophy through modulating inflammatory responses, oxidative stress, mitochondrial function in muscle cells.[313,314] Supplementation of IPA improves the muscle atrophy by reducing the expression of pro-inflammatory cytokines in skeletal muscle. Additionally, IPA promotes myoblast proliferation and increases muscle fiber diameter and the proportion of fast muscle fiber types.[65,313] ILA activates muscle regeneration and reduces inflammatory responses.[315] However, high concentrations of IAA leads to

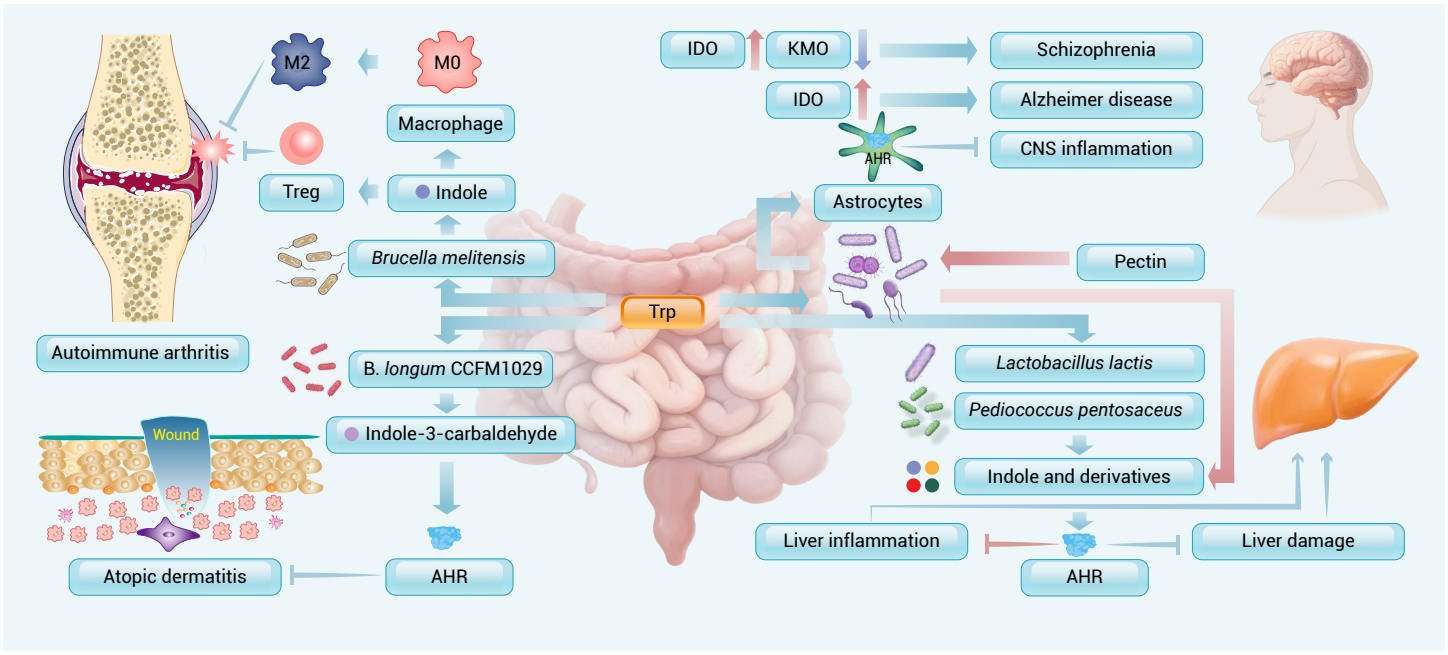

Figure 7. The clinical application of Trp metabolites in diseases control The expression levels of Trp-derived metabolites are often associated with multiple diseases in the body. For instance, the increased activity of indoleamine 2,3-dioxygenase (IDO) activity is present in the brain of patients with Schizophrenia and Alzheimer diseases. While the kynurenine 3-monooxygenase (KMO) expression is reduced in the brain of Schizophrenia patients. Trp metabolites generated by the intestinal commensal bacteria activate the aryl hydrocarbon receptor (AHR) pathway in astrocytes to inhibit central nervous system inflammation. Additionally, indole and its derivatives produced via *Lactobacillus lactis* and *Pediococcus pentosaceus* act as AHR ligands to exhibit anti-inflammatory effects on non-alcoholic fatty liver disease. Indole produced by *Brucella melitensis* modulates macrophage 2 (M2) polarization to produce anti-inflammatory cytokines and promote regulatory T cells (Tregs) function to diminish the severity of autoimmune arthritis. Moreover, indole-3-carbaldehyde generated from *B. longum* CCFM1029 in the gut attenuates atopic dermatitis-associated symptoms by activating AHR signaling pathway.

