BİLKENT UNIVERSITY

MOLECULAR BIOLOGY AND GENETICS

DEPARTMENTAL SEMINAR

Defects in miRNA biogenesis leads to a functional decline in proteostasis

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The gene expression can be regulated post-transcriptionally by short non-coding RNAs called miRNAs. In an effort to study miRNA gene functions, knockouts of miRNA biogenesis genes have been generated, the analysis of the knockouts showed that miRNAs are essential for embryonic and larval development. However, at the same time these findings hampered the efforts to unravel the post-developmental roles of miRNAs. In 2012, a temperature sensitive allele of an essential miRNA biogenesis gene, pash-1 (pash-1ts) has been isolated in *C. elegans*. Using this allele, miRNA production was ceased post-developmentally by a temperature up-shift, which led to rapid aging and motility defects in the mutant animals. Functional decline in proteastasis network (PN) is one of the contributing factors to aging. PN is composed of various components that ensures proper folding or degradation of proteins to maintain the proteome integrity.

In our studies, we first questioned whether the functional decline in the PN is the main cause of accelerated aging in pash-1ts mutant animals. To test this hypothesis, we treated pash-1ts mutant animals with a chemical known to enhance proteastasis. Increase in the proteastasis capacity extended the life span of pash-1ts animals by 40%, but it also rescued the motility defects in these animals by 50-60%. In parallel to these findings, we showed that the loss of miRNA production increases toxicity of the metastable proteins in the muscle cells. In addition, the number of the protein aggregations is higher in the pash-1ts animals compared to wild type animals. Lastly, we examined several components and regulators of proteastasis to understand how their function changes in pash-1ts mutant animals to delineate how miRNAs regulate proteastasis. Collectively, these data indicate that the absence of miRNAs enhance the misfolding of the protein and suggest that aging phenotype of pash-1ts animals, if not all, is mostly due to a functional decline in proteostasis.

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