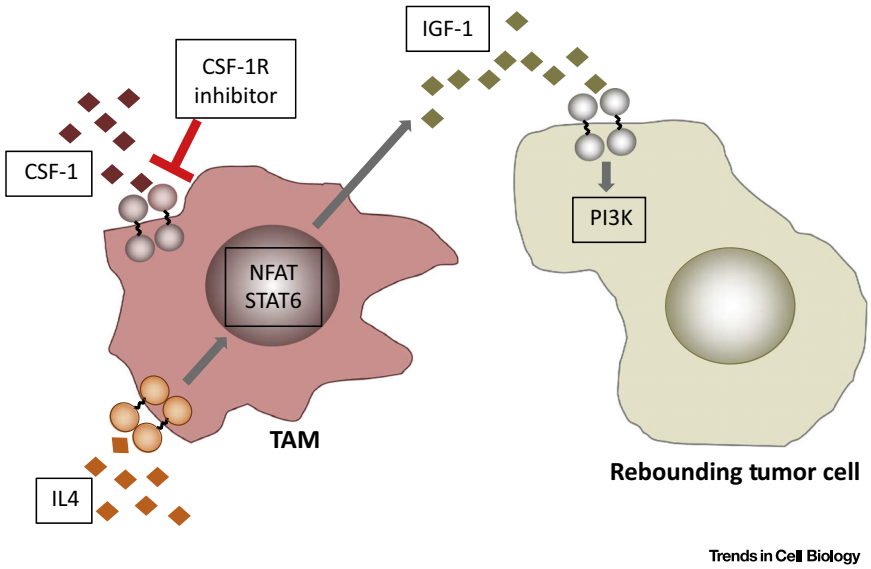

Figure 1. Long-Term Treatment with Colony-Stimulating Factor-1 Receptor (CSF-1R) Inhibitors Promotes Tumor Resistance. After responding to CSF-1R inhibitors, the remaining dormant tumor cells rebound and start proliferating due to the insulin-like growth factor 1 (IGF-1)-mediated induction of the PI3K pathway. IGF-1 is produced by tumor-associated macrophages and microglia (TAMs) in response to the IL4–NFAT/STAT6 pathway.

inhibitors partially prevented tumor recurrence (Figure 1).

The work by Quail *et al.* shows a fascinating interplay between TAMs and tumor cells that evolves during treatment to adapt and escape CSF-1R inhibition. Although TAMs are genetically more stable than tumor cells, TAMs still maintain the versatility to change and facilitate the growth of tumors. Following the parallelism with ecosystems, cancer does not act as an 'organism' in isolation but evolves in intimate contact with its microenvironment to subsist in changing conditions. In a way, tumor cells 'tame' TAMs to resist the selective pressure of anticancer treatments.

The work is performed using animal models and hence the translation of some of the results into human reality could be limited. We know that human tumors are more complex and heterogeneous than those in mice. In addition, we still do not know how the specific genomic makeup of each human GBM will impact the response or resistance to anti-CSF-1R. Moreover, this work raises new questions. Why and how does IL4 suddenly appear in just half (and not all) of the dormant tumors to drive resistance? How will the standard of care (radiotherapy- and chemotherapy) with which patients are treated affect these processes? Most GBM patients exhibit a hyperactive PI3K pathway due to either PTEN alterations or PIK3CA mutations [8] – will this impact the CSF-1R response? The answers to these questions will facilitate quick translation of the findings of Quail *et al.* to the benefit of patients.

Quail and coworkers are advancing the results of clinical trials to prepare for potential resistance to CSF-1R inhibitors and to then act accordingly. We must now wait for the clinical outcome in patients to validate their results and, based on the described findings, be ready to counteract the versatile and evolving tumor-niche ecosystem through rational and effective combinatory treatments.

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Spotlight

Mitochondrial UPR: A Double-Edged Sword

Ye Tian,[1,2] Carsten Merkwirth,[1,2] and Andrew Dillin[1,*]

The mitochondrial unfolded protein response (UPR^{mt}) promotes the recovery of dysfunctional mitochondria. Surprisingly, UPR^{mt} activation inadvertently maintains and propagates the deleterious mtDNA in a heteroplasmic *Caenorhabditis elegans* strain, with detrimental consequences. This study extends our understanding of the UPR^{mt} and provides a possible therapeutic target for diseases associated with mtDNA mutations.

The plethora of human diseases caused by mitochondrial dysfunction is staggering [1]. Many of these diseases are caused not

only by mutations of nuclear-encoded mitochondrial genes but also by mutations in the mitochondrial genome. For example, mtDNA deletions lead to Kearns–Sayre syndrome, which is characterized by paralysis of the eye muscles, heart failure, ataxia, hyperparathyroidism, and a high incidence of diabetes. Moreover, accumulation of mtDNA deletions has been observed in individual muscle cells and neurons during the aging process [2]. How the propagation of deleterious mitochondrial genomes within populations manifest and are maintained is an elusive question that has recently been addressed by Cole Haynes and colleagues.

