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Review

Organ-specific mediation of lifespan extension: More than a *gut* feeling?

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ABSTRACT

Multicellular organisms are composed of an interactive network of various tissues that are functionally organized as discrete organs. If aging were slowed in a specific tissue or organ how would that impact longevity at the organismal level? In recent years, molecular genetic approaches in invertebrate model systems have dramatically improved our understanding of the aging process and have provided insight into the preceding question. In this review, we discuss tissue and organ-specific interventions that prolong lifespan in the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*. These interventions include reduced Insulin/IGF-1 signaling, knockdown of genes important for mitochondrial electron transport chain function and, finally, up-regulation of the *Drosophila* PGC-1 homolog. An emerging theme from these studies is that the intestine is an important target organ in mediating lifespan extension at the organismal level.

1. Introduction

The identification and characterization of genetic mutants that display extended longevity has revolutionized the way we think about and study the aging process (Kenyon, 2005, 2010). Studies in invertebrate model systems, such as the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*, have been at the forefront of these discoveries. While employment of these two invertebrate model systems has mostly focused on producing insights into the aging process at the molecular level, these systems have also allowed for an improved understanding about the relationship between aging at the level of *specific* tissues or organs and organismal lifespan. Many long-lived mutants display a delay in the onset of age-related changes at the level of individual tissues or organs (Biteau et al., 2010; Garigan et al., 2002; Herndon et al., 2002; McGee et al., 2011; Wessells et al., 2004). In addition, the vast array of genetic and molecular tools available in both *C. elegans* and *Drosophila* have allowed investigators to address questions centered on the tissue or organ-specific *requirements* underlying extended lifespan. In other words, genetic studies can be designed to investigate the impact of exclusive manipulation of the aging rate in one tissue or organ on organismal lifespan. In this review, we discuss the large number of studies demonstrating that manipulation of aging-related genes exclusively within one organ—the intestine—results in an increased lifespan. We discuss these findings in terms of: (1) the importance of the intestine to the health and viability of the aging animal and (2) the role of the intestine as a signaling center influencing the rate of aging in responding cells.

2. Insulin/IGF-1 signaling pathway

The first pathway shown to modulate lifespan in animals was the insulin/IGF-1 signaling (IIS) pathway (Kenyon, 2011). Pioneering studies from a number of *C. elegans* researchers showed that mutations in *daf-2*, which encodes a hormone receptor similar to the insulin and IGF-1 receptors, dramatically improve the lifespan of the animal (Kenyon et al., 1993; Kimura et al., 1997). Other mutations affecting downstream IIS components extend lifespan as well (Johnson, 1990; Morris et al., 1996). Lifespan extensions induced by decreasing the activity of DAF-2, or downstream components of the IIS pathway are dependent upon the activity of the worm FOXO transcription factor DAF-16 (Dorman et al., 1995; Larsen et al., 1995; Lin et al., 1997; Ogg et al., 1997), the heat-shock transcription factor HSF-1 (Hsu et al., 2003); and SKN-1 (Tullet et al., 2008), a Nrf-like xenobiotic-response factor. These transcription factors, in turn, regulate the expression of a large number of downstream genes, many of which are important in mediating long life (Hsu et al., 2003; Murphy et al., 2003).

Studies in the fruit fly *Drosophila* provided the first evidence that reduced IIS is a 'public' or evolutionarily conserved mode of life extension (Partridge and Gems, 2002; Russell and Kahn, 2007).

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Specific mutant alleles of the *Drosophila* equivalent of *daf-2*, *InR*, and also *chico*, an insulin receptor substrate, confer extended lifespan (Clancy et al., 2001; Tatar et al., 2001). Other manipulations reported to promote long life include partial ablation of median neurosecretory cells, which produce three of the seven fly insulin-like peptides (Broughton et al., 2005) and a kinase-dead, dominant negative version of *InR* (InR^{DN}) (Slack et al., 2011). Removal of dFOXO, the fly homolog of DAF-16, almost completely suppresses the lifespan extension conferred by reduced IIS in *Drosophila* (Slack et al., 2011; Yamamoto and Tatar, 2011).

In *C. elegans*, the tissue or organ-specific requirements for IIS-mediated longevity have been studied by a number of groups. Altered *daf-2* gene activity in neurons can impact lifespan (Apfeld and Kenyon, 1998; Wolkow et al., 2000), however, the overall importance of the nervous system in IIS-mediated longevity is controversial (Libina et al., 2003). To determine whether increased DAF-16 activity in any single tissue was sufficient to extend the lifespan of *daf-2* mutants, Libina et al. (2003) expressed a DAF-16::GFP fusion in a tissue-specific fashion in a *daf-2*−/− background. As expected, expression of the fusion under the control of the *daf-16* promoter in *daf-16*−/−; *daf-2*−/− animals, almost completely rescued their longevity to *daf-16* (+); daf-2−/− levels. Interestingly, neuronal expression of *daf-16* produced only a modest (∼10%) positive effect on longevity, and expressing *daf-16* specifically in muscles produced no lifespan extension at all. In contrast, expressing *daf-16* in the intestine increased lifespan substantially, by 50–60%. Together, these results indicate that the intestine is an important organ in IIS-mediated lifespan extension in the worm.

