Mitochondrial aging

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Phase separation meets energy generation to boost longevity

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Bai and colleagues show that specialized translation hubs called mitochondria-associated translation organelles (MATOs) form by liquid–liquid phase separation on the mitochondrial surface. MATOs congregate ribosomes and specific mRNAs to supply key proteins on-site and thereby uphold mitochondrial integrity and function. Persistent association of MATOs with mitochondria enhances stress resistance and extends lifespan.

Our bodies are in a constant state of power demand. From the mechanical motion generated by muscle cell contraction to the electric chatter of neurons, every biological process runs on energy that comes largely from mitochondria, the organelles that are often described as the cell's powerhouses. As with any intricate factory, these cellular powerhouses require constant maintenance and quality control to function properly. But how they ensure a steady supply of the specialized proteins needed to maintain their elaborate internal structure and vital functions has remained unclear. A new study published in *Nature Aging* by Bai and colleagues[1] reveals an elegant solution: mitochondria recruit their own dedicated mRNA translation factories, in the form of liquid-like protein condensates that assemble on their surface to manufacture essential components on demand.

Mitochondria contain their own genome (a circular mitochondrial DNA), which, however, only encodes 13 mitochondrial proteins. The vast majority of proteins needed to build mitochondria are encoded by nuclear DNA. This poses the fascinating logistical challenge of how these essential components get made and effectively delivered where and when they are needed. It has long been hinted but never fully understood that mitochondrial biogenesis relies on the selective and local translation of nuclear mRNA transcripts that encode mitochondrial proteins in the vicinity of mitochondria[2,3]. These transcripts are exported from the nucleus in a translationally repressed state and are subsequently delivered to mitochondria, where they become localized to the outer mitochondrial membrane. Previous studies have implicated components of processing bodies (P-bodies) in facilitating the specific localization, storage and degradation of mRNAs that encode mitochondrial proteins on mitochondria[4]. P-bodies are evolutionarily conserved, non-membranous cytoplasmic granules that form through a process of liquid–liquid phase separation (LLPS), and are composed of untranslated mRNAs and associated RNA-binding proteins (RBPs). Their assembly and composition are highly dynamic, and they undergo marked changes during aging and in response to stress[5]. However, the precise mechanism(s) through which the local translation of mitochondrial protein-encoding mRNAs is accomplished remained obscure.

Bai and colleagues now reveal that in the roundworm *Caenorhabditis elegans*, a specific RBP called LARP-1 orchestrates the formation of fit-for-purpose MATOs by LLPS on the surface of mitochondria. The authors conducted a forward genetic screen for mitochondrial defects in *C. elegans*, and isolated a mutant with misshapen, spherical and bloated mitochondria, instead of the canonical, mostly tubular mitochondria seen in wild-type animals. These mutant animals showed poor physiological performance, with reduced ATP output, impaired fertility, lower stress resistance and shorter lifespan. The culprit turned out to be a loss-of-function mutation in *larp-1*, the gene that encodes LARP-1 (a La-related RBP), which belongs to an ancient family of RBPs, involved in RNA processing and mRNA translation regulation[6,7]. Remarkably, heterologous expression of human LARP1 in *C. elegans larp-1* loss-of-function mutants for the most part restored mitochondrial morphology and animal health, which indicates impressive functional conservation across taxa as distant as nematodes and primates.

This raised the question of how the observed pathological phenotypes are brought about upon loss of LARP-1. Digging deeper, the research team uncovered the crux of the problem: without LARP-1, the levels of key mitochondrial proteins plummet. Using proteomics, they found that hundreds of mitochondrial proteins — including those that form the mitochondrial contact site and cristae organizing system (MICOS), and the respiratory chain complexes — were markedly depleted. Yet the corresponding mRNA levels remained unchanged. This pointed to a defect not in gene transcription, but in mRNA translation. Using APEX2 proximity labeling (a technique that tags molecules near a protein of interest), the team found that LARP-1 was nestled on the outer membrane of mitochondria and surrounded by mRNAs, protein synthesis machinery and a constellation of RBPs. Rather than floating freely, these components were gathered into dynamic condensates, liquid-like droplets formed by phase separation — a process that is increasingly recognized as a key organizer of cell compartments[8]. The authors dubbed these droplets MATOs. Unlike traditional membrane-bounded organelles, MATOs are held together by multivalent interactions between proteins and RNAs, which makes them both stable and responsive. These foci were dynamic and highly mobile, and displayed fusion and division events, characteristic of LLPS.

