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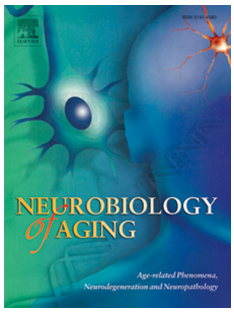

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Genetic or pharmacological activation of the *Drosophila* PGC-1α ortholog *spargel* rescues the disease phenotypes of genetic models of Parkinson's disease

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Running title: PGC-1α activation rescues Parkinsonian phenotypes

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Abstract

Despite intensive research, the etiology of Parkinson's disease (PD) remains poorly understood and the disease remains incurable. However, compelling evidence gathered over decades of research strongly support a role for mitochondrial dysfunction in PD pathogenesis. Related to this, PGC-1α, a key regulator of mitochondrial biogenesis, has recently been proposed to be an attractive target for intervention in PD. Here, we showed that silencing of expression of the *Drosophila* PGC-1α ortholog spargel results in PD-related phenotypes in flies and also seem to negate the effects of AMPK activation, which we have previously demonstrated to be neuroprotective, i.e. AMPK-mediated neuroprotection appears to require PGC-1α. Importantly, we further showed that genetic or pharmacological activation of the *Drosophila* PGC-1α ortholog spargel is sufficient to rescue the disease phenotypes of Parkin and LRRK2 genetic fly models of PD, thus supporting the proposed use of PGC-1α-related strategies for neuroprotection in PD.

1. Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative movement disorder that is characterized pathologically by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain, which results in a severe depletion of striatal dopamine (DA) that is needed for an individual to execute proper, coordinated movements. Although most cases of PD occur in a sporadic manner, a subset of PD cases is inheritable and attributable to mutations in specific genes, which include *Parkin* and *LRRK2* (Martin et al., 2011). Current therapies for PD are largely symptomatic and none of the available medications could stop or slow the insidious neurodegenerative process. Despite intensive research, the etiology of PD remains poorly understood but a broad range of studies conducted over the past few decades have consistently implicated mitochondrial dysfunction

as a key pathogenic culprit (Lim and Zhang, 2013). Not surprisingly, the mitochondrion has emerged as an attractive target for neuroprotection in PD (Schapira and Patel, 2014). Importantly, a recent systems biology-based study identified Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis, as a potential therapeutic focus for intervention in PD (Zheng et al., 2010). Notably, the authors found that bio-energetic genes responsive to PGC-1α are under-expressed in patients with PD, suggesting that the upregulation of PGC-1α may be beneficial. In a related development, we have recently demonstrated that the activation of AMP kinase (AMPK), which activates several downstream targets including PGC-1α, mitigates mitochondrial abnormalities and dopaminergic dysfunction in *Drosophila* genetic models of PD (Ng et al., 2012). Here, we showed that AMPK-mediated neuroprotection involves PGC-1α. We further showed that genetic or pharmacological activation of the *Drosophila* PGC-1α ortholog spargel is sufficient to rescue the disease phenotypes of genetic models of PD, thus supporting the proposed focus on PGC-1α for neuroprotection in PD.

2. Methods

2.1 Fly stocks. Fly lines for *Yellow-white (yw)* control (BL64400), *24B-GAL4* (muscle-specific) and *Ddc-GAL4* (III) (expresses in dopaminergic and serotonergic neurons) (BL7009), *UAS-spargel* and *UAS-mito-GFP* were purchased from Bloomington *Drosophila* Stock Center (Bloomington, IN, USA). *UAS-RNAi-spargel* was purchased from Vienna *Drosophila* RNAi Center (Vienna, Austria). *UAS-dAMPK-TD, LRRK2-WT, LRRK2-G2019S* transgenic and parkin null flies (*park1*) were previously described (Lee et al., 2007; Ng et al., 2009; Wang et al., 2007). The spargel germline homozygous loss of function mutant *srl[KG08646]* was a kind gift from Dr. C. Frei (ETH Zurich, Switzerland).

