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Glial contributions to neuronal health and disease: new insights from *Drosophila*

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Abstract

Glial cells are essential for proper formation and maintenance of the nervous system. During development, glia keep neuronal cell numbers in check and ensure that mature neural circuits are appropriately sculpted by engulfing superfluous cells and projections. In the adult brain, glial cells offer metabolic sustenance and provide critical immune support in the face of acute and chronic challenges. Dysfunctional glial immune activity is believed to contribute to age-related cognitive decline, as well as neurodegenerative disease risk, but we still know surprisingly little about the specific molecular pathways that govern glia-neuron communication in the healthy or diseased brain. *Drosophila* offers a versatile *in vivo* model to explore the conserved molecular underpinnings of glial cell biology and glial cell contributions to brain function, health, and disease susceptibility. This review addresses recent findings describing how *Drosophila* glial cells influence neuronal activity in the adult fly brain to support optimal brain function and, importantly, highlights new insights into specific glial defects that may contribute to neuronal demise.

Introduction

Although it is becoming increasingly clear that glial cells are key players in nervous system development, plasticity, and homeostasis, we know little about the molecular pathways that underlie glia-neuron interactions in the developing and mature brain. The fruit fly *Drosophila melanogaster* is a powerful invertebrate organism model for investigating conserved molecular and cellular features of glia in the embryonic and adult CNS. *Drosophila* are affordable, easy to maintain, and offer unprecedented power to genetically manipulate and visualize cells *in vivo*, even at the single cell level. Moreover, our knowledge of *Drosophila* glial cell anatomy, gene expression, and function is growing exponentially. As in the mammalian brain, *Drosophila* glia can be parsed into discrete subtypes that perform unique functions, including CNS pruning, regulation of synaptic signaling, blood-brain

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Conflict of interest

There are no conflicts to declare.

barrier formation, and neuroprotection (1, 2). This review will not specifically explore the role of *Drosophila* glia during nervous system development as this topic has been addressed in a number of excellent recently published reviews (2–4). Instead, this article will highlight new findings regarding adult glial cell function, with a particular emphasis on brain homeostasis and new insights from *Drosophila* models exploring glia-neuron interactions in the context of injury and neurodegenerative disorders.

Glial diversity in adult *Drosophila*

The distribution and unique morphological classes of glial cells in the adult *Drosophila* brain has only been realized in the last decade (5–8). Currently, adult fly glia are classified into five major subtypes. Cortex glia envelop neuronal cell bodies throughout the cortical regions of the brain. Astrocytes extend highly branched projections into neuropil regions to functionally regulate neuronal signaling. Ensheathing glia enwrap axonal tracts throughout the central and peripheral nervous systems. Finally, subperineurial and perineurial glia comprise a double-layered glial sheath that forms a contiguous surface covering the entire CNS and PNS, which is often referred to as the *Drosophila* blood-brain barrier (BBB) (1, 9) (Figure 1). Ongoing work is providing critical new insight into the molecular and functional fingerprints of mature fly glia and similarities with their vertebrate counterparts. For example, a recent tour de force analysis, which characterized a large collection of novel *in vivo* genetic drivers, now offers more comprehensive information about the morphological diversity of glia, as well as cellular interactions in various brain regions, demonstrating, for example, that homotypic and heterotypic repulsion mechanisms maintain glial tiling in the adult CNS (10). In addition, a novel glial cell type (the “Semper” cone cell), which is strikingly similar to vertebrate Muller glia, has been identified in the *Drosophila* retina (11*) (Figure 1). Both Semper cells and Muller glia radially span the retina and express high levels of crystalline-like proteins to facilitate light scattering throughout retinal tissue. The genetic signatures of Semper cells and Muller glia overlap considerably, as both express critical genes, including inward rectifying potassium channels, Na/K-ATPase, excitatory amino acid transports (e.g. EAAT1), and glucose transporters (e.g. Glut1), to support photoreceptor energetics and signaling. Finally, newly published collections of transcriptional profiling experiments employing FACS sorting and *in vivo* transcript isolation strategies are now providing an unprecedented picture of the genetic profile of glial subtypes in the adult fly brain (11–14). Although glial cell biologists are just beginning to scratch the surface of resolving the varied functional roles of *Drosophila* glia, it is clear that emerging genetic toolkits and *in vivo* profiling strategies will rapidly advance our understanding of glial influences on neuronal function and brain health.

