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Review

Drosophila melanogaster as a model to understand the mechanisms of infection mediated neuroinflammation in neurodegenerative diseases

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Abstract

The innate immune system primarily gets triggered by microbe infiltration, injury, stress, aging, and brain disorders. The hyperactivation of the innate immune system and neuroinflammatory reactions contributes to chronic age-related neurodegeneration. The mechanism for activation of the immune pathway is conserved between *Drosophila melanogaster (D. melanogaster)* and human being. Thus, *D. melanogaster* can serve as a model organism to decipher the cellular and molecular mechanism between infection and neurodegenerative diseases. In *D. melanogaster*, prolonged protective, excessive neuroinflammatory responses in the brain lead to neurodegeneration through antimicrobial peptides mediated neurotoxicity. The prolonged inflammation in the microglial cells helps in the progression of neurodegenerative disease. Therefore, the connection between inflammatory mechanisms in the brain and neurodegeneration pathogenesis in *D. melanogaster* is systematically reviewed.

Keywords: Neuroinflammation; Neurodegeneration; *Drosophila melanogaster*; Infection; Microglia; Astrocytes

1. Introduction

Neurodegeneration is a sequel of the synaptic transmission failure and death of neuronal cells in the brain. Neurodegeneration is seen among patients suffering from neurodegenerative disorders and older adults. During neurodegeneration, autoinflammation occurs, and such a condition is referred to as "inflammaging". Inflammation protects the host from microbe infection/injury by activating microglia and astrocytes in the central nervous system (CNS) [1]. Chronic inflammation alters tissue homeostasis and may culminate in neurotoxicity [2]. An infection in the CNS can also stimulate the local immune response by elevating the cytokine level. Such infection often results in meningitis [3], encephalitis [4], Alzheimer's disease (AD) [5] and other neurological disorders.

Drosophila melanogaster (*D. melanogaster)* shares striking similarities with vertebrates in the context of neural proliferation and brain circuit formation [6]. Therefore, *D. melanogaster* is widely used to decipher the pathways involved in microbes and parasite infection [7–9]. The molecules and signaling pathways involved in *D. melanogaster* and mammalian innate immune response are evolutionarily conserved [10]. Like mammalian systems, cytokine dysregulation and neurodegeneration are also observed in *D. melanogaster* to respond to microbes' infection, tissue injury, and prolonged autoinflammatory response.

2. Learning infection and neurodegeneration in *D. melanogaster*

D. melanogaster is the widely used model organism to explore genetics, metabolism, and physiology. The decades of research in fly genetic have unveiled various metabolic and physiological pathways conserved with higher phylum, including humans. The adaptability, cost-effective rearing, short developmental cycle, well-characterized genomic organization, and easy access to manipulation have endorsed *D. melanogaster* as a principal model for groundbreaking discoveries. In addition, *D. melanogaster* has the advantage of sharing approximately 75% of the disease-causing genes and their function with humans [11].

Host-pathogen interaction suggests conserved innate immune function across species [12]. Vertebrates possess adaptive immune responses, which overshadow innate immune response and thus pose a significant drawback of using a vertebrate model for innate immune response studies. Since *D. melanogaster* does not have adaptive immunity, it is more likely used to decipher the mechanism of action of innate immunity [12]. Although humans are highly evolved organisms, they still share homology with *D. melanogaster* to produce antimicrobial peptides (AMPs), epithelial barriers, and phagocytosis, which are used as defense mechanisms against pathogens. In *D. melanogaster*, the epidermis, gut, and trachea serve as the first barrier to invading pathogens. Fly hemolymph act as the second line of defense by trapping the pathogens with the protein filaments of the clotting factors [13]. The other organs of *D. melanogaster* involved in the immune response are the fat body, differ-

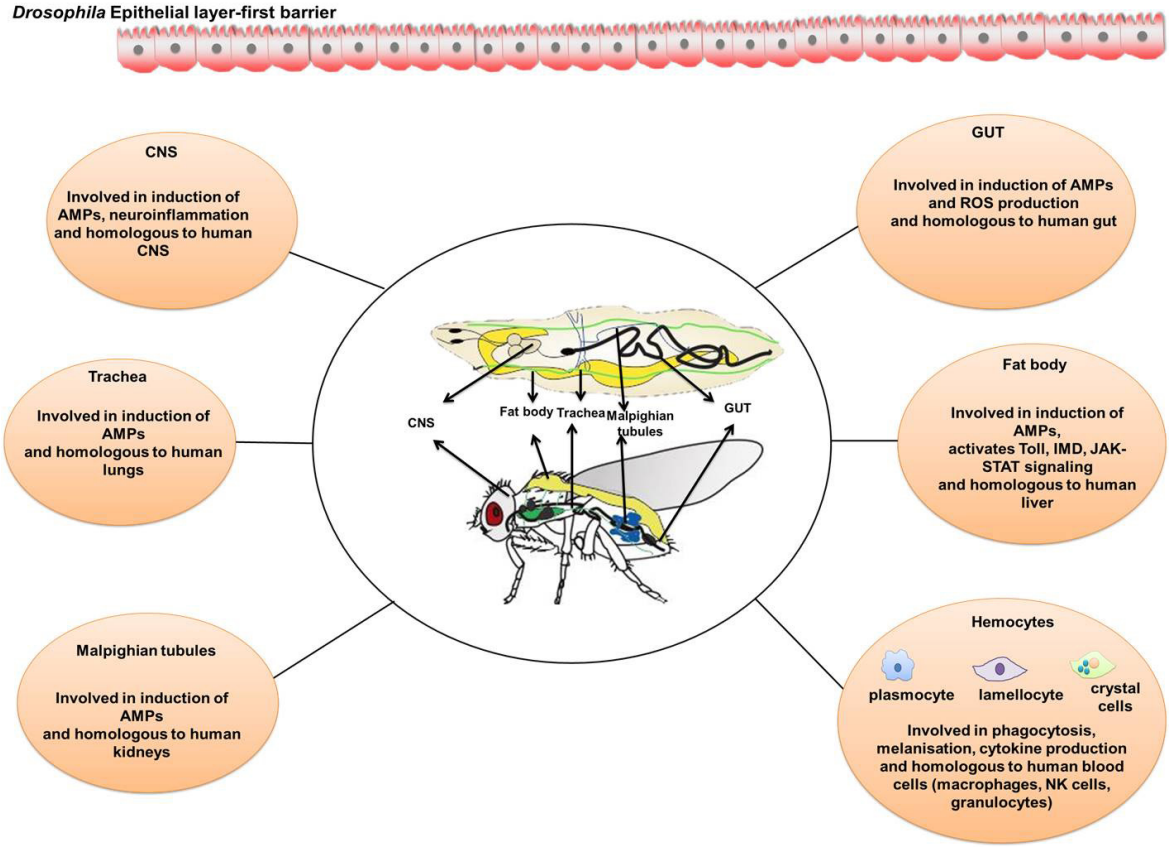

Fig. 1. *Drosophila* organs that are involved in the immune response. The organs of fly, which play a vital role in activating the molecules and signalling of innate immune response, have striking functional similarities with the mammals. The fly CNS, gut, trachea, fat body, malpighian tube and hemocytes mimic the human counterparts and actively participate in the triggering immune pathways, induction of AMPs and ROS, melanisation, production of cytokines and phagocytosis. The image was redrawn from Buchon *et al.* [14] review paper.

ent circulating hemocytes, and malpighian tubules. The organs involved in the *D. melanogaster* immune response are graphically represented in Fig. 1 (Ref. [14]).

