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The Mechanism of lage3 Gene Deficiencies Inducing Developmental Delay in C. elegans.

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Objectives : Galloway-Mowat Syndrome (GAMOS) (MIM 251300) is a rare disorder characterized by the combination of congenital nephrotic syndrome, microcephaly, brain abnormalities, growth retardation, and various clinical manifestations including epilepsy, distinctive facial features, and reduced life expectancy. Recessive mutations in LAGE3 genes of the KEOPS complex have been identified in affected individuals. This study aims to explore the pathogenic mechanisms of LAGE3 mutations in GAMOS.
Methods : Utilizing RNAi technology, we knocked down the lage3 gene in C. elegans to establish GAMOS models. Basic phenotypes, including survival time, development rate, and reproductive function, were collected. RNA-seq analysis was conducted to identify key pathways. Phenotypic validation was performed using C. elegans strains carrying mitochondrial or endoplasmic reticulum stress pathway reporters (hsp-6::gfp or hsp-4::gfp).
Results : 1. The median survival time for the models were statistically significant and shorter than that of the control group ($p < 0.05$). 2. The adult rate in the lage3 knock-down (KD) model was 0% after 50 hours from the L1 stage, compared to 70% in the control group. 3. The average number of progenies in lage3 KD model was decreased (KD vs control, 315.2 vs 369.9, $p < 0.01$). 4. Differentially expressed genes were enriched in pathways related to development, DNA binding, transcriptional regulation, RNA metabolism, endoplasmic reticulum stress and mitochondrial function. Although the activation of the mitochondrial pathway and endoplasmic reticulum was observed, the difference in fluorescence intensity between the lage3 group and the control group was not statistically significant.
Conclusions : The lage3 KD model exhibited shortened life span, developmental defects and impaired reproductive function phenotype. Changes in the gene expression level of the mitochondrial and endoplasmic reticulum pathways were observed in C. elegans. Further discussion is needed to elucidate the biological significance of these results and their implications for understanding the role of the LAGE3 gene in GAMOS.

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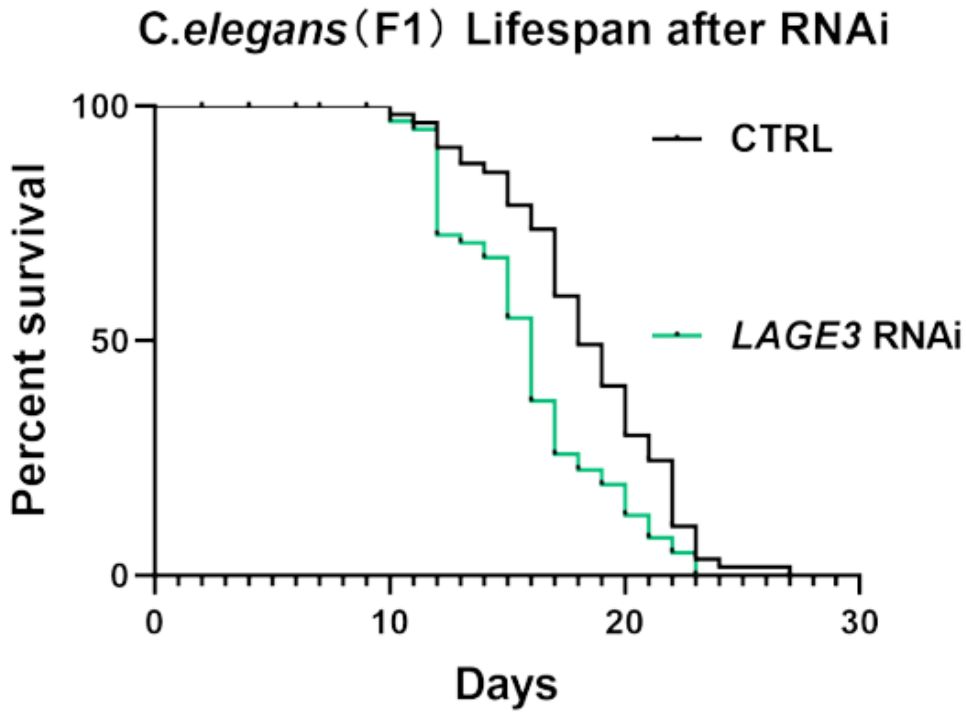

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