Mitochondrial genomes encode 13 genes (12 in *C. elegans*) that are part of the oxidative phosphorylation (OXPHOS) complexes. Most OXPHOS subunits are nuclear-encoded genes whose products are imported into mitochondria. Different from the single genome in the nucleus, hundreds of mtDNAs exist in each cell. A single mtDNA mutation has little impact on the well-being of the host cell and can exist in a process known as heteroplasmy [2]. Within heteroplasmy, the ratio of mutant to wild-type mtDNA determines the onset of clinical symptoms. Typically, a ratio of 60–90% mutated mtDNA is required for the clinical phenotype to develop, but this varies dramatically for different mtDNA mutations. Tissues or organs with the highest energy demands, such as skeletal muscle, brain, and heart, are more susceptible to mtDNA mutations. How mutated mitochondrial genomes expand within cells has been of great interest and an unsolved problem in biomedicine.

When OXPHOS is dysfunctional or unfolded proteins accumulate within mitochondria, cells activate the UPR^{mt}, a transcriptional response mediated by the transcription factor ATFS-1 that promotes the recovery and regeneration of defective mitochondria [3]. Under normal conditions, ATFS-1 is imported into mitochondria, where it is promptly degraded. However, when mitochondrial import efficiency is compromised under conditions of mitochondrial stress, ATFS-1 is less efficiently imported into mitochondria and translocates to the nucleus to induce a broad transcriptional response including the upregulation of mitochondrial chaperones, antioxidant genes, glycolysis genes, and amino acid catabolism pathways [4]. Interestingly, ATFS-1 also limits the accumulation of transcripts that encode the OXPHOS components. In addition to trafficking to the nucleus, a percentage of ATFS-1 also accumulates within mitochondria to repress the OXPHOS transcripts encoded by mtDNA [5]. In summary, UPR^{mt} activation promotes mitochondrial proteostasis capacity and protects mitochondria from further damage.

The protective function of the UPR^{mt} in mitochondria, including bacterial infection, hematopoietic stem cell maintenance, and general aging, has been well studied [6]. A recent study reported in *Nature* suggests a new role for the UPR^{mt} in response to deleterious mtDNA accumulation [7].

In this study, Lin *et al.* examined the role of the UPR^{mt} in the maintenance and propagation of mtDNA harboring a 3.1-kb deletion (ΔmtDNA) encoding four essential OXPHOS subunits within the heteroplasmic *C. elegans* strain *uaDf5* [8]. This strain has been maintained in a stable heteroplasmic state in which ΔmtDNA constitutes 60% of all mtDNAs. Basal oxygen consumption as well as total respiratory capacity is decreased in this strain, indicating that high levels of ΔmtDNA account for the reduced OXPHOS activity that results in UPR^{mt} activation (Figure 1).

Unlike worms harboring mutations in nuclear-encoded OXPHOS components, the development of worms with ΔmtDNA is not affected when UPR^{mt} activation is inhibited by *atfs-1* RNAi. Unexpectedly, *atfs-1* deletion or its knockdown caused a dramatic decrease in ΔmtDNA levels