Using a series of sophisticated experiments, the authors showed that LARP-1 could drive MATO formation both in vitro and in living animals. In turn, MATOs were actively synthesizing essential mitochondrial proteins, such as IMMT-1 (MIC60; a central MICOS subunit) and ATP-2 (the ATP synthase β subunit), right on the mitochondrial surface. In the absence of LARP-1, MATO assembly was impaired and mRNA translation near mitochondria was diminished. The authors next investigated how

MATOs actually attach to mitochondria. The answer involves another set of players: components of the mitochondrial translocase of outer membrane (TOM) complex, which normally helps to import proteins into mitochondria. The authors found that specific TOM proteins could interact directly with LARP-1 and be recruited into the phase-separated droplets. This creates an elegant coupling mechanism: mitochondrial proteins are synthesized in MATOs and immediately handed off to the TOM complex for import into mitochondria, which creates a seamless production and delivery system. Indeed, when TOM subunits were knocked down, MATOs dissociated from mitochondria, which led to mitochondrial fragmentation and – to some extent – recapitulated LARP-1 depletion phenotypes. Notably, previous studies had already implicated the mitochondrial protein import system in the regulation of stress resistance and aging, via metabolic reprogramming[9]. The emerging picture is that of a well-organized assembly line, put together through phase separation (Fig. 1). LARP-1 acts as a master coordinator, by recruiting mRNAs that encode mitochondrial proteins – along with all the molecular machinery needed to translate them into proteins – into phase-separated structures, positioned on top of the mitochondrial protein import channel. This creates a local zone of concentrated translation activity right where the products are needed, on the mitochondrial surface.

The functional significance of MATOs comes into sharper focus during aging or under stress. Bai and colleagues found that as worms grew older, MATOs gradually disappeared from the mitochondrial surface, which coincided with mitochondrial fragmentation and declining cellular health (Fig. 1). Similarly, when young animals were starved, MATOs rapidly dissociated from mitochondria. The authors also exposed worms to low doses of paraquat, a mitochondrial reactive oxygen species generator known to induce adaptive stress responses. In wild-type animals, MATOs expanded in number and recruited additional ribosomes, accompanied by a boost in local translation of mRNAs that encode oxidative phosphorylation components. In MATO-deficient worms, this adaptive response was blunted, which led to respiratory impairment. These animals also aged much faster than wild-type controls. By sharp contrast, when the authors engineered a version of LARP-1 permanently tethered to mitochondria, MATO formation was amplified and they also persisted longer during aging; so did mitochondrial integrity and function. Remarkably, these animals lived up to 43% longer than controls (Fig. 1). Lifespan extension occurred not only in wild-type animals but also in mutant worms with altered insulin signaling and stress response pathways. This suggests that MATOs promote longevity through a mechanism that is at least partially independent of known pathways that modulate lifespan.

Looking forward, the work of Bai and colleagues not only breaks new ground towards understanding critical aspects of mitochondrial biology but also invites intriguing new questions, including what governs the assembly and disassembly of MATOs during aging or under stress. The authors note that LARP-1 is known to be phosphorylated by nodal kinases such as mTOR, Akt and PINK1, which are key players in nutrient sensing and mitochondrial turnover pathways[10–12]. It is tempting to speculate that stress signals or changes in energy demand regulate MATO abundance and dynamics through post-translational modifications of LARP-1, thus tipping the balance between condensate formation and dissolution. Finetuning MATO assembly in response to physiological cues could represent a central element of the cell's stress adaptation toolkit.

