

Review

The Role of *Drosophila* Toll Receptors in the Central Nervous System

Zhuoya Ma^{1,2}, Jianghui Xu^{1,2}, Xue-lu Yu³, Xiakun Wang⁴, Qipei Gu^{1,2}, Hongrui Meng^{1,2,*} 

¹Institute of Neuroscience, Soochow University, 215123 Suzhou, Jiangsu, China

²Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, 215004 Suzhou, Jiangsu, China

³Department of Disease Prevention and Control, Naval Medical Center of People's Liberation Army, Naval Medical University, 200052 Shanghai, China

⁴The Department of Immunology, Basic Medical College, Fudan University, 200032 Shanghai, China

*Correspondence: hrmeng@suda.edu.cn (Hongrui Meng)

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Abstract

Toll-like receptors (TLRs) are evolutionarily conserved pattern recognition receptors that play pivotal roles in innate immunity by detecting pathogen-associated molecular patterns. While initially characterized for their function in dorsoventral patterning and antifungal defense in *Drosophila*, the Toll family is now understood to have undergone a functional expansion in the nervous system. This review synthesizes the current understanding of the nine *Drosophila* Toll receptors (Toll-1 to Toll-9) and their roles in the central nervous system (CNS). We discuss how these receptors, particularly through non-canonical signaling pathways, function as neurotrophin receptors and cell surface recognition molecules. They mediate a wide range of cellular processes, from axon guidance to synaptic partner matching and the regulation of neuronal survival versus apoptosis through the competitive recruitment of adaptor proteins such as dMyD88 and Sarm. We further explore the involvement of Toll signaling in adult brain structural plasticity, sleep homeostasis, and behavioral responses to environmental stressors such as ethanol. Importantly, this article addresses the context-dependent duality of Toll signaling in neuropathology, dysregulation, and aberrant activation, which are closely related to neurodegeneration, lifespan determination, and infection responses. Through this timely summary of current research, this review highlights the molecular switches that govern Toll receptor functional states and their roles in neuro-immune interactions, with implications for understanding neurological diseases in vertebrates.

Keywords: Toll receptors; *Drosophila*; central nervous system; Toll signaling; neuro-immune interactions

1. Introduction

Toll was initially identified for its essential role in establishing the dorsal-ventral axis in the *Drosophila* embryo [1]. Like the homologous Toll-like receptors (TLRs) in mammals, they were subsequently identified to participate in regulating the expression of co-stimulatory molecules and cytokines required for adaptive immune activation [2]. As pattern recognition receptors (PRRs), TLRs detect conserved pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides and nucleic acids as well as endogenous damage-associated molecular patterns (DAMPs), thereby initiating downstream inflammatory and immune signaling pathways [3,4]. Recent studies have revealed that members of the TLR family are also present in the central nervous system (CNS), where they play a pivotal role in activating glia and modulating neuronal signaling. The CNS of *Drosophila*, with its relative simplicity and high degree of genetic conservation, provides a robust model system for dissecting the molecular pathways underlying neuronal development, survival, and plasticity [5]. Given the diverse roles of Toll receptors in the *Drosophila* CNS, it is essential to systematically integrate the latest findings of their functions, with a particular focus on how they shape development and survival, structural plasticity, regulation of

autophagy, neuroinflammation, and the mediation of neuronal pathology.

The *Drosophila* genome encodes nine Toll receptors (Toll-1 to Toll-9) [6,7] and six Spätzle cytokines (Spz-1 to Spz-6) [8,9]. The canonical Toll signaling pathway is activated by proteolytic processing of Spätzle, which generates mature cytokines that bind to Toll receptors at the cell surface [10,11,12]. This binding triggers a cascade of events that culminate in the activation of NF-κB family transcription factors (Dorsal and Dif) through the degradation of Cactus, which inhibits their function [13]. Subsequently, these NF-κB transcription factors undergo nuclear translocation and induce the expression of target genes, primarily antimicrobial peptides (AMPs) [14]. Notably, some Spätzle family members serve as *Drosophila* neurotrophins (DNTs), such as DNT-1/Spz-2 and DNT-2/Spz-5. They are involved in the *Drosophila* Toll receptor signaling and functionally regulate various biological processes. For instance, Toll-6 and Toll-7 act as receptors for neurotrophin-family Spätzles, including DNT-1 and DNT-2, to regulate axon guidance, neuronal targeting, and cell survival [15,16,17]. Toll-7 can also recognize viral glycoproteins independent of the canonical ligand Spätzle, thereby mediating antiviral autophagy [18]. In contrast, Toll-2 appears to play a highly



specialized role in regulating neuronal survival in the pupal and adult central nervous system, influencing structural brain topographic plasticity [19]. Toll signaling is not functionally uniform; subsets of the receptors exhibit distinct ligand specificities and downstream outputs, and are involved in diverse biological processes that extend well beyond classical immunity.

In the nervous system, Toll receptors constitute a dynamic neuro-immune regulatory hub, whose functional states are finely regulated by ligand type, receptor complex composition, and adaptor protein selection [20,21]. A typical receptor-ligand recognition mode, in which Toll-6 and Toll-7 can directly bind to DNT-1 and DNT-2, does not occur in other Toll receptors [15]. Interestingly, in the olfactory circuit, they direct neurite targeting and synaptic partner matching through a non-canonical mechanism that dispenses with the intracellular Toll/Interleukin-1 receptor (TIR) domain [22]. At the signal output level, the same Toll family receptor can recruit different combinations of adaptor proteins in distinct cellular contexts or developmental stages, ultimately eliciting opposing effects such as promoting survival or inducing apoptosis.

This review aims to provide an overview of *Drosophila* Toll receptors in the CNS that function in behavioral regulation, while also discussing the potential molecular basis underlying their functional state transition. The details of the complex interplay between Toll receptors and distinct signaling pathways offer potentially valuable insight into the effect of immune molecules on neuronal processes. The review emphasizes the significance of the *Drosophila* Toll signaling pathway in maintaining neural homeostasis and responding to environmental challenges over the course of evolution, providing a framework for “symmetrical” processes in vertebrates. This overview of Toll signaling interactions and regulatory networks provides a pathway toward harnessing the molecular mechanisms of neuroimmune responses in the context of neuronal health and disease.

2. *Drosophila* Toll Receptors and Signaling Pathways

2.1 Structure of *Drosophila* Toll Receptors

Drosophila Toll receptors belong to the Type I transmembrane protein family and are characterized by three major structural components: an N-terminal extracellular region, a single-pass transmembrane segment, and a C-terminal intracellular signaling domain. The extracellular region primarily mediates ligand recognition, whereas the intracellular region contains the highly conserved TIR domain, which recruits downstream adaptors and initiates intracellular signal transduction cascades [23].

