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AGEING

Live longer with small nucleoli

> "the different longevity pathways converge in the nucleolus"

Lifespan can be prolonged by dietary calorie restriction or by manipulating several evolutionarily conserved metabolic pathways; how these pathways interact to regulate lifespan is still poorly understood. Two recent publications in *Nature Communications* show in different organisms that the pathways converge in controlling the size and function of nucleoli.

The nucleolus is a nuclear compartment where ribosome biogenesis (ribosomal RNA (rRNA) synthesis and ribosome-subunit assembly) takes place. The size of nucleoli correlates with rRNA synthesis levels, and nucleolar function is regulated by growth, metabolic and stress signals. Previous studies in *Caenorhabditis elegans* identified the ribosome-biogenesis inhibitor NCL-1 as an effector of nucleolar size, and *ncl-1* mutants were shown to have larger nucleoli. Tiku *et al.* found that NCL-1 loss reduced the greater longevity of a genetic model of dietary restriction, as well as the longevity of mutants in TOR signalling, insulin signalling, mitochondrial function and protein synthesis. This indicated that NCL-1 is a convergent factor in many longevity pathways.

Although loss of NCL-1 in wild-type nematodes had little effect on lifespan, NCL-1 overexpression reduced nucleolar size and increased lifespan. Similarly, the above longevity mutants and nematodes grown under dietary restriction had smaller nucleoli. Moreover, wild-type nematodes show considerable variability in lifespan, and a strong inverse correlation was found between nucleolar size in the first day of adulthood and longevity.

Next, Tiku *et al.* examined nucleolar function and found that the levels of fibrillarin (which promotes ribosomal biogenesis) and of rRNA and ribosomal proteins increased in *ncl-1* mutants and decreased in nematodes overexpressing NCL-1. In the longevity mutants, the levels of these factors decreased, and this was reversed by loss of NCL-1. Depletion of fibrillarin also reduced nucleolar size and extended lifespan. Thus, the different longevity pathways converge in the nucleolus, and longevity is associated with reduced ribosome biogenesis.

The connection between reduced nucleolar size and function and longevity was corroborated in fruit flies and mice. Furthermore, the authors found a trend towards reduction in nucleolar size in muscle biopsies of elderly humans who reduced their calorie intake and increased exercise.

Hutchinson–Gilford progeria syndrome (HGPS) is a premature ageing disorder caused by the expression of a lamin A mutant termed progerin, which disrupts the nuclear lamina and deregulates nuclear architecture and function. Importantly, progerin expression and its phenotypic consequences also increase during normal ageing. Buchwalter and Hetzer found that fibroblasts derived from individuals with HGPS exhibited an increase in nucleoli size and ribosome biogenesis, which was associated with significantly higher rates of synthesis of nuclear proteins in general.

In wild-type fibroblasts, expression of even low levels of progerin resulted in enlarged nucleoli, whereas high expression levels of a progerin variant that does not cause progeroid phenotypes did not, suggesting that HGPS-causing progerin is sufficient to promote nucleolar expansion. The authors also found a significant correlation between ageing and nucleolar size in healthy individuals; specifically, cells derived from individuals with HGPS exhibited large nucleoli, which were comparable in size to those of old healthy individuals.

The data obtained from the model organisms and HGPS cells show that nucleolar size and activity are cellular hallmarks of longevity and ageing. They also raise the possibility that nucleoli could serve as biomarkers of life expectancy and that inhibition of nucleolar activity could help treat HGPS and possibly even extend human lifespan.

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ORIGINAL ARTICLES Tiku, V. *et al.* Small nucleoli are a cellular hallmark of longevity. *Nat. Commun.* **8**, 16083 (2017) | Buchwalter, A. & Hetzer, M. W. Nucleolar expansion and elevated protein translation in premature aging. *Nat. Commun.* **8**, 328 (2017)
FURTHER READING Kubben, N & Misteli, T. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. *Nat. Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm.2017.68 (2017)