Nuclear autophagy promotes longevity and germline immortality

Under conditions of stress, autophagic degradation of nuclear and nucleolar components was found to promot.e youthfulness and delay aging by preserving nuclear architecture and preventing nucleolar expansion, in somatic cells. We also found that nuclear-material autophagy serves as an essential quality-control mechanism that contributes to sustaining germline immortally.

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The question

Progressive and pronounced deterioration of nuclear architecture is a common and conserved feature of aging, progeria and numerous other disorders associated with aging[1,2]. In addition, progeroid syndromes and aging itself are accompanied by a marked expansion of the nucleolus – the largest well-defined structure within the nucleus, serving as the site of ribosome biogenesis[3,4]. However, the molecular and cellular mechanisms that bring about these changes remain obscure. It is also unclear whether such alterations are simply a corollary of the aging process and age-related pathologies, or have a causative role in progeria and senescent decline. A related, unresolved question pertains to signaling pathways and interventions, such as insulin–IGF1 signaling and dietary restriction, that are well-characterized modulators of lifespan in organisms ranging from nematodes to primates. Whether and how these pathways interface with molecular processes that shape the nucleus, and determine nucleolar size and function during aging, is not known.

The discovery

The preservation of nuclear ultrastructure and recycling of nuclear material is essential for cellular and organismal homeostasis. Nucleophagy, a process of selective targeting and degradation of damaged nuclear components by the autophagic machinery, serves as a nuclear quality-control mechanism[5]. Indeed, aberrant nucleophagy has been implicated in a broad range of pathologies, including DNA damage, cancer and neurodegeneration. We therefore set out to investigate the involvement of autophagic mechanisms in the maintenance of nuclear architecture during aging.

We find that the nuclear envelope anchor protein nesprin 2, and its *Caenorhabditis elegans* orthologue ANC-1, are key nucleophagy regulators. Nesprin 2 and ANC-1 function to maintain small nucleolar size, which is a common denominator of diverse lifespan-extension regimes. In addition, nesprin 2 and ANC-1 prevent nuclear shape abnormalities and the accumulation of lamin, the major structural component of the nuclear lamina (Fig. 1a). We show that selective autophagy of nuclear material is an important determinant of somatic aging and germline immortality, under conditions of stress (Fig. 1b,c). Clearance of aberrant *C. elegans* germ cells during their differentiation in the gonad requires ANC-1-mediated nucleophagy. Notably, perturbation of this clearance pathway causes tumour-like structures in the *C. elegans* germline. Similarly, genetic knockdown of nesprin 2 in female mice causes ovarian carcinomas, indicating that the relevant molecular pathways are evolutionarily conserved across distant phyla.

In total, our findings suggest that nesprin family members serve as key regulators of the autophagic degradation of nuclear material. Impairment of autophagic recycling of nuclear components diminishes stress resistance, undermines animal longevity and precipitates progressive germline mortality. Therefore, nucleophagy is an essential soma longevity and germline immortality mechanism that promotes youthfulness and delays aging under conditions of stress, by preserving nuclear architecture and preventing nucleolar expansion (Fig. 1d).

The implications

Our study offers a mechanistic link that establishes a causative relationship between two parameters that were hitherto merely correlated: the size of the nucleolus and lifespan. We uncover nucleophagy as a molecular mechanism by which diverse physiological signals are integrated to affect nuclear architecture and homeostasis. In addition, we provide substantial insight relevant to the nuclear and nucleolar adaptations that promote or undermine survival and longevity, in response to intrinsic or extrinsic cues. The emerging role of nucleophagy in aging and age-related pathology is multifaceted: For example, it has not escaped our attention that – by regulating the abundance of lamins and ribosomal RNAs – nucleophagy impinges on other vital cellular processes that are implicated in lifespan regulation, such as protein synthesis and proteostasis. Moreover, we identify nucleophagy as a downstream effector of low insulin–IGF1 signaling and dietary restriction on somatic aging. Nucleophagy is also an important pillar that sustains germline immortally. Notably, polymorphisms in the nesprin homologue, *SYNE2*, have been linked to ovarian infertility in women. In essence, nucleophagy upregulation in the soma may endow it with germline-like properties, thereby extending somatic lifespan. The tight evolutionary conservation and ubiquitous expression of the regulatory factors involved suggests that similar pathways may impinge on aging in humans.