Phylogenetic analysis indicates that the Toll receptors of fruit flies are more closely related to one another than to the TLRs present in mammals. The similarities among expanded insect Toll receptors directly correspond to their

evolution in the common ancestor of insect species [24,25]. The characteristic features of Toll receptors include a conserved structural framework with an extracellular leucine-rich repeat (LRR) region, a transmembrane segment, and an intracellular TIR domain (Fig. 1). The N-terminal extracellular region of Toll receptors is dominated by LRR motifs, which typically consist of approximately 24 amino acids arranged around a conserved hydrophobic leucine-rich core [26]. These repeats form a curved solenoid-like structure that provides a versatile scaffold for ligand binding. The stability of the LRR structures is maintained by the shielded, conserved hydrophobic core, with the solvent-exposed residues exhibiting far greater variability [27,28].

Ligand recognition among Toll receptors stems from differences in the sequence composition, organization, and number of LRR motifs. For example, the LRR domain of Toll-1 recognizes the proteolytically processed Spätzle protein dimer, whereas the distinct LRR composition of Toll-7 enables direct interaction with viral glycoproteins (Fig. 2A, Ref. [15,18,19,22,29,30]). The structural arrangement of LRR regions also differs within the family. *Drosophila* Toll-1, Toll-2, Toll-5, Toll-6, and Toll-7 contain two extracellular LRR blocks; Toll-9 has a single LRR block; and Toll-3 and Toll-4 contain multiple shorter LRR segments. These structural variations enable Toll receptor molecules to have potential functional diversification.

2.2 Ligand Recognition and Signaling Transduction Pathways

The signal transduction downstream of Toll receptors is context-dependent. The specific intracellular adapter proteins associated with Toll receptors determine which transcription factors are activated upon receptor stimulation. Five primary adapter proteins, including MyD88, MyD88 adaptor-like (MAL), TIR-domain-containing adaptor inducing interferon- β (TRIF), TRIF-related adaptor molecule (TRAM), and sterile alpha and armadillo motif-containing protein (SARM), are involved in this signaling process in mammals [31]. In *Drosophila*, the canonical Toll signaling pathway primarily relies on dMyD88, while dSarm is involved in the non-canonical pathway [32]. Toll receptors bind ligands through their extracellular LRR domain, sending signals to the conserved intracellular TIR domain, which in turn propagates downstream output.

In the canonical immune signaling pathway, Toll receptor activation by the extracellular ligand Spätzle subsequently recruits adapter proteins. Specifically, the TIR domain of the Toll receptor binds the dMyD88 adapter protein, whereupon the death domain recruits the downstream adapter Tube and the kinase Pelle, forming the core signaling complex [32]. Activated Pelle then phosphorylates and induces the degradation of the inhibitor protein Cactus, thereby releasing the transcription factors Dorsal/Dif, which translocate to the nucleus to initiate target gene expression (Fig. 2B).

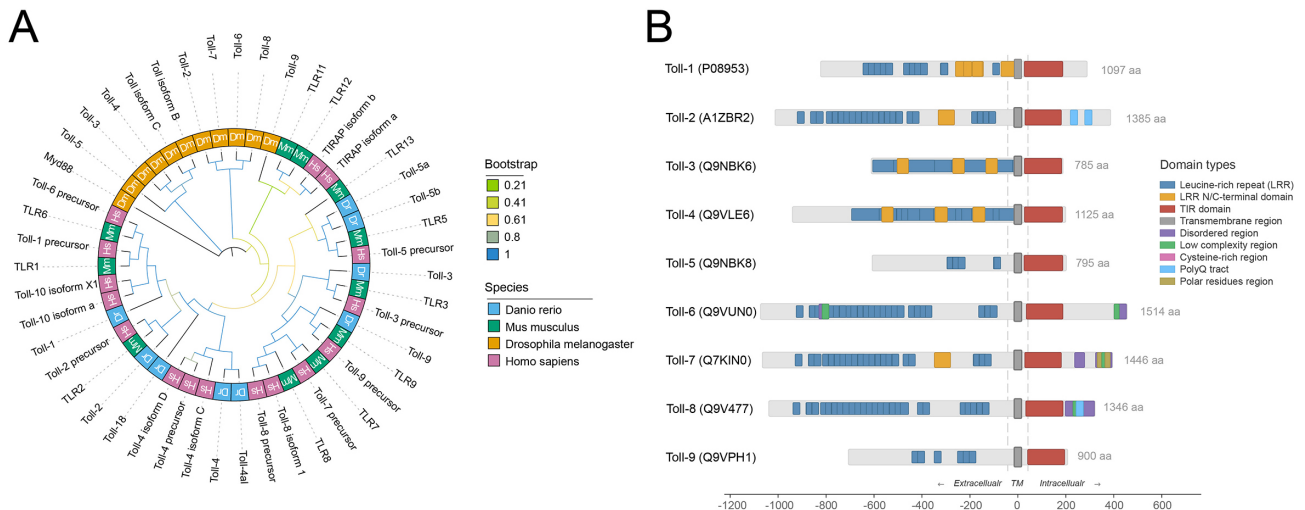


Fig. 1. Evolutionary relationships and structural features of the *Drosophila* Toll receptor family. (A) Neighbor-joining phylogenetic tree constructed from full-length Toll receptor protein sequences retrieved from UniProt. Phylogenetic reconstruction was performed using MEGA12 (<https://www.megasoftware.net/>). Branch colors indicate bootstrap support values. Protein labels are color-coded according to species identity. *Drosophila melanogaster* (Dm), *Danio rerio* (Dr), *Mus musculus* (Mm), and *Homo sapiens* (Hs). (B) Domain architecture of *Drosophila* Toll proteins (Toll-1 to Toll-9). All sequences were derived from UniProt (<https://www.uniprot.org/>). Domain and sequence features were predicted using InterProScan 108.0 and DeepTMHMM 1.0, from which the precise coordinates of the identified domains were extracted. Individual leucine-rich repeat (LRR) units (blue), LRR N/C-terminal capping domains (amber), TIR domains (brick red), and additional features are shown as indicated by the corresponding color code. UniProt IDs are annotated to each Toll protein. Numbers denote the total protein length in amino acids (aa). TM, transmembrane.

