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‘Fly’ing from rare to common neurodegenerative disease mechanisms

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Abstract

Genome sequencing advances have enabled researchers and clinicians to probe vast numbers of human variants to distinguish pathogenic from benign variation. Model organisms have been critical in variant assessment and delineating molecular mechanisms of some of the diseases caused by these variants. The fruit fly, *Drosophila melanogaster*, has played a valuable role in this endeavor, taking advantage of its genetic technologies and established biological knowledge. In this review, we highlight the utility of the fly in studying the function of genes associated with rare neurological diseases that have led to a better understanding of common disease mechanisms. We emphasize that shared themes emerge among disease mechanisms, including the importance of lipids, in two prominent neurodegenerative diseases: Alzheimer’s disease and Parkinson’s disease.

Keywords

Drosophila ; neurodegeneration; mitochondria; lipid; Alzheimer’s disease; Parkinson’s disease

Using flies to study neurological diseases

An ever-increasing trove of human genomic sequences is available but our ability to distinguish **disease-causing variants** (See Glossary) from **benign variation** remains a hurdle to utilizing this information for disease diagnosis or for disease prediction. The rate of genetic sequence acquisition far outpaces our ability to characterize the consequences of individual variants [1,2]. Filling this knowledge gap is critical for our understanding of gene function and disease diagnosis. Increasingly better computational tools together with thoughtful and well-controlled genetic studies are helping to fill this gap [3–6]. Efforts to improve genomic analysis *in silico* together with the addition of hundreds of thousands

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of reference genome sequences to the public domain have helped make great strides in distinguishing genetic signal from noise. While the use of these bioinformatics tools for disease diagnosis is very valuable, it is not always sufficient. Indeed, sequence analysis may reveal multiple putative disease-causing variants, variants of unknown significance, or variants in a gene of unknown function. In these instances, experimental analysis of the variants becomes necessary and model organisms play an important role in this endeavor [4,7–9].

As one of the premier genetic model organisms, the fruit fly, *Drosophila melanogaster*, has been at the forefront of genetic research for over a century [10–12]. The advantages of the fly include fewer gene paralogs compared to vertebrates, the observation that most genes that are associated with or cause human diseases have orthologs in the fly genome, and that most cellular and molecular processes are conserved between fly and human [12–16] (Figure 1). Flies are easy to rear, and it is simple to obtain large numbers of animals in a relatively short period of time, bolstering statistical power. Importantly, the fly community continues to develop and refine open-access tools and resources which are aggregated and curated in the online *Drosophila* database, FlyBase [17]. This unparalleled and growing genetic toolkit includes the use of visible phenotypic markers and **balancer chromosomes**, allowing researchers to follow mutations through generations without the need for genotyping or extensive stock maintenance [18,19]. The fly also offers practical advantages including a short lifespan, allowing researchers to readily perform aging experiments necessary for the study of neurodegenerative disorders [20,21]. These and other advantages set the fly apart from other animal models as particularly useful in studying a broad range of human diseases (Figure 1).

Research efforts using model organisms to understand fundamental cellular and molecular mechanisms have significantly advanced our understanding of the pathogenic mechanism of numerous diseases and identified important therapeutic targets [4,7,22–26]. *Drosophila* has helped elucidate mechanisms of some of the most prevalent neurodegenerative disorders including Alzheimer’s disease (AD) and Parkinson’s disease (PD). Several molecular mechanistic themes have emerged in recent years that are shared between these diseases, including lipid dysregulation and mitochondrial dysfunction [26–31]. In this review, we discuss important advances in rare neurological disease research using the fly that have shed important insights into these two common neurodegenerative diseases, while emphasizing the overlapping disease mechanisms. Finally, we discuss the state of the field and some of the questions that are yet to be answered.

Alzheimer’s disease (AD)

Among all neurodegenerative disorders, Alzheimer’s disease (AD) is the most common in the United States [32], accounting for the majority of dementia cases. While the etiology of AD is complex, it is becoming increasingly clear that lipid dysregulation is a prominent feature of the disease [33]. Glial lipid accumulation in saccules was originally described in patient brains by Alzheimer himself [34,35], but the association of lipid accumulation and lipid dysregulation in AD has only recently become generally appreciated.

Studies utilizing *Drosophila*, initially aimed at studying the role of mitochondrial variants, associated with rare neurological disease [36], have provided insight into the role of mitochondrial function and lipids in these rare diseases as well as in AD [27,37,38]. Leigh syndrome (LS, Phenotype MIM #256000), a rare genetic **neurometabolic disorder**, is characterized by degenerative features of the central nervous system (CNS) in infants including loss of previously acquired motor skills, and progressive respiratory distress [39]. Genetic causes of Leigh syndrome include mutations in one or several genes encoding proteins that function in metabolic pathways. One cause of LS stems from deleterious variants in the *SURF1* gene, which encodes an inner mitochondrial membrane protein involved in the assembly of the of **mitochondrial respiratory chain** complex IV [39,40]. Silencing the fly homolog, *Surf1*, in larvae causes severe deficits in all mitochondrial respiratory chain complexes while silencing in adult flies had a selective impairment in cytochrome c oxidase biogenesis, suggesting differential requirements for *Surf1* during development and adulthood [41]. Using the genetic tools readily available in the fly, the authors reduced expression of the *Surf1* gene specifically in the adult brain and found that this fly mimicked many of the biochemical hallmarks associated with LS, thus providing a suitable animal model in which LS and related mitochondrial disease mechanisms can be probed into the future [42].

