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| Nesprin-2/ANC-1 regulates nuclear autophagy& delays ageing while maintaining germline immortality**Margarita-Elena Papandreou1,2,#, Georgios Konstantinidis1 and Nektarios Tavernarakis1,2**1 Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, Crete, Greece2 Department of Basic Sciences, School of Medicine, University of Crete, Heraklion, Crete, Greece# Presenting author: Margarita-Elena Papandreou, email: m.papandreou@imbb.forth.gr\* Corresponding author: Nektarios Tavernarakis, email: tavernarakis@imbb.forth.gr |

abstract

Recycling of nuclear material is essential for cellular and organismal homeostasis. Alterations in nuclear morphology and aberrant nuclear dynamics are universal hallmarks of ageing and age-related pathologies. Nucleophagy, a process of selective targeting and degrading damaged nuclear components by the autophagic machinery, serves as a nuclear integrity control mechanism and is implicated in neurodegeneration and cancer. We find that the nuclear envelope anchor protein Nesprin 2 and its *Caenorhabditis elegans* orthologue ANC-1 are key nucleophagy regulators. ANC-1/Nesprin 2 restrict nucleolar size, a common denominator of diverse lifespan extension regimes. Their deficiency causes enlargement of nucleoli and accumulation of Fibrillarin, a protein component of nucleolar ribonucleoproteins, in an autophagy-dependent manner. Moreover, we show that ANC-1 confers organismal stress resistance against nutrient deprivation, heat stress and DNA damage in *C. elegans*. Notably we also find that that selective autophagy of nuclear material is an important determinant of germline immortality and somatic ageing under conditions of stress. We identify and characterise a novel germline immortality assurance mechanism, which involves nucleolar degradation at the most proximal oocyte by ANC-1. Clearance of aberrant germ cells during their differentiation by autophagic cell death requires ANC-1 and LGG-1. Notably, perturbation of this clearance pathway causes tumour-like structures in the *C. elegans* germline. Similarly, genetic ablation of Nesprin 2 in female mice causes ovarian carcinomas, indicating that the relevant molecular pathways are evolutionarily conserved, across distant phyla. Thus, autophagic recycling of nuclear envelope-associated and nucleolar components is an essential soma longevity and germline immortality mechanism that promotes youthfulness.