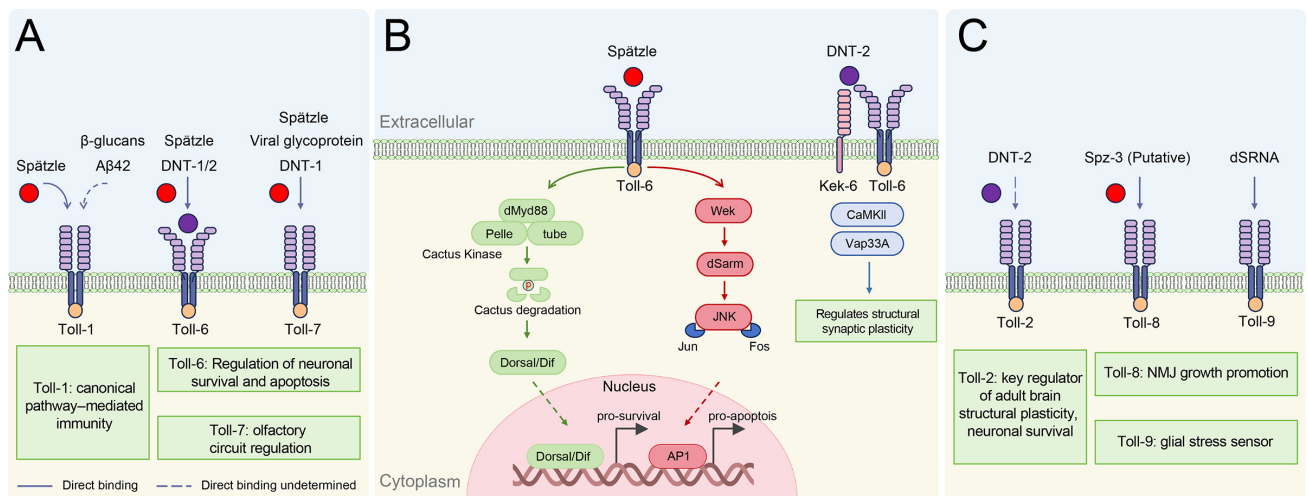


Fig. 2. Functional diversity of *Drosophila* Toll receptors in the CNS. (A) Toll-1 binds Spätzle and signals through the canonical dMyD88 pathway; Toll-6 and Toll-7 bind DNTs to guide axon targeting and synaptic partner matching [15,18,22]. (B) Toll-6 balances survival (via dMyD88) and apoptosis (via Wek/Sarm), and can associate with Kek-6 to regulate synaptic plasticity. (C) Toll-2 regulates structural plasticity of the brain; Toll-8 promotes neuromuscular junction growth through JNK; Toll-9 acts as a glial stress sensor [19,29,30]. CNS, central nervous system; DNT, *Drosophila* neurotrophin; NMJ, neuromuscular junction; JNK, c-Jun N-terminal kinase; dMyD88, *Drosophila* MyD88; Sarm/dSarm, sterile alpha and armadillo motif; CaMKII, Ca²⁺/calmodulin-dependent protein kinase II; Vap33A, VAMP-associated protein 33 kDa; AP-1, activator protein 1; dsRNA, double-stranded RNA.

Toll family signaling diversity manifests at multiple levels. Regarding ligand recognition, the binding pattern by which Toll-7 recognizes viral glycoproteins may resemble that of mammalian TLR4, which has been identi-

fied as a multifunctional viral sensor that can sense bacterial lipopolysaccharide and is capable of coordinating complex antiviral immune responses [33]. As another example of functional diversification, Toll-9 has also been shown

to localize to endosomes, bind dsRNA, induce AKT dephosphorylation, and enhance antiviral RNA interference (RNAi), thereby defending against *Drosophila* C virus infection (Fig. 2C). In terms of signal output, these receptors can also activate non-canonical pathways independent of NF- κ B, providing a compensatory layer of functional diversity. Moreover, Toll signaling processes vary depending on the precise composition of the complex formed when Toll receptors bind distinct adapter proteins. For example, *Drosophila* dMyD88 possesses a C-terminal extension absent in its mammalian homolog, suggesting species-specific functional adaptations and regulatory mechanisms.

2.3 Comparison Between *Drosophila* Toll and the TLR Families in Mammals

Despite the evolutionary conservation of structures and signaling pathways observed when comparing *Drosophila* Toll and mammalian TLRs, significant divergences are evident in ligand recognition, receptor function, and signal adaptation [25]. Both possess extracellular LRR domains and intracellular TIR domains, demonstrating the structural homology indicative of an evolutionarily ancient origin [34]. Mammalian IL-1R or TLR activation recruits MyD88 and activates the interleukin-1 receptor-associated kinase (IRAK), ultimately prompting nuclear NF- κ B translocation and associated induction of gene expression [35,36]. The *Drosophila* Toll-Dorsal/Dif pathway closely parallels the mammalian IL-1R-NF- κ B pathway, with the Spätzle-mediated activation of *Drosophila* Toll-1 triggering the dMyD88-Tube-Pelle cascade, leading to Cactus dissociation and nuclear translocation of Dorsal/Dif to initiate transcription that promotes an antimicrobial response [37].

In contrast to mammalian TLRs, which directly recognize PAMPs and serve as inflammatory regulators [38], the *Drosophila* Toll receptors extend far beyond the confines of the immune response. Several members (e.g., Toll-6, 7, and 8) play roles in guiding axon targeting and neuronal pathfinding via extracellular LRR domains. *Drosophila* lacks obvious orthologs of the mammalian tropomyosin receptor kinase (Trk), p75 neurotrophin receptor (p75NTR), or Sortilin neurotrophin receptor genes, which functionally interact with extracellular neurotrophic factors in mammals [15,39]. A fundamental distinction between flies and mammals thus emerges at the level of ligand identity. Unlike the direct sensing of microbial products by TLRs observed in mammals, *Drosophila* Toll receptors are activated by proteolytically processed Spätzle-family cytokines, which act as functional neurotrophins within the nervous system [40].

Species-specific adaptive evolution is also evident in the specific signaling mechanisms that these pathways employ. Although dMyD88 is homologous to mammalian MyD88, it contains a unique C-terminal extension in *Drosophila*, suggesting additional potential regulatory functions. The activation of certain mammalian TLRs (such

as TLR2 and TLR4) requires the auxiliary adaptor protein TIR domain-containing adaptor protein (TIRAP), reflecting complexity in signalosome assembly. The *Drosophila* Toll and Imd pathways are homologous to the mammalian TLR and tumor necrosis factor receptor (TNFR) signaling pathways, respectively, and both are essential for resistance to infection [41]. Analysis of genes in the Toll and Imd pathways reveals a general principle that downstream signal transducers are subject to stronger selective constraints, while the upstream receptors tolerate greater functional diversification [42]. This positional constraint may elucidate the conservation of core signal transducers in the Toll pathway, such as dMyD88, Tube, and Pelle, with upstream ligand-receptor recognition exhibiting greater diversity to accommodate novel functions.

Apart from mediating transcellular signaling, direct physical interactions between Toll receptors through their intracellular or extracellular domains, either in cis or in trans, have not been experimentally confirmed. In contrast, the ligand-induced heterodimerization of mammalian TLRs has been well documented (e.g., TLR1–TLR2 [43], TLR2–TLR6 [44], and the TLR4–MD-2–LPS complex [45]), and these interactions all occur in cis on the same cell membrane. For *Drosophila* Toll receptors, the only structural evidence available suggests a weak propensity for homodimerization in the ectodomain of Toll-1 [10,46], whereas the dimerization mode of the intracellular TIR domain has been preliminarily explored only through molecular dynamics simulations in mammalian homologs [47], with direct evidence in *Drosophila* still lacking. If such interactions do exist, it remains to be determined whether they involve transcellular engagement to provide positional cues for developing neurons.