Other studies aimed at elucidating mechanisms of LS identified a glial **lipid droplet** (LD) accumulation phenotype upon loss of genes important for mitochondrial function including the mitochondrial chaperone protein, *sicily* [27,36,37]. Mutations in the human homolog of *sicily*, *NDUFAF6*, are known to cause LS and variants in this gene have recently been identified as risk factors for AD [36,39,43–45]. The studies in the fly demonstrate that neuronal **reactive oxygen species** (ROS), caused by defective mitochondria, induce **lipogenesis** and **peroxidation** of newly synthesized lipids. Peroxidated lipids are shuttled from neurons to glia where they are sequestered in LDs (Figure 2A). The fly model of ROS-induced glial LD formation allowed researchers to probe neuron-glia interactions and the transfer of lipids between these cell types. It was shown that glial LD formation requires the **apolipoprotein** Glial lazarillo (*GLaz*). The highest known genetic risk factor for developing AD is a variant in a homologous human lipoprotein, *Apolipoprotein E*, termed APOE ε4 (APOE4) while other common APOE variants ε2 (APOE2) and ε3 (APOE3) do not confer AD risk [46]. Use of a humanized fly model, in which the expression of the *GLaz* was replaced with the expression of APOE2, APOE3, and APOE4, demonstrated that expression of APOE2 and APOE3, but not APOE4, rescue glial LD formation, suggesting that APOE4 is a loss-of-function (LOF) mutation in neuron-to-glia lipid transfer. These findings suggest that LD formation and intercellular lipid transport play roles in the pathogenesis of AD, which is bolstered by growing evidence of the importance of lipid regulation in neurodegenerative diseases like AD [29,33,47].

A recent study utilizing the fly model of ROS-induced glial LD accumulation identified a tissue-specific role for several known AD risk genes identified in GWAS and other studies [44,45,48–50], in neuron-to-glia lipid transport and LD accumulation [38]. This study showed that AD risk genes that function in APOE lipidation are required in neurons, while genes important for APOE uptake are required in glia for LD formation. These

findings suggest that AD risk may be conferred by altered gene function in neurons or glia and that multiple insults synergize to cause disease (Figure 2B).

The link between elevated ROS levels in neurons and LD accumulation in glia is not confined to genes that cause LS. Rather, ROS and LD formation is a shared phenotype resulting from mutations in proteins important for mitochondrial function which are associated with rare neurological diseases. Examples of this include a mitofusin protein encoded by the *MFN2* gene (*Marf* in flies), which is associated with Charcot-Marie-Tooth Disease Type 2A2A/2A2B (Phenotype MIM#609260 and 617087), and a mitochondrial Methionyl-tRNA synthetase encoded by the *MARS2* gene (*MetRS-m* or *Aats-met* in flies), which is associated with autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL, Phenotype MIM #611390) [27,51,52]. Additionally, one study aimed at probing the mechanistic underpinnings of a rare form of hereditary spastic paraplegia (Spastic Paraplegia 39 [SPG39], Phenotype MIM #612020) and other rare syndromes [53], revealed links between mitochondrial abnormalities, ROS accumulation, and LD formation in the fly brain. SPG39 is caused by variants in the gene *patatin like phospholipase domain containing 6*, *PNPLA6*, which encodes an enzyme that facilitates the breakdown of phosphatidylcholine in membranes [54]. The fly ortholog of *PNPLA6*, *swiss cheese* (*sws*), shares high conservation with human *PNPLA6* [53]. Loss of *sws* in the fly leads to a dramatic loss of neurons in the brain, causing behavioral abnormalities, memory deficits, and shortened lifespan. Moreover, knockdown of *sws* specifically in neurons or in glia activates the production of neuronal ROS and triggers the upregulation of antioxidant genes [53,55]. Consistent with previous reports [27,37,38], loss of *sws* and the concomitant activation of ROS in neurons leads to enhanced LD formation. Overall, the links between ROS, LD formation, and neurodegeneration in this study are striking and have implications for the etiology of SPG39. The cell-specific effects observed in this case and other studies highlights the complexities of both rare and common neurological disease. Certainly, studies that utilize tissue-specific inquiry for neurological disease research will be key to understanding disease as well as therapeutic discovery.