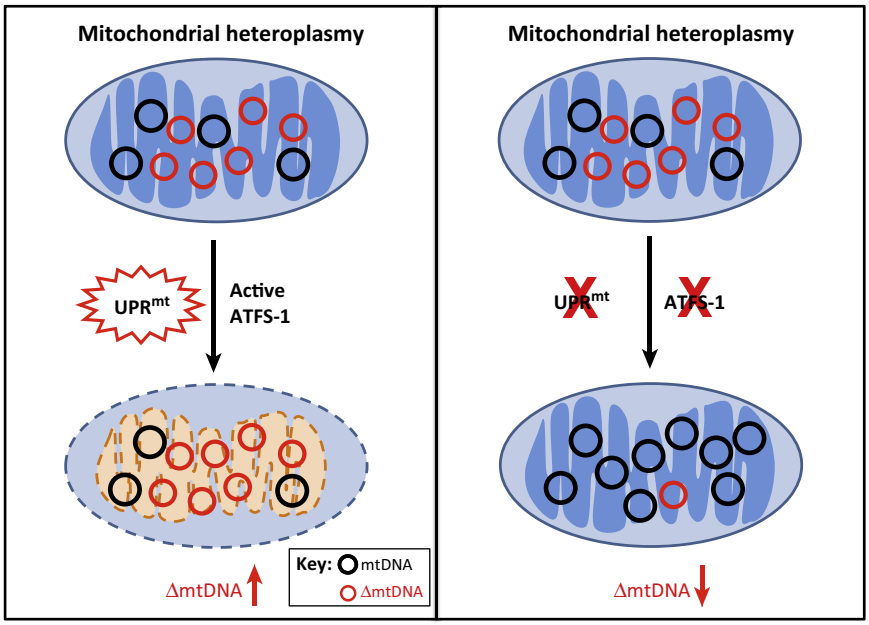

Figure 1. The Role of ATFS-1 in ΔmtDNA Maintenance and Propagation. Activation of the mitochondrial unfolded protein response (UPR^{mt}) and functional ATFS-1 maintain and propagate deleterious mitochondrial genomes (ΔmtDNA) in the context of mtDNA heteroplasmy (left panel). Impaired UPR^{mt} signaling due to loss of ATFS-1 activity results in a reduced load of deleterious ΔmtDNA molecules (right panel). Black circles, wild-type mtDNA; red circles, ΔmtDNA.

from 60% to 7% (Figure 1). Similar results were also observed in worms without germ cells, to exclude the possibility that the shift in ΔmtDNA occurred during germline development and supporting the idea that ATFS-1 and the UPR^{mt} function in post-mitotic somatic cells to maintain deleterious ΔmtDNA levels. Constitutive activation of ATFS-1 further increased ΔmtDNA, from 63% to 73% (Figure 1), resulting in further OXPHOS impairment, reduced mitochondrial membrane potential, defective crista formation in mitochondria, and accumulation of autophagosome-like structures around mitochondria.

It is well established that mitophagy is important for the elimination of mitochondria with high levels of ΔmtDNA [9]. Mitophagy inhibition increased the level of ΔmtDNA in the heteroplasmic *C. elegans* strain. However, such an increase did not fully restore the ΔmtDNA level in *atfs-1*-deleted worms, indicating that ATFS-1 promotes ΔmtDNA propagation independent of mitophagy. Notably, ATFS-1 controls a mitochondrial biogenesis program in response to mitochondrial dysfunction to compensate for the loss of OXPHOS activity. Therefore, mitochondrial mass is increased on UPR^{mt} activation as well as the total mtDNA copy number, including both wild–type and deleterious mtDNAs. In the heteroplasmic cells, it is possible that a replicative advantage for shorter mtDNA molecules results in the accumulation of ΔmtDNA when mitochondrial biogenesis is induced on UPR^{mt} activation. In addition, mitochondrial fusion and fission also limit the accumulation of deleterious mtDNAs in individual mitochondria to promote tolerance to deleterious mtDNAs in the cell. Therefore, the combined effects of UPR^{mt} activation due to deleterious mtDNA accumulation results in robust induction of multiple genes involved in mitochondrial biogenesis, mitochondrial dynamics, and mitophagy, which produces stoichiometric imbalance for ΔmtDNA maintenance and provides a favorable environment for ΔmtDNA propagation but is detrimental to the host cells.

This work raises several intriguing questions. Is the role of ATFS-1 in the maintenance of mutated mtDNA molecules restricted to deletions or does it also propagate mtDNA molecules carrying point mutations? Another important aspect to consider is the dual role of the UPR^{mt} in lifespan regulation, especially regarding prolonged UPR^{mt} activation in a heteroplasmic background such as inherited mitochondrial deletions or cancer cells. An urgent question in the field is whether the UPR^{mt} in mammals acts in a similar fashion to that in *C. elegans*. Future challenges will be to identify the homologous UPR^{mt} regulators in higher organisms, especially the transcription factor ATFS-1. Ultimately, understanding the molecular roles of ATFS-1 and the UPR^{mt} in the maintenance and propagation of deleterious mtDNA in specific tissues in different disease models may pave the way for the treatment of human diseases associated with mitochondrial mutations.

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Forum

Does Longer Lifespan Mean Longer Healthspan?

Malene Hansen[1,*] and Brian K. Kennedy[2,*]

Once thought to be impossible, it is now clear that changing the activity of several conserved genetic pathways can lead to lifespan extension in experimental organisms. In humans, however, the goal is to extend healthspan, the functional and disease-free period of life. Are the current pathways to lifespan extension also improving healthspan?

Lifespan versus Healthspan

It is likely that we will look back on the first half of the 21st century in health care as the age of aging. The world is getting older and the numbers are staggering: up to 20% of the globe will be over 60 years old in the near future and health-care costs will rise. Chronic diseases of aging are increasing and are inflicting untold costs on human quality of life and there is a growing recognition that solutions must be found to keep people healthy longer.

Most medical research is targeted at diseases in isolation and yet evidence is mounting that physiologic changes associated with aging underlie a vast majority of chronic disease states. If this is true, slowing aging might prevent multiple morbidities simultaneously.