submaximal exercise, while fatty acid (FA) concentrations are not affected by maximal exercise but increase after submaximal exercise (Lee et al., 2014) and exposure to cold, at least in BAT positive subjects (Orava et al., 2013). In this context, shivering may be regarded as “low-intensity minimal exercise,” which may be important for the irisin response (Lee et al., 2014). The resulting browning of subcutaneous WAT may help meet the need for excess oxidation sites for released FAs in response to cold, acting in concert with heat production. Alternatively, submaximal exercise may be regarded as “high-intensity shivering,” leading to similar responses including the activation of thermogenesis along with the oxidation of glucose and FAs in working muscles.

Overall, the results by Lee et al. (2014) suggest that irisin and FGF21—induced submaximal exercise, shivering or cold—collaborate in promoting the browning of adipose tissue in order to meet the increased demand for fat (and/or glucose) oxidation. In the future, it will be interesting to explore how these signals linking muscle and adipose tissue are regulated in obesity and whether they could function as a treatment for subjects with nonfunctional BAT. Moreover, these two players, though important, are only part of the puzzle, and new factors will likely add to our understanding of muscle-adipose tissue communication and the possibilities for treatment.

REFERENCES


Independent Control of Aging and Axon Regeneration

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Axon regeneration capacity often declines with age. One might assume that loss of regeneration is an obvious consequence of organismal aging. However, in the latest issue of Neuron, Byrne et al. (2014) demonstrate that regeneration ability and aging are regulated cell-autonomously within neurons, and can be decoupled.

In animals, the juvenile state is often associated with better tissue-repair ability. Ample evidence suggests that this is also the case for axon regeneration, an essential step of neural repair after brain and spinal cord injury. For example, in contrast to immature neurons with robust growth ability, the terminally differentiated neurons in the adult mammalian central nervous system possess limited regenerative regrowth after injury. Such aging-associated decline of regenerative growth has also been observed in the mammalian peripheral nervous system and other species. These observations suggest a possible connection between axon regeneration ability and aging. However, this issue has never been formally tested due to the complexity of the system. In an attempt to address this question, Byrne and colleagues analyze how aging affects axon regeneration in C. elegans, and find that age-dependent decline of axon regeneration ability is independent of the life span of the animals. (Byrne et al., 2014).

C. elegans is a particularly well-adapted model to address the relationship between axon regeneration and aging. Axon regeneration can be easily assessed in vivo by laser axotomy, and C. elegans is a leading model for aging study. Byrne and colleagues first observe a 3-fold decrease in axon regeneration capacity between young and old adult worms, corroborating the hypothesis of age-dependent decline of regeneration. They then ask whether conditions that delay aging and increase lifespan could overcome this effect. They therefore assess the regeneration capacity of old worms in three different mutants known to increase life span (sig-2, eat-2, and daf-2) (Figure 1). They observe that only the mutation in daf-2, the worm homolog
of insulin/insulin-like growth factor 1 receptor, enhances regeneration in aged adults, whereas sir-2.1 and eat-2 mutants do not affect regeneration, demonstrating that some mechanisms extending life span have no influence on neuronal regeneration.

The increases in both life span and regeneration induced by daf-2(−) are mediated by the daf-16/FOXO transcription factor. Thus, the daf-2-daf-16 pathway controls these two different processes. There are two possible explanations for this finding: either axon regeneration is secondary to delayed organismal aging, or the same pathway controls life span and regeneration independently. To differentiate between these possibilities, the authors tested tissue-specific daf-16 expression in a daf-2(−); daf-16(−) background. daf-16 expression in the intestine increases life span but not youth-like axon regeneration, while neuronal expression of daf-16 maintains axon regeneration in adults without extending life span. These results provide compelling evidence for independent control of life span and regeneration by the daf-2-daf-16 pathway.