Additional support for the links between ROS, LD formation, and neurological dysfunction related to rare neurological disease and AD have been discovered using the fly [37,56,57]. Intercellular transport of lipids and glial LD formation is part of normal brain development [56,58,59] as well as a consequence of cell stress [27,38,60,61]. This transfer relies on apolipoproteins [37,38,62–64]. As APOE4 is a risk-factor for AD, these and other findings [65–68] suggest that a better understanding of AD will require careful probing of tissue-specific consequences of genetic variants required for LD formation. Furthermore, these studies implicate mitochondrial dysfunction and subsequent ROS production in glial LD accumulation, suggesting that therapeutic interventions aimed at reducing the effects of ROS may prove effective at preventing neurodegeneration and dysregulation of lipids in the brain. It should be emphasized that antioxidant therapies for AD and neurological disorders utilize a potent blood-brain-barrier (BBB) penetrating compound that can be administered prior to the onset of disease which is safe to administer over a long period of time. One compound that has these features is N-acetylcysteine amide (NACA) [69]. In flies, this compound alleviates ROS-mediated neurodegeneration and relieves glial LD accumulation [27,37,38] as well as strongly suppresses neurodegenerative phenotypes in a fly model of ACOX1

deficiency [70]. Hence, further exploration of NACA or similar compounds in AD and other ROS-associated disorders is warranted. A better understanding of cell-specific lipid biology in the brain will be critical to understand the etiology of neurodegenerative diseases and to identify therapeutic strategies for these illnesses.

Parkinson's disease (PD)

Parkinson's disease (PD) is a common neurodegenerative movement disorder characterized by chronic loss of dopaminergic neurons in the **substantia nigra** (SN) and the presence of abnormal protein inclusions called **Lewy bodies** [71]. α-synuclein (α-Syn), one of the primary protein components of Lewy bodies, forms aggregates in neurons and can also be found in glia of PD patients [72–74]. Indeed, *SNCA*, the α-Syn encoding gene, is one of the strongest risk factors of sporadic PD [75–77] and mutations as well as copy-number variants in *SNCA* cause familial PD [78]. During the past decades, multiple cellular pathways have been associated with PD pathology, however the mechanisms underlying PD are not yet fully understood. Recent findings reveal that lipids play a key role in the pathogenesis of PD and here we discuss several fly studies that indicate lipid metabolism is a common mechanism in PD and related rare diseases.

Dysregulated ceramide metabolism as an emerging mechanism shared by Parkinson's disease and PLA2G6-associated neurodegeneration

The phospholipase A2 Group 6 (*PLA2G6*) gene encodes an enzyme that catalyzes the release of fatty acids from **phospholipids** [79]. Studies carried out in *in vitro* systems and cultured cell lines have shown that this group of genes play critical roles in maintaining homeostasis of cell membranes and lipid signaling [80]. Dysfunction of *PLA2G6* has been observed to cause dysregulated lipid metabolism in the CNS of a knock-out mouse model, and has been reported to be associated with several human neurological diseases [81,82]. Autosomal recessive mutations in *PLA2G6* have been identified in a group of rare diseases collectively termed PLA2G6-associated neurodegeneration (PLAN). PLAN disorders have a broad clinical spectrum and can be classified into three major types including infantile neuroaxonal dystrophy (INAD, Phenotype MIM #256600), atypical neuroaxonal dystrophy (aNAD, Phenotype MIM #610217), and PLA2G6-related dystonia-parkinsonism (Phenotype MIM #612953). The age of onset and severity of disease vary greatly between the three [83–85]. Possible explanations for this clinical heterogeneity include distinct tissue distribution of PLA2G6 isoforms, derived via alternative splicing [79,86], and different pathogenic alterations that may impose selective effects on protein function [87]. Variants in *PLA2G6* have been associated with NBIA (neurodegeneration with brain iron accumulation) disorder [88,89]. However, elevated levels of iron are only observed in a subgroup of INAD and in aNAD patients but not in PLA2G6-related dystonia-parkinsonism patients [89]. Hence, the precise mechanisms that underlie the pathogenesis of PLAN are still not fully understood.

A study in flies identified phenotypes associated with loss of the fly homolog of *PLA2G6*, *iPLA2-VIA*, including sleep disturbances and loss of dopaminergic neurons [90]. The authors documented a change in phospholipid composition in the brain of *iPLA2-VIA*$^{-/-}$ flies as they contain shortened phospholipid acyl chains when compared to wild-type