D. melanogaster has a multi-layered defense mechanism categorized into (a) systemic immune response-release of NF-$\kappa\beta$, Toll and immune deficiency (IMD) pathways induced AMPs, in the fly fat body (homolog of the mammalian liver) into the hemolymph, (b) an enzymatic response—produce melanization near wound site and (c) cellular response-hemocytes mediated engulfment of the pathogen [15]. AMPs and reactive oxygen species (ROS) are also capable of stimulating the immune response [7,16]. The pathogenic agents trigger the hemocyte differentiation into plasmocytes, crystal cells, and lamellocytes involved in the phagocytosis of pathogens. The production of melanin kills the microorganism and encapsulates the larger parasite [17]. The hemocytes having phagocytic activity originate from the lymph gland's progenitor cells, a specialized hematopoietic organ in a fly. Thus the lymph gland of *D. melanogaster* is the homolog of the bone marrow of humans [18,19]. In *D. melanogaster*, hematopoiesis is also regulated by ROS. In addition, *D. melanogaster* and humans also share a similarity in the signaling pathway that participates in the blood cell differentiation [20].

In various studies, *D. melanogaster* is modeled to understand the immune activation by bacteria, fungi, parasites, and viruses [8,9,21,22]. *D. melanogaster* Toll receptor that can evoke the immune response in fly has homolog named Toll-like receptors in vertebrates. Also, *D. melanogaster*'s innate immune system targets different classes of molecules present on the surface of the different pathogen. For example, AMPs like drosomycin, defensin, and drosocin respond to fungi, Gram-positive and Gram-negative bacteria, respectively [7]. The mechanism of action of multiple signaling pathways such as JAK/STAT and AMPs sequence is evolutionarily conserved between humans and *D. melanogaster* [23]. In fruit flies, stimulation of signaling cascade by pathogenic invasion leads to activation of NF-$\kappa\beta$ transcription factors Dif (belong to *toll* pathway) and Dorsal homolog and Relish (belonging to *Imd* pathway) leads to the release of AMPs from the fat body [7]. In addition to bacterial or fungal infection, *Drosophila* is also an excellent model for understanding the mechanism of viral infection [24].

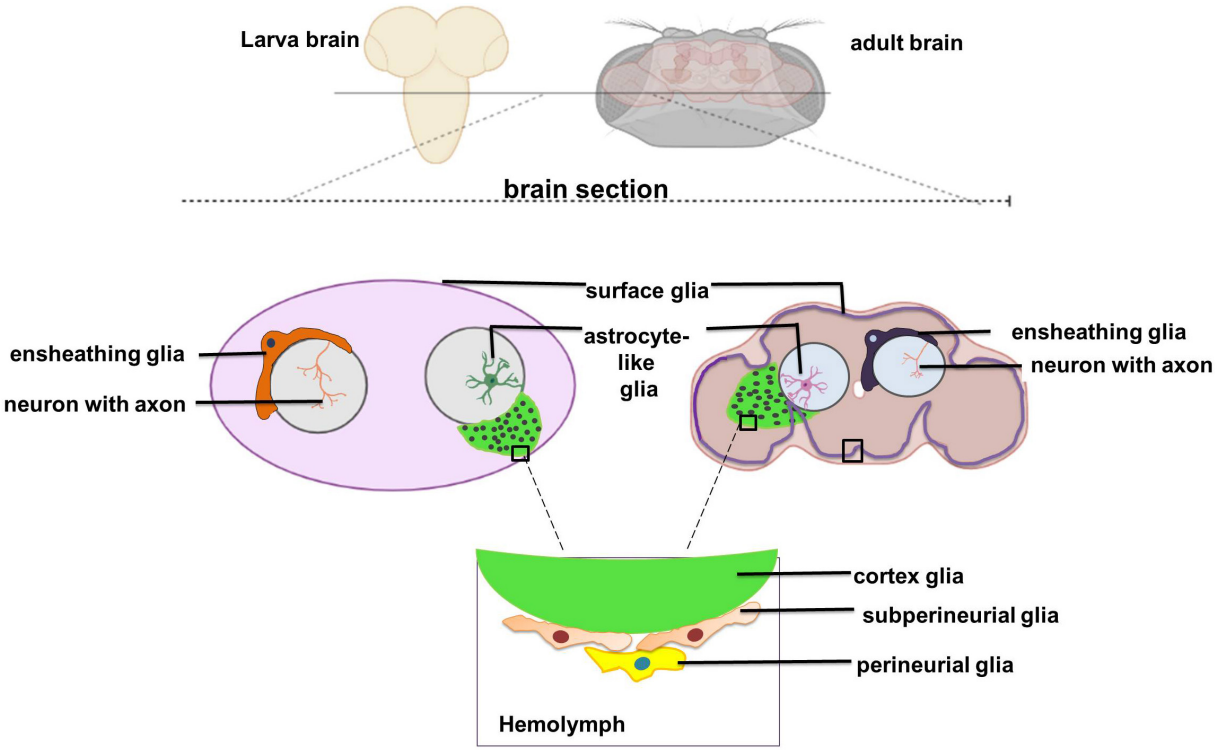

Fig. 2. *Drosophila* brain section showcasing the glia and subtypes. Fly CNS comprised of variety of glia. The surface glia, cortex glia, perineurial and sub-perineurial found in fly system are homologs of mammalian pericytes. Astrocyte-like cells and ensheathing glia and reticular glia display high degree conservation with mammalian astrocytes and microglia cells respectively. Drosophila glia cells display morphological and functional similarities with the mammalian system. The role of glia cells in neuroinflammation between fly and mammal is highly conserved. The image was redrawn from https://coutinhobuddlab.com/about-us/.

It has been reported that in humans, any breakdown in the innate immune system leads to several diseases, including neurological disorders [25–27]. In the mammalian system, a prolonged inflammatory response against the infection not only activates the local immune cells like microglia, and macroglia (astrocytes, pericytes and oligo-dendrocytes) [28] but also leads to infiltration of the peripheral immune cells into CNS, which results in cell/neuronal death and ultimately may result in neurodegeneration and such inflammation that occurs in response to foreign particles in the CNS is referred to as neuroinflammation.

Activated innate immune system and neuroinflammation play a vital role in the pathogenesis of neurodegeneration in mammals [29]. Besides dissimilarity between fly and mammalian brain anatomy, some crucial similarities between both structures still persists [30]. Fly CNS is formed primarily by the fusion of four ganglia namely, the sub esophageal ganglion, the protocerebrum, the deutocerebrum, and the tritocerebrum [31]. Protocerebrum, the largest ganglion covers majority of the adult fly brain and is analogous to the cerebrum of the mammals. Mushroom body, found in fly brain is associated with learning, olfactory discrimination, processing sensory inputs from olfactory and antennae lobe. This mushroom body is analogous to the mammalian hippocampus [32].

