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REVIEW

The tryptophan metabolic pathway of the microbiome and host cells in health and disease

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Abstract

The intricate and dynamic tryptophan (Trp) metabolic pathway in both the microbiome and host cells highlights its profound implications for health and disease. This pathway involves complex interactions between host cellular and bacteria processes, producing bioactive compounds such as 5-hydroxytryptamine (5-HT) and kynurenine derivatives. Immune responses to Trp metabolites through specific receptors have been explored, highlighting the role of the aryl hydrocarbon receptor in inflammation modulation. Dysregulation of this pathway is implicated in various diseases, such as Alzheimer's and Parkinson's diseases, mood disorders, neuronal diseases, autoimmune diseases such as multiple sclerosis (MS), and cancer. In this article, we describe the impact of the 5-HT, Trp, indole, and Trp metabolites on health and disease. Furthermore, we review the impact of microbiome-derived Trp metabolites that affect immune responses and contribute to maintaining homeostasis, especially in an experimental autoimmune encephalitis model of MS.

Keywords: brain disease, GPR35, immune cell, kynurenic acid

Introduction

The tryptophan (Trp) metabolic pathway within the microbiome and host cells constitutes a complex and dynamic system with profound implications for health and disease (1–6). This pathway involves an intricate interplay between host cellular and bacteria processes involving Trp, which is an essential amino acid. In health, the Trp metabolic pathway plays a pivotal role in maintaining homeostasis and supporting physiological functions. Interactions between the microbiome and host cells contribute to the production of bioactive compounds, including 5-hydroxytryptamine (5-HT) and kynurenine (Kyn) derivatives, exerting far-reaching effects on both local and systemic processes (7–9).

Therefore, dysregulation of the microbiome–host cells Trp metabolic pathway has been implicated in the pathogenesis of various diseases (10–16). This review provides a comprehensive overview of the Kyn and 5-HT pathways and their functional implications in neuronal diseases, autoimmunity, and cancer, incorporating recent research findings. Both pathways commence with the utilization of Trp. Trp plays a pivotal role in mammalian physiology and exerts diverse effects on various aspects of human health. First, we describe the tryptophan metabolic pathway and discuss its role in homeostasis.

The roles of Trp

Trp is one of the 20 standard amino acids that are building blocks of proteins and are incorporated into polypeptide chains during protein synthesis, thereby contributing to protein structure and function (17–20). Trp is also a precursor for the synthesis of 5-HT (21, 22), a neurotransmitter that plays a crucial role in mood regulation, sleep–wake cycles, and appetite (23, 24). Trp is also a precursor for the synthesis of melatonin, a hormone that regulates the sleep–wake cycle (25, 26). In the pineal gland, Trp is converted to 5-HT, and then to melatonin, through a series of enzymatic reactions. Moreover, Trp serves as a precursor for the synthesis of niacin (vitamin B3) (27), which is essential for various physiological processes including energy metabolism (28, 29), DNA repair (30), and cell signaling (31–33). Trp can be metabolized to produce nitric oxide (34), a signaling molecule with various physiological functions, including regulation of blood vessel dilation and immune responses (11).

Trp also has antioxidant properties that contribute to host cells' defense against oxidative stress (35). It participates in the synthesis of molecules with antioxidant activity, helping neutralize free radicals. Trp is involved in the synthesis of collagen (36), a structural protein that provides strength and support to tissues, such as the skin, bones, and cartilage.

Notably, Trp availability can be influenced by dietary factors, and a balanced diet that includes sufficient protein sources is crucial to meet the body's Trp requirements. In addition, certain medical conditions or medications may affect Trp metabolism (37). The major Trp metabolic pathways are (i) the 5-HT pathway, (ii) the indole pathway, and (iii) the Kyn pathway. As well as a detailed description of these pathways, we will mention which pathways are dominant in various host cells and bacteria.

Trp pathway in the host cells and bacteria

Most tryptophan metabolites are produced by both the host cells and bacteria (1, 38–40). However, it remains unclear whether these metabolites are synthesized *in vivo*, as the data indicating their production capacity were obtained from gene sets with the potential to convert tryptophan metabolites (41). In this study, bacterial genes were identified using AnnoTree (version 2.0.0) (default parameters) (42) searches targeting K numbers associated with tryptophan metabolism (map00380) in the KEGG pathway (43) (Supplementary Figure 1). Tryptophan metabolites, such as *N*-formyl kynurenine (NFK) and Kyn, can be digested by both the host cells and bacteria. Indole and indole-3-acetamide are only produced by the microbiome, whereas indole-3-pyruvate and 5-HT are produced by the host cells. Based on their genes, the predominant metabolic pathway differs between the host cells and bacteria (Fig. 1).

The Trp digestive pathway differs from that of the host cells and bacteria. Many bacteria possess enzymes that can break down tryptophan to indole and indole-3-carboxaldehyde (I3A) in the indole pathway. On the other hand, host cells have enzymes involved in the Kyn pathway with continuous expression of indoleamine 2,3-dioxygenase (IDO) (44–46). Immune cells, macrophages, and dendritic cells, in which the Kyn pathway mainly dominates, upregulate IDO in response to stimuli (47, 48). The Kyn pathway is dominant in astrocytes and microglia in the brain, whereas the 5-HT pathway is dominant in serotonergic neurons in the central nervous system (CNS) (49–51). Other cells in the peripheral tissues such as hepatocytes express tryptophan 2,3-dioxygenase (TDO) (52). Therefore, the Kyn pathway is thought to dominate in these cells.

The 5-HT pathway is primarily associated with serotonergic neurons in the CNS that produce and release 5-HT (51, 53). The 5-HT pathway is dominant in enterochromaffin (EC) cells in the gastrointestinal tract, resulting in the synthesis and release of 5-HT (54–57) (Fig. 2). Platelets and mast cells do not synthesize 5-HT but they can store and release it after they are activated (51, 58, 59). Platelets can enter the blood–brain barrier (BBB) and are a major source of 5-HT. Trp and Kyn can pass BBB, on the other hand, other metabolites, 5-HT, kynurenic acid (KYNA), and quinolinic acid (QA), cannot pass the BBB, which means these metabolites in the brain are derived from the neurons, astrocytes, and microglia or from the platelets that carry 5-HT (60–66).

The 5-HT pathway

The 5-HT metabolic pathway involves the conversion of Trp into various important molecules including 5-HT and melatonin (Fig. 1). This pathway is essential for the synthesis of neurotransmitters and plays a crucial role in regulating mood, sleep–wake cycles, and other physiological functions (67–69). 5-HT is stored in vesicles within nerve terminals (70, 71). Upon neuronal stimulation, 5-HT is released into the synaptic cleft, where it binds to receptors on the postsynaptic neurons and transmits signals (72–74).