Significant functional diversification also exists among members of the *Drosophila* Toll family. Unlike the relatively conserved members (e.g., Toll-1, -6, -7, and -8), Toll-3 and Toll-4 exhibit characteristics of rapid gene turnover and male-specific expression. Their knockout does not cause severe developmental defects, suggesting they may have shed core developmental functions and adopted species- or sex-specific specialization [48]. Their functions in the nervous system, along with those of Toll-5, remain key areas of focus for future research. Although Toll-9 is structurally the most similar to vertebrate TLRs and may represent an ancestral form of these Toll receptors, loss-of-function mutants have shown that Toll-9 is not required for basal antibacterial immunity or inducible immune responses. This suggests that Toll-9 may not possess conventional immune functions, and its biological role remains to be further explored [49].

3. Roles of Toll Receptors in Neural Plasticity and Survival

The nine Toll receptors encoded by the *Drosophila* genome exhibit distinct expression patterns, ligand recog-

nitition, and signaling pathways in the brain (Table 1, Ref. [10,11,12,15,18,19,22,29,30,32,48,50,51,52,53,54]). Toll-1 is broadly distributed across multiple neuropils, while Toll-2 and Toll-6 are enriched in Kenyon cells and the antennal lobe, Toll-7 and Toll-8 are expressed in the protocerebral bridge and motor neurons, respectively, and Toll-9 is restricted to glial cells [19]. During the larval stage, Toll receptors participate in axon guidance, synaptic partner matching, and the establishment of neuromuscular junctions. In adults, they regulate experience-dependent structural plasticity, sleep homeostasis, and stress responses. Among these receptors, Toll-6 and Toll-7 mediate the remodeling of dopaminergic circuits through non-canonical signaling pathways [22,51]. This functional specialization is further manifested in the dynamic expression of distinct receptors in specific cell types and at defined developmental stages, laying the foundation for the subsequent detailed elaboration of the multiple roles of Toll receptors in CNS development and plasticity.

3.1 Axon Guidance, Pathfinding, and Neural Circuit Assembly

Within the nervous system, Toll receptors recognize neuronal surface cues via their extracellular LRR domains, which in turn guide the growth cone and direct axons toward their correct targets. This involvement underpins their roles in developmental processes such as axon elongation, neuronal pathfinding, and the assembly of complex neural circuits.

Toll receptors provide axonal guidance through mechanisms that are potentially related to their roles in directing cell migration during early development. One previous study identified a regulatory region that controls Toll gene expression in the midline cells of the CNS [55]. During embryogenesis, Toll-2, Toll-6, and Toll-8 provide planar-polarity signals to cells, thereby coordinating their intercalation [56,57]. The core mechanism that does so involves the localized activation of the Src/PI3K signaling axis to remodel the cytoskeleton [58], which likely guides the precise pathfinding of neurites during growth cone navigation.

In the assembly of the *Drosophila* olfactory circuit, Toll-6 and Toll-7 act in a cell-autonomous manner to direct the precise targeting of specific classes of projection neuron dendrites and olfactory receptor neuron axons, respectively [22]. This neural-specific function is independent of Spätzle and dMyD88 and does not strictly rely on the intracellular TIR domain. Loss of Toll-6 function leads to erroneous pathfinding of axon terminals [51], and recent research has established a spatial model describing how Toll receptors achieve appropriate connectivity. Briefly, Lyu et al. [59] discovered that olfactory circuit assembly does not involve a direct search within a complex 3D space but is instead simplified through a “dimensionality reduction” principle: ORN axons first contact PN dendrites on a 2D surface within the antennal lobe, after which axons

of each ORN type precisely meet their partner dendrites along a specific, pre-determined curved trajectory. This model reduces the complex 3D search problem to a 1D pathfinding task. Within this refined framework, the transcellular recognition signals mediated by Toll-6 and Toll-7 likely comprise the molecular basis for defining and guiding these specific trajectories, ultimately “locking” synaptic partners at the correct locations. These findings indicate that Toll receptors, particularly Toll-6 and Toll-7, provide a crucial recognition code that guides olfactory circuit assembly through their diverse extracellular interactions [60]. Furthermore, a repulsive interaction system involving the interplay between pairs of proteins (e.g., Toll-2/Ptp10D and Fili/Kek1, among others) ensures precise synaptic matching and prevents the formation of erroneous neuronal connections during this process [61].

3.2 Synapse Formation and Coordinated Regulation of the Neuromuscular Junction

The *Drosophila* neuromuscular junction (NMJ) synapse exhibits developmental plasticity and can achieve functional plasticity while maintaining a specific connection pattern [62,63]. Toll receptors coordinate transcellular signaling and actively regulate NMJ growth with respect to the connection between nerve and somatic musculature [63,64]. Toll-8 expression in motor neurons is necessary for the regulation of NMJ growth, as it functions by activating the c-Jun N-terminal kinase (JNK) signaling pathway and altering the phosphorylation of c-Jun and puc-lacZ, thereby promoting NMJ growth [29].

The process of NMJ growth also relies on retrograde signals from the muscle. DNT2, produced by muscle cells, acts as a key retrograde factor and binds to receptor complexes on motor neurons [19]. The binding of DNT2 to the Toll-6/Kek6 complex triggers Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) activation, linking the extracellular signal to neuronal calcium signaling (Fig. 2B) [65]. Toll receptors dynamically regulate the structural growth of the NMJ (i.e., synapse size and morphology), but are largely dispensable for maintaining its basic physiological transmission function.

3.3 Brain Structural Plasticity and Regulation of Adult Neurogenesis

During embryonic and larval development, Toll receptors are involved in neural circuit formation and the coordinated regulation of overall brain volume [19]. In adulthood, these receptors continue to mediate experience-dependent structural remodeling of the brain during critical periods. In the adult brain, specific Toll receptors (e.g., Toll-2, -6, -7, and -8) exhibit precise topographical distribution patterns that demarcate the boundaries of distinct brain regions [19]. This distribution forms the anatomical basis for brain structural plasticity.

Table 1. The expression patterns, ligands, signaling pathways, and functions of the *Drosophila* Toll proteins in the CNS.