Glial support of metabolism and brain health

Glial cells perform the very important task of maintaining metabolic homeostasis in the nervous system. Glia-neuron metabolic coupling has been well documented in mammals, between myelinating glia and axons, as well as astrocytes and synapses (15–18), and recent work investigating metabolic regulation in *Drosophila* now highlights the evolutionary conservation of energy homeostatic mechanisms. In insects, including *Drosophila*, the sugar trehalose is the major energy metabolite that circulates within the hemolymph, the fluid that

flows through the insect's open circulatory system and bathes all organs. Until recently, it was unknown how trehalose and derived metabolites were transferred to the CNS. Volkenhoff and colleagues (2015) now show that *Drosophila* employ a "glia to neuron" shuttling system to provide these critical metabolic factors to neurons. The perineurial glial cells of the blood brain barrier specifically express the trehalose transporter Tret1-1 to absorb trehalose from the hemolymph (19). Within this subset of glia, trehalose is first broken down to glucose and then further metabolized to alanine or lactate, which can be taken up by local neurons to meet energy demands. Although the perineurial glia express ample glycolytic enzymes to break down trehalose, glycolytic gene expression is strikingly low in neurons, which renders neurons dependent on glia for precious energy sources. Notably, glial-specific knockdown of glycolysis results in neurodegeneration, while neuronal glycolysis is largely dispensible (19, 20). Looming questions still remain as to how metabolites are transferred from glia to neurons and, potentially, also between glial cells. It will also be important to determine if and how metabolite transfer occurs in an activity-dependent manner. Nonetheless, this metabolic compartmentalization between neurons and glia is clearly an evolutionarily conserved strategy, which underscores the importance of glial-neuron metabolic interplay and emphasizes the value of *Drosophila* as a powerful model to resolve the molecular details of CNS energy metabolism.

Glia in the context of healthy aging and acute injury

Age-related changes in glial cells and glial-neuron signaling networks profoundly influence CNS plasticity, cognition, and overall organismal function. Thus, scientists are eager to define the cellular and molecular changes that occur in senescent glia. Several recent studies have provided new insight into how changes in innate immune function contribute to brain aging, as well as susceptibility to neural damage and disease.

One highly conserved glial immune pathway includes Draper (known as MEGF10 in mammals), an engulfment receptor that is required in flies and vertebrates for proper glial clearance of degenerating neuronal projections, synapses, and apoptotic neurons during development (21–26). Draper couples to several downstream signaling pathways via tyrosine kinases, including the c-Jun N-terminal kinase (JNK) cascade, to alter cytoskeletal remodeling, gene transcription, and phagocytic function in glial cells (27–29). In *Drosophila*, Draper is also required for glial engulfment of degenerating axons after acute nerve axotomy in adults (23, 27, 29, 30). Notably, neurodegeneration occurs in aged *draper* mutant animals (31, 32), and this phenotype is rescued by glial expression of target of rapamycin 1 (TORC1), one factor implicated in proper processing of phagocytosed material (32). The neurodegenerative phenotype in *draper* mutants may arise, at least in part, from incomplete clearance of neuronal corpses during development. However, it is important to consider that dysfunctional glial engulfment (due to lack of Draper) in mature glia may also contribute to a decline in CNS health.