The first step in the 5-HT pathway involves the enzymatic conversion of Trp to 5-hydroxytryptophan (5-HTP), catalyzed by tryptophan hydroxylase (TPH), wherein tetrahydrobiopterin (BH4) plays a crucial role (75). Subsequently, L-tryptophan decarboxylase (TDC) decarboxylates 5-HTP to produce 5-HT (21). 5-HT can be metabolized by monoamine oxidase to form 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in urine. This step is crucial for terminating the expression of 5-HT in the synaptic cleft (23, 76). 5-HT can also be metabolized to form melatonin in the pineal gland. This pathway is important for the regulation of circadian rhythms and sleep–wake cycles. The 5-HT pathway is not only important for the synthesis of 5-HT and melatonin but also contributes to the production of various biologically active compounds (77, 78).

As 5-HT is a key neurotransmitter involved in mood regulation, disturbances in this pathway can have implications for mental health. Selective 5-HT reuptake inhibitors are commonly used to treat conditions, such as depression, by modulating 5-HT levels in the brain (79). Furthermore, intestinal neurons sense 5-HT and regulate their movement rhythms (80). As previously mentioned, 5-HT in serum does not cross the BBB. 5-HT in the brain are mostly derived from platelets. EC cells produce 5-HT and release it into the serum (Fig. 2). In addition, serum 5-HT concentrations in germ-free (GF) mice were reduced when juxtaposed with specific pathogen-free (SPF) mice, providing evidence for the impact of gut bacteria on 5-HT levels (81, 82).

The indole pathway

The gut microbiota converts Trp into indole and its derivatives such as indoleacrylic acid, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), indole-3 acetaldehyde (3-IAld), and tryptamine (83) (Fig. 1). The fecal indole level in GF mice was lower than that in SPF mice (84). *Anerostipes*, *Bacteroides*, *Clostridium*, *Bifidobacterium*, and *Lactobacillus* spp. catabolize Trp into its indole derivatives (85). *Lactobacillus* spp. metabolizes Trp to I3A; *Clostridium sporogenes* and *Ruminococci* convert Trp to tryptamine; and *Staphylococcus*, *Providencia*, and *Pseudomonas* convert Trp to IAA (41, 86). Furthermore, tryptamine induces 5-HT in EC cells (39). A recent study reported that supplementation with 3-IAld elicited antidepressant effects in mice subjected to stress (87). The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor activated by the indole pathway derivatives Kyn and KYNA (88–91). The BBB exhibits increased permeability in adult GF mice and monocolonization with *Bacteroides thetaiotaomicron* and *Clostridium tyrobutyricum* with sodium butyrate decreases the permeability of the BBB (92). These data suggest that microbiota-induced metabolites affect the permeability of BBB, and one of the candidate metabolites is the AHR ligand (93–95) (Fig. 2).

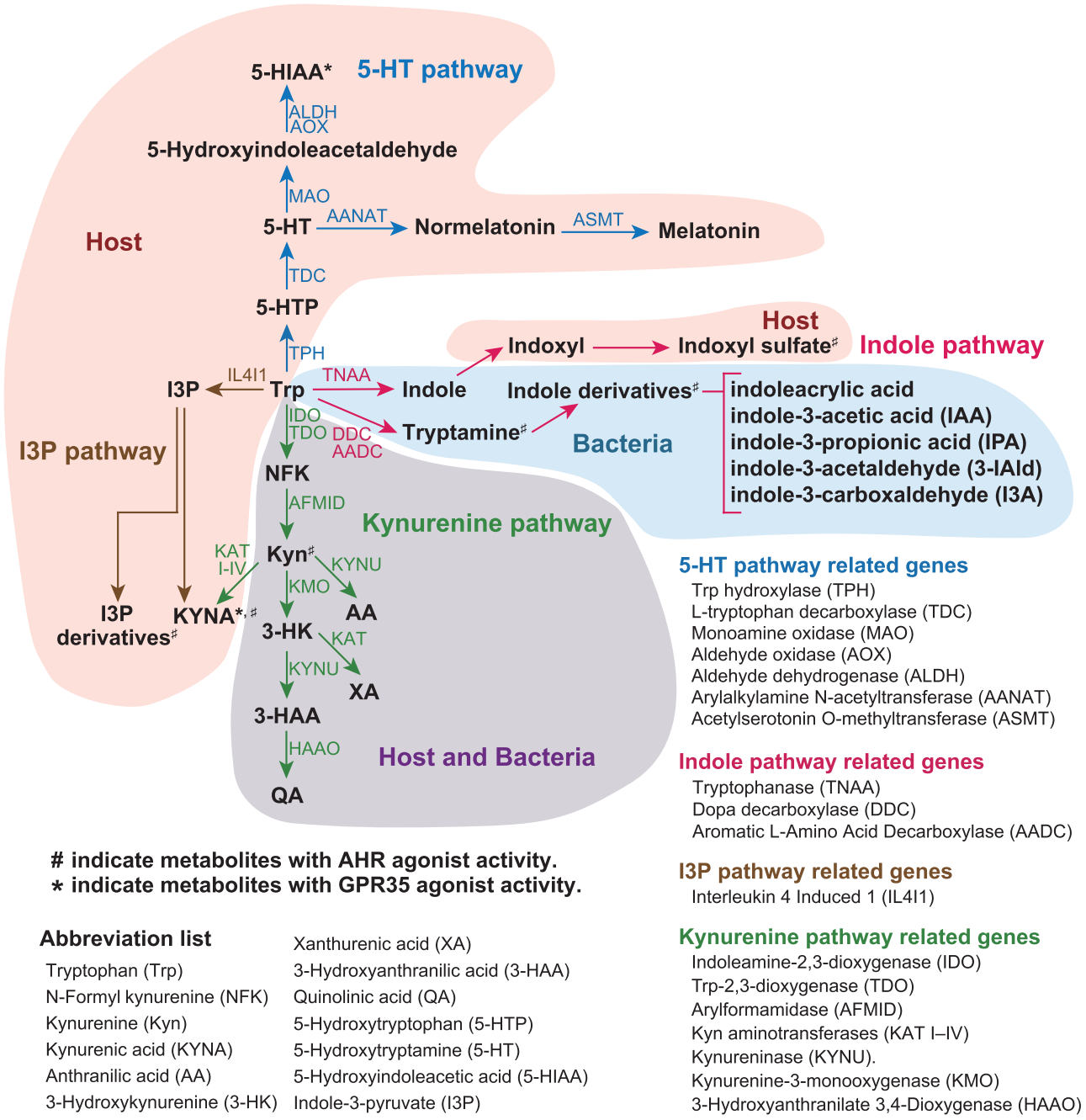
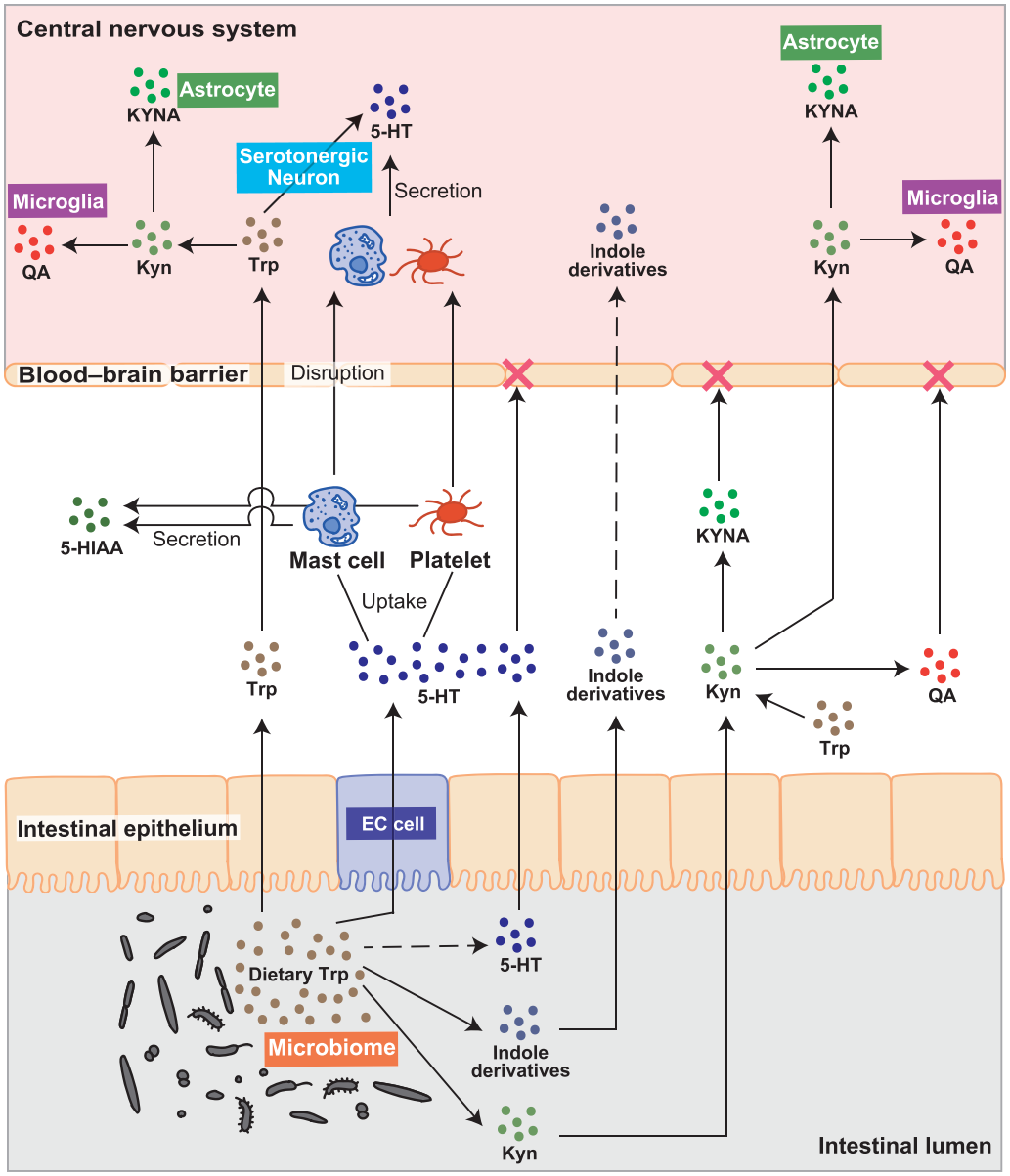