2.2 Immunohistochemistry, TEM analysis and dopamine assay. Immunohistochemical analysis of whole-mount adult fly brains was performed according to published protocols (Whitworth et al., 2005) and stained with rabbit anti-TH (1:300, Pel-Freez Biologicals, Milwaukee) as primary antibody before analysis using an Olympus Fluoview Upright Confocal Microscope. DA neurons were quantified according to published methods (Whitworth et al., 2005). The size of mito-GFP puncta was measured using Image J program and expressed as mean $\pm$ S.D. ($n \geq 10$ DA neurons per experimental group). For TEM analysis, indirect flight muscles were prepared according to previous protocol (Ng et al., 2012) and specimens were sent for commercial EM analysis at the EM Research Services, Newcastle University (UK). For dopamine measurement, 10 fly heads were homogenized in 0.1 M perchloric acid and the lysates were filtered through 0.1 µm Durapore Ultrafree Centrifugal filters (Millipore, USA) prior to HPLC measurement.

2.3 Climbing assay and drug treatment. Climbing assays were carried out according to previously described methods (Ng et al., 2009). To study the effects of drugs, flies were fed with cornmeal-agar medium supplemented with 0.3 mM Pyrroloquinoline quinone (PQQ) (Sigma), at day 35 post eclosion (for LRRK2 flies) for a period of 25 days.

2.4 Statistical Analysis. Unless otherwise stated, statistical significance for all the quantitative data obtained were analyzed using one way ANOVA with Tukey's HSD *post hoc* test (*$P < 0.05$, **$P < 0.001$).

3. Results

To address the role of PGC-1α in the maintenance of mitochondrial and dopaminergic neuron homeostasis in *Drosophila*, we examined mutant flies that are deficient in the

expression of *spargel* (an ortholog of the mammalian *PGC-1α*). Notably, spargel loss of function mutant flies have previously been reported to result in mitochondrial abnormalities in larval fat body (Tiefenbock et al., 2010). Interestingly, a recent study using a RNAi approach to knock down spargel function in adult *Drosophila* documented a reduced locomotion ability (Merzetti and Staveley, 2015). Consistent with this, we found that spargel deficiency promotes an age-dependent impairment in the climbing ability of adult flies (Fig. 1A). Further, we also recorded a significant loss of TH-positive neurons in the PPL1 as well as PPM3 dopaminergic clusters (Fig. 1B & C) that is associated with a remarkable depletion of dopamine level in the mutant fly brain, which is comparable to that exhibited by LRRK2 and parkin mutant flies (Fig. 1D). Given the intimate role of PGC-1α in mitochondrial homeostasis, we next examined the morphology of mitochondria in the dopaminergic neurons of control and mutant flies and found that spargel deficiency results in significantly smaller mitochondrial size (Fig. 1E). As the spargel mutant arose from a germline mutation, we also examined the status of mitochondria in their flight muscles. We found that spargel mutant flies exhibit visibly more fragmented mitochondria relative to their control counterparts (Fig. 1F). As an extension of these findings, we generated *spargel* knockdown flies via the RNAi approach. When driven by the muscle-specific *24B-GAL4* driver, the silencing of spargel expression similarly results in more fragmented mitochondria relative to those harboring the driver (i.e. 24B/+) alone. The same scenario is observed when we knockdown spargel in dopaminergic neurons via the *Ddc-GAL4* driver (also expresses in serotonergic neurons), which leads to marked loss of TH-positive neurons in the PPL1 cluster (Fig. 1C & G) and again smaller-sized mitochondria (Fig. 1E). Curiously, *Ddc-GAL4*-mediated silencing of spargel expression did not result in apparent climbing impairment (Fig. S2A), which perhaps reflects a more modest RNAi silencing effect in the absence of co-expressed Dicer-2. Notably, the effect observed by Merzetti and Staveley in their spargel RNAi flies is also

rather modest (Merzetti and Staveley, 2015). Notwithstanding this, our results when taken together suggest that optimal expression of spargel is essential for the maintenance of mitochondrial and dopaminergic neuronal integrity.