Toll protein	Localization		Ligands	Signaling pathway	Neurological function		Reference
Toll-1	Photoreceptor	cells	Processed Spätzle	dMyD88-Tube-Pelle-Dorsal/Dif (NF-κB)	Axon	guidance	[10,11,12,19,32,52,53,54]
	Fan-shaped	body			Neuronal	survival	
	Ellipsoid	body			Sleep	regulation	
	SOG				Ethanol tolerance		
Toll-2	Kenyon	cells	Unknown	dMyD88-NF-κB Non-canonical pathway	Synaptic	matching	[19]
	Antennal	lobe			Critical period structural brain plasticity		
	Fan-shaped	body			Lamina neurons survival		
	Optic lobe						
Toll-3	Fan-shaped Optic lobe lamina	body	Unknown	Unknown	Male-specific expression		[19,48]
Toll-4	Low expression precise CNS localization un-clear		Unknown	Unknown	Male-specific expression		[19,48]
Toll-5	Kenyon cells (mushroom bodies) Medulla (optic lobe) Protocerebral bridge Antennal lobe Fan-shaped body		Unknown	Unknown	Unknown		[19]
Toll-6	Kenyon	cells	DNT1/Spz-2	dMyD88-NF-κB	Axon	guidance	[15,19,22,51]
	Antennal	lobe	DNT2/Spz-5	Wek-Sarm-JNK	Neuronal	survival/apoptosis	
	Fan-shaped	body	Processed Spätzle-5		Structural	plasticity of	
	SOG				dopaminergic	circuits	
	Motoneurons				Motor function and memory		
	Dopaminergic neurons						
Toll-7	Kenyon	cells	Viral glycoproteins	Autophagy	Antiviral	autophagy	[15,18,19,22]
	Protocerebral	bridge	DNT1/Spz-2	Non-canonical signaling	Axon guidance		
	Ellipsoid	body	Processed Spätzle				
	Specific PNs/ORNs						
Toll-8/Tollo	Kenyon Antennal SOG, Motoneurons	cells lobe	Spz-3 (Putative)	JNK signaling	Synaptic growth (NMJ)		[19,29]
Toll-9	Glial cells		dsRNA (Putative)	p38 MAPK/JNK (SAPK)	Stress sensor in aging and neurodegeneration Neuroprotection		[30,50]

NMJ, neuromuscular junction; SAPK, stress-activated protein kinase; DNT, *Drosophila* neurotrophin; NF-κB, nuclear factor kappa B; SOG, sub-oesophageal ganglion; JNK, c-Jun N-terminal kinase; PNs, projection neurons; ORNs, olfactory receptor neurons; dsRNA, double-stranded RNA; MAPK, mitogen-activated protein kinase.

Toll-2 is a particularly important regulator of structural plasticity in the adult brain. Functional experiments have demonstrated that conditional activation of Toll-2 signaling in the adult *Drosophila* brain is sufficient to increase cell numbers in the optic lobe medulla and the central brain, and to cause an overall increase in brain volume. Conversely, knockdown of Toll-2 or its downstream effectors, Wek and Yki, can rescue this phenotype, confirming that Toll-2 promotes neural cell proliferation and regulates brain size via the Yki pathway [19]. The neurotrophin-Toll axis enables the situationally appropriate regulation of specific neural circuits. For example, Toll-6 and its ligand DNT-2 form a sophisticated regulatory feedback system that induces structural plasticity in circuits and modifies behavior. Functional deficiencies in DNT-2, Toll-6, and the Kek-6 signaling axis lead to the loss of dopaminergic (DA) neurons and synapses, reduced synaptogenesis, impaired locomotion, and worsened long-term memory [51].

Although strong evidence suggests that activity-dependent cell proliferation occurs during the adult critical period (e.g., adjustments to neuronal connections, remodeling of neural circuits, and behavioral adaptation) and that the Toll pathway is involved in these processes, the existence of sustained, widespread neurogenesis in the adult *Drosophila* brain remains a topic of ongoing debate. Future studies will be essential to clarify the specific target of the Toll pathway in this process and to determine whether it acts directly on progenitor cells or indirectly by altering the microenvironment.

3.4 Regulation of Neuronal Survival and Apoptosis

Bioinformatic homology searches using the Spätzle sequence as a query probe identified a six-member Spätzle family in the *Drosophila* genome [9]. Their neurotrophic activity was subsequently validated by functional recombinant proteins that promoted neurite outgrowth and supported neuronal survival in primary embryonic neurons [8]. To dissect the ligand processing mode, differential proteolytic cleavage was employed to generate precursor and mature forms. Subsequent quantitative cell survival assays demonstrated that the mature forms of these proteins promote neuronal survival, whereas the precursor forms induce apoptosis [39,66]. The physical interaction between DNT-1/2 and Toll-6/Toll-7 was confirmed by a protein pull-down assay, showing that these ligands specifically bind to the extracellular domains of the corresponding Toll receptors [15].

Ligand cleavage patterns provide an initial titer of regulatory control over signaling outcomes. DNTs exist as either precursors (pro-DNTs) or cleaved mature forms, which preferentially induce neuronal apoptosis and promote survival, respectively [39,66]. Toll receptors also possess inherent signaling biases. For instance, Toll-6 promotes neuronal survival via the dMyD88-NF- κ B pathway, but can also induce cell death via the Wek-Sarm-JNK pathway

[51]. These relationships are further complicated by Toll receptors that form functional complexes with co-receptors, thereby refining signal output. Toll-6 forms a complex with the kinase-truncated, Trk-like receptor Kek-6, jointly receiving retrograde signals from DNT-2 to participate in the structural plasticity and neuronal survival of DA circuits [51,65]. Downstream of Toll-6, the pro-survival adapter dMyD88 and the pro-apoptotic adapter Wek-Sarm compete, with their relative abundance and activation status subject to spatiotemporal specificity that is dependent on cell type, developmental stage, and neural circuit (Fig. 2B). Additionally, during neuronal apoptosis, Spz-5 is processed and activated, whereupon it signals through Toll-6 in glial cells to regulate the expression of the engulfment receptor Draper through a dSarm-mediated transcriptional pathway [67]. Furthermore, broad Toll signaling, not limited to specific subtypes, has been reported to induce caspase-dependent apoptosis by activating the JNK pathway and promoting reactive oxygen species (ROS) production [68].

4. Toll Receptors in the Control of CNS Homeostasis and Behavior

4.1 The Role of Toll Receptors in the Sleep-Wake Cycle

Despite clear evidence that sleep is subject to homeostatic regulation, the underlying molecular and cellular mechanisms have long remained unclear [69]. In recent years, studies in *Drosophila* have identified astrocytes as key cells that sense sleep need through activity-dependent Ca^{2+} dynamics. Sleep deprivation or prolonged wakefulness significantly elevates intracellular Ca^{2+} levels in astrocytes, particularly in their fine processes. This elevation is not a passive correlate but rather an instructive signal. It is progressively amplified through a positive feedback loop involving the monoamine receptor TyrRII, eventually reaching a threshold that triggers the transcriptional upregulation and secretion of the Spätzle [52,53].

Spätzle serves as a secreted relay factor in this context, translating astrocytic sensing into neuronal output. Specifically, Spätzle acts on downstream sleep-promoting R5 neurons located in the ellipsoid body within the central complex of the *Drosophila* brain. Knockdown of Toll receptors in R5 neurons effectively suppresses their enhanced excitability following sleep deprivation and blocks the compensatory homeostatic increase in sleep [52,53]. Toll activity thus lies at the core of this neuro-glial signaling axis.

