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# Tryptophan metabolism: entering the field of aging and age-related pathologies

**Annemieke T. van der Goot and Ellen A.A. Nollen**

University of Groningen, University Medical Centre Groningen, European Research Institute for the Biology of Aging, 9700 AD Groningen, The Netherlands

**Aging is an important risk factor for many debilitating diseases, including cancer and neurodegeneration. In model organisms, interfering with metabolic signaling pathways, including the insulin/insulin-like growth factor (IGF) 1 (IIS) and TOR pathways, can protect against age-related pathologies and increase lifespan. Recent studies in multiple organisms have implicated tryptophan metabolism as a powerful regulator of age-related diseases and lifespan. Its high conservation throughout evolution has enabled studies that begin to dissect the contribution of individual enzymes and metabolites. Here, we focus on the emerging view of tryptophan metabolism as a pathway that integrates environmental and metabolic signals to regulate animal biology and health.**

## Aging and age-related diseases

The past few decades have seen an increase worldwide in both life expectancy and the relative proportion of older individuals in the population [1]. One consequence of an aging population is an increased incidence of age-related diseases, such as cancer and neurodegenerative disorders. Thus, these demographic changes pose a major societal and economic burden.

Studies, mainly from the past two decades, have shown that dietary alterations or genetic interference in nutrient-sensing pathways can increase lifespan in several model organisms [2]. These findings have changed the view of aging from a merely stochastic process to a process that is regulated by multiple signaling pathways and downstream transcription factors. Importantly, extending lifespan by interfering with these pathways has been shown to protect against a broad range of age-related pathologies (Table 1). Therefore, understanding the molecular mechanisms underlying aging and finding new components involved in the aging process could reveal new targets for treating age-related diseases and thereby promote a healthy life.

## Nutrient-sensing pathways as central regulators of aging and age-related diseases

Dietary restriction is one of the most reproducible and best-studied interventions to extend lifespan in multiple organisms (reviewed in [2,3]), and several nutrient-sensing pathways have been reported to be involved in lifespan regulation by dietary restriction. In particular, components of the mechanistic target of rapamycin (mTOR; also mammalian target of rapamycin) and the insulin/insulin-like growth factor (IGF) 1 (IIS) pathways appear to mediate the effects of dietary restriction, depending on the type of intervention [4]. Genetic or pharmacological inhibition of the IIS and mTOR pathways, without a reduction in food intake, can extend lifespan in multiple species, including *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Mus musculus* (Table 1 and reviewed in [5]).

Both the IIS and mTOR pathways sense nutrient availability and subsequently adjust the metabolism, growth, and fecundity of the organism. When environmental conditions are favorable and food is abundant, growth and reproduction are stimulated. However, when environmental conditions are harsh and food is scarce, these nutrient-sensing pathways control the shift in energy resources from growth and reproduction to cellular stress defenses and repair. This allows the animal to survive until more favorable conditions are encountered [5].

Several studies have shown that the mTOR pathway acts in parallel to the IIS pathway, but there is crosstalk and functional interaction between the two pathways at multiple levels [6]. For instance, in *C. elegans* it has been shown that mTOR signaling acts mostly independent of the Forkhead box (FOXO) transcription factor DAF-16, in contrast to the IIS pathway [7,8]. Similar to IIS mutants, mTOR signaling does require the nrf-like xenobiotic response factor SKN-1 [8,9]. Moreover, inhibition of mTOR in long-lived *C. elegans daf-2* mutants does not further increase lifespan [7]. In some IIS fly mutants, rapamycin treatment could extend lifespan even more than changes to the IIS pathway depending on the degree of IIS downregulation [10].

These data indicate that lifespan extension through dietary restriction and the IIS and mTOR pathways can be achieved by both overlapping and distinct mechanisms. Nevertheless, how these pathways interact is not yet completely understood.