Next, we examined the effects of spargel overexpression in flies. Notably, transgenic overexpression of spargel alone in *Drosophila* does not have any negative effects on its climbing performance, dopaminergic neuronal integrity, neuronal mitochondrial size or dopamine level (Fig. S1A-D). Given our previous report that the activation of AMPK, a key upstream regulator of PGC-1α, mitigate the pathological phenotypes of parkin deficient flies (Ng et al., 2012), we speculated that spargel overexpression would similarly be neuroprotective against the loss of parkin function. As anticipated, we found that the climbing performance of parkin null flies is markedly improved in the presence of spargel overexpression (Fig. 2A), a phenomenon that is likely related to the ability of spargel to rescue the widespread mitochondrial pathology of parkin null flies, particularly in their flight muscles (Fig. 2B). Since spargel overexpression can apparently compensate for the loss of parkin function, and given our previous demonstration that parkin activity can protect against LRRK2-induced neurotoxicity (Ng et al., 2009), we further speculated that spargel overexpression can also ameliorate the disease phenotypes of *Drosophila* expressing LRRK2 G2019S mutant. Again, as expected, spargel overexpression in LRRK2 G2019S flies via the *Ddc-GAL4* driver rescues their climbing deficits (Fig. 2C) and also protects against the loss of their PPL1 dopaminergic neurons (Fig. 2D) to a similar extent to that brought about by a constitutively active AMPK mutant (i.e. AMPK-TD) that we have previously shown to protect against LRRK2-induced neurotoxicity (Ng et al., 2012) (Fig. 2C-D). Moreover, the reported abnormal enlargement of mitochondrial size associated with LRRK2 mutant (Ng et al., 2012) is restored in the presence of spargel overexpression (Fig. 2E). Collectively, these results demonstrate that enhanced spargel/PGC-1α activity is neuroprotective in *Drosophila*

parkin and LRRK2 PD models and suggest that the transcriptional coactivator acts downstream of AMPK. Supporting this, we found that AMPK-mediated protection of LRRK2-induced climbing deficits and dopaminergic neuronal loss is abolished in the presence of RNAi-mediated silencing of spargel expression (Fig. 2F & G). Notably, AMPK-TD co-expression has no appreciable beneficial effects on the dopaminergic neuronal number of *spargel* knockdown flies (Fig. S2B). Thus, our results suggest that AMPK-mediated neuroprotection possibly requires spargel/PGC-1α.

Finally, we tested whether pharmacological activation of PGC-1α might also work. For this purpose, we treated LRRK2 mutant flies with PQQ, which was reported to stimulate mitochondrial biogenesis through increasing PGC-1α expression (Chowanadisai et al., 2010). Consistent with our results above, PQQ treatment of LRRK2 mutants ameliorates its disease-associated phenotypes including dopaminergic neuronal loss (Fig. 2H) and enlarged neuronal mitochondria (Fig. 2I). Taken together, our results suggest that genetic or pharmacological activation of PGC-1α may be of therapeutic value to PD.

4. Discussion

Emerging studies suggest that the enhancement of PGC-1α activity may offer neuroprotection in PD (Islam et al., 2012; Peng et al., 2016). This is an attractive proposition considering that the PGC-1α transcriptional co-activator is able to induce mitochondrial biogenesis as well as antioxidant defenses (St-Pierre et al., 2006) – both of these processes appear to be dysfunctional or sub-optimal in the PD brain (Zheng et al., 2010). Supporting this, human induced pluripotent stem cell-derived PD models exhibit defects in MEF2- PGC-1α transcriptional network, leading to mitochondrial dysfunction and neuronal death (Ryan et al., 2013). Moreover, polymorphic variations in the PGC-1α gene are known to modulate the risk and age of onset of PD in the human population (Clark et al., 2011). Notably, mice

deficient in PGC-1α expression are more sensitive to the degenerative effects of the parkinsonian neurotoxin MPTP (St-Pierre et al., 2006) and α-synuclein overexpression (Ciron et al., 2015). Similarly, both our group (this study) and others (Merzetti and Staveley, 2015) have demonstrated that the deficient expression of spargel, the *Drosophila* PGC-1α ortholog, results in locomotion defects. However, Merzetti and Staveley also documented an increased mean lifespan in spargel-deficient flies despite their PD-like phenotypes (Merzetti and Staveley, 2015), which is rather curious and contradicts a previous report by others showing that spargel overexpression (rather than deficiency) promotes longevity (Rera et al., 2011). Importantly, we further showed in this study that genetic overexpression or pharmacological activation of PGC-1α activity mitigates the examined disease-associated phenotypes of parkin null and LRRK2 G2019S mutant flies. It is noteworthy to highlight that for LRRK2 mutant flies, we have assumed that its expression is not compromised in the presence of the co-expressing spargel transgene, notwithstanding that we have previously reported that LRRK2 expression in the fly brain essentially remains unchanged in the presence of AMPK or Parkin co-expression (Ng et al., 2012). At the same time, we demonstrated in this study that PGC-1α activity appears to be needed for its upstream activator AMPK to exert its neuroprotection, although more work clearly needs to be done to confirm this. This is nonetheless an important clarification as AMPK activation is known to modulate multiple processes (besides promoting mitochondrial biogenesis) to regulate intracellular energy metabolism. Interestingly, PGC-1α deficiency is also featured prominently in Parkin-related PD cases. This is due to the ability of Parkin to regulate the expression of PGC-1α indirectly through its ability to down-regulate PARIS (Shin et al., 2011), which is a major transcriptional repressor of PGC-1α. Thus, it is logical to expect that the enhancement of both AMPK and PGC-1α activities may compensate for the loss of Parkin function and be neuroprotective in Parkin-deficient models, which is precisely what we have observed