The fly glial cells are evolutionary and display some degree of morphological and functional parallelism with vertebrate microglia. *Drosophila* CNS does not possess oligodendrocytes but have lower proportion (10–20%) of glial cells that have functional similarity with the microglial and astroglial cells of vertebrate CNS [28,33]. *Drosophila*, consist of vertebrate glial like cells and subtypes such as (i) surface, perineural, and cortex glia (Pericyte-like cells) (ii) astrocytes like glia (iii) ensheathing glia and reticular glia (microglial cells). The surface, perineural, and cortex glia form a barrier, analogous to vertebrate blood-brain-barrier (BBB), separating fly CNS from the hemolymph [34]. Fly astroglia are homologous to the mammalian astrocytes and perform variety of tasks such as metabolic, maintenance, transporting, development of dopaminergic axons, providing neurotrophic aid to fly eye and neuronal survival [35–37]. Microglia residing in mammalian CNS has a counterpart in *Drosophila*, namely ensheathing glia, performed a wide array of function ranging from pathogen clearance, neuronal phagocytosis, and leukocyte recruitment into the brain [38,39]. However, other studies have defined some microglia in fly perform neurotropic and neuroprotective role similar to astrocytes and thus named as reticular glia [40,41] (Fig. 2). Thus, both ensheathing glia and reticular glia in *D. melanogaster* CNS are considered as homologs on

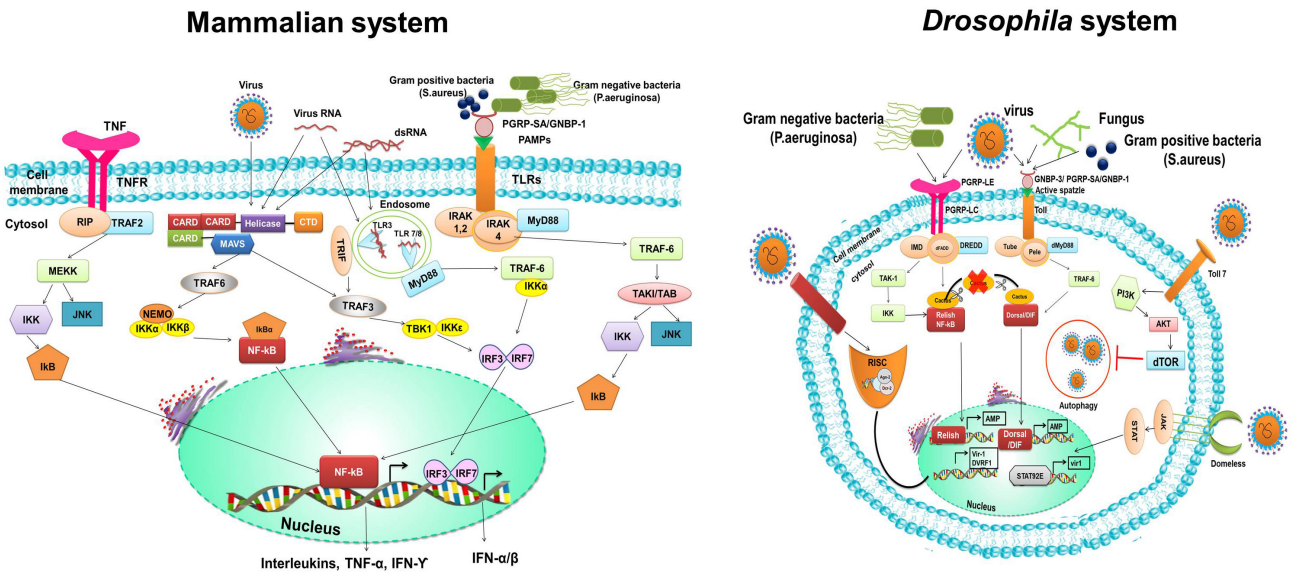

Fig. 3. Immune response upon infection. Activation of innate immune signalling such as Toll, IMD pathway and toll-7 and domeless elicited by bacterial and viral infection in *Drosophila* share a high degree homology with the mammalian innate immune signalling. In invertebrate, the molecules involve in innate immune signalling and mechanisms of activation of these molecules exhibit evolutionary conservation with the vertebrate except for some difference in downstream pathway of immune response. The image redrawn from Valanne *et al*. [55] paper.

mammalian microglial cells. Microglial phenotype polarization is witnessed in the vertebrate CNS as a vital feature of innate immune system during both healthy and diseased condition. Microglia exhibits three morphological and two polarization phenotypes depending on the neurons, neighboring environment and other microglia. They were categorized as: (i) M1 microglia- round in structure and found in diseased adult CNS (ii) M2 microglia- extended process and highly ramified in morphology usually found in the healthy vertebrate CNS along neural tract and near neuropil and synapses respectively [42–44]. *Drosophila* also displays microglial polarization and morphologies similar to the vertebrate microglial system. Ensheathing glia are morphologically flattened cell bodies with small processes that showed striking resemblance to mammalian M1 microglia. Similarly, reticular glias are characterized by longer, ramified extensions, structurally mimicking mammalian M2 microglia in healthy CNS [38,45].

D. melanogaster having many striking similarities with the human immune response and glia cells, thus can be used to elucidate the host-pathogen interaction, mechanism of defense/inflammation, and also to establish a connection between the chronic infections mediated neurodegenerative disease onset/progression.

3. Infection induced immunological response in *D. melanogaster*

In mammals, microbial invasion is first defended by the body's innate immune system. It serves as the first line of defense, which later activates the adaptive immunity—the second line of defense for long-term protection against pathogens [46]. Immune system activation is orchestrated by the initiation of a critical process called inflammation. Inflammation-induced by infection or injury later stimulates the production of various immune cell types and cytokines [1]. Inflammation for a short period protects the body against the infection by eradicating the pathogens, but chronic inflammatory responses have detrimental effects such as tissue/neuron cell damage. The brain was previously considered an immune-privileged organ. Still, it is now known that prolonged inflammatory response in the CNS may lead to various neurological disorders and significant mortality globally [2].

In *D. melanogaster*, foreign invaders such as bacteria, fungi, and viruses can cause infection-mediated immune system activation. *Drosophila* immune proteins that can recognize the bacterial components are generally called pattern recognition receptors (PRRs) which are broadly classified into two families: (i) the peptidoglycan recognition proteins (PGRPs) and (ii) Gram-negative binding proteins (GNBPs) [47]. Thirteen PGRPs have been identified in the fruit fly, out of which only three PGRPs, namely PGRP-SA, PGRP-LC, and PGRP-LE, could recognize the invaders and increase immune sensitivity [47]. Out of three PRRs belonging to the GNBP family in *D. melanogaster*, only GNBP1 can recognize the bacterial component (LPS) and fungal cell component (b-1, 3-glucan) when challenged by Gram-negative bacteria and fungus [48]. The Gram-negative and Gram-positive bacterial infection activates the Toll pathway and IMD pathway, respectively (Fig. 3). The

binding of Gram-positive bacteria or fungus initiates Toll receptor dimerization which then recruits heterotrimeric complexes comprising Myd88 protein, Pelle, and Tube [49]. The heterotrimeric complexes mediated activation of kinases (interleukin-1 receptor (IL-1R) associated kinase (IRAK)) leads to hydrolysis of the Cactus which in turn initiates the nuclear translocation of Dorsal and Dorsal related immunity factor (Dif) [50]. However, both Dorsal/Dif play a crucial role in immune response in fruit flies by activating the expression of drosomycin [50]. A *Drosophila dTRAF2* (homolog of mammalian TNF-receptor-associated factor-6 (TRAF-6) protein) interacts with Pelle to stimulate drosomycin expression [51]. Toll is also activated in *D. melanogaster* by cytokine-like protein Spaetzle (spz) [52]. IMD signaling, provoked by Gram-negative bacteria, activates the member of NF-$\kappa\beta$/Rel family named as Relish. *D. melanogaster* infected with Gram-negative bacteria, activate IMD pathway, which then stimulates the large adaptor complex comprising Fas-associated death domain (dFADD) [53], and death-related ced-3/NEDD2-like protein (DREDD) [54]. The components of the adaptor complex interact with the growth factor-β (TGF-β)-activated protein kinase 1 (dTAK1 80), which simultaneously leads to the activation of Relish by degrading cactus and finally produces AMPs such as Diptericin B (DptB). Fungus is recognized by Gram-negative binding protein-3 (GNBP-3), which then activates the Toll pathway (Fig. 3). Besides Toll and IMD pathways, viruses can activate JAK/STAT, Toll 7, RNAi and autophagy, in the fly host, leading to the release of anti-virulence factors such as Vir-1 (Fig. 3, Ref. [55]).