Figure 1. Overview of tryptophan metabolism via the kynurenine, 5-HT, indole, and I3P pathway.

The Kyn pathway

Trp is metabolized to Kyn via a series of enzymatic reactions (Fig. 1). Kyn can be further metabolized, leading to the synthesis of various neuroactive compounds, including KYNA and QA. The initial and rate-limiting steps of the Kyn pathway involve the enzymatic conversion of Trp to Kyn catalyzed by TDO or IDO, depending on the tissue, such as the brain, lung, liver, small intestine, and colon (78, 96–100). Kyn can be metabolized further, producing KYNA, a neuroactive compound (101). This conversion is catalyzed by kynurenine aminotransferases (97). Kyn can also be converted to QA. Kyn is first transformed to 3-hydroxykynurenine (3-HK), which is catalyzed by kynurenine 3-monooxygenase (KMO). Next, 3-HK is transformed into 3-hydroxyanthranilic acid (3-HAA) catalyzed by KYNU. Finally, 3-HAA is converted to QA by 3-hydroxyanthranilate 3,4-dioxygenase. QA is converted to nicotinamide adenine dinucleotide (NAD^+), an important



Tryptophan metabolites derived from the host cells and gut microbiota and the blood-brain barrier

Figure 2. Tryptophan metabolites derived from the host cells and gut microbiota and the blood–brain barrier.

coenzyme in energy production, cell division, and mitochondrial function, by QA phosphoribosyltransferase and NAD synthase (102).

Involvement of the Kyn and 5-HT pathways in immune diseases

Trp metabolites can transmit signals through cellular receptors that exhibit tissue-specific expression and are regulated by their circumstances. These receptors include AHR, alpha 7 nicotinic acetylcholine receptor (α7nAChR), and G-protein-coupled receptor (GPR) 35. IDO1 and TDO, which are involved in the initial steps of Trp metabolism, are constitutively expressed in tumors. However, the expression of these genes is induced in immune and epithelial cells by inflammatory signals. Local and systemic inflammation induce the initial expression of IDO1 in epithelial and myeloid cells (103, 104). Kyn amplifies the IDO1–Kyn–AHR loop to suppress inflammatory mediators through AHR signaling in immune and epithelial cells (105) (Fig. 3A).