controls. These lipid alterations reduce the binding affinity of α-Syn and phospholipids, which in turn promotes α-Syn aggregation. Another study in flies demonstrated that loss of *iPLA2-VIA* causes an excessive ceramide buildup in neurons, impaired retromer function, lysosomal dysfunction, and neurodegeneration [83]. iPLA2-VIA interacts with retromer proteins, including VPS35 and VPS26, and loss of *iPLA2-VIA* leads to a reduction of these proteins, causing excessive trafficking of protein and membrane lipids to lysosomes, resulting in lysosomal expansion and dysfunction. These observations have been confirmed by studies in many other tissue culture and model systems including mice and rats, and are also consistent with observations that variants in *VPS35* cause familial PD [91,92]. The authors proposed that excessive ceramide levels leads to stiffened cellular membranes, based on biophysical data (reviewed in [93]), and documented that ceramide-reducing drugs are able to significantly rescue observed neurodegenerative phenotypes (Figure 3). Another link between ceramide accumulation and PD comes from observations of excessive ceramide as well as a retromer dysfunction in fly PD models in which α-Syn is overexpressed [83]. These phenotypes are strongly suppressed by feeding flies with food containing drugs that lower the ceramide levels. Together, these studies connect variations in *PLA2G6/iPLA2-VIA* with rare neurological diseases as well as PD. Indeed, dysregulations of ceramides are found to be associated with PD progression. The plasma ceramide levels are increased in PD patients [94,95], especially in those who have cognitive impairment [96]. In the postmortem PD brains and cerebrospinal fluid, lipidomic analyses also revealed an unbalanced ratio of sphingolipid metabolites [97–99]. However, these observations in human samples do not address the causal relationship between disrupted ceramide metabolism and PD pathogenesis. Luckily, studies in flies provide new evidence for a possible underlying mechanism. Fly *pink1* is the ortholog of human *PTEN-induced kinase 1 (PINK1)*, which is associated with an autosomal recessive familial form of early-onset PD. *PINK1* is involved in mitochondrial quality control, and loss of *PINK1* leads to dysfunction in mitochondrial activities as well as defective clearance of damaged mitochondria [100,101]. In a recent study, lipidomic analyses of mitochondria isolated from *pink1* deficient flies also documented and increase ceramide levels [102]. Genetic or pharmacological reduction of ceramide levels in flies rescued the mitochondrial phenotypes of *pink1* mutants and restored normal flight behavior. Hence, ceramide reduction may be a potential therapeutic strategy in the treatment of PD [83,103].

Dysregulated ceramide metabolism shared by lysosomal storage disease and Parkinson's disease

Additional insight into the role for ceramide dysregulation in Parkinson's disease has come from studies using the fly aimed at defining the molecular mechanisms of Gaucher disease (GD, Phenotype MIM#230800 Type I, #230900 Type II, #231000 Type III), a lysosomal storage disorder. Variants in the lysosomal acid β-glucocerebrosidase (GCase) encoded by *Glucocerebrosidase* (*GBA1*) lead to accumulation of glucosylceramides (GluCer) in phagocytic '**Gaucher cells**' [104]. While autosomal recessive LOF alleles of *GBA1* cause GD, heterozygous mutant alleles of *GBA1* are genetic risk factors for PD and dementia with Lewy bodies (Phenotype MIM #127750) [105]. GD patients and carriers of GD-associated mutations have a higher propensity to develop PD, and develop a faster progression of both motor and cognitive deficits associated with disease [106,107]. How *GBA1* mutations

influence PD etiology, including α-Syn aggregation, is under intensive investigation and still remains to be fully elucidated (reviewed in [108,109]).

Several *GBA1* mutant fly models have been generated by different groups to elucidate the signaling pathways and cellular processes underling disease pathogenesis [110–115]. Flies have two orthologues of *GBA1*, *Gba1a* and *Gba1b*, and it is the loss of *Gba1b* that accounts for the phenotypes resembling symptoms observed in PD patients [104,105,110,114,115]. *Gba1b* is expressed in the brain and **fat body**, consistent with its role in neurological function and lipid metabolism [112]. Proteomic analyses of *Gba1b* null mutants revealed dysregulation of proteins involved in **extracellular vesicle** (EV) biology, and GCase deficiency was shown to promote protein aggregate spread between cells and tissues via dysregulated EVs [115]. *Gba1b* deficiency affects a specific subset of ceramides that are critical for EVs and alters the cargo components of EVs. The pathogenic effects of ceramide dysregulation were also observed in preformed α-synuclein fibrils (PFF) treated SH-SY5Y cell line, and treating the cells with myriocin, a ceramide synthesis inhibitor, rescued the cellular phenotypes associated with PD [116]. These and other studies (reviewed in [29,117]) implicate ceramide homeostasis as an important candidate for PD therapeutic intervention (Figure 3). Although the working models of the interaction between *GBA1* and PD are complex and have not been well-tested in different cellular contexts [113,118–120], the links between *GBA1* and PD identify new therapeutic targets and strengthen evidence for PD being a lipidopathy (reviewed in [121–123]).