Interestingly, reducing the activity of the IIS or mTOR pathways not only increases lifespan but it also delays the onset of several age-related pathologies (Table 1). Tumor growth is suppressed upon genetic inhibition of the IIS pathway in worms [11] and mice [12], and reduced insulin/IGF-1 signaling has been shown to protect against the toxic

*Corresponding author:* Nollen, E.A.A. (e.a.a.nollen@umcg.nl).
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**Table 1. Examples of metabolic pathways and their role in aging and age-related diseases**

| Pathway | Organism | Aging | | |
|---|---|---|---|---|
| | | Cancer | Neurodegeneration[a] | Longevity |
| IIS pathway | *Caenorhabditis elegans* | Genetic inhibition of *daf-2* inhibits germline tumor growth [11] | Genetic inhibition of *daf-2* protects in an AD model [14], and genetic inhibition of *age-1* protects in a polyQ model [13] | Genetic inhibition of *daf-2* [72,73] and *age-1* [74] extends lifespan |
| | *Drosophila melanogaster* | Not reported | Not reported | Genetic inhibition of the insulin receptor substrate *chico* [75] or the *insulin-like receptor InR* [76] extends lifespan |
| | *Mus musculus* | Liver-specific IGF-1-deficient mice show a reduced tumor incidence and decreased frequency of metastasis upon implantation with colon adenocarcinoma tissue fragments [12] | Genetic inhibition of the insulin receptor substrate 2 (*Irs2)* [15], or neuronal loss of IGF-1 receptor [16], and loss of one allele of the IGF-1 receptor [17] ameliorate neurodegeneration in AD models | Loss of one allele of the insulin-like growth factor type 1 receptor (IGF-1 receptor) [77], or fat-specific knockout of the insulin receptor [78], or reduced insulin receptor-2 (Irs2) signaling in all tissues or just in the brain [79], or insulin receptor substrate (IRS) 1 knockout [80] extends lifespan |
| mTOR pathway | *C. elegans* | Not reported | Not reported | Genetic inhibition of *let-363*/TOR [7], TORC1 components: *daf-15*/Raptor [8,81], *rheb-1*/Rheb [8,82], *raga-1* [8], *ragc-1* [8], and TORC2 component: *rict-1* [8], or pharmacological inhibition with rapamycin extends lifespan [8] |
| | *D. melanogaster* | Not reported | Pharmacological inhibition of mTOR with rapamycin suppresses toxicity in a polyQ [83] model. Genetic inhibition of Rheb, TOR, or gain of function of Tsc1/2 rescues from tau- [84] or htt-mediated toxicity [85] | Genetic inhibition of dTOR/TOR [86,87], or gain of function of *dTsc1/2*/TSC1/2 [86], or pharmacological inhibition with rapamycin extends lifespan [10] |
| | *M. musculus* | Pharmacological inhibition of mTOR with rapamycin suppresses tumor growth in cancer-prone animals [18] | Pharmacological inhibition of mTOR with rapamycin ester CCI-779 suppresses aggregation and toxicity of polyQ [83,88] | Pharmacological inhibition of mTOR with rapamycin extends lifespan [89–91] |
| Kynurenine pathway | *C. elegans* | Not reported | Depletion of *tdo-2* suppresses proteotoxicity on models for PD, AD, and polyQ diseases [21] | Depletion of *tdo-2* extends lifespan [21] |
| | *D. melanogaster* | Not reported | Loss of function of *vermillion* and genetic or pharmacological inhibition of *cinnabar* suppresses toxicity in a polyQ model [33] | Loss of function of *vermillion* extends lifespan [22] |
| | *M. musculus* | Pharmacological inhibition of IDO/TDO suppresses tumor growth and promotes tumor rejection [28–31]. Knockout of IDO prevents tumor formation [92] | Pharmacological inhibition of KMO ameliorates neurodegeneration in models for AD and HD [34] | Not reported |

[a]Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease.

effects of aggregation-prone disease proteins involved in neurodegeneration in worms [13,14] and mice [15–17].

Inhibition of mTOR signaling suppresses aging-related pathologies. Pharmacological inhibition of the mTOR pathway with rapamycin suppresses tumor growth in mice [18], and although the exact mechanisms by which rapamycin suppresses tumorigenesis remain unknown, alterations in autophagy, cell proliferation, angiogenesis, and recruitment of immune cells have been proposed to play a role. Similarly, pharmacological or genetic inhibition of mTOR signaling is protective in multiple fly and mouse models of neurodegeneration (reviewed in [19]). Various protective mechanisms have been reported, including autophagy, an attenuation of translation, and cell-cycle inhibition, which may suppress neurodegeneration because they increase the removal of disease proteins, decrease their synthesis, and increase the expression of stress response proteins and detoxifying enzymes.