In addition to revealing a specific pathway governing sleep homeostasis, a study published by Blum et al. [52] has shifted the focus to the broader network of neuro-glial interactions. This raises questions regarding how non-canonical signaling downstream of Toll receptors specifically modulates the excitability of R5 neurons. Moreover, the differential responses of wake- versus sleep-promoting circuits to astrocytic Spätzle may be dictated by cell-type-specific complements of Toll receptors or downstream adaptors. It should be noted that Spätzle is recognized as a func-

tional analog of the mammalian pro-inflammatory cytokine interleukin-1 (IL-1), rather than a sequence homolog. Both *Drosophila* Spätzle and mammalian IL-1, in addition to their immune functions, can modulate sleep architecture within the CNS [70]. Although the role of Spätzle/IL-1 in sleep is evolutionarily conserved, the upstream mechanisms that initiate astrocytic Ca^{2+} signaling in response to sleep pressure exhibit marked differences. Notably, the initial Ca^{2+} influx in *Drosophila* depends on L-type voltage-gated calcium channels (Ca- α 1D), whereas in mammals, it primarily involves IP₃ receptor- and stromal interaction molecule 1 (STIM1)-mediated release from intracellular stores [71]. In both mammals and *Drosophila*, immune signals can be harnessed within the CNS to sense sleep pressure, highlighting a conserved neuro-immune mechanism by which Toll/IL-1 family signaling contributes to CNS homeostasis across evolution.

4.2 The Role of Toll Receptors in Alcohol Tolerance and Addiction

Drosophila possess a conserved reward system, making them an ideal model for interrogating the molecular and neural mechanisms underlying drug addiction and alcohol tolerance [72]. Indeed, ongoing work employing well-defined behavioral assays and genomic tools is progressively clarifying the basis for alcohol-related behaviors in this species [73]. In mammals, TLR4 was the first TLR to be linked to alcohol response [74], and the innate immune signaling Toll pathway in *Drosophila* was subsequently identified as a key regulator of alcohol tolerance. Whole-genome expression analyses revealed that ethanol exposure coordinately upregulates multiple innate immune signaling pathways, including the Toll and Imd pathways, and subsequent functional assays have further demonstrated that increasing Toll activity enhances ethanol resistance, whereas decreasing it increases sensitivity [54].

This Toll pathway-associated regulation of alcohol tolerance may involve interactions with shared neural circuits relevant to sleep, learning, and memory [75,76]. For instance, alcohol consumption disrupts sleep, and the Toll pathway is implicated in regulating both processes. Conversely, circadian rhythms modulate some, but not all, behavioral responses to alcohol exposure. The underlying mechanism likely operates at multiple levels, as ethanol exposure rapidly induces the expression of innate immune effector genes downstream of the Toll pathway, potentially representing a defensive response to chemical stressors. Notably, the activation of the Toll pathway appears to be part of a common transcriptional program through which *Drosophila* respond to various environmental chemical stressors (e.g., acetic acid, 2-phenylethanol) [77]. This suggests that the Toll pathway, through neuro-immune modulation, can mediate behavioral plasticity towards alcohol and other chemical stressors.

5. Context-Dependent Role Switching of Toll Receptors in Neuropathology

In addition to playing an instrumental role in brain development, *Drosophila* Toll receptors, when dysfunctional, also directly contribute to the progression of neurodegenerative processes through complex pathways. In pathological states such as infection, protein aggregation, or cellular stress, Toll receptor signaling output can shift from developmental guidance and survival support toward the activation of pro-apoptotic and inflammatory cascades. This functional transition reflects changes in ligand availability, adaptor protein recruitment, and downstream pathway engagement under disease-relevant conditions (Fig. 3).

5.1 Neuroinflammation, Immune Surveillance, and Pathogen Hijacking

Within the CNS, Toll receptors constitute a crucial innate immune barrier, initiating neuroinflammatory responses upon recognition of PAMPs to eliminate invaders and maintain tissue homeostasis. In fungal infections, cell wall components, particularly β -glucans, are sensed by upstream host recognition systems and further promote the activation of Toll signaling cascades. Toll-7, in particular, can directly sense viral glycoproteins and mediate antiviral autophagy through a process that also participates in clearing damaged organelles and abnormal protein aggregates [78]. However, this sophisticated immunosurveillance system has become a target for certain pathogens. Notably, neuroinvasive fungi can secrete specific effector proteins that “hijack” the host Toll pathway, thereby evading immune-mediated clearance and inducing CNS pathology [79]. This hijacking does not usually involve direct mimicry of Toll ligands; rather, it reshapes Toll pathway output through steps such as degradation, blockade, or inhibition of Spätzle processing, receptor activation, or downstream adaptor recruitment. For instance, the fungus *Metarhizium* secretes the effector ETS1, which directly targets and inhibits Spätzle activity, thereby disrupting Toll pathway activation at its source and facilitating successful fungal invasion of the CNS [80]. In addition, the effector protein Fkp1 targets and inhibits host cathepsin activity, thereby blocking the maturation of the danger-sensing protease Persephone (Psh) and ultimately suppressing Spätzle processing and Toll pathway activation [81] (Fig. 3).

In the CNS, such interference is particularly concerning given that Toll signaling is functionally coupled not only to antimicrobial defense but also conservatively involved in neuronal survival, glial responses, and the maintenance of neural homeostasis [82,83]. A previous study indicates that the Toll downstream effector peptide Baramicin A (BaraA) does not directly kill pathogens; instead, it acts in glial cells to protect neurons from toxins such as Destruxin A, enabling flies to recover from toxin-induced paralysis [84]. Therefore, pathogen-mediated suppression or misdirection of Toll signaling may shift the balance from protec-