An additional line of evidence for independent regulation of life span and regeneration emerged when the authors tested the regeneration capacity of the daf-18/PTEN mutant, which increases TOR activity and decreases the life span of the animals (Figure 1). In other species PTEN deletion activates neuronal intrinsic regenerative ability (Park et al., 2008, Song et al., 2012). Consistently, the results show an increase of regeneration capacity in young and old worms through TOR pathway activation, demonstrating that both daf-2 and daf-18 mutants promote regeneration despite their opposite effects on life span.

In analyzing the transcriptional targets of DAF-16/FOXO, the authors identify 1526 DAF-16 binding sites, consistent with its implicated roles in diverse processes, such as metabolism, life span, synapse formation, and axon morphology (Murphy, 2006). One DAF-16 target, dlk-1, is a known critical regulator of axon regeneration in C. elegans and other species. DLK-1 is a conserved dual-leucine zipper kinase MAPKK that functions in axon regeneration by activating mkk-4/ZIPPER kinase MAPKK and pmk-3/MAPK (Hammarlund et al., 2009; Yan et al., 2009, Shin et al., 2012). DAF-16/FOXO directly binds the dlk-1 promoter and induces its expression. Importantly, dlk-1 is necessary for the axon regeneration induced by both daf-2(−) and daf-18(−) mutants. On the other hand, dlk-1 expression declines in aged worms. These results suggested that DLK-1 might act as a key age-dependent sensor in neurons, representing a relevant target of DAF-16/FOXO in regulating neuronal regenerative ability.

The precise mechanisms by which these pathways control regeneration remain to be determined. For a successful regenerative event to occur, an injury signal needs to be generated in the lesion site and relayed to the neuronal cell bodies. Then, based on competence levels, injured neurons will dictate specific responses, such as survival and/or regeneration. Mature, intact neurons primarily focus their metabolism toward maintaining homeostasis, producing ATP through catabolic processes to sustain ion transport and other basic functions. However, injured neurons need increased anabolic synthesis of macromolecules to support regenerative growth. In this regard, mTOR is a good candidate for regulating this process. By regulating biosynthetic processes such as cap-dependent protein translation, it drives the production of macromolecules and other building blocks fundamental for cell growth. However, not all types of axon regeneration depend on mTOR. For example, it has been shown that the axon regeneration of mammalian sensory neurons is not affected by rapamycin, an mTOR inhibitor (Sajilata et al., 2013). It would be interesting to investigate what other pathways compensate for mTOR function. In this regard, a recent study suggests that ribosomal S6 kinase inhibits intrinsic axon regeneration capacity via AMP kinase in C. elegans (Rhubert et al., 2014), underscoring the complex control of cell metabolism in injured neurons.

On the other hand, DLK-1 appears to be a critical component of an evolutionarily conserved injury signal pathway. From C. elegans to mammals, DLK-1 is required for many types of axon regeneration. After injury, axonal DLK-1 is activated by a Ca2+-dependent switch that turns inactive heteromeric to active homomeric DLK-1 protein complexes. Thus, a plausible model is that in adult aging neurons decreased DLK-1 expression might lead to a reduced injury response and regeneration. Intriguingly, a recent study suggests that in Drosophila, dendrite injury elicits DLK-independent regeneration (Stone et al., 2014). Although this result might be explained by the unique localization of DLK-1 to axons, it would be interesting to determine the molecular nature of the injury signals after dendrite injury and any aging-dependent alteration of dendrite injury responses.

Altogether, this study provides new insights into a fundamental yet complicated
question regarding the regulation of life span of an organism and neuronal regeneration. Although seemingly interconnected (Figure 1), the daf-2/insulin receptor—
daf-16/FOXO and the daf-18/PTEN—
mTOR pathways appear to regulate these processes independently. How these pathways are coordinated in regulating specific injury responses remains to be
determined. Further, it would be interesting to assess the relevance of these findings to the axonal pathologies in age-dependent neurodegenerative
diseases.

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