Together, these studies show that cellular protection machineries that are thought to be compromised and decline during aging are boosted and maintain a more youthful state when insulin/IGF-1 and mTOR signaling are lowered. Moreover, these studies point out that there is great potential in targeting metabolic pathways for the

treatment of a broad range of age-related diseases. However, the mechanisms and downstream targets required for mediating these beneficial effects remain largely unknown. It will be crucial to elucidate the roles of tissue specificity, timing requirements, and crosstalk between the different nutrient-sensing pathways in order to design effective therapies with limited side effects.

## An emerging role for tryptophan metabolism in aging and age-related diseases

Recently, several independent studies have identified a role for tryptophan metabolism in aging and age-related diseases in multiple model organisms, including yeast, worms, flies, and mice (Table 1). Most free tryptophan is metabolized by what is called the kynurenine pathway of tryptophan degradation through a series of metabolic reactions (Figure 1A, reviewed in [20]). The first and rate-limiting step in this series of reactions is the opening of the indole ring, which can be catalyzed by either one of two heme-dependent enzymes, namely, indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). The kynurenine pathway of tryptophan degradation is conserved, although there are also species-specific differences (Figure 1A). We have recently found that depletion of TDO in *C. elegans* results in an increased lifespan [21]. Similarly, inactivation of fly TDO extends lifespan [22], suggesting that lifespan regulation by TDO is evolutionarily conserved. In worms, this extension of lifespan