Lipid droplet biology as a functional node in PD and rare diseases

There is also growing evidence that PD pathology is associated with the presence of LDs. *In vitro* data show that α-Syn can accumulate on LD surfaces and may affect the turnover of LDs, but this mechanism has not been confirmed *in vivo*. LD membranes contain perilipin proteins, and perilipin 1 (PLIN1) is the major scaffold protein that encircles the LDs in adipocytes [124,125]. PLIN1 regulates the homeostasis of LDs as a lipid store gatekeeper for the coordinated assembly and disassembly of lipolytic complexes upon phosphorylation and dephosphorylation [125,126]. *PLIN1* is associated with familial partial lipodystrophy type 4 (FPLD4, Phenotype MIM #613877), characterized by childhood or young adult onset lipodystrophy, severe dyslipidemia and insulin-resistant diabetes mellitus [127]. In *Drosophila*, there are two genes encoding fly perilipins, *Lipid storage droplet-1* (*Lsd-1*) and *Lsd-2*. The ortholog of human *PLIN1*, *2*, *3* and *5* is *Lsd-2* [128] and it is ubiquitously expressed. As in vertebrates, Lsd-2 is considered to be the guardian of LDs by limiting the access of lipases [129–131]. The fly eye provides an *in vivo* model to study the relationship of α-Syn and LDs and an accumulation of LDs can be promoted by expression of *Lsd-2* as well as *Lsd-1* in photoreceptor neurons [132]. Interestingly, the overexpression of α-Syn initiates LD accumulation. Moreover, α-Syn aggregation is enhanced in the presence of LDs (Figure 3). Hence, these data provide evidence that LDs contribute to α-Syn aggregation in the progression of PD pathology.

Additional studies have shed light on the role that the protein Split Ends (SPEN), an RNA-binding protein, plays in lipid regulation in PD [133]. Heterozygous truncating mutations in *SPEN* are associated with a rare neurodevelopmental disorder called Radio-Tartaglia

syndrome (RATARS, Phenotype MIM #619312), characterized by global developmental delay and variable behavioral abnormalities [134]. Recently, *SPEN* was also found to be associated with PD using microarray analysis from the substantia nigra of PD patients [61] (Figure 3). In *Drosophila*, loss of *spen* leads to the inhibition of fat catabolism, which delays larval development, indicative of a failure to generate energy to fuel proper development [135]. *spen* also regulates LD number, size, and localization in glia. Knockdown of *spen* in glia leads to increased PLIN2 levels and a dramatic accumulation of LDs in the *Drosophila* brain [61]. Moreover, glial-specific knockdown of *spen* causes enhanced sensitivity to paraquat, a model of PD, while overexpression of *spen* in glia protects against paraquat-induced neurotoxicity [61]. Together, these data support an important role for *SPEN* in the control of lipid metabolism, and implicate *SPEN* and lipid dysregulation in neurodegeneration associated with PD.

These and other studies [136–138] demonstrate that lipid dysregulation in the nervous system is a key component of PD and related neurological disorders. Therapeutic interventions aimed at restoring proper balanced lipid production and preventing buildup of toxic lipid species may be important in PD prevention.

Concluding Remarks

In the pursuit to delineate cell biological mechanisms, including those involved in human diseases, it is critical that researchers have access to genetic models with a history of translational success. There are numerous recent examples of successful rare disease studies using *Drosophila* that have not only shed light into the rare disease diagnosis and pathogenesis, but have also led to insights into common disease [70,139–142]. Continued emphasis on model-organism-based research will fuel insights into rare and common disease mechanisms as well as shed light on therapeutic strategies and identify targets of therapeutic value. Obviously, as with any model system, *Drosophila* has limitations which need to be carefully considered [143–145], but studies in flies balance utility and translatability.

As researchers continue to probe the etiology of both rare and common diseases, common themes emerge. For AD, PD, and related disorders, a key role for mitochondria, ROS, and lipid biology emerges as driving forces for disease, with mitochondrial dysfunction driving lipid dyshomeostasis and peroxidation, leading to neurodegeneration. While general mechanistic themes of disease etiology emerge, the detailed differences of cellular changes as well as the nature of affected lipids distinguish one neurodegenerative disease from another. Future investigation will yield specific molecules for which focused therapeutic intervention will likely aid the prevention or cure of these diseases. A broader therapeutic strategy that aims to prevent general lipid dysregulation and mitochondrial dysfunction might also prove effective at preventing disease with common mechanisms. One such therapeutic strategy is the administration of antioxidants. While this intervention has been tried with mixed success, it is possible that a better knowledge of the genetic make-up of individuals will allow administration of potent, BBB-penetrating antioxidants prior to the onset of disease symptoms for AD. Similarly, lowering ceramide levels may have beneficial effects in individuals that carry variants associated with PD. While many outstanding questions remain (see outstanding questions box), the future of neurodegenerative disease

research as well as therapeutic interventions aimed to prevent them will inevitably be led by the use of model organisms, including the fly.