In the initial steps of the immune response, antigen-presenting cells and dendritic cells (DCs) play a crucial role in both the initiation and maintenance of immune responses. IDO1 expression in DCs is increased by lipopolysaccharide (LPS), extracellular and intracellular DNA, and type I and type II interferons (106). Kyn, which is initially released by

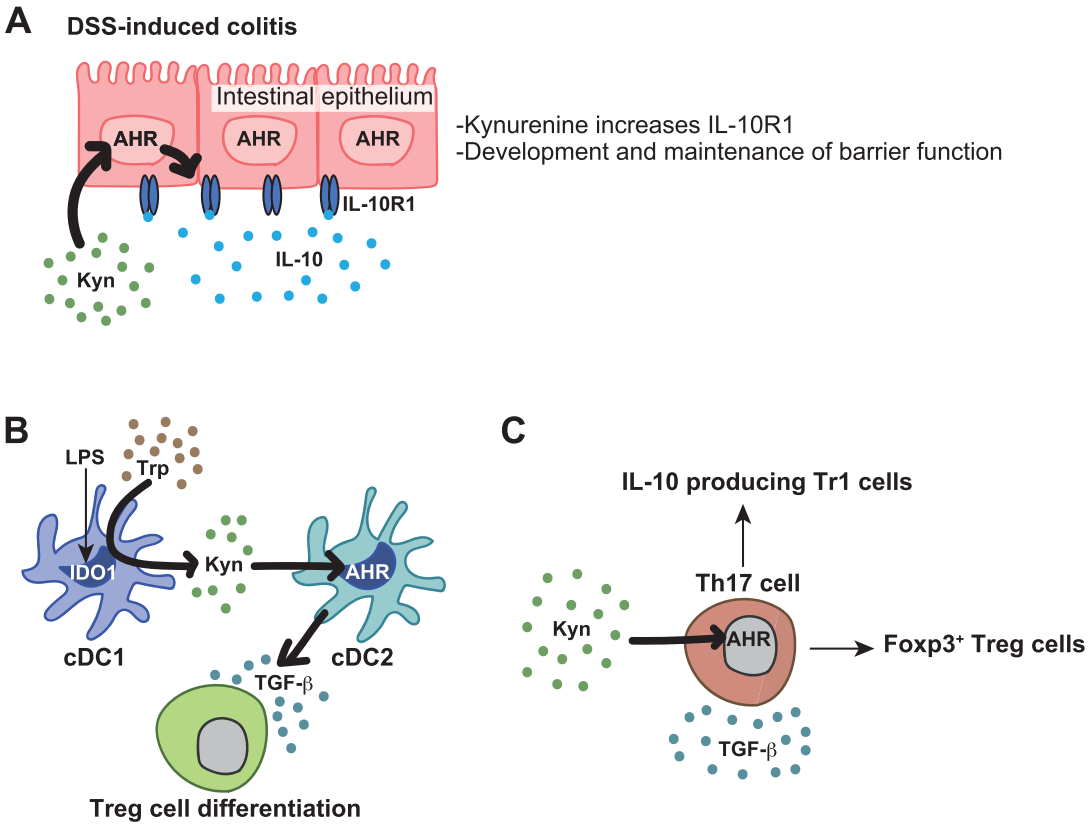


Figure 3. The role of the Kyn pathway in immune regulation. (A) In DSS-induced colitis, kynurenine via the intestinal epithelial AHR leads to an increase in IL-10 receptor-1 (IL-10R1) expression. This consequently exerts an anti-inflammatory effect through IL-10 signaling. (B) The IDO1-AHR axis in the induction of infection resistance upregulates TGF-β and induces Tregs. (C) The collaborative interaction between TGF-β and AHR plays a pivotal role in the transdifferentiation process of Th17 cells, leading to the generation of IL-10-producing Tr1 cells and Foxp3$^+$ Treg cells.

IDO1-expressing type 1 conventional DCs (cDC1s), recruits AHR-expressing cDC2s. cDC2s produce transforming growth factor-β (TGF-β), which induces anti-inflammatory forkhead box protein 3$^+$ (Foxp3$^+$) regulatory T cells (Tregs) (Fig. 3B). The TGF-β–IDO1–AHR loop is crucial for the generation of tolerogenic DCs, resulting in self-tolerance and LPS tolerance. However, its direct effect on tolerogenic DCs differentiation remains unclear.

T helper (Th)17 cells and Tregs play a central role in immune function during colitis and cancer progression (107–113). AHR plays a role in the induction of the effector cytokine interleukin (IL-)17A and is expressed in both Th17 cells and Tregs (114). AHR expression in Tregs enhances their immunosuppressive function (115). TGF-β and AHR promote Th17 cell differentiation into IL-10-producing type 1 regulatory T (Tr1) cells especially in the resolution phase of intestinal inflammation (116) (Fig. 3C).

Tumour-associated macrophages (TAMs) play a crucial role in tumor progression. Tumour cells elicit AHR expression and activation in TAMs by releasing IL-1β/IL-6 and Kyn (117). In addition, AHR-enhanced macrophages have the potential to differentiate into TAMs, suppressing the antitumour activity of CD8$^+$ T cells. Higher levels of IDO1 and TDO2 are associated with the immunosuppressive function of Tregs in tumors. Overexpression of IDO1/TDO2 in tumor cells can enhance tumor progression by suppressing the function of Tregs and M2-TAMs (118). Additionally, KYNA exerts an anti-inflammatory role in human invariant natural killer (iNK) cells through activation of GPR35 (119–121). GPR35-mediated KYNA sensing plays a crucial role in preserving the integrity of the intestinal barrier against damage in dextran sulfate sodium (DSS)-induced enteritis (122). Conversely, 5-HIAA released by platelets and mast cells recruits pathogenic neutrophils and eosinophils to induce inflammation (123, 124) (Fig. 4A and B). Moreover, mast cells in the subepithelial dome secrete 5-HIAA to attract GPR35$^+$ cDC2s. This sequential cascade of events leads to the augmented synthesis of immunoglobulin A (IgA) by plasma cells (125) (Fig. 4C).

Furthermore, individuals with inflammatory bowel disease (IBD), multiple sclerosis (MS), or chronic kidney disease exhibited elevated concentrations of serum KYNA (126–131). Meanwhile, serum metabolomic analysis in patients with coronavirus disease 2019 (COVID-19) showed elevated KYNA levels and an increased KYNA:Kyn ratio in male patients. The clinical prognosis of COVID-19 is less favorable in males than in females, and this sex-based disparity is attributed to immune responses. These metabolite alterations are positively associated with age, as well as with inflammatory cytokines and chemokines (132).