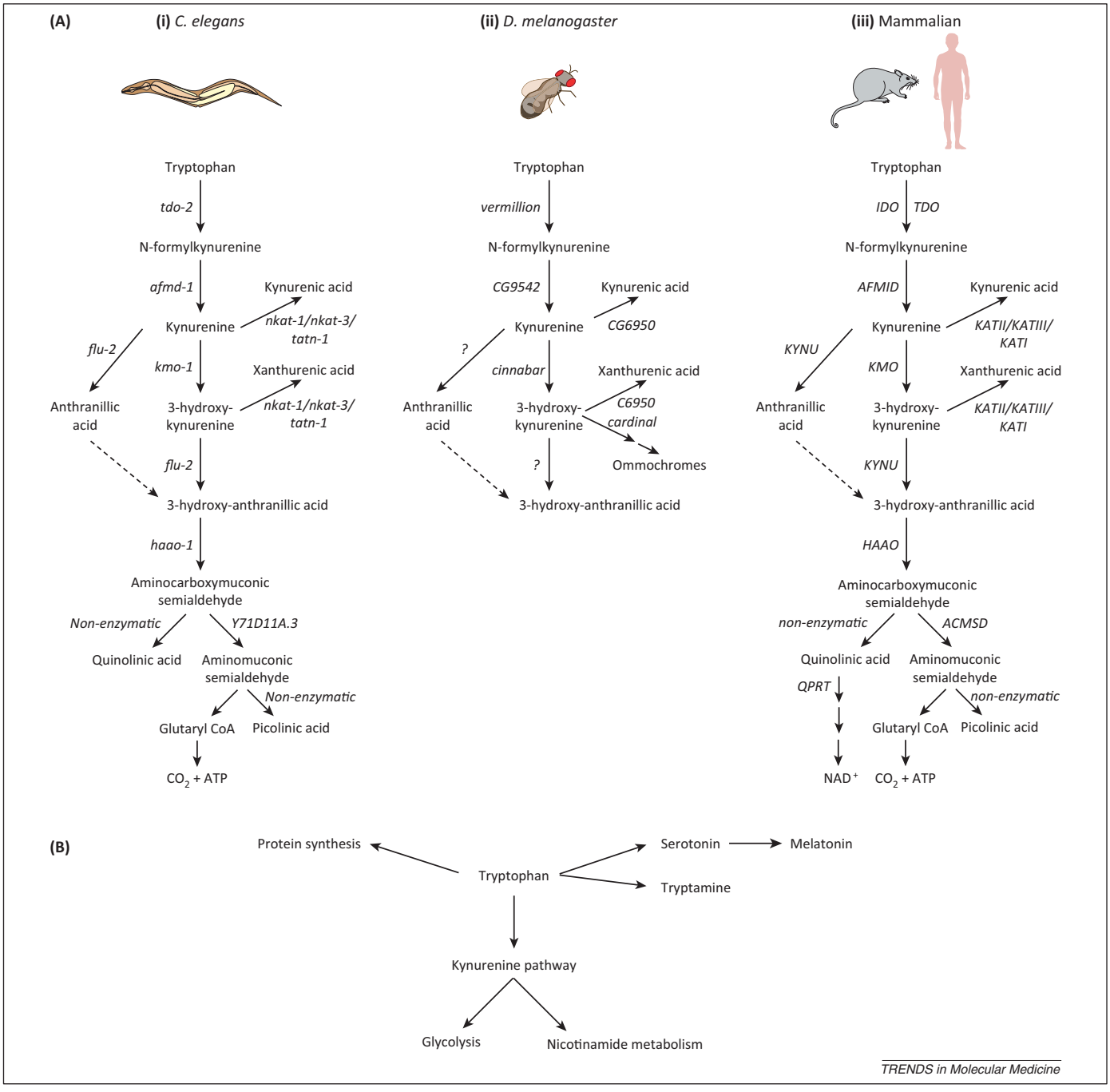


**Figure 1**. Schematic representation of the kynurenine pathway in different organisms. **(A)** Overview of the kynurenine pathway in *Caenorhabditis elegans, Drosophila melanogaster*, and mammals. **(B)** Tryptophan metabolism contributes to a variety of metabolic processes, as shown here.

depends on the FOXO transcription factor DAF-16 [21], which is required for mediating the effects of multiple longevity mechanisms including the IIS pathway, indicating that TDO might act through or converge on some of the known longevity factors. Related to this, the TOR inhibitor rapamycin inhibits IDO activity in blood cells *in vitro*, suggesting a connection between the TOR pathway and tryptophan metabolism as well [23]. Given that TDO or IDO knockout mice are viable and show no gross abnormalities [24,25], it will be interesting to learn whether inhibition of the first step in tryptophan degradation regulates lifespan in higher organisms as well. If any of the other enzymes in the kynurenine pathway play a similar role in lifespan regulation remains to be investigated.

Two independent studies found that the kynurenine: tryptophan ratio, reflecting the tryptophan degradation rate, was increased in people of old age, suggesting that aging is accompanied by the accelerated degradation of tryptophan through the kynurenine pathway [26,27]. Moreover, one of these studies showed that a higher kynurenine:tryptophan ratio at the start of the study predicted higher mortality in a group of individuals in their nineties [27]. Although these data on altered tryptophan metabolism during aging are correlative, they suggest that tryptophan metabolism might play a role in regulating lifespan in humans as well. Alternatively, pathologies, such as infections or cancer, could be responsible for the observed increase in IDO activity and enhanced tryptophan degradation could reflect an increase in the occurrence of these pathologies with age.

Inhibition of several enzymes in the kynurenine pathway has recently provided direct evidence for a role for tryptophan metabolism in the regulation of age-related pathologies. Pharmacological inhibition of IDO or TDO in mice suppresses the growth of tumors expressing these enzymes [28–31]. Moreover, combining pharmacological inhibition of IDO with various cytotoxic agents could promote the regression of established tumors that did not respond to treatment with single agents [30].

The first direct evidence for the involvement of the kynurenine pathway in neurodegeneration came from a genetic screen in a yeast model for Huntington disease; loss-of-function mutations in the enzyme kynurenine 3-monooxygenase (KMO) suppressed toxicity of a mutant huntingtin fragment [32]. Genetic or pharmacological inhibition of KMO was subsequently shown to reduce neurodegeneration in a fly model for Huntington's disease and mouse models for Alzheimer's and Huntington's diseases [33,34], suggesting evolutionary conservation for the function of KMO in regulating neurodegeneration. In addition, genetic inhibition of TDO reduced proteotoxicity in the same fly model for Huntington's disease [33] and in *C. elegans* models for Alzheimer's, Huntington's, and Parkinson's diseases [21]. Together, these data implicate tryptophan metabolism as a potent metabolic regulator of ageing and age-related diseases, offering new avenues for disease intervention. In addition, owing to the high conservation of tryptophan metabolism throughout evolution, small model organisms provide powerful tools to dissect the molecular roles of individual enzymes and metabolites in a wide range of disease models.