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Glossary Box

Apolipoproteins
Proteins that are associated with lipids to form lipoproteins. Apolipoproteins stabilize lipoprotein complexes and aid in lipid solubilization

Balancer chromosomes
Genetically engineered chromosomes that carry a recessive lethal or sterile allele as well as a dominant allele that causes a visible phenotype (marker). Balancers also contain multiple chromosomal inversions that inhibit the formation of viable recombinant chromosomes, therefore allowing maintenance of the desired mutation(s) or transgene(s) in future generations

Benign variation
One or more genetic alterations that do not induce any obvious phenotype or cause disease

Disease-causing variants
One or more genetic alterations that cause or are associated with a particular disease

Extracellular vesicle (EV)
Particles released from cells surrounded by a phospholipid bilayer to transport cargo proteins, lipids, etc

Fat body
The fly tissue containing adipocytes which facilitate lipid metabolism and storage as well as protein synthesis and secretion

Gaucher cells
Monocyte-macrophage cells that accumulate unprocessed glucocerebrosidase. These cells are typically characterized by their large size, small and eccentrically placed nuclei, spindle or rod-shaped membrane-bound inclusion bodies, and numerous small tubules in the cytoplasm

Lewy bodies

Inclusion bodies in which abnormal protein aggregations (composed of the protein α-synuclein in association with ubiquitin, neurofilament protein, alpha B crystalline, etc.) form and which serve as a pathological marker for PD

Lipid droplet (LD)
A phospholipid monolayer-bound organelle containing lipids (esp. di- and tri-acylglycerols and sterol esters) together with embedded proteins. LDs serve as lipid stores and are most prevalent in adipose tissue

Lipogenesis
The process of fatty acid synthesis. Lipogenesis occurs predominantly in the liver, adipose tissue, and small intestine

Mitochondrial respiratory chain
Five enzymatic protein complexes (I-V) critical for the production of energy in the form of adenosine triphosphate (ATP)

Neurometabolic disorders
Genetic disorders that result from abnormalities of enzymes that cause a deficiency or an accumulation of certain essential metabolites or cause the accumulation of toxic compounds, impairing the development or function of the nervous system

Peroxidation
The process of chemical degradation of lipids by oxidants. Polyunsaturated fatty acids, containing multiple carbon-carbon double bonds, are particularly susceptible to peroxidation

Phospholipid
A type of amphiphilic lipid that is composed of two fatty acids (hydrophobic “tails”), a phosphate group (hydrophilic “head”), and a glycerol molecule. Phospholipids comprise the key components of cell membranes often forming a bilayer with oppositely oriented molecules (heads out)

Reactive oxygen species (ROS)
Radical oxygen-containing molecules that readily oxygenate and alter cellular molecules

Substantia nigra (SN)
Meaning “black substance,” the SN is a part of the basal ganglia in the midbrain which looks like a darkened streak in the unstained brain. The SN itself is made up of two anatomically and functionally distinct portions: the substantia nigra pars compacta (SNpc), mainly consisting of dopaminergic neurons, and the substantia nigra pars reticulata (SNpr), mainly consisting of GABAergic neurons

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Outstanding Questions Box

- What is the prevalence of lipid dysregulation in neurodegenerative diseases beyond AD and PD?
- Are there signatures of alterations in lipid accumulation and metabolism that can be used as biomarkers and diagnostic tools?
- What is the role of different brain cell types in neurodegenerative diseases? Which cell types are affected first?
- Which organelles are relevant to neurodegenerative diseases? Which organelles are affected first?
- Can therapeutics be generated that selectively target specific proteins and lipids in different cell types?
- How can researchers more readily translate observations in fly studies to human disease?

Highlights

- The study of rare neurological disease using the fruit fly, *Drosophila melanogaster*, has shed valuable insight into common neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.
- Mitochondrial dysfunction and lipid dysregulation are shared features of many rare neurological disorders and common neurodegenerative diseases.
- Studies aimed at delineating mechanisms in flies have shed light on disease pathogenesis and identified novel therapeutic targets for the treatment of neurological disease.