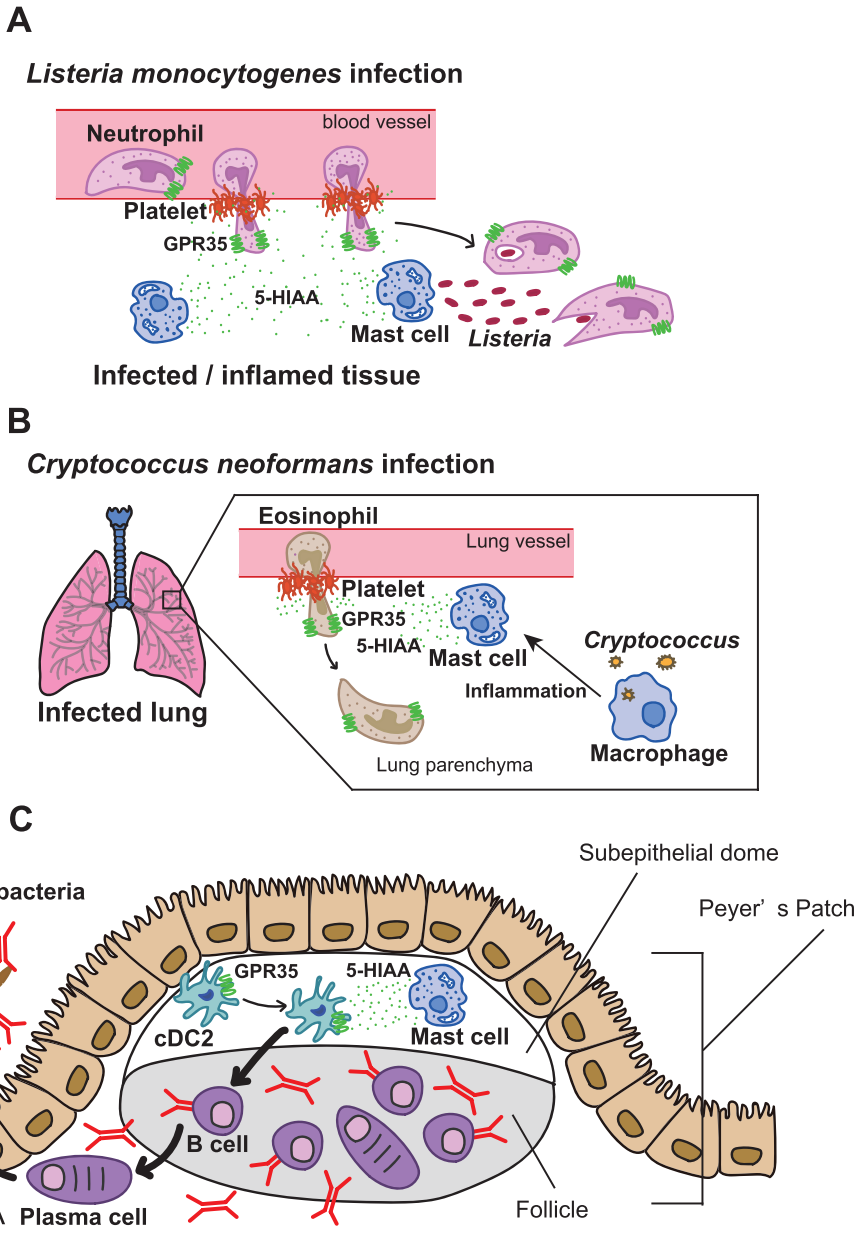


Figure 4. The 5-HIAA-GPR35 axis is implicated in the recruitment of immune cells (A) platelet- and mast cell-derived, a metabolite of serotonin, 5-HIAA serves as a ligand for the chemoattractant receptor GPR35, facilitating GPR35$^+$ neutrophil transendothelial migration and their recruitment to inflammatory tissue during *Listeria monocytogenes* infections. (B) When *Cryptococcus neoformans* infects the lungs, it produces 5-HIAA derived from platelets and mast cells through macrophage-mediated inflammation. This process promotes the recruitment of GPR35$^+$ eosinophils to the infected lung, leading to the exacerbation of the disease. (C) Mast cells located in the subepithelial dome produce 5-HIAA to recruit GPR35$^+$ cDC2s. This consecutive series of events results in an increased synthesis of immunoglobulin A (IgA) by plasma-cells.

In summary, Trp plays a crucial role in modifying the response of immune cells, particularly in reducing inflammation. However, the specific roles of other Trp metabolites, such as 5-HIAA, remain unclear.

Involvement of the Kyn and 5-HT pathways in CNS diseases

The Kyn and 5-HT pathways are interconnected and play crucial roles in maintaining normal brain function. Dysregulation of these pathways has been implicated in the development and progression of various brain diseases, including neurodegenerative diseases, mood disorders, and autoimmune conditions.

Neurodegenerative diseases

Individuals with Alzheimer's disease had increased brain levels of Kyn and its metabolites, such as QA (133, 134). These metabolites may contribute to neuroinflammation and neurotoxicity. Meanwhile, an altered Trp metabolism has been observed in Parkinson's disease, leading to changes in the

Kyn pathway (135). Imbalances in the Kyn pathway may contribute to oxidative stress and brain inflammation.

Mood disorders

Dysregulation of the Kyn pathway has been implicated in the pathophysiology of depression. Increased levels of Kyn and its metabolites, along with reduced 5-HT levels, may contribute to depressive symptoms (136). Furthermore, abnormalities in Trp metabolism are associated with schizophrenia, and changes in Kyn pathway metabolites may contribute to the cognitive and neuroinflammatory aspects of this disorder (137, 138).

Autoimmune conditions

The Kyn pathway has been implicated in the pathogenesis of MS (128, 139–141). Imbalances in Trp metabolism may contribute to neuroinflammation and CNS demyelination.

Connection between KYNA/QA and neurons

KYNA also exhibits neuroprotective properties (142–145). High levels of KYNA competitively inhibit ionotropic glutamate receptors (146, 147). Moreover, it selectively decreases the activity of the glycine co-agonist side of the N-methyl-D-aspartate (NMDA) receptor, which is involved in excitatory neurotransmission (148–150). Administration of low KYNA concentrations reduces glutamate levels by 30%–40% (146). KYNA also putatively acts as a negative allosteric modulator at the α7nAChR (151–154). KYNA also acts as an agonist at GPR35, which was thought to be an 'orphan' receptor, modulating cAMP production and inhibiting the N-type Ca^{2+} channels of sympathetic neurons and astrocytes, causing suppression of many inflammatory pathways (120, 155). By blocking this receptor, KYNA regulates the balance of neurotransmitters and prevents excessive excitotoxicity (156, 157).

In contrast, abnormal QA levels are implicated in neurodegenerative disorders. QA is an NMDA receptor agonist that exhibits neurotoxic effects (158–161), inhibits glutamate reuptake by astrocytes, and contributes to excitotoxicity when present in excessive amounts. QA generates reactive oxygen species (ROS), promotes tau phosphorylation, and disrupts the BBB. In addition, QA acts on astrocytes to produce inflammatory mediators (162). A balance between the production of neuroprotective KYNA and neurotoxic QA is crucial in maintaining normal brain function.

Trp metabolites and the microbiome

The microbiome has been shown to affect the immune system. Intestinal bacteria are involved in the induction of specific immune cells as well as activating immune cells as antigens. For example, *Lactobacillus* spp. digest dietary Trp and produce the AHR ligand indole-3-propionic acid (I3P) (Fig. 1), and these metabolite polarizations of tumor-promoting TAMs and other *Limosilactobacillus* (*Lactobacillus*) *reuteri* induce intraepithelial lymphocytes (IELs) in the small intestine (163, 164). Recently, in two distinct cohorts of pancreatic ductal adenocarcinoma (PDAC), a noteworthy correlation was observed between the therapeutic response and levels of IAA, a Trp metabolite derived from the microbiota that serves as an AHR ligand (165, 166) (Fig. 5A). Indole derivatives produced by *L. reuteri* have shown anticancer properties (167, 168) (Fig. 5B).