previously (Ng et al., 2012) and in the current study. That both strategies apparently also work in rescuing LRRK2-induced disease phenotypes emphasize the need to examine the poorly understood relationship between LRRK2 and mitochondrial homeostasis beyond current favored models of LRRK2-induced neurotoxicity that includes its role in causing vesicular trafficking defects and protein synthesis dysregulation (Martin et al., 2014).

In essence, our study provides *in vivo* evidence supporting the use of PGC-1α-related strategies for neuroprotection in PD. However, we wish to highlight that more work needs to be done to establish this particularly in view of recent reports demonstrating that PGC-1α overexpression actually resulted in dopamine depletion associated with reduced Pitx3 levels and enhanced sensitivity of these neurons to MPTP-induced toxicity (Ciron et al., 2012; Clark et al., 2012). Future work should clarify if the neuroprotective effect of PGC-1α is dosage-dependent.

Disclosure Statement

The authors have no conflicts of interest to disclose

Acknowledgments

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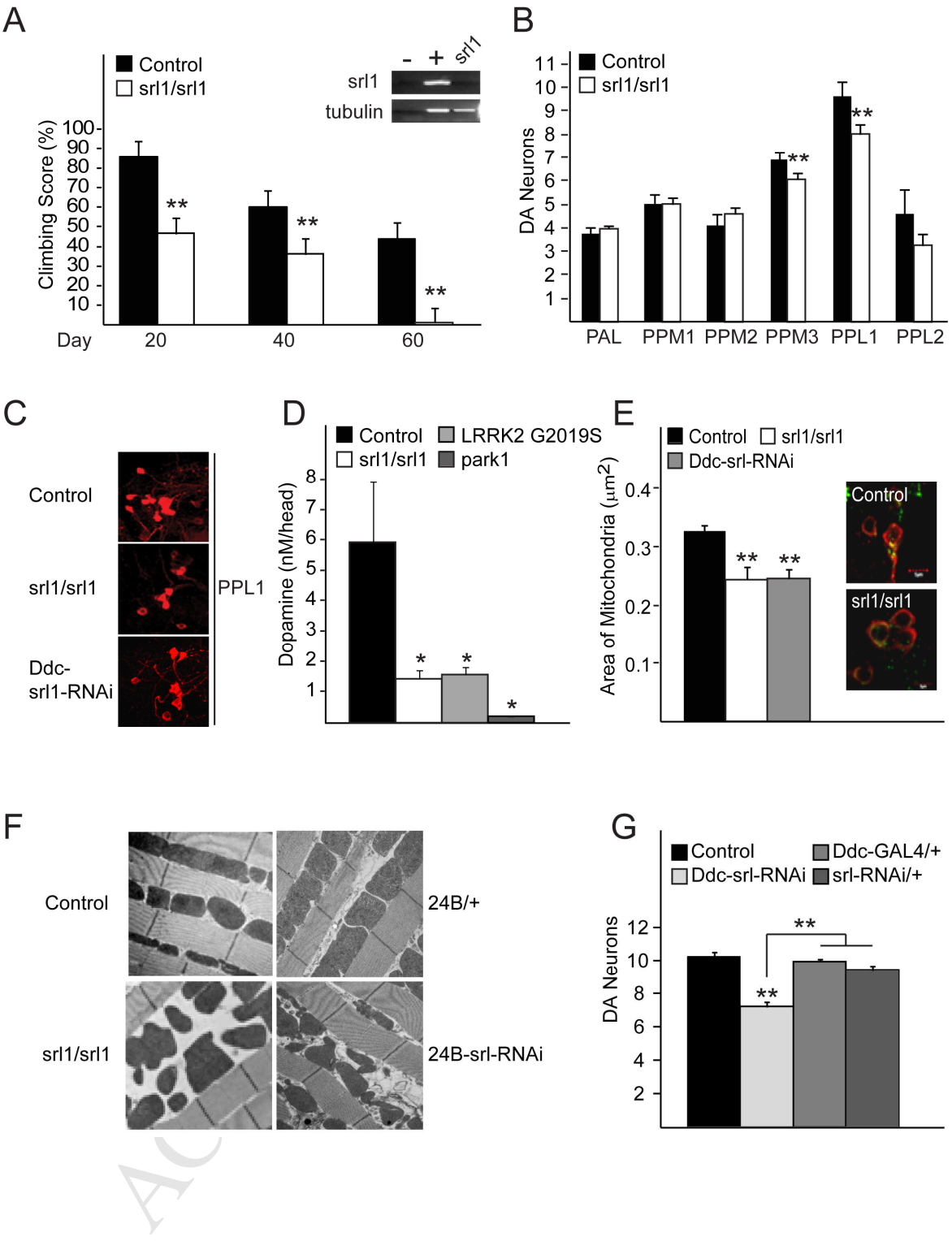
Figure Legend