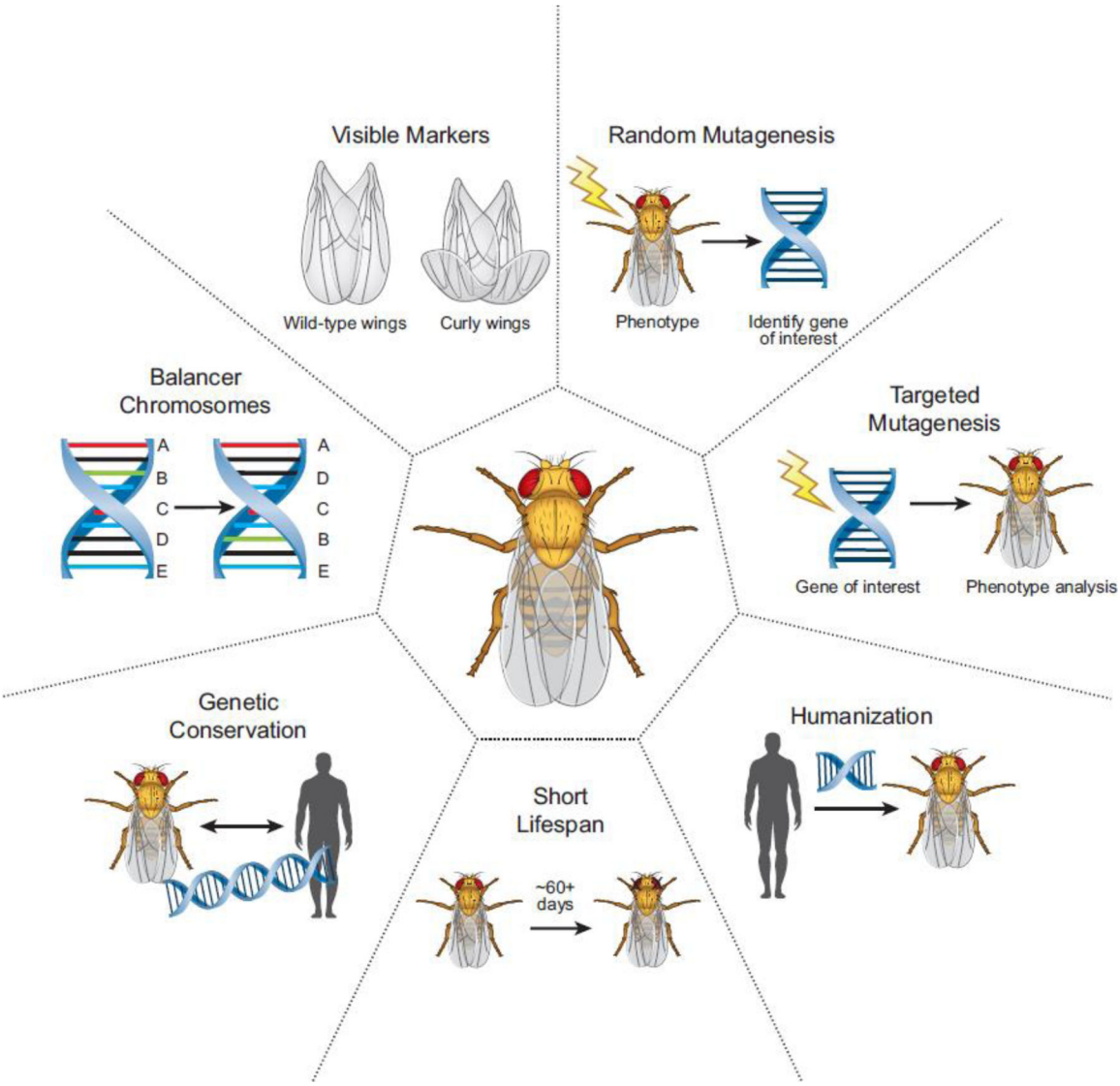

Figure 1. Advantages of fly biology together with innovative genetic technologies make *Drosophila melanogaster* a valuable genetic tool

The fly is a valuable screening platform for random or targeted mutagenesis with visible markers and balancer chromosomes to help track mutations without the need for genotyping. The high degree of genetic conservation between human and fly genes together with humanization strategies widely available in the fly provide a useful resource to probe causes of human genetic disease. The biology of the fly, including a short lifespan, allow for simple and rapid assessment of age-dependent phenotypes including neurodegeneration.