## Tryptophan metabolism

### *Regulation*

To understand how tryptophan metabolism contributes to health and disease, it is important to know how it is regulated and to which physiological processes it contributes. Tryptophan is an essential amino acid that can only be taken up through diet. In addition to protein synthesis, it is used in a variety of processes, including the production of biogenic amines such as serotonin, melatonin, tryptamine, and tryptophan degradation products collectively called kynurenines. In mammals and yeast it contributes to the synthesis of nicotinamide adenine dinucleotide ($NAD^+$), a coenzyme important for energy metabolism (Figure 1B).

Systemic and cellular tryptophan levels are determined by food intake as well as the activity of pathways that convert or degrade tryptophan. More than 95% of free tryptophan is degraded through the kynurenine pathway described in Figure 1. The enzymes IDO and TDO, which catalyze the first and rate-limiting step of tryptophan degradation, are expressed in different tissues and their expression is induced upon exposure to different stimuli, suggesting they have distinct functions in health and disease (Figure 2). TDO is present in both eukaryotes and bacteria, but IDO has been found only in mammals and yeast. Mammals express both IDO and TDO. TDO is expressed mainly in the liver and its expression is induced by tryptophan itself or by corticosteroids, secretion of which occurs in response to stress. By contrast, IDO is found in most mammalian cells, including macrophages and cells of the central nervous system (reviewed in [35]). IDO is induced by the proinflammatory cytokine interferon (IFN)-γ and other immune stimulants, including lipopolysaccharide [36,37]. TDO influences systemic tryptophan levels by controlling tryptophan levels in the blood, whereas IDO acts locally to modulate tryptophan levels in response to inflammation. Moreover, enzymes of the kynurenine pathway downstream of TDO or IDO are also expressed in different cell types and tissues, and as a consequence determine the presence and relative abundance of subsequent metabolites. Hepatocytes are the only cells in which all of the enzymes of the kynurenine pathway are found. In the brain, most of the kynurenine pathway metabolites are formed in microglia and astrocytes, with the synthesis of 3-hydroxykynurenine and further downstream metabolites occurring in microglia, and the synthesis of kynurenic acid occurring in astrocytes [38]. In addition, there is evidence for interplay between tryptophan metabolites in the periphery and in the central nervous system, which are separated by the blood–brain barrier. Tryptophan, kynurenine, 3-hydroxykynurenine, and anthranillic acid can cross the blood–brain barrier easily. Because of this, fluctuations in the blood levels of these metabolites can affect metabolism in the kynurenine pathway in the brain. Kynurenic acid, 3-hydroxyanthranilic acid, and quinolinic acid cross the barrier poorly [39].

The use of tryptophan for the production of serotonin and melatonin also occurs in distinct cell types. Serotonin is mainly present in the nervous system and gut, whereas melatonin is mainly produced in the pineal gland. Both neurotransmitters are known to regulate animal behavior.