Figure 1. Spargel deficiency promotes mitochondrial abnormalities and dopaminergic dysfunction in *Drosophila*. (A) Climbing score of wild type and spargel mutant flies at

different age post-eclosion, as indicated. *Inset*, expression of spargel in wild type (+) and mutant (srl1) mutant flies as detected by RT-PCR. (-) refers to negative control. (B) Bar-graph showing the number of TH-positive DA neurons in different clusters of wild type and spargel mutant flies at 60 day post eclosion. (C) Representative confocal microscopy images showing TH-positive (red) dopaminergic neurons in the PPL1 cluster of control, spargel mutant, and *Ddc-GAL4* driven srl-RNAi flies at 60 days post eclosion. (D) Dopamine level in control, spargel mutant, LRRK2 G2019S and parkin null (park1) flies as measured by HPLC. (E) Bar-graph showing the average size $\pm$ S.D. of mito-GFP puncta in control and spargel mutant flies and also those whose spargel expression is silenced (srl-RNAi). *Inset*, Representative confocal microscopy images showing the expression and localization of mito-GFP in TH-positive neurons (red) of control and spargel mutant flies. (F) TEM images of indirect flight muscles of control, *24B-GAL4* driver line and spargel mutant flies, as indicated. (G) Bar-graph showing the number of TH-positive DA neurons in the PPL1 cluster of control, srl1-RNAi (*Ddc-GAL4* driven), *Ddc-GAL4* alone and *UAS-srl-RNAi* alone flies at 60 days post eclosion.

Figure 2. Overexpression of *spargel* rescues the disease-associated phenotypes of parkin and LRRK2 mutant flies. (A) Climbing score of control and parkin null (*park1*) flies in the absence or presence of spargel overexpression (*park1, 24B>srl*) at 25 days post eclosion. (B) TEM images of indirect flight muscles of parkin null flies in the absence or presence of spargel overexpression at 25 days post eclosion. (C) Climbing score and (D) DA neuronal number (PPL1 cluster) of control, wild type LRRK2 and LRRK2 mutant flies in the absence or presence of a constitutive active AMPK mutant (AMPK-TD) or spargel overexpression, as indicated. (E) Bar-graph showing the average size $\pm$ S.D. of mito-GFP puncta in control and mutant LRRK2 flies (G2019S) in the absence or presence of spargel overexpression (GS +