It is well established in mammals that microbe invasion could lead to acute or prolonged inflammation in the CNS, which may later culminate in significant degeneration of specific neuronal population associated with a plethora of neurological disorders such as meningitis [3] encephalitis [56], AD [57], and PD which is presented in Table 1 (Ref. [25,58–66]). Moreover, an infection caused by bacteria or the neurotrophic virus (such as the Zika virus) in the brain may lead to the onset of severe brain disorders such as schizophrenia and depression [67]. These neurotropic viruses' replication elicits the expression of the Interferon (IFN) regulatory factors (IRFs), kappa-light-chain-enhancer nuclear factor (formed by B cell activation signaling), and the effector molecules downstream to the signaling in CNS. This immune activation causes infiltration of the microglia and astrocytes into the CNS, which recognizes the pathogen by PRRs and induces neuroinflammation [68]. If neuroinflammation continued for an extended period, it might result in neurotoxicity and neurological pathogenesis. Infection in *D. melanogaster* triggers a cytokine-based regulatory signal. This inflammatory response includes the production of AMPs, recruitment of hemocytes, and release of cytokines and chemokines by activated immune cells [69,70]. These inflammatory events profoundly affect the tissue involved in the inflammatory response and neural tissues, and the animal as a whole [71]. Thus, *D. melanogaster* serves as an excellent model organism to delineate the role of innate immune response individually (in the absence of adaptive immune response) and inflammation in the development of neurodegenerative diseases.

4. The interrelation of neuroinflammation and neurodegeneration

The prolonged structural and functional loss of the neurons is evident when neurodegeneration occurs in CNS. The neurodegeneration culminate in functional and mental impairments in CNS [72]. The sources of neurodegeneration are not well understood yet. However, one of such sources that increase the probability of neurodegeneration is aging [73]. The neurodegeneration in the CNS could lead to the incidence of neurodegenerative diseases such as AD, Multiple sclerosis (MS), PD, Amyotrophic lateral sclerosis (ALS), Polyglutamine Diseases, Ataxia Telangiectasia, Traumatic (Brain) Injury, Tauopathies, Frontotemporal Dementia, and Progressive Supranuclear Palsy. The characteristic features of these neurodegenerative diseases are altered and unfolded protein which leads to the formation and aggregation of β-structures. These β-structures are toxic to neuronal cells and can damage different parts of the brain. The improperly folded tau, α-synuclein, and polyglutamine protein accumulation in the neuron trigger the pathological conditions of AD and tauopathies, PD, and polyglutamine diseases, respectively. This inappropriate protein folding is not only specific to aging-mediated neurodegenerative disorders but also occurs during infection-induced inflammation-mediated neurodegeneration [74] (Fig. 4, Ref. [75]).

4.1 Alzheimer's disease

AD is a neuropsychiatric ailment; found most frequently in people above 65 years, has affected millions of people worldwide. The World Health Organization (WHO) [76] has described the disease as a cognitive impairment that gradually affects behavior, mood, memory, and learning [77,78]. Neurofibrillary tangles (NFTs) are derived from the paired helical filaments (PHFs), which are the hyperphosphorylated forms of the axonal protein "tau". Proteases cleave the senile plaques (SPs), which are derivatives of the amyloid precursor protein (AβPP) to form Aβ protein. The intracellular (NFTs) and β-amyloid (Aβ) peptide oligomer deposition are evident in AD. The aggregation and spreading of these oligomeric structures to the extracellular environment and all over the brain can cause synaptic toxicity and neuronal death [79,80]. It is also evident that the NFTs and Aβ peptide accumulation increases with age. The aggregated Aβ and tau protein may leak from the brain to the external environment, such as cerebrospinal fluid (CSF) [81]. However, extensive research on neurodegeneration has explained several factors other than aging, which can

Table 1. Neurodegeneration in infectious disorders in mammals.

Infectious agent	Neurodegeneration	Immune response	Literature references
Japanese B Encephalitis	Neuronal death	Increase in pro-inflammatory mediators, iNOS, COX-2, IL-6, IL-1β, TNF-α, and CCL2	[58]
Bacteroides fragilis (B. fragilis)	Sporadic Alzheimer's disease (AD) in the brain	Generation of the inflammatory transcription factor NF-$\kappa\beta$ (p50/p65 complex)	[25]
Chlamydia pneumoniae	Alzheimer's	Enhanced cytokine levels	[59,60]
Borrelia burgdorferi (*B. burgdorferi*)	Alzheimer's, Parkinson's disease	Higher α-Syn and IL-1β and IL-6 expression Increased beta-amyloid protein (Aβ) levels and inflammatory cytokines (i.e., interferon-γ, tumor necrosis factor α, interleukin-1β, and interleukin-6)	[60,61]
Helicobacter pylori (*H. pylori*)	Alzheimer's, Parkinson's disease	Higher α-Syn and IL-1β and IL-6 expression Increased beta-amyloid protein (Aβ) levels and inflammatory cytokines (i.e., interferon-γ, tumor necrosis factor α, interleukin-1β, and interleukin-6)	[60,61]
Coronavirus	Neuro invasion, cerebral edema, neuronal degeneration, encephalitis, meningoencephalitis, acute disseminated encephalomyelitis, encephalopathy, and stroke	Excessive production of cytokines such as interleukin (IL)-1β, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-4, and IL-10	[62]
Human herpesvirus 6	Meningoencephalitis and leucoencephalitis, death of neurons undergoing neuronophagia	Lymphocytes and microglia activation	[63]
Epstein-Barr virus	Encephalopathy and acute quadriparesis with diminished reflexes, horn cell degeneration, and edema, the paralysis with diminished reflexes	EBV antibodies, IL-10 production	[64]
Bacterial meningitis	Neuronal loss and death, apoptosis	TLR induced microglia activation	[65]
Human immunodeficiency viruses (HIV)	Dementia	Activation of macrophages and migration into CNS	[66]

trigger the accumulation of NFTs and Aβ. One of such neuromodulation, induced by inflammation, also results in the development and progression of AD.

In mammals, the microglia present in the brain is the key factor that links neuroinflammation and neurodegeneration. Microglia can be activated by several factors such as infectious agents (bacteria, viruses, fungi), advanced glycation end products (AGE) receptors, Aβ and tau protein, and neurotoxins that include antibodies, cytokines, iron-rich-complement factors, and chemokines (such as toll-like receptors TLRs) [82]. These are considered as danger signals that may pose a threat to CNS homeostasis. In general, the activated microglia serves as the first line of defense that releases inflammatory molecules to combat infection and toxins, regulates astrocytes' activation, and engulfs the tau and Aβ by phagocytosis [83]. It plays a major neuroprotective role in the inflammatory processes, which involves activation of astrocytes and release of signaling molecules, mainly neurotoxic factors like (superoxide radicals (O_2^-), nitric oxide (NO) and ROS), growth factors, major histocompatibility complex II (MHC-II) molecular pattern recognition receptors (PPRs), tumor necrosis factor-alpha (TNF-α) and cytokines (interleukin (IL) 1 beta (IL-1β), IL-6, IL-12 and interferon (IFN) gamma (IFN-γ)) [84,85]. These signaling then possibly change the blood-brain barrier (BBB) permeability and generate various lesions in the brain and CNS [86]. The activated microglia and the neuro-immunomodulatory signaling can switch the role from neuroprotective to neurotoxic and pose a risk of development and progression of AD [87].