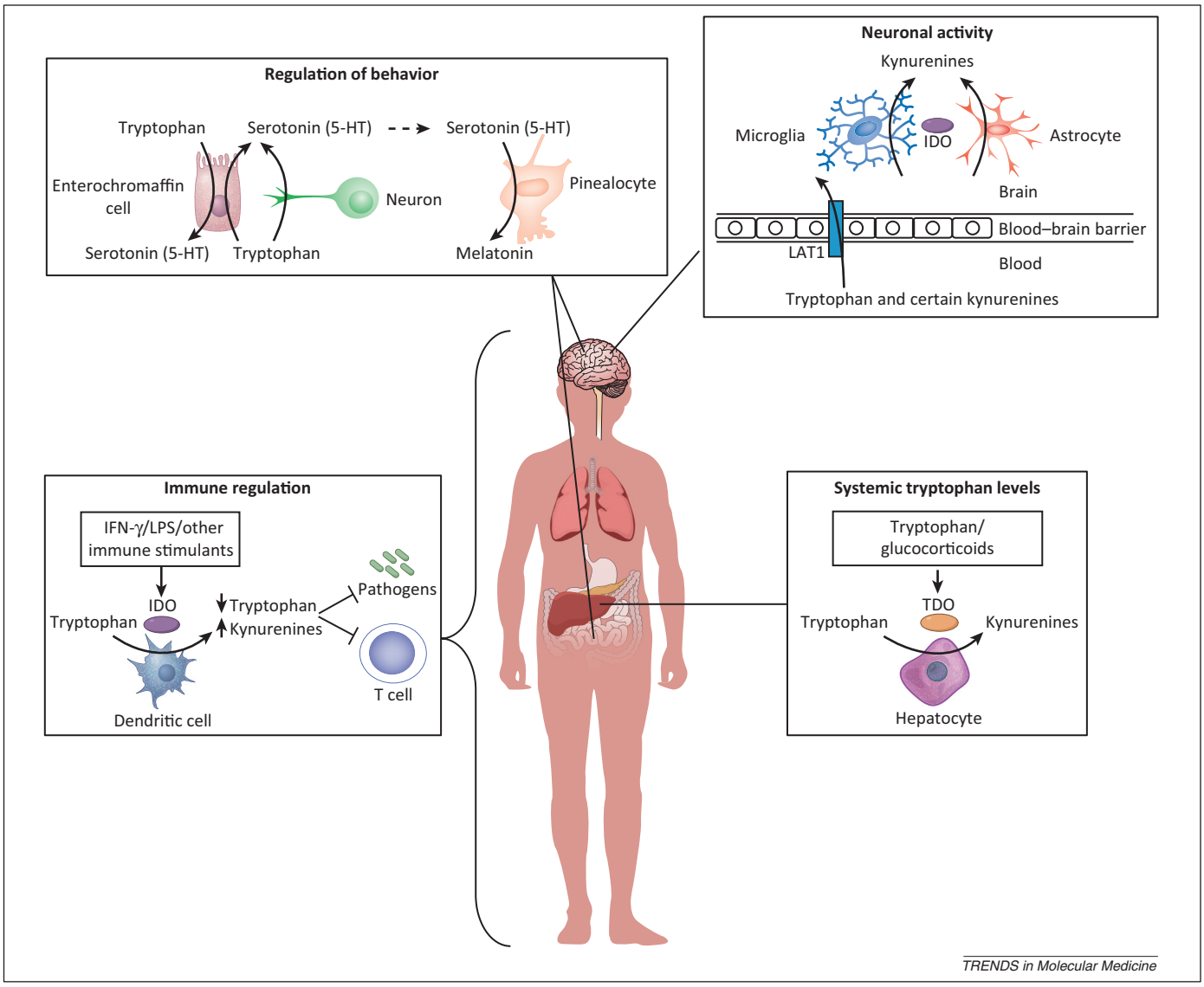


**Figure 2**. Tryptophan metabolism in health and disease. The regulation of tryptophan metabolism is cell type-dependent and can be controlled locally or systemically by different stimuli. Tryptophan metabolism plays a role in neuronal activity, immune regulation, and behavior. Abbreviations: IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; LAT1, large neutral amino acid transporter; IFN-γ, interferon-γ; LPS, lipopolysaccharide.

For instance, serotonin is implicated in regulating mood, appetite, and reproduction, whereas melatonin has been implicated in the regulation of circadian rhythm. Local or systemic alterations in tryptophan metabolism, therefore, could result in profound behavioral changes.

Together, these data show that the regulation of tryptophan metabolism is sensitive to environmental conditions and can affect both physiological and behavioral processes. It differs between species, cell types, induction agents, and can be modulated by interactions between tissues (Figure 2). Given that tryptophan is the rarest amino acid found in food, and the enzymes responsible for its degradation or conversion to other substances can be controlled, tryptophan levels may be used to adjust animal biology to survive under changing environmental conditions.

### *Role in immune regulation*

One of the biological functions of tryptophan metabolism, and more specifically of IDO, is immune regulation. This was first recognized by the observation that IDO can be induced by IFN-γ and other immune stimulants [36,37] and is expressed in inflamed tissues. IDO is thought to be part of the innate immune defense against various pathogens, especially those that cannot synthesize their own tryptophan. Upon infection, IDO expression is induced and causes the local depletion of the essential amino acid, thereby inhibiting growth of the pathogen [40–42]. At least *in vitro*, these effects seem to rely on the depletion of tryptophan because supplementing the medium with extra tryptophan reverts the antimicrobial effects.