These findings dovetail nicely with a recent report from Purice and colleagues (2016), which reveals that translation of the Draper receptor declines significantly with age due to reduced phosphoinositide-3-kinase (PI3K) signaling (33). Consequently, in the senescent brain, glial cells are sluggish responding to axon injury, and glial clearance of degenerating axonal

debris is significantly delayed (33). Interestingly, in a *Drosophila* model of Huntington's Disease, Draper is also required for glial uptake of neuronally-derived mutant huntingtin (Htt) aggregates (34**). Draper-dependent transfer of mutant Htt aggregates promotes the prion-like pathogenic conversion of soluble wild type Htt peptides within glial cells (34**). Thus, due to a decline in Draper levels, aged glia may be poor at clearing a variety of neurotoxic factors, contributing to a heightened risk for damage and disease. Finally, with regard to proteinopathies, glial cells are viable candidates for transmission of protein aggregates from cell to cell or from one brain region to another, implicating Draper/MEGF10 as a new candidate intervention point to block protein aggregate spreading in specific neurodegenerative disorders.

Aging is associated with impaired PI3K signaling, and the above findings raise the following important question: Which upstream pathways are altered with age to inhibit glial PI3K activity and, subsequently, reduce Draper production? One interesting candidate is the insulin-like signaling pathway, which controls energy homeostasis, cellular growth, and cell survival. In vertebrates, the ILS receptor family includes the insulin receptor and insulin-like growth factor receptors, while the *Drosophila* genome contains only one related gene, the insulin-like receptor (InR). In all species, this class of receptors initiates a highly conserved canonical cascade that includes PI3K (35). Recent work has revealed a unique role for the insulin-like pathway in the context of glial immune responses to nerve injury in adult flies (36*). Musashe and colleagues (2016) now show that transection of the olfactory nerves in flies triggers increased insulin-like signaling in local ensheathing glia, the glial subtype responsible for phagocytically clearing degenerating axons in the adult brain (36*). Ensheathing glia typically upregulate Draper as they infiltrate injury sites and engulf degenerating olfactory projections (23, 27, 30). Genetic inhibition of the insulin-like pathway in ensheathing glia blocks injury-induced Draper upregulation and delays clearance of severed projections. Importantly, forced expression of Draper in glial-InR depleted flies provides significant rescue with regard to axon engulfment, indicating that the insulin-like pathway as an important upstream positive regulator of Draper and glial phagocytic function (36*). It is well established that systemic insulin-like signaling pathways gradually decline with age across species (37); future work will reveal if this contributes to age-related loss of Draper/MEGF10 and attenuated glial immune responses in older animals. Interestingly, genetic deletion of insulin-like signaling pathway components, including the InR and PI3K, extends lifespan in *C. elegans, Drosophila*, and mammals, although increased longevity may occur at the cost of optimal metabolic fitness and overall health (38). Selected manipulation of PI3K and insulin-like cascades in a cell type specific and temporal manner may prove to be the most ideal method of optimizing glial immune gene expression and immune-like responses in the aged brain.

Another set of well-characterized immune cascades are the Toll and Imd (immune deficiency) pathways, which both activate conserved Nuclear Factor–κB (NF-κB)-related transcription factors (known as Relish and Dif in flies) to drive expression of immune genes, including those that encode secreted antimicrobial peptides (AMPs). These NF-κB-dependent pathways have been well characterized in the systemic immune system and are essential for destroying invading pathogens and defending overall organismal health (39). We now know that these pathways are also activated in the *Drosophila* brain and can

profoundly influence neuronal survival. For example, glial overexpression of secreted AMPs is sufficient to promote neurodegeneration (40). In fly models of Ataxia-Telangiectasia, activation of the NF-κB homolog Relish in adult glia is also a primary driving force for neurodegeneration (41). Finally, work from Kounatidis and colleagues (2017) also reveals that IMD/NF-κB activity increases as part of normal aging and adversely influences locomotor activity, metabolism, and longevity (42*). Collectively, these studies further emphasize the notion that manipulating glial immunity pathways could serve as a useful strategy to extend health span.

Glia-neuron signaling and implications for neurodegenerative disease

For decades, *Drosophila* has served as a tractable genetic model to investigate basic molecular mechanisms that underlie neurodegenerative disease pathogenesis (43). The more recent explosion of work related to *Drosophila* glial cell biology has now poised to us to tackle the role of glia-neuron interactions in the context of disease.

