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Longevity regulation by NMD-mediated mRNA quality control

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Key words: nonsense-mediated mRNA decay, aging, *daf-2*/insulin/IGF-1 signaling, *smg-2*, *Caenorhabditis elegans*

Abbreviations: NMD, nonsense-mediated mRNA decay; IIS, insulin/IGF-1 signaling; *C. elegans*, *Caenorhabditis elegans*

Running title: NMD-mediated longevity regulation

Abstract

Proper maintenance of biological components is crucial for longevity and healthy aging. Although the role of homeostatic maintenance systems for DNA and protein in longevity is established, it remained largely unknown for RNA. In our recent work, we show that nonsense-mediated mRNA decay (NMD) promotes longevity in the roundworm *C. elegans* by enhancing RNA quality control. We find that the activity of NMD decreases during aging, raising the possibility that RNA quality declines in old animals. We then show that key components of NMD complex are required for long lifespan in *C. elegans*. We further demonstrate that animals with reduced insulin/IGF-1 signaling (IIS), a representative longevity model, display increased NMD activity. We propose that up-regulation of NMD plays crucial roles in longevity conferred by reduced IIS via enhancing mRNA quality control. As both IIS and NMD pathways are evolutionarily conserved, mammals including humans may be equipped with similar RNA quality control systems to achieve longevity.

Main text

DNA and protein quality control systems deteriorate with aging, and this causes diverse aging-related diseases such as Werner syndrome and Alzheimer's disease. However, whether RNA quality control is affected by aging or it regulates aging remains largely unexplored. For the last several years, our group in collaboration with Dr. Hong Gil Nam's group has been addressing this issue by using the roundworm *C. elegans*, an excellent model for aging research.

We have focused on RNA helicases that are involved in diverse aspects of RNA biology ranging from transcription, splicing, translation to RNA degradation. We first performed a large

scale RNA interference-based lifespan screen upon knocking down each of 82 genes that encode proteins that contain RNA helicase domains in *C. elegans* (Seo M, et al. *Proceedings of the National Academy of Sciences of the United States of America* 2015, 112:E4246-4255). We identified 11 RNA helicases, which are crucial for longevity conferred by reduced insulin/IGF-1 signaling (IIS), an evolutionarily conserved aging-regulatory genetic pathway. We reported the functional characterization of two RNA helicases, HEL-1 (DEAD-box helicase 39A/UAP56/BAT1) (Seo M, et al. *Proceedings of the National Academy of Sciences of the United States of America* 2015, 112:E4246-4255) and SACY-1 (DEAD-box helicase 41 (Seo M, et al. *Cell cycle (Georgetown, Tex)* 2016, 15:1821-1829). Here, we will introduce our most recent paper showing the life-extending roles of SMG-2 (UPF1 RNA helicase), a core component of nonsense-mediated mRNA decay (NMD) responsible for mRNA quality control.

NMD degrades aberrant RNAs such as premature termination codon (PTC)-containing mRNAs. As PTC-containing mRNAs are translated into potentially toxic truncated proteins, NMD is critical for maintaining normal cellular physiology. NMD is also known to degrade other endogenous mRNAs, such as upstream open reading frame (uORF)- and long 3' untranslated region (UTR)-containing transcripts. We show that NMD activity decreases during *C. elegans* aging by using a green fluorescent protein (GFP)-fused PTC-containing NMD reporter. We then find that the levels of various NMD targets, including PTC-, uORF- and long 3' UTR-containing transcripts, are decreased in long-lived insulin/IGF-1 (insulin-like growth factor-1) receptor mutant animals, which display reduced IIS and delayed aging phenotypes. Furthermore, we show that reduced IIS increases the degradation rate of NMD target transcripts. Thus, age-dependent decreases in NMD activity appear to play causative roles in *C. elegans*

longevity.

Different tissues have distinct roles in the aging of a whole organism, and therefore we asked in which tissues NMD contributes to longevity in *C. elegans*. Interestingly, NMD in neurons plays the most important roles in long lifespan. Through the analysis of neuron-specific RNA-seq. data (Kaletsky R et al. *Nature* 2016, 529:92-96), we find that the levels of NMD targets are down-regulated in the neurons of animals with reduced IIS. In addition, we show that RNA quality in neurons is better maintained in aged worms compared to other tissues. These data point to the importance of the neuronal NMD for *C. elegans* longevity. Interestingly, most neurons in mammalian central nervous system (CNS) are post-mitotic and may need to maintain cellular components longer than those in other tissues. Therefore, we speculate that perhaps NMD in the neurons of mammalian CNS may also be enhanced, compared to that in other tissues.

We then aimed to identify key NMD target transcripts for longevity. We show that the level of a *yars-2* (tyrosyl-tRNA synthetase 2) splice variant, a canonical NMD target, is decreased by reduced IIS. Importantly, down-regulation of *yars-2* is responsible for long lifespan in animals with reduced IIS. These data imply that reduced IIS enhances NMD, which decreases the levels of the *yars-2* transcript, and this in turn promotes longevity. As tRNA synthetases are essential components for mRNA translation, our data raise the possibility that enhanced NMD may extend lifespan by regulating both mRNA decay and translation. Our data are also in agreement with previous reports showing that translation rates are down-regulated in *C. elegans* with reduced IIS (Stout GJ, et al. *Molecular systems biology* 2013, 9:679) and that genetic inhibition of several tRNA synthetases increases lifespan (Lee SS et al. *Nature genetics* 2003,

33:40-48; Kim Y and Sun H *Aging cell* 2007, 6:489-503).

