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A gutsy way to extend longevity

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A commentary on

Modulation of longevity and tissue homeostasis by the *Drosophila* PGC-1 homolog by Rera, M., Bahadorani, S., Cho, J., Koehler, C.L., Ulgherait, M., Hur, J.H., Ansari, W. S., Lo, T. J., Jones, D. L., and Walker, D. W. (2011). *Cell Metabol.* 14, 623–634.

Aging is a complex biological process characterized by declining physiological functions. One of the most prominent age-associated declines is a loss of mitochondrial function. Progressive loss of mitochondrial activity and biogenesis negatively affects longevity whereas preservation of mitochondrial biogenesis results in life span extension (Guarente, 2008; Cho et al., 2011). For instance, beneficial effects and longevity extension associated with dietary restriction are closely related to increased mitochondrial biogenesis in a variety of species (Guarente, 2008). The PGC-1 family of transcription coactivators promotes mitochondrial biogenesis through coactivation of nuclear transcription factors (Scarpulla, 2011). Together, they induce expression of genes encoding mitochondrial proteins to enhance mitochondrial activity. The recent publication by Rera et al. (2011) offers additional evidence for the role of mitochondrial biogenesis in aging. They found an age related decrease in the levels of *dPGC-1* (*Drosophila* PGC-1 or *spargel*) mRNA and investigated if an increase in *dPGC-1* levels in the whole body or in a tissue specific manner could affect fly longevity. While overexpression of *dPGC-1* in the whole body increases mitochondrial activity, it also decreases fly life span. However, overexpression of *dPGC-1* specifically in the *Drosophila* midgut promotes intestinal homeostasis and extends fly longevity. Their findings indicate a key role for mitochondrial biogenesis in intestinal stem cell (ISC) homeostasis and longevity and provide the link between two important areas of aging research, ISCs, and mitochondrial biogenesis.

Midgut maintenance and homeostasis has recently emerged as an important determinant of fly life span (Biteau et al., 2010). The *Drosophila* midgut is maintained by multipotent ISC activity. ISCs undergo asymmetric division, giving rise to an identical daughter ISC and an immature enteroblast (EB) with differentiation potential (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). In old flies, ISCs hyper-proliferate, but ISC daughter cells do not differentiate, which results in the accumulation of misdifferentiated ISC daughter cells, a phenotype thought to contribute to gut aging. For instance, genetic or environmental manipulations that prevent tissue maintenance have been associated with accumulation of ISCs, irregular ISC proliferation and differentiation patterns, and shorter lifespan (Biteau et al., 2010). Likewise, genetic manipulations that preserve ISCs homeostasis extend longevity (Biteau et al., 2010). Rera et al. (2011) demonstrated that the age related decline in mitochondrial activity observed in the midgut epithelia may be a key component in the loss of ISCs homeostasis. The authors showed that increasing levels of *dPGC-1*, specifically in the immature cells and their progeny in the midgut is sufficient to extend longevity. The transcription factor *escargot* (*esg*) is a marker for ISCs and EBs. They used the *esgGal4/dPGC-1/UAS* and the *5691GeneSwitch/dPGC-1* UAS system, to drive expression of *dPGC-1* in *esg*-positive cells. *dPGC-1* overexpression in *esg*-positive cells resulted in preservation of mitochondrial membrane potential and increased activity of mitochondrial complexes I and II.

dPGC-1 AND TISSUE HOMEOSTASIS

Age-associated hyper-proliferation and accumulation of misdifferentiated cellular aggregates in the midgut is associated with increased exposure to mitochondrial free radicals. Prolonged exposure to oxidative stress triggers persistent ISC proliferation in an attempt to restore damaged tissue. When the rate of proliferation exceeds the ability

for faithful differentiation, it results in accumulation of misdifferentiated cells (Biteau et al., 2010). Upregulation of *dPGC-1* activates ROS-detoxifying enzymes, which reduce age related oxidative damage in the midgut (Rera et al., 2011). Consequently, *esg* targeted *dPGC-1* overexpression resulted in a significant decrease in both proliferation and cellular misdifferentiation in aged flies when compared to controls.

Aged flies often exhibit irregular intestinal tissue architecture or deterioration due to impaired ISC function, which fails to replace recent regions of apoptosis (Biteau et al., 2010). *esgGAL4* driven expression of *dPGC-1* was sufficient to maintain intestinal integrity. Long-lived flies overexpressing *dPGC-1* in the gut ISCs have decreased levels of triglycerides but have the same fecundity, weight, food consumption, and response to hyperoxia and starvation as control flies. These results suggest that longevity effects of *dPGC-1* are independent from the stress resistance and reproduction.

CONCLUDING THOUGHTS

The studies conducted by Rera et al. successfully demonstrate a new role for *dPGC-1* and mitochondrial biogenesis in ISC homeostasis and longevity. How does it all work? *dPGC-1* overexpression increases levels of anti-oxidative enzymes to decrease oxidative damage and conserve ISC homeostasis. Preserved ISC homeostasis is required for gut maintenance, which is necessary for normal energy supply and/or prevention of microbial or toxin overload. All of these factors may contribute to delaying the onset of age related phenotypes. As Zhou et al. (2011) suggested, it is also possible that an unknown factor/s released by PGC-1 overexpression in ISCs/EBs regulates longevity directly or through affecting other longevity pathways. This work highlights the complex influence of *dPGC-1* on aging at the cellular level as well as at the organismal level. Overall the data presented by Rera et al. (2011) links two major components of aging and has uncovered an attractive target for the modulation of aging.

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