abnormal arrangement of muscle fibers, disruption of muscle contraction function, and cause damage to muscle cells.[316] Indoxyl sulfate induces intestinal inflammation and oxidative stress to cause muscle atrophy and inhibit muscle protein synthesis.[317,318] Increased level of NAD^+ and ILA have been shown to improve sarcopenia.[319,320]

CLINICAL IMPLICATIONS OF TRYPTOPHAN METABOLITES IN DISEASES PREVENTION AND TREATMENT

Potential for targeting Trp metabolism in CNS, metabolic, and autoimmune diseases

In schizophrenia patients, the IDO activity in the brain and peripheral serum is enhanced, while the kynurenine-3-monooxygenase (KMO) activity is reduced in the brain. The levels of Kyn, KYNA, Kyn/Trp, and KYNA/Kyn as well as Trp are increased, while the level of 3-hydroxykynurenine and the KMO/Kyn ratio are reduced in CNS.[321] Increased IDO activation and the association between high level of quinolinic acid and the neuronal damages are observed in the Alzheimer's disease models.[322,323] Therefore, the increased IDO activity may be one cause of neurological disorders in the brain. Metabolism of Trp by intestinal microbiota also affect CNS diseases. Mice with herpes simplex encephalitis exhibits intestinal microbiota dysbiosis and altered Trp-nicotinamide metabolism. Supplementing with nicotinamide N-oxide generated by *Lactobacillus gasseri* and *Lactobacillus reuteri* is able to restore NAD^+-dependent mitophagy, thus inhibiting microglia activation and alleviating the progression of herpes simplex encephalitis.[324] Meanwhile, commensal bacteria-derived Trp metabolites modulate the transcription of astrocyte factors and CNS inflammation via activation of AHR. In the multiple sclerosis models, Trp limits encephalitogenic T cell responses and alleviates intestinal inflammatory response.[325]

Tryptophan metabolites also play important regulating roles in metabolic diseases. Pectin supplementation diminishes liver damage in the alcoholic liver disease model by increasing Trp metabolites and activation of the AHR pathway.[326] In the condition of a leucine-deficient diet, *Blautia Coccoides* improves insulin sensitivity and reduces body fat to alleviate metabolic disorders by metabolizing Trp into IAA and its activation of AHR.[327] In Western-style diet-induced NAFLD model, indole generated by *Lactobacillus lactis* and *Pediococcus pentosaceus* exhibits anti-inflammatory effects and restores the liver-to-body weight ratio, liver enzymes, cholesterol concentration, and cytokines.[328] In two clinical cohort studies, Trp bacterial metabolites indole-3-pyruvic acid and 5-OH-indole-3-acetic acid are closely associated with the incidence of major adverse cardiovascular event and poorer survival.[329] In addition, blood IPA level is significantly reduced in patients with coronary heart disease and is inversely associated with the risk and severity of atherosclerotic cardiovascular disease.[330]

Autoimmune diseases are often accompanied by low grade and chronic inflammation. The autoimmune-associated changes of microbiota composition may explain the mechanism of IFN-γ-related chronic inflammation and the important roles of Trp metabolism in autoimmune diseases.[87] A metabolically engineered bacterial strain *Brucella melitensis,* with the ability to produce indole, can polarize M1 macrophages to M2 macrophages producing anti-inflammatory cytokines and promoting Treg functions to control inflammation in autoimmune arthritis.[331] In the autoimmune disease model of systemic lupus erythematosus, the level of Kyn is increased while its protective effect is decreased after antibiotic treatment. Interestingly, a low level of dietary Trp prevents autoimmune pathology in lupus erythematosus by inhibiting the production of anti-dsDNA IgG, whereas a high dietary Trp exacerbates this disease.[332] Therefore, the Trp metabolism appears to play bidirectional roles in controlling autoimmune diseases (Figure 7).