In conclusion, our study demonstrates that proper removal of mRNAs via NMD-mediated RNA quality control, in particular in neurons, is pivotal for organismal longevity (Fig. 1). Interestingly, we and others recently reported that factors regulating mRNA splicing are also important for *C. elegans* longevity (Seo M, et al. *Cell cycle (Georgetown, Tex)* 2016, 15:1821-1829; Heintz et al. *Nature* 2017, 541:102-106). Therefore, precise regulation of mRNA quality at multiple steps, including splicing and degradation, appears to regulate organismal lifespan. As these RNA-processing mechanisms are evolutionarily conserved, it will be interesting to test whether similar RNA quality control systems play roles in longevity in mammals, including humans.

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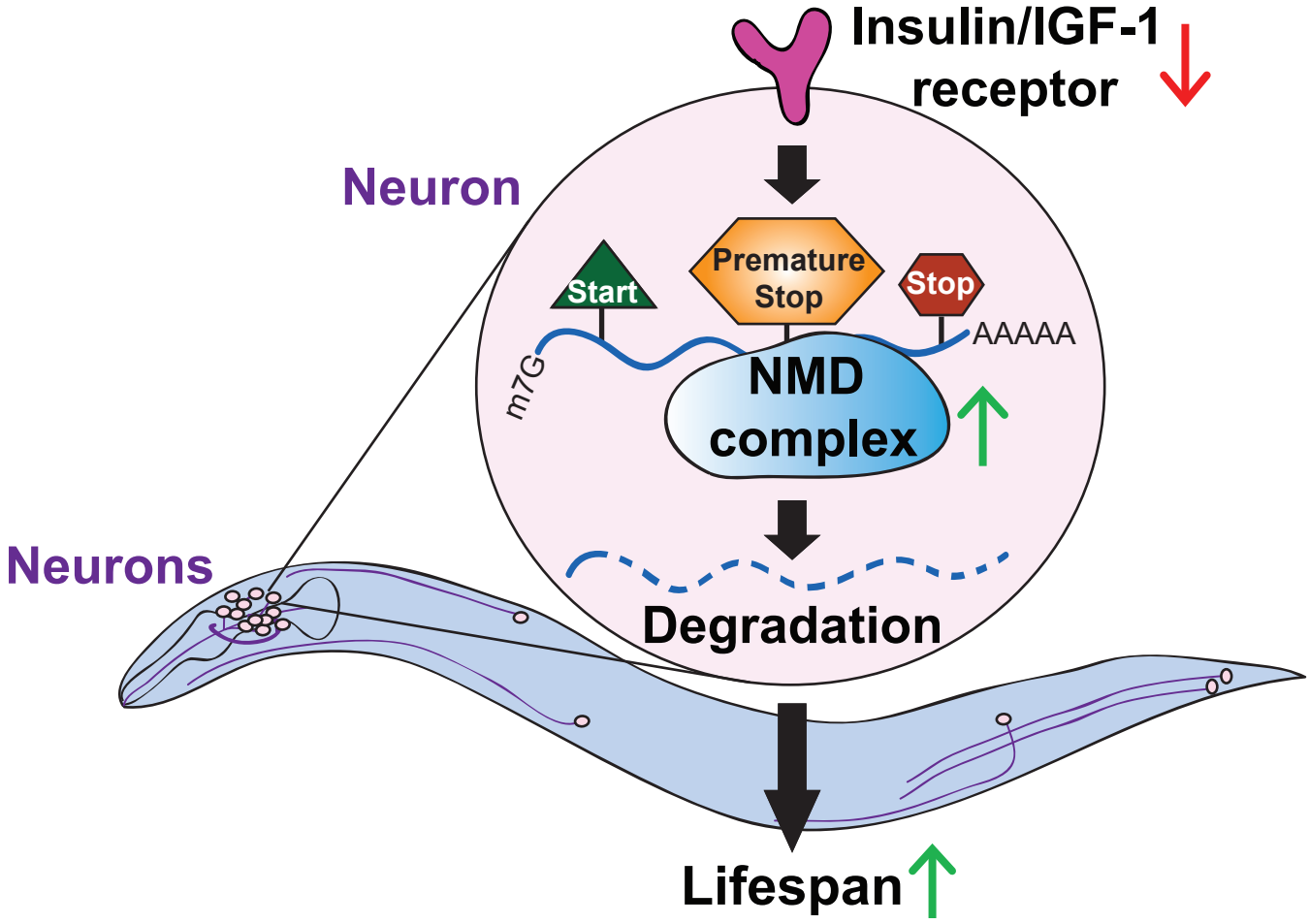
Figure legends

Fig. 1. A model for the roles of nonsense-mediated mRNA decay (NMD) in *C. elegans* longevity. When insulin/IGF-1 signaling is reduced, for example by genetic inhibition of insulin/IGF-1 receptor, NMD is enhanced. The NMD complex then degrades aberrant mRNAs such as

87 premature termination (stop) codon-containing transcripts, and this contributes to lifespan
88 extension. Among several tissues, NMD in neurons is the most crucial for longevity.


Insulin/IGF-1
receptor
Neuron
Premature
Stop
Start
Stop
AAAAA
m7G
NMD
complex
Degradation
Neurons
Lifespan