Trp metabolites at the interface between the microbiota and host cells are important for maintaining body homeostasis. Organs utilize Trp metabolites produced by bacteria under inflammatory conditions to induce AHR upregulation in epithelial and immune cells. Indole derivatives from intestinal bacteria enhance the intestinal barrier function by promoting the production of IL-*22* through AHR expressed on innate lymphoid cells (ILCs) 3 (169–174) (Fig. 6).

AHR activated by indole derivatives can stimulate the expansion of Tregs and concurrently suppress experimental autoimmune encephalitis (EAE) (175). AHR signaling in microglia, which is mediated by indole derivatives, induces alterations in immune signaling within astrocytes, leading to a reduction in disease severity in EAE (176, 177). Trp-deficient and Trp metabolite-deficient diets induce chronic tissue inflammation, as IELs, Th17 cells, Tregs, and ILC3s express AHR, which is involved in mucosal homeostasis in the gut. In contrast, host cells affect the composition of the microbiota. Deletion of *CARD9*, an IBD-related gene, leads to exacerbated colitis owing to a reduction in Trp metabolites in *Lactobacillus* spp (178). These results imply that intestinal bacteria and immune cells live in symbiosis with Trp.

Bacteria-mediated Trp metabolite, KYNA induces EAE

EAE is used as an animal model for MS in humans. Trp metabolites act on AHR in astrocytes, reducing the inflammation of encephalitis (Fig. 6) (177). Moreover, these astrocytes are controlled by AHR in microglial cells via TGF-α expression (176). Trp-deficient diets exacerbate EAE because of the reduced stimulation of microglial and astrocyte AHR, and I3S supplementation ameliorates EAE. On the basis of this evidence, Trp metabolites are beneficial neuroprotective metabolites.

The microbiome was shown to have the potential to induce EAE, as GF mice did not develop EAE (179). The involvement of the microbiota in EAE and MS remains unclear; however, studies on humans have implied that the composition of the microbiota in MS differed from that in other populations (180–183). In addition, *L. reuteri* enhances the disease score of EAE because it possesses a peptide that mimics myelin oligodendrocyte glycoprotein (MOG). Moreover, *Erysipelotrichaceae* bacteria (*EB*) act as an adjuvant to enhance Th17 cell responses in the small intestine (184, 185). Although *L. reuteri* and *EB* enhance the disease activity of EAE with the accumulation of the Th17 cells in the spinal cord (SC), the proportion of Th17 cells in the small intestine did not increase. Furthermore, the levels of the Th17 cell driver serum amyloid A were not increased in the small intestine. It is unclear whether T cells course through the small intestine and SC in EAE.

Recently, blocking the pathway that involves α4β7-integrin and its ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which mediates T cell migration to the intestine, was found to ameliorate encephalitis (186). Moreover, Schnell *et al.* and Miyamoto *et al.* showed that Th17 cells in