Liu et al. (2015) took a broad approach to investigate how defects common to many neurological disorders influence glial cell function (44**). Using the adult *Drosophila* retina as a model, they stressed neurons *in vivo* by genetically inhibiting mitochondrial activity and promoting the production of reactive oxygen species (ROS). Interestingly, these neuronal defects encouraged the formation of lipid droplets (LD) non-cell autonomously in local glial cells, which was followed by neurodegeneration; inhibiting LD formation in glia provided neuroprotection. They went on to show in a mouse model for the neurodegenerative disorder Leigh syndrome that LD formation in astrocytes and microglia preceded neuronal death in various brain regions (44**), suggesting that similar neuron-glia crosstalk mechanisms are conserved in higher organisms. LDs typically serve as storage sites for triglycerides and cholesterol, and the mechanistic significance of LDs in the context of neuronal stress or disease is not yet clear. Nonetheless, because mitochondrial dysfunction and oxidative stress are core components of many neurological disorders, this works offers a new twist on how glia may contribute to disease progression, specifically through altered lipid metabolism.

Drosophila has also furthered our understanding of the complex pathology of Alzheimer's disease (AD), including molecular, cellular, and behavioral dysfunction. Fly models that express human amyloid precursor protein (APP), amyloid-β42, and/or tau have all provided valuable information about how these neurotoxic peptides influence synaptic signaling and structure, as well as behavioral phenotypes including locomotor defects (45). The fly genome contains one APP-related gene, APP-like (APPL), which, when mutated, causes defects in neuronal outgrowth, synaptic stability, and behavior, and *Appl* mutant flies have provided important insight into endogenous APP signaling mechanisms in the CNS (46). Across all model organisms, an overwhelming number of studies have explored the role of neuronal APP, but relatively little is known about the function of glial APP, despite the fact that APP is also expressed in mammalian oligodendrocytes, astrocytes, and microglia (21, 47). A recent study explored how glial APPL influences sleep-wake cycles in adult flies. There is a clear reciprocal relationship between Alzheimer's disease and sleep disruption (48), and this phenomenon extends to *Drosophila* (49). Farca Luna and colleagues (2017) found that knockdown of APPL in adult fly glia, specifically in cortex glia or astrocytes,

alters sleep patterns. *Appl* mutant flies sleep more overall and display more consolidated sleep during the night, while overexpression of APPL in glia has the opposite effect. Interestingly, boosting glial cells' ability to uptake glutamate reverses the *Appl* mutant sleep phenotypes. Notably, glial depletion of APPL also inhibits the expression of a) glutamine synthetase, an enzyme that converts glutamate to glutamine, and b) innexin 2, a component of gap junctions, which allow small molecules to pass between specific glial subtypes (50*). Together, these findings raise the intriguing possibility that disruption of glial APP function or processing promotes intrinsic changes within glial cells to disturb glutamate metabolism and/or recycling, which, in turn, contributes to altered sleep patterns in Alzheimer's disease patients.

The glial-based leukodystrophy disorder Alexander disease, which presents with developmental delays, loss of myelin, and dementia, is a result of mutations in the gene for glial fibrillary acidic protein (GFAP). Wang and colleagues (2011) developed a robust model for Alexander disease in *Drosophila* by expressing mutant forms of human GFAP in glia, which recapitulates key features of the disease including abnormal protein folding, dysfunctional glutamate transport, seizures, and neurodegeneration (51). Exploiting the rapid genetic capabilities of the fly, they performed an unbiased forward genetic modifier screen and identified nitric oxide (NO) as a key player in glial-mediated neuronal death induced by GFAP toxicity. After probing candidate upstream and downstream regulators, their work revealed that pathogenic versions of GFAP promote upregulation of the inducible nitric oxide synthase (iNOS) gene via the transcription factor STAT. In turn, excess NO levels non-cell autonomously induce cyclic guanosine monophosphate (cGMP) signaling and apoptosis in neurons (51). An independent *in vivo* pharmacological screen of FDA-approved drugs identified a cohort of muscarinic acetycholine receptor (mAChR) antagonists that reverse toxicity in Alexander model flies (52). Notably, brain tissue from Alexander model mice and patients also display increased iNOS and mAChR expression in the CNS, although the mechanisms driving the latter change are still unclear (51, 52). Continued screening efforts and histological analysis in flies will likely provide new insight into the mechanisms of this disease and the specific contributions of glial cells.