The oligomer Aβ formed in mammals is possibly phagocytosed by the activated microglia, which promotes the NLRP3 inflammasome activation, triggering microglia to release the cytokine interleukin-1β (IL-1β). The phagocytosed Aβ then activates the death of the lysosomes, followed by production of the cathepsin B from it. The released cathepsin B now activates caspase-1, which further triggers the production of IL-1β from the pro-IL-1β. Subsequently, more microglia was activated by the IL-1β maturation [88]. Reports have proposed that the lower the caspase-1 and IL-1 IL-1β activation in the brain, the higher the Aβ phagocytosis, which subsequently reduces the probability of spatial memory loss and AD related deficiencies [89]. However, a study on the murine model (APP/PS1) of AD

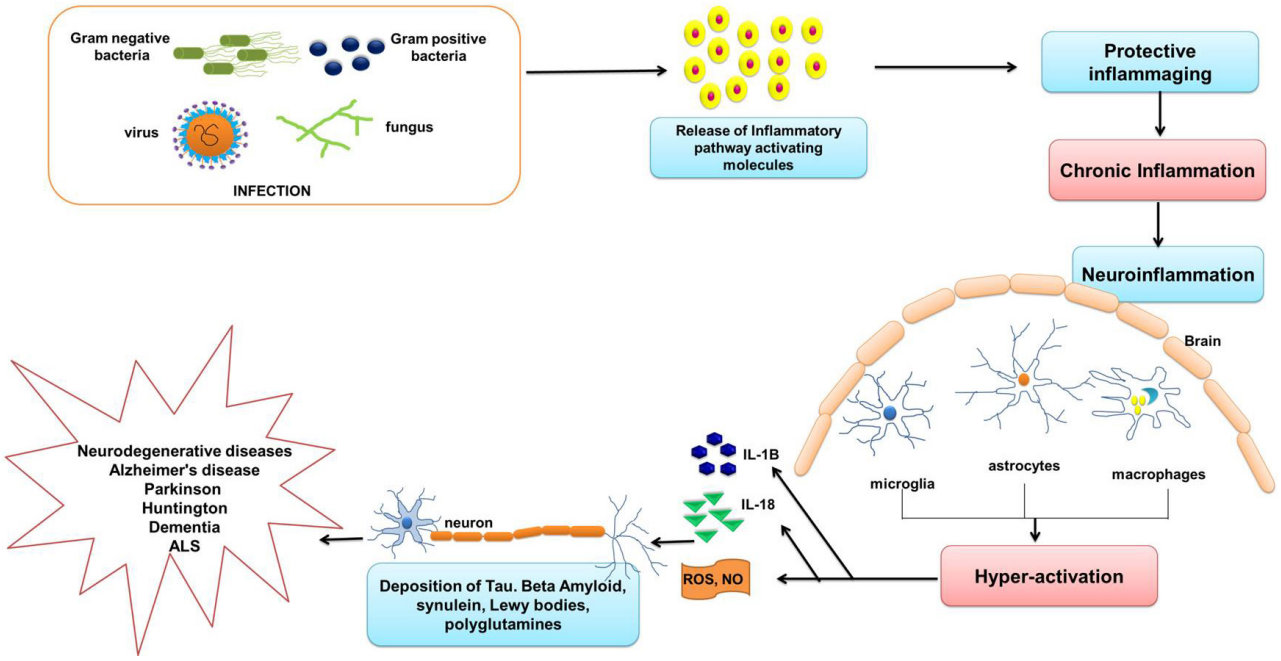

Fig. 4. Infection mediated neuroinflammation and neurodegeneration. Invasion of pathogens is a danger signal to the resting microglia. Pathogens activate the immune signalling and lead to the release of the molecules which further activates the macrophages and glia cells in the CNS. In this model, prolonged activation of the macrophages and glia cells constantly produces cytotoxic factors such as proinflammatory cytokines and ROS. These further promote damage to neurons (mainly motor neurons, hippocampal neurons, and dopaminergic) which culminate in development of neurodegenerative disorders such as AD, ALS and PD, etc. The image was redrawn from Chen *et al*. [75].

deficient in NLRP3 inflammasome has reported a decline in the Aβ deposition suggesting the importance of NLRP3 in AD onset and progression [90].

It has been observed that the patients with AD have an upregulated IL-1-NF-$\kappa\beta$ immune signaling, but the mechanism of disease is still poorly understood [91]. Research on the mammalian model suggested that glial cell receptors can identify different forms of Aβ. They further activate different pathways; for instance, the advanced glycation end products (AGES) or CD36 receptors could recognize fibrillar Aβ to sensitize Toll-like receptors (TLRs). In contrast, the CD36 receptor recognizes soluble (nonfibrillar) Aβ and triggers its phagocytosis by microglia [92]. Similarly, nonfibrillar Aβ matured from soluble Aβ leads to the formation of NOD-like receptor protein 3 (NLRP3) inflammasome, promoting IL-1 IL-1β [73], which later may facilitate the onset of AD.

On the other hand, in *D. melanogaster*, the Aβ deposits are recognized by the glial engulfment receptor called Draper, which activates the Draper/STAT92E/JNK signaling pathway and downstream protein degradation lysosomal-related pathways to phagocytose Aβ deposits [93]. The AD flies deficient with the IMD pathway are marked with the Draper activated glial cells accumulation around the β-amyloid plaques [94]. Earlier reports on *D. melanogaster* suggested that loss of function of Draper intensifies the ç42-induced toxicity, which then leads to impaired locomotion and a short life span. At the same time, overexpression of Draper reduces Aβ42-induced toxicity and moderately improves fly longevity and defective locomotion [93]. Mammalian TNF-R pathway, homolog Imd pathway play a neuroprotective role in *D. melanogaster* by activating the NF-$\kappa\beta$ signaling, which then induces the microglial-mediated engulfment of extracellular Aβ pools [94]. A study revealed that mutation in the transmembrane receptor '*D. melanogaster* Toll (Tl) gene', a homolog of the mammalian IL-1 receptor, reduces the Aβ42 neuropathological activity in *D. melanogaster,* but the gain of function of the toll receptor enhances the Aβ42 neurotoxicity activity. Thus, when the Tl- NF-$\kappa\beta$ pathway is suppressed genetically, it causes a reduction in the neuropathological activity of Aβ42 [91].

Previous reports suggest that deposits of Aβ in mammal activates and recruits the microglia which in turn phagocytoses them and releases pro-inflammatory cytokines but mechanism after the phagocytosis of Aβ still not known [95], so *D. melanogaster* can be used to decode inflammation-mediated AD pathogenesis.