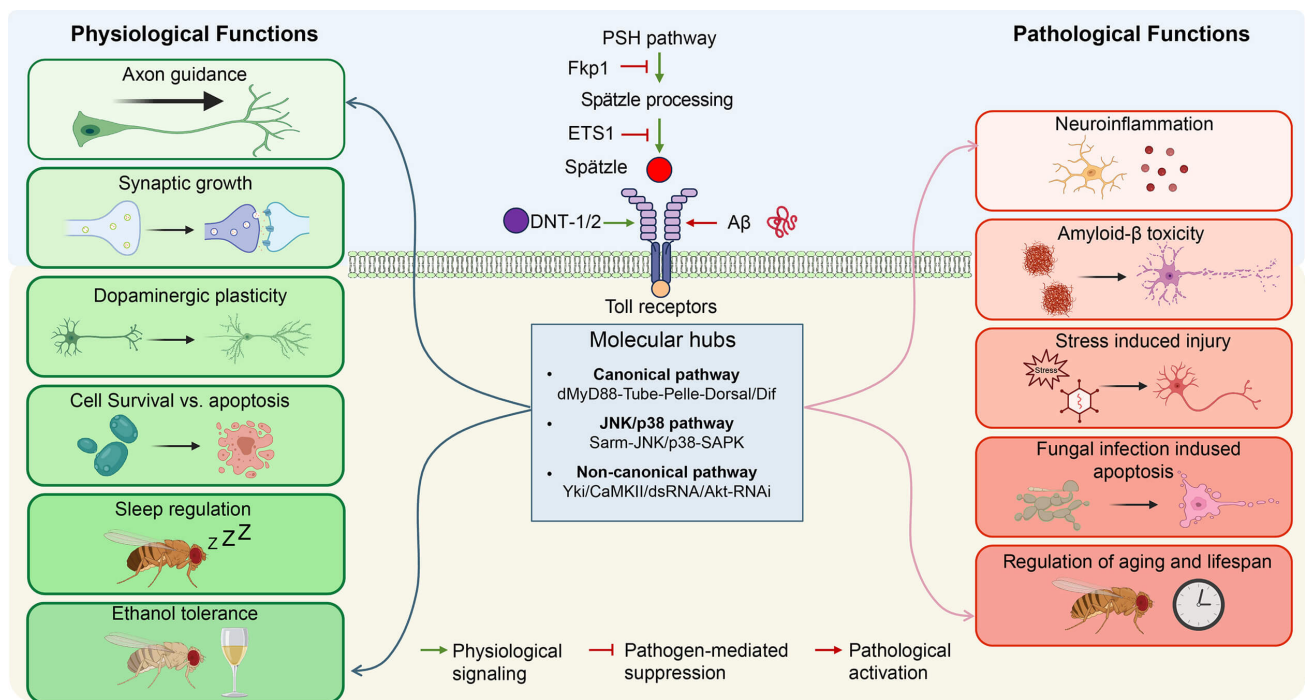


Fig. 3. Overview of physiological and pathological functions of Toll receptors in the *Drosophila* CNS. This figure illustrates the central molecular hubs through which Toll receptors mediate diverse physiological and pathological processes in the *Drosophila* central nervous system. Under physiological conditions, Toll receptors respond to ligands such as Spätzle (Spz) and *Drosophila* neurotrophins (DNT-1/DNT-2) to regulate key neural functions, including axon guidance, synaptic growth, the balance between cell survival and apoptosis, sleep homeostasis, ethanol tolerance, and dopaminergic circuit plasticity. These functions are mediated by adaptor proteins and downstream signaling pathways, as well as by cellular processes such as autophagy. Under pathological conditions, aberrant Toll signaling contributes to neuroinflammation, amyloid β ($A\beta$) toxicity, stress-induced injury, fungal infection-induced apoptosis, and the modulation of aging and lifespan. Drawing this figure was partly sourced from BioRender (<https://www.biorender.com>).

tive surveillance toward persistent infection, maladaptive neuroinflammation, or neurodegenerative damage. Such pathogenic manipulation underscores the role of Toll biology in the nervous system, such that the signaling that maintains CNS integrity can, when dysregulated or exploited, drive neural dysfunction.

5.2 The Role of Toll Receptors in Lifespan and Age-Associated Functional Decline

Specific activation of Toll/NF- κ B signaling in neuroendocrine insulin-producing cells and neuroblasts significantly shortens lifespan, whereas inhibiting this pathway extends lifespan and enhances resistance to lethal stress [85]. Notably, simultaneous inhibition of Toll signaling in both these cell types produces additive lifespan-extension effects, suggesting independent regulatory mechanisms exist. Toll-9 acts as a stress sensor in aging and neurodegeneration, with its expression being specifically upregulated in glial cells of the aged fly brain. While its loss does not affect normal lifespan, it impairs resistance to oxidative stress and exacerbates neurodegeneration in a Tauopathy model. These protective effects depend on the maintenance of p38 MAPK/JNK (SAPK) kinase signaling activity [30].

Functional experiments confirm that systemic knock-down of Toll receptors in adult flies extends lifespan, whereas constitutive activation of the pathway causes immune dysregulation and shortens lifespan [86]. This indicates that maintaining age-related immune homeostasis via the Toll pathway is an important evolutionary basis for lifespan determination. Dietary interventions exert lifespan-extending benefits by suppressing the Toll/Imd pathway. The life-extending effects of periodic protein restriction (PPR) and rambutan peel polyphenol extracts, for instance, both involve inhibition of the Toll signaling pathway [87,88]. PPR indirectly suppresses the pathway by reducing palmitic acid levels, while polyphenol extracts directly downregulate Toll/Imd pathway gene expression, ultimately extending the lifespan. Silibinin, extracted from milk thistle, can boost antioxidant capacity and prolong the lifespan of *Drosophila* through an effect achieved by inhibiting the Toll signaling pathway while upregulating the activity of antioxidant-related superoxide dismutase and catalase [89]. These findings provide evidence that the Toll pathway may be involved in an effective strategy for delaying aging through dietary regimens.

Notably, the age-associated activation of the Toll pathway extends from the CNS to peripheral organs. Recent studies of the *Drosophila* intestine indicate that the Toll pathway is one of the two most significantly upregulated innate immune pathways during aging, with the other being the Imd pathway [90]. In the gut of aged female flies, coordinated increases in gene expression across the entire Toll pathway are evident from microbial-sensing mediators to various proteases in the proteolytic processing cascade. This suggests that the disruption of intestinal immune homeostasis with age is partly due to the systemic activation of the Toll/Imd pathway. Research shows that the lack of endogenous substances, such as intestinal lipase Liph, accelerates gut aging and shortens lifespan by activating the Toll/Imd pathway [91]. This suggests that dietary interventions and medications may inhibit the overactive Toll/Imd pathway in the intestines, improving barrier function and stem cell homeostasis to extend lifespan. Recent studies have shown that Toll signaling plays a central role in the regeneration of intestinal stem cells, with its activation regulating their proliferation and differentiation, thus shaping the density of commensal bacteria [92]. During aging, dysregulation of the intestinal Toll pathway can disrupt epithelial homeostasis associated with microbiota dysbiosis [93]. These peripheral changes may further impact CNS function, constituting a novel mechanism of aging regulation at the level of the gut-brain axis.