How exactly MATOs extend lifespan also remains an open question. One possibility is that by supporting mitochondrial cristae,

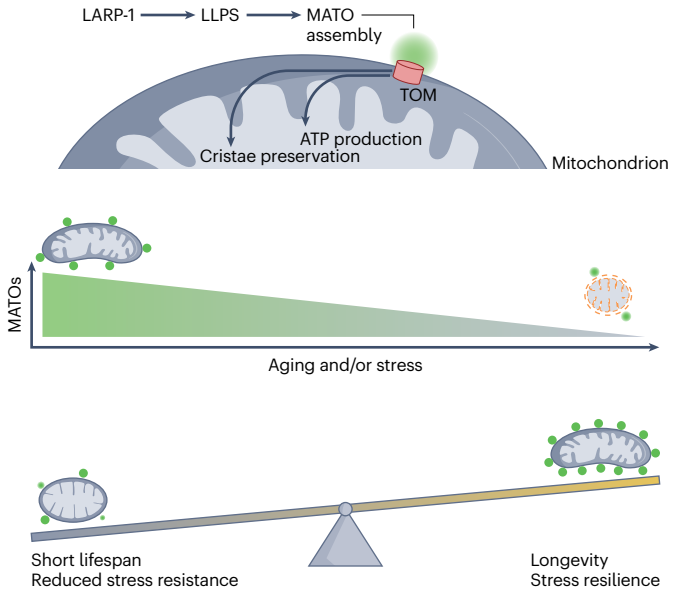

Fig. 1 | MATOs serve as local protein synthesis hubs on the surface of mitochondria to sustain energy metabolism and promote longevity. Top, MATOs assemble through LLPS, driven by the RBP LARP-1. Anchored to the TOM import machine, MATOs cluster ribosomes, and mRNAs that encode respiratory chain and mitochondrial membrane-shaping proteins, including subunits of the MICOS complex, and ATP synthase components. By channeling newly synthesized proteins directly into mitochondria, MATOs maintain cristae structure and efficient ATP production. Middle, during aging and/or stress, most MATOs dissociate from mitochondria. Bottom, by contrast, persistent association of MATOs with mitochondria supports mitochondrial integrity, augments stress resilience and extends organismal lifespan.

MATOs ensure efficient electron transport and ATP production, which reduces the build-up of damaging reactive oxygen species[13]. Alternatively, they may buffer against proteostatic stress, and keep key mitochondrial components in ready supply. Moreover, the molecular logic that underlies the recruitment of specific mRNAs into MATOs remains unclear. Are there specific sequence motifs, adaptor proteins or simply concentration-driven equilibria at play? Another open question is whether there are distinct 'flavors' of MATOs: do different sets of mRNAs, RBPs and translation factors form specialized condensates tuned to specific needs, or are these universal hubs are all created equal, synthesizing whatever is needed on demand? The authors identified several RBPs that co-assemble with LARP-1 into MATOs. Some of these proteins could independently undergo LLPS, whereas others required LARP-1 to form droplets. This indicates that MATOs are built through a network of interactions between multiple factors, with no single molecular linchpin.

In addition, it is worth considering how universal MATOs are across species. Whether MATOs exist and function similarly in humans remains to be seen, but the conservation of LARP-1 function between nematodes and mammals offers hope. If analogous structures exist in humans, they could influence a range of physiological and pathological processes – perhaps having a role in aging, neurodegeneration or metabolic decline. Neurons, with their long axons and spatially distributed energy requirements, might particularly benefit from local mitochondrial translation. In this context, MATO defects could exacerbate neurodegenerative diseases associated with aging, for which

both mitochondrial dysfunction and impaired protein homeostasis are hallmarks[14,15]. Given that MATOs preserve mitochondrial function during aging, it is compelling to envision interventions that manipulate and stabilize these structures as means to counter mitochondrial decline in age-related diseases. For example, in muscle cells, enhancing MATO function could help to sustain mitochondrial performance during aging, and potentially mitigate sarcopenia. Indeed, the findings of Bai and colleagues suggest that bolstering MATOs could become a potential strategy to improve mitochondrial health across a range of contexts, from neurodegeneration to metabolic disease.

Ultimately, the broader significance of this work lies in how it links the emerging field of biomolecular condensates to organelle homeostasis and organismal aging. We now appreciate that cells use LLPS to compartmentalize biochemical processes without membranes, forming structures such as stress granules, nucleoli and P-bodies. MATOs become a new entry to this growing list, and demonstrate that phase separation can be used to localize and coordinate mRNA translation on organelle surfaces. Their discovery is a fine example of how cells meet logistical challenges with elegant molecular mechanisms, and provides a fresh perspective on cellular maintenance and how it falters with age: long-term survival may hinge on something as ephemeral and fluid as a droplet.

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Competing interests

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