4.2 Parkinson's disease

PD is the second most common neurodegenerative disease after AD, accounting for approximately 2% of the population. Patients suffering from PD have difficulty in movement (bradykinesia), dementia such as LB demen-

tia (DLB), multiple-system atrophy (MSA), and neuropsychiatric dysfunction, and rest tremor, instability in body posture, rigid movements, hallucinations, hypotension, and constipation [96–98]. PD is a multifactorial disease caused by various factors such as the deposition of α-synuclein (α-syn) oligomers, dysfunctional oligomers, neuroinflammation, oxidative stress, and aging. PD patients have mainly marked with degeneration in neurons of substantia nigra pars compacta that contains neuromelanin. The major hallmark of PD is the degradation of the dopamine and aggregation of Lewy bodies (LBs-the cytoplasmic protein) composed of α-syn filaments [99]. Thus, dopamine amendments consequently promote dysregulation in the basal ganglia, which then triggers dysfunctional motor activities.

PD can occur from multiple damage signals such as endogenous proteins, pathogens, toxins or toxic agents, dying neuron products, and aging. It has been reported that the vascular channels connecting the brain to the skull employing meninges might direct the microbes or the non-cerebral immune cells to enter into the brain region [100] to evoke the damage signals. The inflammatory cascade activated by damage signals causes synaptic impairment, leading to the penetration of more inflammatory molecules to the mid-brain and triggers more microglia production, increasing ROS and eicosanoid generation dopaminergic neurons death that ultimately results in PD associated neurovascular dysfunctions [101]. PD patients are found with an enhanced inflammatory response such as activation of the peripheral lymphocytes and releasing the pro-inflammatory serum cytokines IL-2, IL-6, IFN-γ, and TNF-α, leading to the development of neurotoxicity [102]. Martin *et al.*'s [103] study on mice PD model suggested that induction of the inflammatory processes causes elevation of the MHC II in astrocytes and microglia residing in ventral midbrain. The bone marrow-derived leukocytes are also capable of triggering neuroinflammation in the brain tissue and leading to the onset or progression of PD and other brain pathologies [104].

PD pathogenesis caused by infections often mediates neuroimmunomodulation. Neuroimmunomodulation includes an increase in aggregation of substrates such as adenosine triphosphate, α-syn, metalloproteinase-3 (MMP-3), and neuromelanin from degenerated neurons [103]. Watson *et al.* [105] demonstrated the activation of microglia and inflammation in the α-Syn overexpressed mouse. The α-syn also causes MyD88 activity-dependent microglial activation by activating TLR 1/2 [106]. The degenerated neurons are the outcomes of multiple factors such as α-syn-mediated phagocytosis, activated TLR4 microglia, presence of proinflammatory cytokines (IL-6β, TNF-α, TGF-β, and IFN-γ), presence of ROS, and incidence of α-syn activated astrocytes localized in nigrostriatal regions and CSF of PD patients [107–109]. The activated microglia can engulf the α-syn and initiate its degradation by the lysosome. Still, failure in the degradation of α-syn aggregates triggers cathepsin B from lysosomal chamber and also activates NLRP3 inflammasome formation, which ultimately causes pathogenesis of PD [110]. The elevated level of key inflammatory molecules contributes to inflammation-related neurotoxicity in PD [111,112].

In PD-affected people, the role of lysosomal dysfunction is well studied. The lysosomal autophagy system (LAS) and the ubiquitin-proteasome system maintain the proper amount of intracellular α-syn [95]. Lysosome plays a significant role in fibrils (α-syn) trading through tunneling nanotubes (TNTs) present in the middle of the neuron, stimulating misfolding, and deposition of soluble protein [113]. But a lysosomal dysfunction can initiate the escaping of the α-syn to neighbor cells which may cause brain invasion and disease progression [114]. These α-syn are cleaved by caspase-1 and aggregate as Lewy bodies in the dopaminergic neurons of mammals and activate the microglial cells. These further stimulate excessive production of tumor necrosis factor-a (TNF-a) and IL-1 IL-1β in the *substantia nigra pars compacta* regions resulting in neuroinflammation mediated neuron death [106].

D. melanogaster also exhibits complex behaviors such as aggression, grooming, courtship, learning, conditioning to fear, and locomotory activities such as climbing, flying, and walking [115] which gets, impaired by PD pathogenesis. PD mutant flies are observed with loss of DA neurons and defective motor activity. The paraquat-induced *Drosophila* PD model is witnessed with activated signaling factor of Toll, IMD and c-Jun N-terminal kinase (JNK) [116]. Maitra *et al.* have also demonstrated the crucial role of Relish to rescue mobility defects and neuronal loss in flies. Infection-mediated Relish activation via IMD signaling leads to the induction of NF-$\kappa\beta$ signaling in *D. melanogaster* that finally culminates in increased AMP production [117,118]. This rise in the *Relish*-dependent AMPs level can lead to neurodegeneration.

Mammalian mitochondria featuring multiple functions can be a central driver of diseases owing to their dysfunction caused by aging, disease (autoimmune diseases, cancer, metabolic disorders, and neurodegeneration), exposure to toxicants of the environment, and pathogenic infection. Dysfunction of mitochondria results in impaired oxidative phosphorylation (OXPHOS) and metabolism, accumulation of unfolded proteins, loss of membrane potential, and enhanced ROS generation. It regulates a wide range of cellular processes and houses the molecules involved in the antiviral and inflammasome signaling and endogenous damage-associated molecular patterns (DAMPs). These mitochondrial DAMPs engage the innate sensors/PRRs to activate pro-inflammatory and type I IFN responses [119]. Numerous studies have revealed the association of mitochondrial dysfunction with the pathogenesis of PD in humans [120]. Mammalian mitochondria also possess many sophisticated systems that participate in the proper func-

tioning of the protein and maintain the cell's structural integrity. These systems, comprising AAA proteases, the ubiquitin-proteasome system, mitochondrial-derived vesicles (MDVs) and mitophagy, and fission/fusion regulatory system, taken together is referred to as mitochondrial quality control (MQC) [121]. In the past few years, the role of PTEN-induced putative kinase 1 (PINK1) and PRKN in the activation of the MQC machinery in response to mitochondrial dysfunction has been extensively studied [122,123]. Under unpleasant conditions (mitochondrial damage, mutagenic stress, and proteotoxicity), the intermembrane transport of PINK1's N-terminus from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM) is impaired, resulting in PINK1 accumulation on the OMM. The accumulated PINK1 triggers autophosphorylation, which facilitates kinase activation and promotes binding to the Parkin and ubiquitin [124,125]. Now activated Parkin facilitates the formation of the ubiquitin chains and attracts more Parkin to the mitochondria, thereby amplifying the damage detecting signals received by PINK1 [126]. The recruited Parkin leads to ubiquitination of many cytosolic targets such as Parkin Interacting Substrate (PARIS, ZNF746) and AIMP2, whose accumulation may cause neurotoxicity and cell death of nigral DA neurons [127,128].

Moreover, mutations in these genes are linked to the autosomal recessive forms of PD in mammals [129,130]. Autosomal recessive juvenile parkinsonism (ARJP) results from the dysfunctional LAS and E3 ubiquitin-ligase system produced from a mutation in the parkin gene [131]. However, the mechanism of the development of ARJP pathogenesis is still not clearly understood. Loss of function PINK1/Parkin MQC machinery may alter the correlation between CNS and peripheral immune system and evoke an adaptive immune response against mitochondrial proteins. Thus, compromised PINK1/Parkin MQC engages the peripheral immune system in an attack against CNS. Loss of Parkin impairs the generation of mitochondrial-derived vesicles (MDVs) required for bactericidal activity, resulting in the defect in clearance of infection causing chronic infection and enhanced cytokine production [132].