spargel). (F) Climbing score and (G) DA neuronal number (PPL1 cluster) of control, LRRK2 mutant flies, and LRRK2 G2019S/AMPK-TD double mutant flies that are silenced of spargel expression (GS + TD + srl-RNAi). (H) DA neuronal number (PPL1 cluster) and (I) average size ± S.D. of mito-GFP puncta of wild type LRRK2 and LRRK2 mutant flies in the absence or presence of PQQ treatment. All the analyses for LRRK2 flies were done at 60 days post eclosion.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50
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Control
srl1/srl1
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srl1/srl1
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24B/+
24B-srl-RNAi
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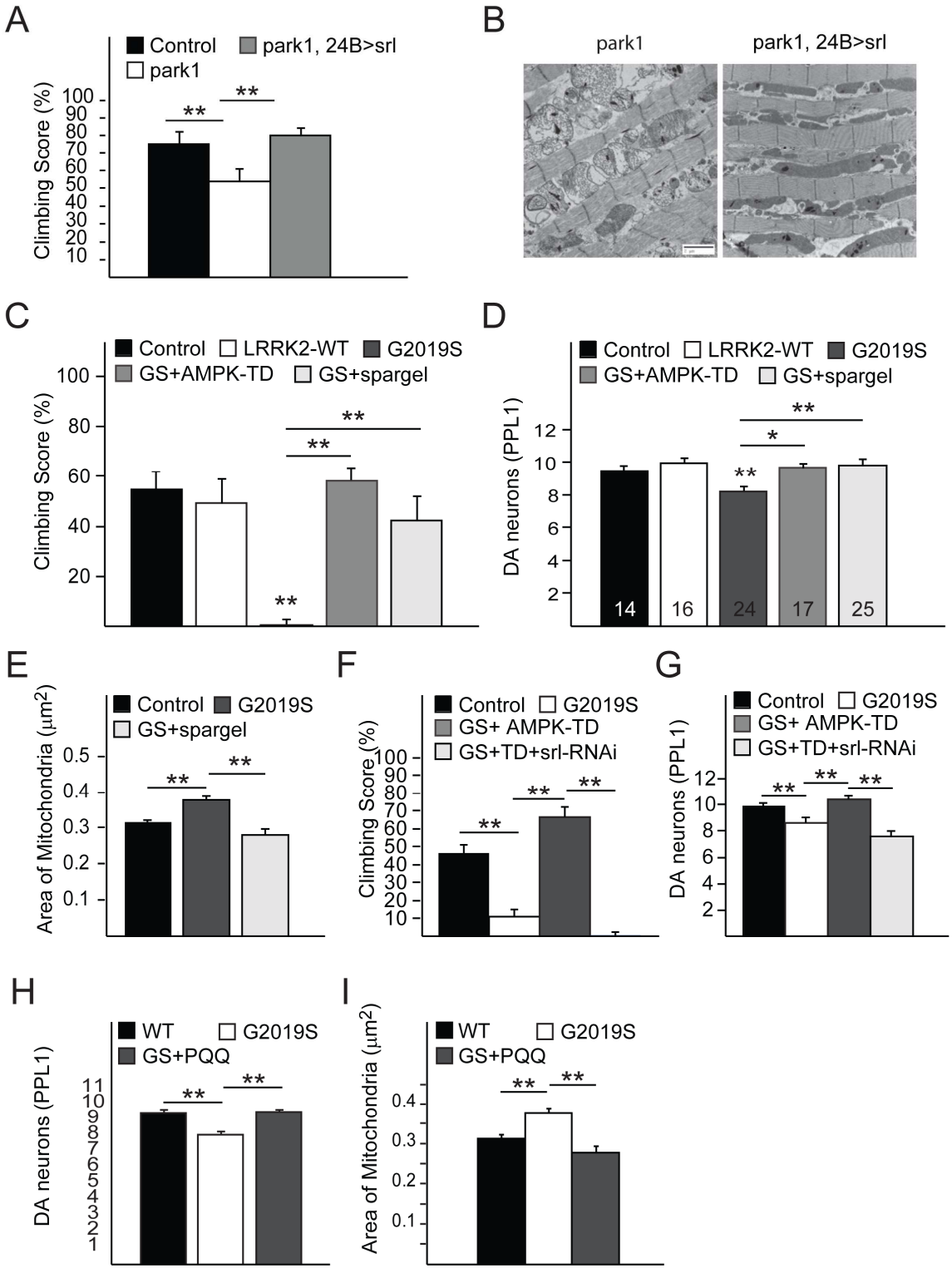
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park1, 24B>srl
park1
Climbing Score (%)
B
park1
park1, 24B>srl
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Control
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G2019S
GS+AMPK-TD
GS+spargel
Climbing Score (%)
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DA neurons (PPL1)
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24
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Area of Mitochondria (μm2)
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GS+ AMPK-TD
GS+TD+srl-RNAi
G
H
WT
G2019S
GS+PQQ
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Highlights

- Silencing of PGC-1α/spargel expression promotes Parkinsonian phenotypes in flies
- PGC-1α/spargel expression silencing blocks AMPK-mediated neuroprotection
- PGC-1α/spargel activation rescues disease phenotypes of PD flies
- Our findings support the use of PGC-1α-related strategies for neuroprotection in PD