Therapeutic interventions and ongoing clinical research

At present, regulation of metabolic pathways of Trp to prevent and control diseases in some clinical trials have been carried out. For example, melatonin supplementation can improve circadian disorders and control body weight in night shift workers.[333] Clinical improvement of the severity of immune-related diseases by targeting the Trp metabolism has also been conducted. In particular, the application of IDO inhibitors in cancer immunotherapy has attracted significant attention from both the scientific community and the industry sides, because of its ability to inhibit the immune system within tumor microenvironment. Inhibition of the IDO pathway with indoximod has been shown to reverse the immunosuppressive effects of low Trp and high Kyn that result from IDO activity in the advanced melanoma model. Combination of pembrolizumab and indoximod exhibits antitumor efficacy.[334]

A preliminary phase I/II clinical trial of the IDO inhibitor BMS-986205 presents the initial effectiveness in patients with hepatocellular carcinoma when combined with another IDO inhibitor nivolumab which exhibits partial

responses in advanced solid tumors in combination with atezolizumab.[335,336] Combining IDO1 inhibitors with other therapeutic drugs also manifests their potential in optimizing the effectiveness of cancer immunotherapy.[337] IDO forms an immunosuppressive tumor microenvironment by facilitating the expansion of Tregs and myeloid-derived suppressor cells that drive immune aging.[338] Thus, IDO inhibitors may play critical regulatory roles in prevention or treatment of immunosenescence and tumors.

Preclinical study on melanoma showed that 3-IAld released by intratumoral *Lactobacillus reuteri* can drive antitumor immunity dependent on the activation of AHR signaling in $CD8^+$ T cells.[339] In two independent cohorts of pancreatic ductal adenocarcinoma, the IAA level is positively correlated with the therapy efficacy in the clinical trial.[340] Indole-3-carbaldehyde derived from *B. longum CCFM1029* has been found to improve atopic dermatitis symptoms by activating AHR-mediated immune pathways.[93] Notably, the individual patients exhibit varied characteristics in genetic background, gene expression, physiological conditions, and disease types, all of which may interfere with the treatment efficiency. Therefore, it is worth to further utilize multi-omics strategies by combing genomics, proteomics, microbiomics, and metabolomics to develop stratified treatment schedule of diseased patients and implement personalized therapies. This may help to more effectively treat patients through the regulation of Trp metabolism in conjunction with drug intervention.

CONCLUSIONS

Tryptophan metabolism regulates physiological functions and pathological processes in the body via modulating the intestinal microbiota-mediated inter-organ interactions. Despite the large involvement of Trp metabolism in the pathogenesis of various diseases in the host, translating these findings into clinical applications remain a big challenge. In particular, individual variability in host genetics, immune status, environmental conditions, and microbial composition may substantially affect therapeutic outcomes. Personalized treatment approaches by integrating and optimizing multi-omics, like genomics, proteomics, metabolomics, microbiome, not only enhance the methodology to elucidate the complex interactions between Trp metabolites and host physiology, but also build a path toward more effective and curative treatments for metabolic diseases to ultimately improve health and life quality for diseased individuals. Whilst not the main focus of this review, emerging studies have started to explore the use of synthetic Trp-based nanoparticles as a novel drug delivery platform. These early findings suggest that the unique chemical properties of Trp may offer advantages in the development of targeted therapeutic systems, particularly in neurological and oncological applications. Although current data are still limited, this area represents a promising direction for future research. Further comprehensive investigation are needed to evaluate the design, safety, and efficacy of Trp-derived nanomaterials in different clinical contexts.

Tryptophan has also been implicated in anti-cancer research, particularly in the area of cancer immunotherapy. For instance, the Trp-Kyn pathway is often hijacked by cancer cells to evade the immune system. Cancer cells overexpress IDO that catalyzes the conversion of Trp to Kyn, which in turn suppresses the immune response by inhibiting the activation and function of T cells. Trp-derived metabolites capable of inhibiting IDO activity and enhancing immune response against cancer cells are good candidates for the reversion of the immune evasion. Therefore, it is of great interest to further explore the potential application of synthetic Trp-derived nanoparticles in cancer treatment.

Tryptophan allocation is a complex process and its regulation is determined by both internal and external factors. How three Trp metabolic pathways are precisely allocated to either cooperate or act independently to modulate physiological functions in distinct organs under normal or diseased conditions still lacks investigation. Moreover, in addition to the intestinal microbiota-mediated inter organ communication, some Trp metabolites also capable of participating in signaling transduction between organs outside the intestine. It is possible that distinct Trp metabolic pathways are preliminary allocated to different organs, which in turn initiate the organ interactions. These challenges/questions await further experimental and clinical investigation. Finally, important results from basic science and few clinical studies focused on the implication of Trp metabolism in both host cells and lodged bacteria among the intestinal microbiota have been obtained. Anomalies of Trp metabolism have been identified in various physiological and pathophysiological situations. This state of the art should stimulate further efforts for the prevention and treatment of pathologies associated with alterations of the metabolism of this amino acid.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

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DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.