In *D. melanogaster*, PINK1/Parkin shows similarities in pathways to maintain mitochondrial fidelity with mammals but differs in its localization [133]. Greene *et al.* [134] studies demonstrated dysfunctional mitochondria and damaged flight muscle phenotypes in the *D. melanogaster* model mutant for the parkin gene. Moreover, these parkin mutant flies have also shown higher oxidative stress levels and altered levels of parkin and oxidative stress genes. Lastly, when they induced the innate immunity genes in the parkin mutant flies, the cell cycle and the endoplasmic reticulum stress regulatory pathways are altered, resulting in the inflammation-mediated ARJP pathogenesis. The PINK1/Parkin KO mutant flies are observed with a decline in male sterility and life span, impaired locomotor activity, mitochondrial dysfunction in muscle and brain, and defective DA neuron morphology [135,136]. Loss of function of Parkin in *Drosophila* leads to the reduced motor activity, shrinkage of DA neurons, and decline in the level of tyrosine hydroxylase [137]. Flies with PINK1 mutation have similar phenotypic defects (impaired locomotion, defective DA neurons, and reduced life span) as that of *parkin* mutant flies [136]. Additionally, loss of function of PINK1 causes defective thorax phenotype in young flies (3 days old) and leads to age-dependent DA neurons deficiency in PPL1 cluster in 30 days old flies [138].

4.3 Amyotrophic lateral sclerosis (ALS)

ALS is a fatal neurodegenerative disorder evident in approximately 2 people per 100,000 and usually causes the death of the patients within 3–5 years [139–141]. Men are slightly more prone to the disease than women. ALS patients exhibit weakness of limbs and are thus diagnosed with upper and lower body motor neurons defect [142]. Along with motor disorders, ALS patients are also diagnosed with dementia, sensory abnormalities, and autonomic dysfunction [143–145]. Many factors play a role in the pathogenesis of ALS, such as environmental hazards, immunological disorders, and inflammation. ALS is identified with a genetic mutation in the superoxide dismutase 1 (SOD1) [146]. The mutation in SOD1 covers only 20% of the total identified ALS cases suggesting probability of mutations in other genes. Modification of the gene encoding transactive response DNA-binding protein-43 (TDP-43), i.e., TARDBP and mutation in the gene encoding sarcoma fusion/translocation in liposarcoma, is also responsible for ALS [147].

Meissner *et al.* [148] reported that the endocytosed mutated SOD1, when relocated to the cytosol, acts as a danger signal, leading to activation of the caspase1 in the mammalian SOD1 mutant microglial cells. Then the activated caspase-1 activates IL-1 IL-1β, which in turn causes neuroinflammation-induced motor neuron disease progression, a hallmark of ALS. Another common feature of ALS is the massive accumulation of the TDP-43 in certain brain regions affecting the motor neurons and activating the relocation of the NF-$\kappa\beta$ from the cytoplasm of microglial cells to its nucleus [149]. Several studies have also reported the involvement of the CD14 in the IL-1 IL-1β production from microglial cells and on the TDP-43 mediated NLRP3 inflammasome activated phagocyte surface [150].

D. melanogaster acts as a good model to investigate the TDP-43 neurotoxicity and related disease. Zhan *et al.* [151] has reported the vital contribution of the leucine kinase Wallenda (Wnd) and p38 and JNK (downstream components) in the TDP-43 mediated neurotoxicity, and thus any genetic variation in the Wnd expression or its antagonist may improve the fly life-span by canceling the negative effect of TDP-43. Furthermore, overexpression p38b or loss-of-function of Basket (Bsk), a homolog of JNK, has exhibited a shorter fly life span and increased TDP-43-associated

lethality [151]. In a nutshell, the cytoprotective role and cytotoxic effect of the JNK signaling and p38 signaling, respectively, have been well-studied in the *D. melanogaster* model. However, the conversation of the same in humans still needs to be explored.

4.4 Polyglutamine diseases

The Polyglutamine (poly Q) diseases are of 9 types, namely; Huntington's disease (HD), dentatorubral-pallidoluysian atrophy, spinobulbar muscular atrophy, and spinocerebellar ataxias types 1, 2, 3, 6, 7, and 17; featuring CAG-trinucleotide repeats expansion along with the open reading frame (ORF) in the corresponding genes [152]. These groups of genetic diseases are marked with the deposition of the multiple inclusion bodies comprising polyglutamine-rich proteins (insoluble) that can bring about neurodegeneration in different brain regions [153]. HD is a well-studied autosomal polyQ disease featuring CAG repeats in the Huntingtin (HTT) gene. Genetic abnormality caused due to mutated HTT subsequently causes progressive atrophy of the cortex and striatum [89].

The samples collected from plasma and affected regions of HD patient's brains exhibit increased TNF levels hinting at the role of inflammation (microglia cells recruitment and proinflammatory cells activation) in producing an unpleasant physiological state in the brain and disease progression [154]. Elevated levels of IL-1 IL-1β, hyper activated glia cells, higher levels of complement pathway components (C3 and C9), overexpression of cytokines in the brain areas of HD patients are evidence of inflammatory responses [155].

To elucidate onset/progression of polyQ diseases mainly HD and spinocerebellar ataxia type 3 (SCA3), *D. melanogaster* is recently used as a model organism. Transgenic flies' mutant for transgenes encoding for ATXN3 and HTT are generated to investigate cellular and molecular mechanisms of the disease [152]. Jackson *et al*. have reported adult fly retinal degeneration in the SCA3 and HTT mutant flies [152,156,157]. Thus, *D. melanogaster* retina can be used as a model to decipher the link between the polyQ mediated neurodegeneration in the retina and pathogenesis SCA3 and HD mutants [152]. Evolutionary conserved innate immune (Toll and IMD) pathways in *D. melanogaster* play a pathological role in developing polyQ-mediated neurodegeneration. These immune signalling in *D. melanogaster* are involved in the inhibition of the Yorkie (Yki) a transcriptional coactivator of the Hippo pathway, by accumulated polyQ, leading to enhanced AMPs expression and the onset of neurodegeneration. Altogether, this validates an interrelation between immune pathway and neurodegeneration. Dubey and Tapadia have reported that Yki in humans can negatively regulate the innate immune pathways and reduce the polyQ neurotoxicity either by overexpressing Yki or by triggering cyclin E/bantam mediated cell proliferation in the affected cells [158].

Shieh and colleagues characterized 160 genes responsible for differential expression signatures, including genes associated with innate immune responses in the fly model having CAG repeat-associated neurodegeneration. The authors have also explored a correlation between inflammation and polyQ mediated neurodegeneration as they observed overexpression of Hsp70 and AMPs, especially metchnikowin in CAG repeat fly model [159]. Involvement of Hsp70 is also found in the human polyQ and other human neurodegenerative disease suppression [160]. These works suggest that the mechanism of inflammation-mediated neuro-pathogenesis is highly conserved between flies and humans. Shieh *et al*. [159] also identified genes, namely; *DpId, Orb2, and Tpr2* in flies which can modify the Ataxin-3 polyQ protein toxicity and CAG-repeat RNA-based pathogenicity. Altogether, these reports suggest that the genetic modifiers identified in flies can be targeted in the mammalian model to establish a relationship between RNA/protein toxicity mediated polyQ pathogenicity [157].

