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RESEARCH HIGHLIGHT

Time is of the essence: microRNAs and age-associated neurodegeneration

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Aging is a key risk factor in neurodegenerative disease; however, little is known about cellular pathways that mediate age-associated degeneration of the brain. The Bonini lab has identified a conserved microRNA, miR-34, that plays a neuroprotective role in the aging *Drosophila* brain and suggests that it functions in temporal control of gene expression.

Fact and folklore across cultures tell of our obsession with the pursuit of longevity. Thanks to medical advances and preventative care, average human lifespan has greatly increased over the past few decades. Further progress can be anticipated as we come to better understand the molecular and cellular underpinnings of aging [1, 2]. In this context, age-progressive neurodegenerative disorders that impair cognitive, sensory and motor functions pose a growing challenge.

Neurodegenerative diseases are characterized by the progressive loss of function of specific subsets of brain cells, and aging is a key risk factor of disease onset [3]. In recent years microRNAs have come to attention for their roles in neurodegenerative diseases. MicroRNAs (miRNAs) are short non-coding RNAs that control the expression of protein-encoding messenger RNAs. Changes in the levels of some miRNAs have been observed in brain tissue from patients with neurodegenerative diseases [4, 5]. Using genetic models, miRNAs have been linked to neuronal function [6, 7] and cell survival [5, 8, 9]. miRNAs have also been linked to accumulation of the disease-related proteins α-synuclein and Ataxin1 [10, 11]. These studies have suggested that exploring the functions of microRNAs and their targets could provide new insights into mechanisms that influence healthy and disease-related aging of the brain.

In a recent report, Liu *et al*. [12] show that a conserved microRNA, miR-34, has a neuroprotective role. In the absence of miR-34, flies show early-onset movement disorder associated with age-progressive loss of neurons. The Bonini lab had previously reported that blocking microRNA biogenesis enhanced poly-Q-induced neural degeneration [8]. Even without PolyQ expression to sensitize the system, Liu *et al*. now find that miRNA-deficient animals had shortened lifespan and exhibited early-onset neurodegeneration. They examined age-dependent changes in miRNA expression and found that miR-34 was upregulated in older brains. Mutants for miR-34 showed a severe age-progressive form of movement disorder compared to age-matched controls. Interestingly, young flies were unaffected by the absence of miR-34. Defects became apparent with age and progressively worsened, culminating in early death. Behavioral impairment was accompanied by premature neural degeneration. To explore this process in more depth, the authors took a genome-

Figure 1 The 'aging' fly, as imagined here by David Foronda, will have experienced gradual age-progressive impairment of motor coordination and other brain functions, as well as changes in metabolism, stress responses, etc. The finding that a microRNA mutant can show premature aging opens new avenues to explore the biology of aging.

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wide approach to identify molecular correlates of aging. By transcriptional profiling they identified 173 genes whose expression correlated with normal brain aging. A majority of the upregulated genes showed a premature increase with age in miR-34 mutants. The picture that emerges from these studies suggests accelerated brain aging in the mutant.

miRNAs function by guiding ribonucleoprotein complexes to target mRNAs, leading to transcript destabilization and/or translational repression. Target prediction algorithms typically predict hundreds of candidate targets. Targetscan predicts 98 targets for miR-34 (www.targetscan.org). For reasons unspecified, Liu *et al*. focused on one of these, Eip74EF, which encodes a transcription factor regulated by the steroid hormone ecdysone. Interestingly, they observed that expression of the E74A protein isoform encoded by Eip74EF showed a reciprocal pattern of temporal expression to miR-34. E74A protein expression was high in young flies, when miR-34 expression was low. Reciprocally, E74A levels were low in later life when miR-34 levels increased. In miR-34 mutants, E74A protein levels were increased.

The authors next tackled the question of whether the elevated levels of E74A that occur in the mutant are responsible for the degenerative and behavioral defects. If this were the case, downregulation of E74A in the mutant would be predicted to rescue these deficits, whereas overexpression of E74A would be predicted to mimic the loss of miR-34. Both predictions were validated, showing that too much E74A is detrimental. The rising level of miR-34 miRNA contributes to lowering the levels of its target in the aging brain. Failure to do so has severe consequences.

The appearance of misfolded protein aggregates in the brain is characteristic of neurodegenerative diseases [13]. Interestingly, loss of miR-34 also resulted in an increase in the number of brain inclusions. The Bonini lab had previously shown that expression of bantam microRNA could suppress neurodegeneration induced by the ataxin-3 polyglutamine (PolyQ) disease protein without affecting the formation of protein inclusions [8]. In the case of miR-34, they found that the miRNA was able to slow the formation of PolyQ inclusions. It would be interesting to know whether the upregulation of E74A in the miR-34 mutants contributed to the formation of the PolyQ inclusions. This would strengthen the link between inclusion formation, brain vacuolization and the other age-related defects of miR-34. Finally, since miR-34 appeared to have age-dependent neuroprotective functions, the authors asked whether upregulation of miR-34 could enhance lifespan. This proved to be the case.

Bonini and colleagues present the intriguing suggestion that the role of an adult-expressed miRNA, such as miR-34, may be to repress developmental genes such as E74A whose later expression is harmful to the organism. This notion of temporal reciprocity is a variation on the spatial reciprocity model in which miRNAs have been proposed to limit spatial expression of targets that would be harmful if expressed in the miRNA-expressing cells [14]. Temporal reciprocity between miRNAs and targets has also been observed during the dramatic changes in gene expression that occur during the mid-blastula transition in the fly embryo [15]. The observation that miRNAs confer reciprocity is interesting, but it begs the question of why use miRNAs instead of transcriptional repression or epigenetic silencing mechanisms? Tissue repair in response to injury may require cells to maintain a level of developmental plasticity. They can do this via epigenetic reprogramming, but a more reversible state mediated by miRNAs could offer advantages.

The identification of age-associated roles for miR-34 raises the question of what aging-related signal regulates its function. One candidate is the currently controversial family of sirtuins, which has been shown to regulate control of neuronal function via a miRNA-based mechanism [6].

In light of its neuroprotective roles and its relevance to aging, the evolutionary conservation of miR-34 is tantalizing. Unfortunately the molecular mechanism reported in this study does not suggest a conserved microRNA-target relationship. Yet, the changes in miRNA and target gene expression provide a molecular signature of the aging brain. Comparing aging data from transcriptional profiling of different species to try to identify conserved pathways might point to the way to disease-relevant processes in humans [2, 3]. Taking the long view, we can look forward to turning our understanding of the fundamental mechanisms of brain aging into new approaches to managing neurodegenerative disease.

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