In addition to its role in innate immunity, IDO was also shown to play a role in immunosuppressive and anti-inflammatory activities mediated primarily by T cells of the adaptive immune system. Pharmacological inhibition of IDO in pregnant mice results in the rejection of allogeneic fetuses, mediated by maternal T cells. These data, therefore, suggest that IDO expression at the maternal–fetal interface contributes to maternal tolerance towards

the fetus [43,44]. Subsequent studies implicated IDO in the regulation of immunosuppressive effects mediated by T cells in autoimmune disorders, transplant medicine, and tumor immunology (reviewed in [45]). How TDO and IDO exert these immunomodulatory activities is not completely understood, but two mechanisms have been proposed to mediate these effects: the depletion of tryptophan and an increase in the generation of kynurenines with immunomodulatory properties. Similar to its effects on the growth of pathogens, the depletion of tryptophan induces cell-cycle arrest of T cells [46] and sensitizes these cells to apoptosis [47]. Low levels of tryptophan might be detected by the mTOR [48,49] or the integrated stress response (ISR) pathway [50,51], both of which respond to low levels of amino acids. Indeed, the stress-responsive kinase GCN2, a downstream mediator of the ISR pathway, has been shown to be required for the immunoregulatory effects of IDO in T cells [52,53]. It is possible that an increase in the amount of uncharged transfer RNA (tRNA) in the cell activates GCN2 (general control non-derepressible 2), which then initiates downstream signaling. The downstream targets that mediate the immunoregulatory effects remain to be identified, but previous studies have shown that activation of the ISR pathway can result in cell-cycle arrest, lineage-specific differentiation, metabolic adaptation, or cell death [52]. Alternatively, kynurenines could have immunomodulatory properties. Kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid inhibit proliferation and induce apoptosis when applied exogenously to cultured T cells [54–56]. The mechanisms by which these kynurenines affect T cells remain unknown. They may be directly toxic or might bind to receptors and activate signaling pathways.

Inflammation has also been implicated in cardiovascular diseases. A decrease in tryptophan concentration, likely reflecting enhanced IDO activity, has been observed in patients [57–59]. Because these data are correlative, it remains to be established whether tryptophan degradation has a causal role in cardiovascular diseases or whether the observed increase in tryptophan degradation reflects a response of the immune system to inflammation associated with cardiovascular diseases.

In the context of cancer, IDO or TDO expression by tumors can contribute to their immune escape, and pharmacological inhibition of IDO or TDO suppresses the formation of tumors by promoting T cell-mediated tumor rejection [28–31]. In addition, the proinflammatory microenvironment of the tumor could promote expression of IDO in tumor cells and other cells present in the tumor tissue, such as antigen-presenting cells invading the tumor [28,60,61]. Expression of IDO or TDO by tumor cells and antigen-presenting cells results in the depletion of tryptophan from the tumor microenvironment while increasing the abundance of kynurenines. The generation of kynurenine by TDO-expressing tumors was recently shown to suppress T cell-mediated tumor rejection and to promote tumor cell survival by activating the aryl hydrocarbon receptor (AHR) and upregulation of its downstream target genes [62]. Whether and how the depletion of tryptophan, or the increased generation of other kynurenines, contributes to T cell-mediated tumor rejection *in vivo* remains to be investigated. The fact that a large number of human tumors express IDO, TDO, or a combination of both enzymes [29,31] illustrates the therapeutic potential for targeting IDO or TDO in the treatment of cancer.