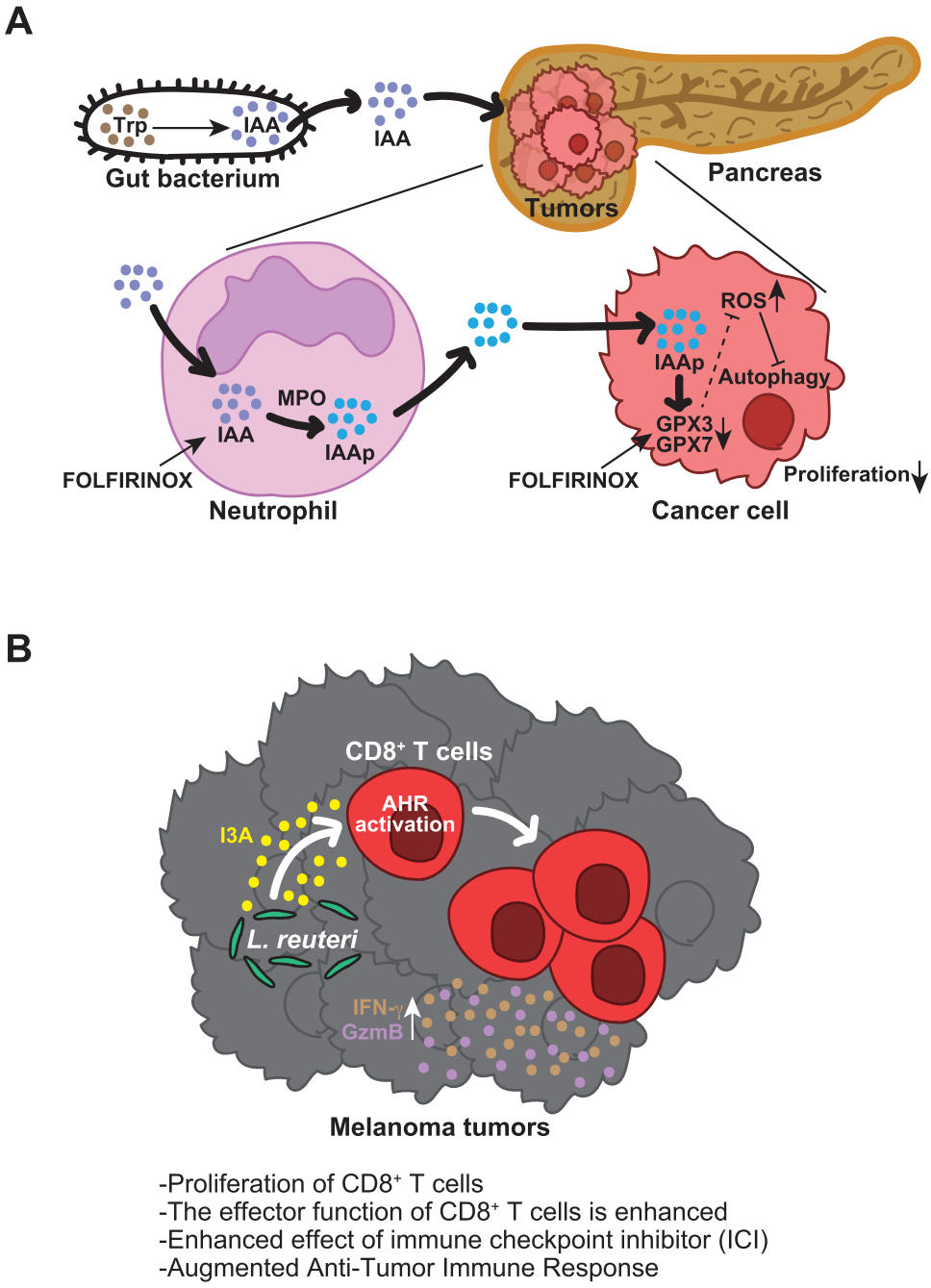


Figure 5. Indole derivatives derived from bacteria serve as facilitators for augmenting the efficacy of chemotherapy and ICI in cancer. (A) Trp metabolites originating from the gut microbiome accelerate the chemotherapy response in pancreatic cancer. Intestinal bacteria generate IAA from absorbed dietary Trp. IAA is transported to PDAC through the bloodstream, where it may undergo oxidation to produce toxic molecules (IAAp) facilitated by myeloperoxidase (MPO) and cytotoxic anticancer drugs such as 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) within intratumoural neutrophils. Subsequently, IAAp and FOLFIRINOX jointly contribute to the downregulation of GPX3/7, enzymes responsible for degrading ROS, leading to the accumulation of ROS within cancer cells. Ultimately, elevated ROS levels inhibit the autophagy pathway, a crucial process in cancer cell proliferation. (B) *L. reuteri* translocates to, colonizes, and persists within melanoma, where, through the release of its dietary tryptophan catabolite I3A, it locally enhances the generation of IFN-γ-producing $CD8^+$ T cells, thereby augmenting the efficacy of ICI. Furthermore, I3A was found to be both necessary and sufficient to stimulate antitumour immunity, and the loss of AHR signaling within $CD8^+$ T cells abolished antitumour effects.

the small-intestinal circuit directly enter the neural circuit to induce encephalitis in photoconversion 'Kaede mice' (187, 188). Kaede mice emit green fluorescence constitutively in all the cells. After irradiation with violet light to the mesenteric lymph nodes draining from the small intestine, green-to-red photoconversion occurs only in the exposure site, to enable us to track the cells and monitor precise cellular movement *in vivo* (189). We observed the red cells in the SC of the

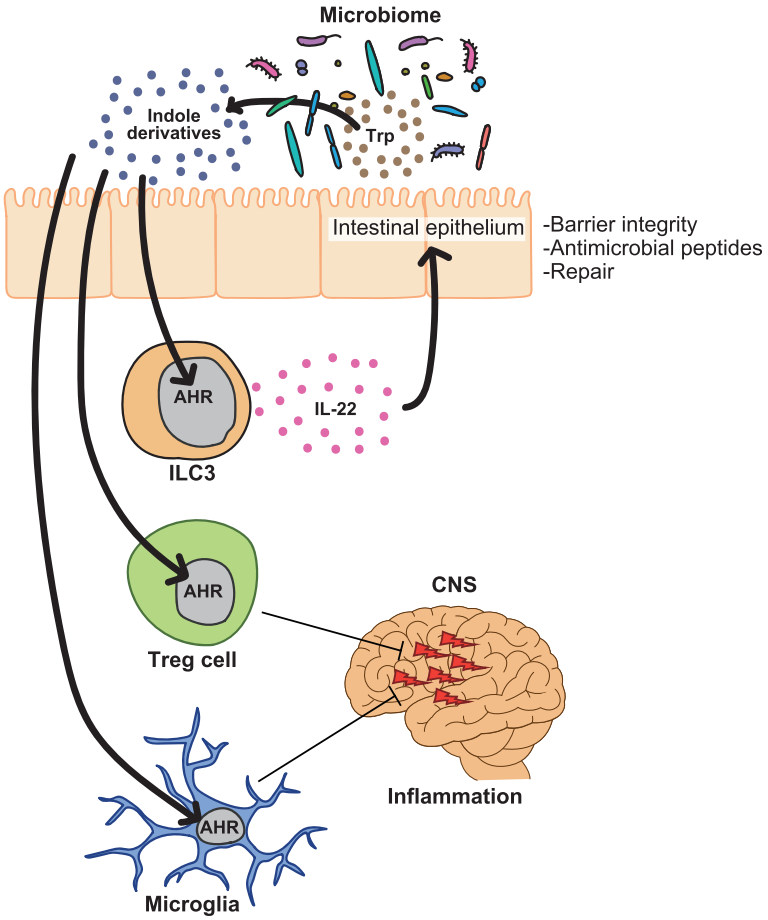


Figure 6. Indole derivatives originating from the gut microbiota exert anti-inflammatory effects through the AHR. Indole derivatives, generated by the microbial conversion of dietary Trp, can activate AHR in Group 3 innate lymphoid cells (ILC3s), thereby promoting IL-22-mediated tissue protection. Indole derivatives can activate AHR in T cells, leading to the generation of Tregs and subsequent reduction in inflammation, resulting in improved disease outcomes in EAE. Additionally, AHR in microglia contributes to the suppression of inflammation in EAE.

EAE mice. Taken together, these findings suggest that certain T cells originating from the small-intestinal population may translocate to the SC, playing a role in the induction of myelitis.

Intestinal Th17 cells are induced by antigen-presenting cells. Miyamoto *et al*. showed that CX3CR1^{+} Ly6C^{+} GPR35^{+} macrophages potentially induce the accumulation of Th17 cells in the small intestine of EAE mice (188). The major GPR35 ligands are cGMP, lysophosphatidic acid, 5-HIAA, and KYNA (131, 190). The concentration of KYNA increased in the small intestine of EAE mice, whereas the others did not increase, compared with non-EAE mice. Furthermore, the expression levels of *afmid, kat1*, and *kat2* (see Fig. 1) were higher in EAE mice than in non-EAE mice. Notably, the expression levels of *Ido1* did not increase in EAE mice (Fig. 7).

Interestingly, the microbiome potentially harbors a Kyn pathway that digests Trp to form NFK and Kyn. Intestinal bacteria possess the enzyme groups EC:1.13.11.11, which converts Trp to NFK, and EC:3.5.1.9, which converts NFK to Kyn. The expression of EC:1.13.11.11, but not of EC:3.5.1.9, increased in fecal bacteria in both EAE mice and patients with MS (180). Previous reports have shown that *EB* are increased in EAE mice (188), but *EB* do not possess EC1.13.11.11. *Sporosarcina pasteurii* (*SP*), *Staphylococcus lentus*, *Pseudoxanthomonas mexicana*, and *Sphingomonas* are potential possessors of the EC:1.13.11.11 gene. Notably, the abundance of *SP* was higher in fecal samples of EAE mice than those of non-EAE mice. Miyamoto *et al*. inserted the EC:1.13.11.11 gene into the *Escherichia coli* JCM1649 (EC^{WT}) and generated a strain that can convert Trp into NFK (EC^{KynA}) (188). Mice mono-associated with EC^{KynA} exhibited significantly higher EAE scores than mice mono-associated with EC^{WT} following MOG induction.