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EXPERT OPINION

"The authors discovered that the giant outer nuclear envelope protein ANC-1/nesprin and autophagy components promote somatic longevity in *C. elegans* by creating small nucleoli via nucleophagy. Nucleophagy defects also elicited sterility within 10 generations, suggesting a heritable form of nucleolar damage. A role for nucleophagy in promoting germ cell immortality may be consistent with the long-standing model that improved nucleolar stability prolongs the replicative lifespan of yeast mother cells." **Shawn Ahmed, University of North Carolina, Chapel Hill, USA.**

FIGURE

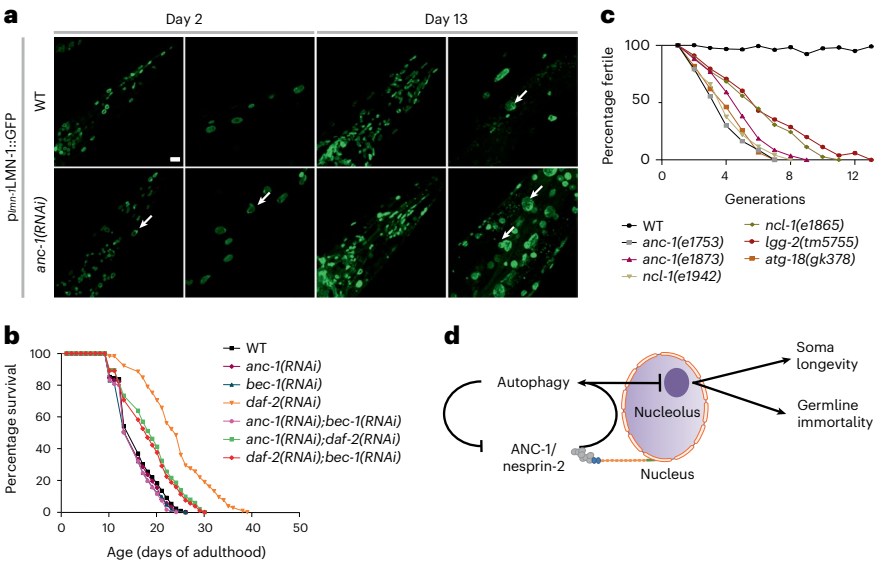

Fig. 1 | Nucleophagy promotes longevity of the soma and germline immortality by maintaining nuclear architecture. a, Imaging of control (WT) and *anc-1*(RNAi)-silenced worms of the indicated age (day 2, D2; day 13, D13), expressing a nuclear lamina reporter (p_{lmn-1}LMN-1::GFP). Arrows indicate irregular nuclei. Scale bar, 20 µm. **b**, Lifespan analysis of WT or long-lived, DAF-2-deficient worms (where autophagy is induced) upon knockdown of *anc-1* or *bec-1* (which encodes a protein involved in early-stage autophagy). **c**, Fertility of indicated nematode strains across generations. **d**, Schematic of an autophagic pathway that recycles nuclear and nucleolar components to preserve germline immortality and delay aging. © 2022, Papandreou, M.-E. et al.

BEHIND THE PAPER

We have always been intrigued by the dichotomy between two diametrically opposed, fundamental phenomena in biology: soma mortality and germline immortality. The prospect of uncovering the molecular underpinnings of this sharply idiosyncratic character of cell types, within a single organism, provided ample motivation for us to embark on a research journey, towards tackling such questions. We decided to focus on nuclear morphology in somatic cells, which deteriorates during aging. By contrast, the overall architecture of the nucleus is preserved in the germline. Our hypothesis was that a homeostatic mechanism effectively maintains the structure of germ cell nuclei, whereas it fails during aging in the soma. We were surprised to find that autophagic recycling of nuclear material is an important factor, preserving nuclear architecture and restricting nucleolar size. Interestingly, nucleophagy interfaces with nodal, prolongevity signal transduction pathways, highlighting the complex crosstalk of the molecular mechanisms that influence aging. **N.T.**

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FROM THE EDITOR

"Nuclear morphology changes with aging, but the role of these changes and the underlying mechanisms are not fully understood. The authors here find that the nuclear envelope anchor protein ANC-1 in worms, and its counterparts nesprin 1 and 2 in mammals, promote the degradation of nuclear components to limit nuclear size, and this process emerges as an important regulator of longevity and germline immortality." **Editorial Team**, ***Nature Aging*.**