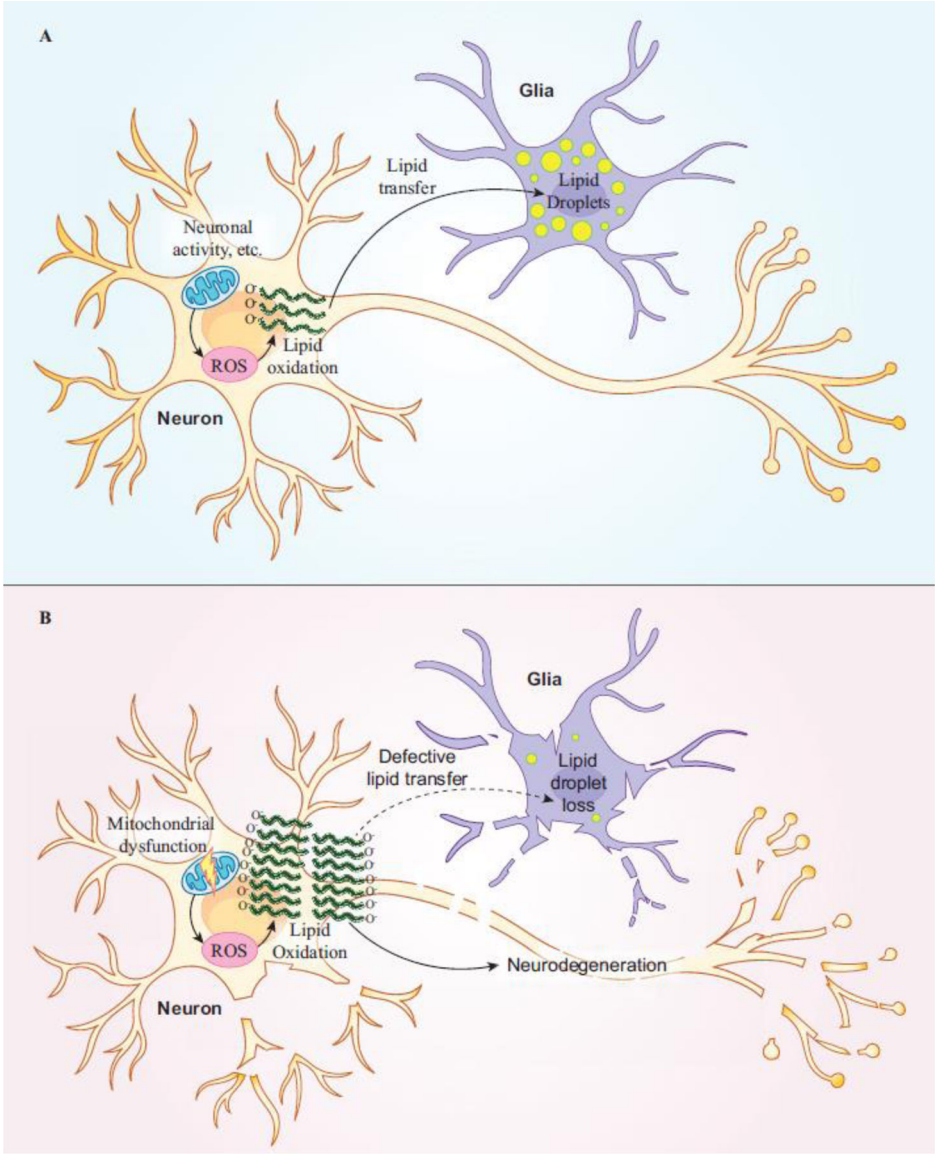

Figure 2. Oxidated lipids produced upon neuronal ROS are shuttled to glia and sequestered in glial LD which protects neurons from damage

(A) Glial LD formation defends against neurotoxicity caused by oxidative stress in the form of ROS. Neuronal ROS production from mitochondria induces lipogenesis and lipid oxidation. Oxidated lipids are shuttled from neurons to glia where they become sequestered in LDs.

(B) Loss of glial LD formation leads to neurodegeneration. Elevated ROS (due to aging, genetic risk, etc.) together with defects in neuron-to-glia lipid transfer leads to the accumulation of oxidated lipids in neurons and in the extracellular space where they induce neurodegeneration. Genes important for lipid transfer overlap with AD risk factors suggesting an important role for glial LD formation in disease.

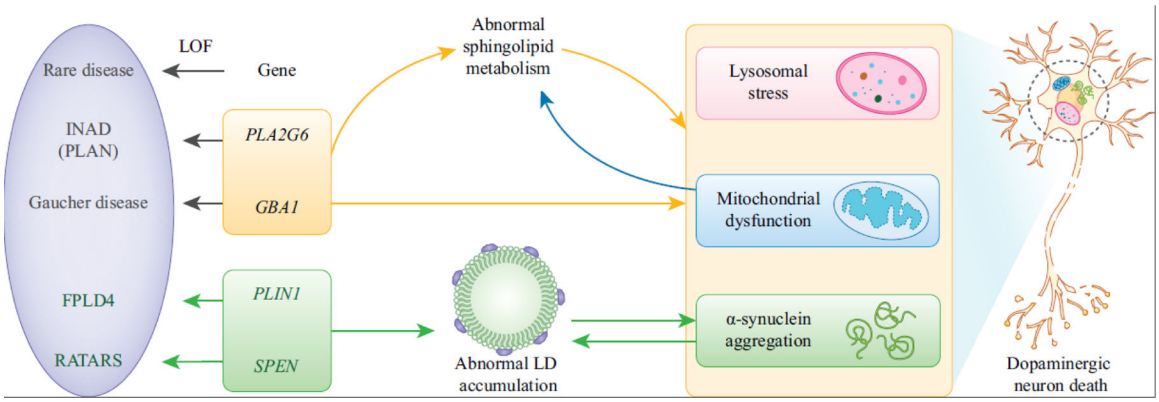

Figure 3. The involvement of rare disease-associated genes in lipid metabolism as a common mechanism in PD

Autosomal recessive mutations in *PLA2G6* are associated with INAD (PLAN). Autosomal recessive LOF alleles of *GBA1* cause Gaucher disease (GD). Loss of *PLA2G6* or *GBA1* causes abnormal sphingolipid metabolism. Dysfunction of *PLA2G6* or *GBA1* causes lysosomal stress, mitochondrial defects and α-Syn aggregation, leading to the dopaminergic neuron death in PD. In addition, mitochondrial stress causes ceramide accumulation. *PLIN1* regulates the homeostasis of LDs as a lipid store gatekeeper. Heterozygous frameshift mutations in *PLIN1* are associated with FPLD4. Heterozygous truncating mutations in *SPEN* are associated with RATARS. Disruption of *PLIN1* or *SPEN* causes accumulation of LDs, which contributes to α-Syn aggregation in the progression of PD. In addition, overexpression of α-Syn also causes LD accumulation.