As mentioned above, the worm homolog of Nrf2, called SKN-1, a member of the cap-n-collar family that induces expression of genes encoding antioxidant and detoxifying enzymes, is an important downstream component of IIS-mediated longevity (Tullet et al., 2008). Specifically, SKN-1 is required for the stress tolerance and longevity phenotypes of *daf-2* mutant worms. This requirement is intriguing as it indicates that the longevity of *daf-2* mutants (which also requires DAF-16) is mediated in a parallel and non-redundant fashion by both DAF-16 and SKN-1. Interestingly, SKN-1 is expressed in both the intestine and in the ASI chemosensory neurons of the worm. In both locations it has been shown to play a role in lifespan determination-but, in response to different signals. SKN-1 activity in ASI neurons, but not in the intestine, has been reported to be required for dietary restriction (DR)-mediated lifespan extension—suggesting that the role of SKN-1 in these neurons is to regulate the organism-wide response to nutrition (Bishop and Guarente, 2007). In contrast, it appears that SKN-1 activity in the intestine is important in IIS-mediated longevity (Tullet et al., 2008). In response to reduced IIS, changes in the nuclear localization of SKN-1 and upregulation of SKN-1 target genes were observed exclusively in intestinal cells. Moreover, expression of constitutively nuclear SKN-1 in the intestine is sufficient to extend life span (Tullet et al., 2008). Therefore, the intestine appears to play an important role both for DAF-16- (Libina et al., 2003) and also SKN-1-mediated (Tullet et al., 2008) lifespan extension in *C. elegans*. Given the importance of these molecules in mediating the pro-longevity effects of reduced IIS, these findings provide a compelling argument for a central role for the intestine in this context.

In *Drosophila*, the inducible Gene-Switch system (Osterwalder et al., 2001; Roman et al., 2001) has been used to activate dFOXO in different tissues of adult flies. Overexpression of dFOXO with two driver lines, *$S_1$106* (Giannakou et al., 2004, 2007) and *$S_1$32* (Hwangbo et al., 2004), has been reported to increase longevity. Initially, these findings were interpreted as demonstrating that activation of dFOXO in adipose tissue was sufficient to extend lifespan. However, subsequent characterization of both *$S_1$106* (Alic et al., 2011; Poirier et al., 2008) and *$S_1$32* (Poirier et al., 2008) have shown that both of these driver lines are also expressed in the intestine. Moreover, recent work with the *Drosophila* homolog of the human insulin-like growth factor binding protein 7, IMP-L2, supports the idea that the intestine is an important organ in IIS-mediated longevity in the fly (Alic et al., 2011). Increased expression of *Imp-L2* results in phenotypic changes consistent with reduced IIS (Alic et al., 2011; Honegger et al., 2008). Furthermore, adult-onset induction *Imp-L2* with *$S_1$106* results in an increased lifespan (Alic et al., 2011). Interestingly, in response to the inducing agent, an increase in IMP-L2 protein levels was detected in the intestine. However, no increase in IMP-L2 was detected in the fat body of long-lived flies. These data suggest that the intestine may be the most relevant organ in *$S_1$106*-mediated life extension, including the dFOXO studies.

These studies raise an interesting question: are there specific cell types within the intestine that are important in IIS-mediated life extension? The *Drosophila* midgut displays functional and morphological similarities with the mammalian small intestine, as well as with other vertebrate barrier epithelia. Tissue homeostasis in the midgut is maintained by multipotent intestinal stem cells (ISCs), which are distributed along the basement membrane (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). Division of an ISC gives rise to one daughter cell that retains stem cell fate and another daughter cell that becomes an enteroblast (EB), both expressing a transcription factor called Escargot (esg). In the intestine, the *5961-GeneSwitch (GS)* driver line is expressed exclusively in ISCs and EBs (Mathur et al., 2010). At the same time, this driver line shows no detectable expression in muscle tissue or major organs such as the brain and gonad (Biteau et al., 2010). Therefore, *5961GS* provides a powerful tool to refine our understanding of the relationship between the intestine, IIS and longevity. Remarkably, recent work has shown that moderate inhibition of IIS in ISCs/EBs is sufficient to extend lifespan (Biteau et al., 2010). More specifically, adult-onset induction of InR^{DN}, $DP110^{DN}$ or RNAi of Akt, with *5961GS* results in enhanced longevity (Biteau et al., 2010). To identify candidate downstream mediators of this effect, the authors activated certain FOXO target genes in ISCs/EBS and examined lifespan. Interestingly, up-regulation of two stress protective genes, *Hsp68* and *Jafrac1*, was sufficient to extend lifespan. Therefore, expressing selected FOXO target genes in the ISC/EBs is sufficient to recapitulate the effects of reduced IIS in these cells. Taken together, the data with the *$S_1$106* and *5961GS* driver lines support a model where reduced IIS in the fly intestine can lead to a longer life.

3. Mitochondrial electron transport chain

Mitochondria have been implicated in the aging process in a number of ways (Balaban et al., 2005; Guarente, 2008; Wallace, 2005). Interestingly, perturbation of genes important for mitochondrial electron transport chain (ETC) function has been reported to extend lifespan in diverse species including yeast (Kirchman et al., 1999), worms (Dillin et al., 2002; Feng et al., 2001; Lee et al., 2003), flies (Copeland et al., 2009) and mice (Dell'agnello et al., 2007; Lapointe and Hekimi, 2008). However, a detailed understanding of the relationship between respiratory chain *activity* and lifespan determination in these models is lacking. As in the case of IIS-mediated longevity, ETC-mediated longevity has been most extensively studied in *C. elegans*. Mutations in *clk-1* (Wong et al., 1995), i*sp-1* (Feng et al., 2001) and *nuo-6* (Yang and Hekimi, 2010b) lead to enhanced lifespan. *clk-1* encodes an enzyme necessary for the biosynthesis of ubiquinone (Ewbank et al., 1997), an electron transporter of the respiratory chain, and *isp-1* and *nuo-6* encode subunits of the respiratory complexes. In addition, a number of studies have shown that knockdown of worm genes encoding ETC