4.5 Ataxia telangiectasia

Mutation in the gene Ataxia telangiectasia mutated (ATM) (that encodes for a protein kinase responsible for maintaining genomic integrity) results in a recessive autosomal neurodegenerative disease called Ataxia telangiectasia (A_T), observed with clinical features such as cerebellar ataxia, immunodeficiency, occulocutaneous telangiectasia, and sensitivity towards radiation [161]. An impaired ATM gene function produces chromosomal instability, leading to dysfunctional immune response and thus activates systemic inflammatory signaling that participates in the onset of neurodegeneration, speeding up the aging process, tampering the cardiovascular system, and developing autoimmune disease similar to the pathological features of A_T [162].

McGrath-Morrow *et al*. [163] had identified more than 300 genes expressed in the A_T patients and showed the association of some of the identified genes with the immune/inflammatory pathway when their peripheral blood mononuclear cells were compared with the healthy control (without A_T disease). The authors have also found an increase in the level of IL-8 in serum, uncontrolled/prolonged inflammatory response, and free activation of the innate immune system, indicating the role of inflammation in the A_T pathogenesis; which is more likely to develop in malignancy/death in 4–6 years: yet to be discovered.

Petersen *et al*. [164] have used flies, with mutated ATM genes, as a model to decipher the mechanism of inflammation-mediated A_T-related neurodegeneration in the brain. Subsequently, the authors have modified the amino-acid in the C-terminal region of the *D. melanogaster* ATM gene to inhibit the protein kinase activity, and this impaired ATM in the glial cells contributes significantly to sustained immunological responses, which in turn impairs glial mobility or cause glial/neuronal cell death [165]. The authors have also reported that the regulatory molecules

(NF-$\kappa\beta$ factor) of the IMD pathway, Relish, play a vital role in the onset of neurodegeneration in the glial cells of the ATM mutant flies [164]. Overall, the work on glial cells of ATM mutated *D. melanogaster* model system decrypted the mechanistic basis of inflammation-mediated A_T-associated neurodegeneration. Although a correlation between inflammation and neurodegeneration is established in the fly model events leading to the unrestricted inflammatory responses in the human A_T patients still needs to be understood.

4.6 Traumatic (brain) injury

Traumatic brain injury (TBI) is a consequence of the primary or secondary injuries in the head due to external mechanical forces, which subsequently trigger functional defects in the individual's behavior, cognition, and physical responses. The severity of the secondary injuries depends on how the host cellular and molecular function responds to the external mechanical stress on the brain primarily [166]. TBI is categorized into subcategories [167], such as (i) based on skull and dura condition; (ii) closed head injuries (no damage observed in dura and skull); (iii) penetrating injuries (damage observed in both dura and skull); (iv) based on the clinical characteristics (v) length and state of consciousness; (vi) incidence of amnesia and (vii) neurological disorders.

Csuka *et al*. [168] had reported that dysregulation of the innate immune responses via cytokines can stimulate secondary injuries in humans, indicating the role of inflammation in the pathogenesis of TBI. On the contrary, some studies on TBI patients have also reported the beneficial role of cytokines to rescue the neural system [169]. TBI patients are observed with an elevated level of TNF in the CSF which indirectly affects the patient negatively. Thus, targeting TNF serves as a potential therapeutic for TBI treatment [170].

Recently, as *D. melanogaster* is modeled in various studies related to inflammation and neurodegeneration, Katzenberger *et al*. [166] developed 'high-impact trauma'. This adjustable device primarily imposes closed-head TBI conditions in flies. These close head-TBI fly models are found with elevated expression of genes such as 'metchnikowin' and 'spz' of Toll and IMD pathways, respectively. Consequently, hyper-activated immune pathway has also been reported in the TBI fly model, inducing damage in the neural system similar to that of aged flies undergoing neurodegeneration [171].

Unrestrained AMPs expression leads to neurodegeneration mediated vacuolar lesion formation in the neuropil (area of nervous system comprising dendrites, unmyelinated axons, and glial cells) of the human brain [115]. The vacuolar lesions analogous to the brain are identified in the nervous system (neuropil area) of the flies used as TBI model. These lesions in the TBI *Drosophila* model vary from as small as 1.0 μm in diameter to somewhat large. The size variation of the vacuolar lesion depends on the age of the flies [166]. The larger the size of the lesion, the older is the fly. However, the role of varied dimension of these lesions on survivability of the TBI flies or development of neurodegenerative disease/pathologies has not been elucidated yet. Hence, the significance of these vacuolar lesion size variations in the AMP-induced inflammation-mediated TBI neurodegeneration can be studied in the future.

5. Conclusions

Neuroinflammation is one of the major aspects of the chronic innate immune response in the CNS. Infiltration of foreign invaders or neuronal injury provokes the activation of pro-inflammatory molecules secreted from the host immune system and triggers the accumulation of microglial cells, causing a deregulated brain tissue homeostasis, which exaggerates into neurotoxicity or neurodegeneration. The glial cell-derived prolonged expression of proinflammatory cytokines, or AMPs (in *D. melanogaster*) in the CNS cause elevated deposition of the endogenous non-infectious ligands like tau, α-synuclein, Aβ and, poly glutamates result in neurodegenerative pathogenesis. Although the function of microglial cells has been studied in detail, the role of other brain cells such as astrocytes in neurodegeneration is yet to be discovered. It is known that fruit fly Amps have both protective and pathological functions in the brain, but how the switching between two functions is regulated remains unclear. We have limited knowledge about the mechanism of inflammatory state-derived neurotoxicity. Understanding such mechanisms using different model organisms, including *D. melanogaster*, will help to develop novel diagnostic tools and therapeutics for neurodegenerative diseases.

Abbreviations

CNS, central nervous system; AMPs, antimicrobial peptides; ROS, reactive oxygen species; IRFs, Interferon (IFN) regulatory factors; PGRPs, peptidoglycan recognition proteins; GNBPs, Gram-negative binding proteins; IL-1R, interleukin-1 receptor; DIF, Dorsal-related immunity factor; TRAF-6, TNF-receptor-associated factor-6; spz, Spaetzle; dFADD, Fas-associated Death Domain; DREDD, death-related ced-3/NEDD2-like protein; dTAK1, Drosophila transforming growth factor activated kinase 1; NO, nitric oxide; GNBP-3, Gram-negative binding protein-3; GNBP-1, Gram-negative binding protein-1; RNAi, RNA interference; DptB, Diptericin B; AD, Alzheimer's disease; MS, multiple sclerosis; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; WHO, World Health Organization; NFTs, Neurofibrillary tangles; PHFs, paired helical filaments; SPs, senile plaques; AβPP, the amyloid precursor protein; CSF, cerebrospinal fluid; TLRs, toll-like receptors; AGE, advanced glycation end products; MHC-II, major histocompatibility complex II; TNF-α, tumor necrosis factor (TNF) alpha; IL-1β, in-

terleukin (IL) 1 beta; IFN-γ, interferon (IFN) gamma; BBB, blood brain barrier; MSA, multiple-system atrophy; α-syn, α-synuclein; LBs, Lewy bodies; MMP-3, metalloproteinase-3; ARJP, Autosomal recessive juvenile parkinsonism; SOD1, superoxide dismutase 1; TDP-43, DNA-binding protein-43; Bsk, Basket; polyQ, Polyglutamine; HD, Huntington's disease; ORF, open reading frame; HTT, Huntingtin; Yki, Yorkie; ATM, Ataxia telangiectasia mutated; TBI, Traumatic brain injury.

Author contributions

NN did the literature review and wrote the paper. MM did drafting and critical revision of the article.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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