### *Role in neurodegeneration*

The beneficial effects in many neurodegenerative disease models upon manipulation of the kynurenine pathway, but especially upon inhibition of KMO, are suggested to be mediated by changes in the levels or relative abundance of several kynurenines. A role for kynurenines in the nervous system has been studied extensively (reviewed in [63,64]). Among the kynurenines thought to possess biological activity are 3-hydroxykynurenine and 3-hydroxyanthranilic acid, both generators of free radicals, the metabolite quinolinic acid, which can excite neurons by acting as an agonist at the *N*-methyl-D-aspartate (NMDA)-sensitive population of glutamate receptors, and kynurenic acid, a glutamate receptor antagonist [63,64]. These properties suggest that the beneficial effects of manipulating the kynurenine pathway could be mediated by changing their levels, possibly reducing the generation of reactive oxygen species (ROS), reducing excitotoxicity, or increasing the scavenging of free radicals [32–34]. Experimental evidence for a role of these kynurenines in neurodegeneration mainly comes from studies in flies and mice. In mice, pharmacological peripheral inhibition of KMO raised kynurenic acid levels in the brain and ameliorated neurodegeneration in Alzheimer's disease and Huntington's disease models [34]. These beneficial effects were suggested to be the result of the observed increase in levels of the neuroprotective kynurenic acid and a decrease in glutamate levels in the brain, leading to a reduction in synaptic loss [34]. How alterations in these metabolite levels exactly regulate neurodegeneration and which receptors are involved remains unknown. Similarly, in flies inhibition of KMO or TDO increased the levels of kynurenic acid relative to 3-hydroxykunurenine [33]. In the case of KMO, it was shown that feeding flies 3-hydroxykynurenine reduced the protective effects of KMO inhibition, providing more evidence for a causative role of this metabolite. Furthermore, genetic inhibition of *cardinal* in flies, which results in elevated levels of 3-hydroxykynurenine, leads to age-dependent learning and memory deficits and synaptic pathology [65]. Although these studies clearly indicate a role for kynurenines in neuronal activity and neurodegeneration, their relative contribution and specific biological activities remain to be investigated.

Recently, we found that inhibition of TDO results in a very strong suppression of proteotoxicity in *C. elegans* models for protein misfolding. Genetic studies in combination with analyses of a range of kynurenines revealed that TDO did not suppress proteotoxicity by preventing the formation of toxic degradation products. This suggests that an effect upstream of TDO and independent of kynurenines can mediate the beneficial effects upon inhibition of TDO. Moreover, when we supplemented the food with extra tryptophan, we observed a similar suppression of proteotoxicity [21]. Our data imply a role for tryptophan itself or for metabolites requiring tryptophan for their synthesis. In contrast to its effect on

**Box 1. Outstanding questions**

- Is tryptophan metabolism also associated with aging and age-related diseases in humans?
- Is altered tryptophan metabolism a cause or consequence of aging?
- Which step of the kynurenine pathway of tryptophan degradation is the best target for intervention?
- Will there be any negative effects of interference in tryptophan metabolism, and what will they be?
- Does tryptophan metabolism interact with other metabolic signaling pathways that regulate aging or does it function in parallel?
- Which downstream mechanisms are involved in regulating the beneficial effects of tryptophan?
- Do other amino acids play similar roles?

longevity, suppression of proteotoxicity by inhibition of TDO was completely independent of DAF-16, suggesting that TDO regulates lifespan either downstream or independent of its role in regulating protein homeostasis [21]. How TDO regulates protein homeostasis and which signaling routes are involved remains to be determined (Box 1).

To date, evidence for a role of the kynurenine pathway in patients is mostly correlative. For example, in Alzheimer's disease patients serum tryptophan levels are decreased, serum kynurenine levels are increased, and these changes correlate with the level of cognitive decline [66,67]. Similarly, brain levels of quinolinic acid, kynurenic acid, and 3-hydroxykynurenine are reported to be elevated in early phases of Huntington's disease [68,69], in line with findings in mouse models [70]. These studies support the idea that restoring the balance in tryptophan metabolism may provide therapeutic benefits in patients with neurodegeneration.

## Concluding remarks and future perspectives

Studies in yeast, worms, flies, and mice have now firmly established that tryptophan metabolism can function as a regulator in age-related pathologies and lifespan. Owing to its high conservation, the use of small model organisms in studying this complex route provides powerful tools to test the involvement of individual enzymes and metabolites in a quantitative manner. The fact that two unbiased genome-wide screens, in different organisms expressing different disease proteins, identified the kynurenine pathway as a modifier for neurodegeneration illustrates the potential of these small model organisms [32,71]. These models could also be instrumental in identifying receptors and pathways that mediate the effects of altered tryptophan metabolism.

Interfering with these pathways using pharmacological inhibitors or natural metabolites through diet offers new routes to explore for the treatment of age-related diseases. Furthermore, understanding the involvement of tryptophan metabolism in all aspects of animal biology will help to design additional strategies with the potential to improve health and extend lifespan.

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