5.3 The Role of Toll Receptors in Neurodegeneration

Activation of the innate immune system in the CNS has increasingly been recognized as a pivotal mechanism underlying the molecular pathogenesis of numerous neurodegenerative diseases [94]. In models of Huntington's disease mediated by expanded repeats (e.g., rCAG.rCUG₋₁₀₀), the toxicity of double-stranded RNA has been shown to depend on Toll signaling [95]. This RNA toxicity can disrupt multiple pathways, including innate immunity, and its pathogenicity can be alleviated by genetically suppressing the Toll pathway. In Alzheimer's disease (AD) models, ectopic expression of human A β 42 in the *Drosophila* eye induces severe cell death and tissue degeneration, and this neuropathological effect critically depends on the Toll signaling pathway, which in flies transduces signals through the downstream transcription factors Dorsal and Dif. Genetic evidence demonstrates that Toll loss-of-function mutations significantly suppress A β 42 toxicity, whereas pathway activation exacerbates the associated pathological phenotype [96]. In human cell models, A β (25–35) activates the homologous TLR4/NF- κ B and p38 MAPK/NF- κ B pathways, and this inflammatory response can be alleviated by the soluble epoxide hydrolase inhibitor 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU), which downregulates pro-inflammatory cytokines such as TNF- α and IL-1 β . This indicates that A β pathogenicity is not entirely autonomous and is instead ex-

cuted by hijacking the host's innate immune pathway. Interventional strategies targeting this pathway show therapeutic potential [97].

Following fungal infection, Toll receptors functionally transition to pathological effectors that contribute to excessive or sustained activation, leading to neuronal death in AD models. When Toll signaling becomes aberrantly or persistently activated in response to pathogen infection or other pathogen stimuli, it thus appears to precipitate an imbalance between pro-inflammatory and pro-apoptotic responses, thereby causing its normally protective activity to become destructive. In AD model flies, the fungal pathogen *Beauveria bassiana* activates the Toll-1/Wek/Sarm signaling axis, which operates independently of traditional immune responses, leading to neuronal apoptosis and subsequent brain cell loss [79]. This reveals another important route for Toll receptor-mediated neurotoxicity defined by a shift from pro-inflammatory to direct pro-apoptotic signaling. These findings provide evidence linking Toll pathway activation to neuroinflammation and neuronal damage in neurodegenerative processes [98].

6. Discussion and Perspectives

Over the past decade, several studies have firmly established that the role of Toll family members extends far beyond classical immunity, regulating neural development, neural circuit assembly, synaptic plasticity, and behavioral modulation [51,71,99]. These findings outline an intricate signaling network whose functions are deeply embedded in cellular processes within the CNS. Understanding the molecular switches that govern the transition between Toll receptor functional states is of paramount importance. The same receptor can promote neuronal survival or trigger apoptosis depending on the cellular context, developmental stage, or pathological state. This “switch” is likely orchestrated at multiple levels, such as proteolytic processing of DNT ligands, competitive recruitment of downstream adaptor proteins, and combinatorial assembly of receptor complexes. Admittedly, definitive evidence for direct physical interactions—whether in cis or in trans—between two Toll family receptors remains lacking. This is largely attributable to the considerable technical challenges associated with applying recombinant protein binding assays, cell-surface interaction studies, proximity ligation assays, Förster resonance energy transfer, cryo-electron microscopy, and crystallography in the *Drosophila* model, despite its well-established advantages with respect to genetic interaction, functional synergy, and phenotypic analysis. In contrast, compelling experimental evidence supports both the homo- and heterodimerization of mammalian TLRs, although these interactions remain confined to ligand-induced dimerization on the same cell membrane.

The CNS-related functions of Toll receptor subtypes remain to be elucidated. The sex-specific expression of Toll-3 and Toll-4 suggests potential roles in dimorphic neu-

ral development or male-specific behaviors. The expression of Toll-9, the structurally most ancestral family member, is induced in glial cells in response to stress, and its endogenous ligand and precise signaling pathways remain unknown. Furthermore, emerging evidence from single-cell analyses indicates that proper Toll receptor function may depend not only on timely activation but also on their programmed silencing during specific developmental windows. For instance, persistent Toll-8 expression disrupts salivary gland morphogenesis, hinting at analogous developmental constraints in the nervous system [100].

Translating these insights to mammals requires confronting a fundamental divergence: *Drosophila* Tolls often function as guidance or adhesion molecules during neural development, whereas mammalian TLRs primarily regulate immune surveillance and microglial plasticity within the CNS. The ability to genetically target specific neuronal populations in *Drosophila* through intersectional strategies [101,102,103] opens the door for dissecting the roles of Toll receptors in glial–neuronal interactions in mammals. Nevertheless, certain downstream signaling modules appear to be conserved across species. For example, the Toll/TLR-Sarm axis mediates developmental axon degeneration in mammals and executes pro-apoptotic signaling in *Drosophila* neurons. This suggests that while the receptors themselves have undergone functional specialization, their core effector pathways may still represent conserved functional targets. Identifying specific Toll subtype(s) and their downstream signal transduction pathways will thus offer greater insight into fundamental principles of neuron–glia communication.

Finally, adopting a systemic, cross organ perspective will broaden our understanding of the Toll protein family. Recent studies have begun to reveal the functional integration of the immune and sensory systems at the molecular level. For example, odorant-binding proteins have been found to interact with Toll-like receptors, thereby regulating antimicrobial responses and intestinal microbial homeostasis [104]. Investigating how hyperactive Toll signaling in peripheral organs, such as the gut, influences systemic aging processes and brain health is essential for understanding the organism-wide mechanisms by which dietary or pharmacological interventions delay aging.

7. Conclusions

This review provides comprehensive evidence that the *Drosophila* Toll receptor family plays diverse roles in the CNS that extend far beyond canonical immunity. The *Drosophila* model clearly reveals the significant functional expansion of the TLR family, from immune recognition to the regulation of neural functions. These receptors are involved in guiding neural development and neural circuit assembly, as well as contributing to behavioral regulation and brain homeostasis. Toll receptor functions exhibit a high degree of context-dependency such that the receptor can ex-

ert strikingly diverse effects. In various neuropathological models, including Alzheimer's disease, stress-induced injury, and fungal infections, the aberrant or sustained activation of Toll signaling pathways is a key driver of neurodegenerative processes. Future research that focuses on establishing a nuanced paradigm for investigating the intrinsic pathways underlying Toll functional state transitions will be beneficial for understanding the maintenance of nervous system homeostasis and the pathogenesis of related diseases.

Abbreviations

TLRs, Toll-like receptors; CNS, central nervous system; DNTs, *Drosophila* neurotrophins; PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; LRR, leucine-rich repeat; TIR, Toll/Interleukin-1 receptor; Spz, Spätzle; Ca²⁺, calcium; NMJ, neuromuscular junction; SOG, sub-oesophageal ganglion; PNs, projection neurons; ORNs, olfactory receptor neurons; SAPK, stress-activated protein kinase; PPR, periodic protein restriction; TPPU, 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea; AD, Alzheimer's disease.

Availability of Data and Materials

No experimental datasets were generated in this study. Sequence data used for bioinformatic analyses were obtained from publicly available databases.

Author Contributions

Design and conception, HRM; Literature review, ZYM, JHX, XLY, XKW, and QPG; Table and figures preparation, ZYM, HRM, JHX, XKW; Writing (original draft), ZYM, JHX, XKW, and QPG; Review and editing, ZYM, JHX, XLY, and HRM; Supervision, HRM; Funding acquisition, HRM. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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