Overall, these results indicate that KYNA in the small intestine plays an inflammatory role in EAE, whereas KYNA has a neuroprotective role. In addition, the Trp metabolic pathway and microbiome harbor both the indole and Kyn pathways, especially the initial step of Trp conversion to Kyn. Further investigations focusing on Trp metabolites and their pathways are required to understand their action on neurons and immune cells. Inhibitors of rate-limiting enzymes that play crucial roles in Trp metabolism, such as IDO/TDO, KMO, and TPH, are candidates for modulating Trp metabolites in neuronal diseases or tumors. Modulation of the gut microbiome may also regulate Trp metabolites. The specific mechanism remains unknown; however, controlling Trp

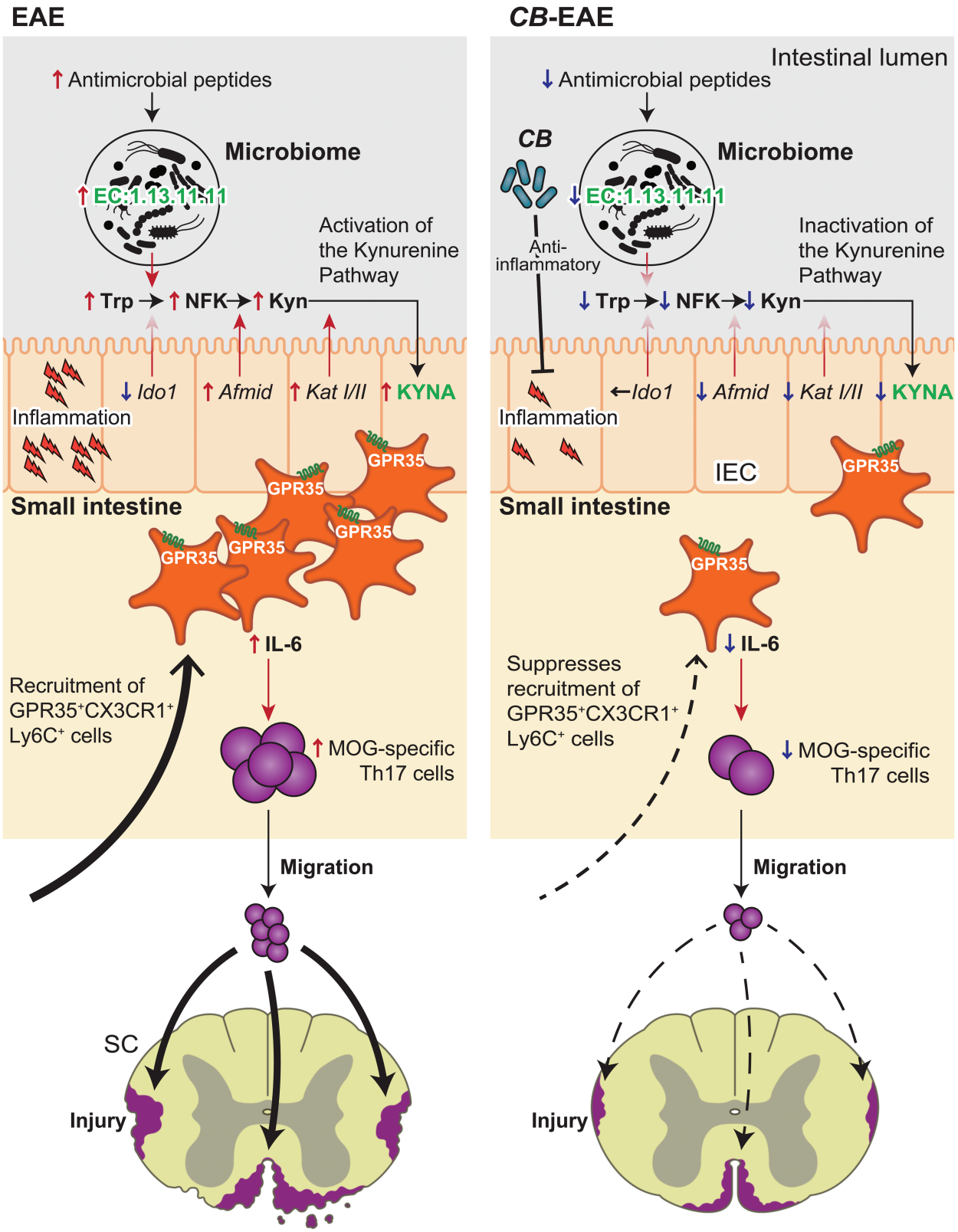


Figure 7. The gut microbiota-induced KYNA recruits GPR35⁺ macrophages to promote experimental encephalitis. (Left) Inflammation was initiated in the small intestine prior to the manifestation of the phenotype in the EAE model of MS. Inflammation elevated antimicrobial peptides and modified the microbiome. The intestinal epithelium cells (IECs) and microbiome collaborated in the production of KYNA. GPR35⁺ CX3CR1⁺ Ly6C⁺ cells utilizing KYNA as a chemokine ligand were recruited to the small intestine. GPR35⁺ CX3CR1⁺ Ly6C⁺ cells exhibit high levels of IL-6 expression and an expanded population of pathogenic myelin-responsive Th17 cells. Pathogenic myelin-responsive Th17 cells migrated to the SC, triggering inflammation. (Right) The administration of CB led to the suppression of inflammation in the small intestine. CB altered the microbiome and gene expression in the IECs, leading to the inactivation of the Kyn pathway. The diminished KYNA levels resulted in a reduced recruitment of GPR35⁺ CX3CR1⁺ Ly6C⁺ cells. The number of pathogenic myelin-responsive Th17 cells induced by GPR35⁺ CX3CR1⁺ Ly6C⁺ cells was decreased. Inflammation was attenuated due to a decrease in the number of pathogenic myelin-responsive Th17 cells migrating to the SC. The potential preventive effect of CB on MS was suggested.

metabolites by modulating the composition of microbiota is a safe and promising method in discovering therapeutic options. *Clostridium butyricum* MIYAIRI 588 (*CB*) is known to reduce the disease activity of EAE following a reduction in Trp metabolites (Fig. 7).

Conclusion

Trp metabolites play key roles in immune function, neuronal excretion, and energy metabolism. An imbalance in these metabolites induces neuropsychiatric disorders and inflammation. These pathways are complicated because (i) they interact with each other and are not independent; (ii) Trp metabolites are generated not only by vertebrates but also by bacteria; and (iii) Trp metabolites act differently on each cell. For example, KYNA has a neuroprotective role in astrocytes but is pathogenic to intestinal macrophages in the EAE model.

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Supplementary data

Supplementary data are available at *International Immunology* online.

Conflict of interest statement. K.M. is an employee of Miyarisan Pharmaceutical.

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