Conclusion

Our understanding of glial cell biology is still in its infancy, but resolving how glia differentiate, influence brain metabolism, and signal reciprocally with neurons throughout life is essential in order to fully comprehend how the nervous system becomes vulnerable to stress and disease. Here, we briefly describe key recent advances that highlight *Drosophila* contributions to the fields of normal aging, energetic homeostasis, immunity, and neurodegenerative disease progression. These findings expose novel glia-neuron signaling pathways and further show that invertebrate and vertebrate glia employ common molecular pathways to ensure optimal neuronal function and to defend CNS fitness. Emerging advances in genetic manipulation (e.g. CRISPR/Cas9), high resolution light microscopy, and live microscopy imaging methods promise to strengthen the rich insight we can gain from invertebrates about this utterly important but poorly understood cell type in the brain.

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Highlights

- *Drosophila* glia are strikingly similar to mammalian counterparts in form and function
- Glial immune responses decline naturally with age
- Innate immune responses influence brain health and disease progression

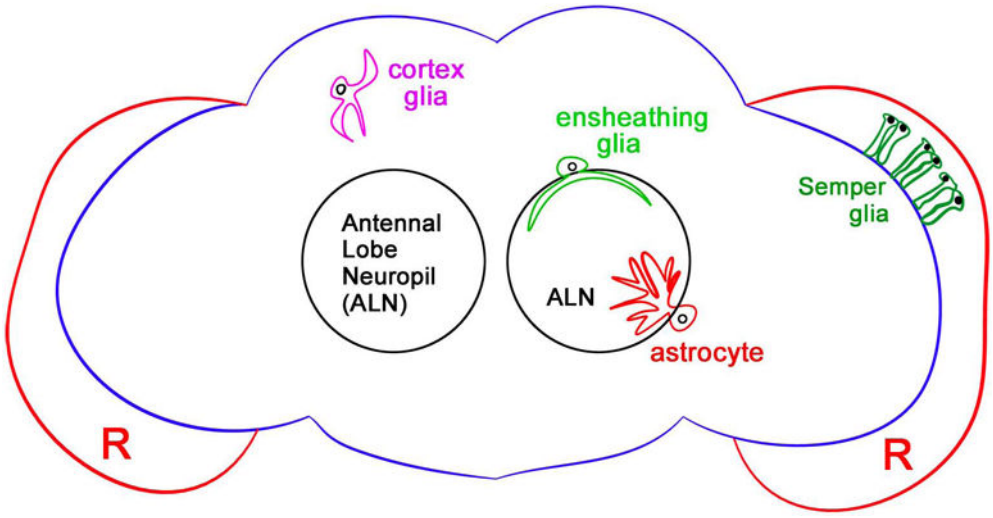

Figure 1. Glial subtypes in the adult Drosophila CNS

Schematic diagram of the adult fly brain illustrates representative classes of glia. In the cortical regions of the CNS, cortex glia (magenta) surround neuronal cell bodies, likely providing important metabolic and functional support. Neuropil areas of the central brain, which house axonal and dendritic projections, contain two major glial subtypes: Ensheathing glia (light green) enwrap neuronal extensions and appear to serve as the primary immune responders in adult animals, while astrocytes (red) modulate synaptic signaling. Representative diagrams of ensheathing glia and astrocytes within the antennal lobe neuropil (ALN) are shown. The entire nervous system is covered by a double layer of surface glial cells (blue outline), which offers a protective barrier between the CNS and the circulating hemolyph. A more recently identified cohort of glial cells in the adult retina (R), Semper cells (dark green), regulate photoreceptor function in a manner comparable to mammalian Mueller glia.