Memory of neuronal mitochondrial stress being passed on to their descendants

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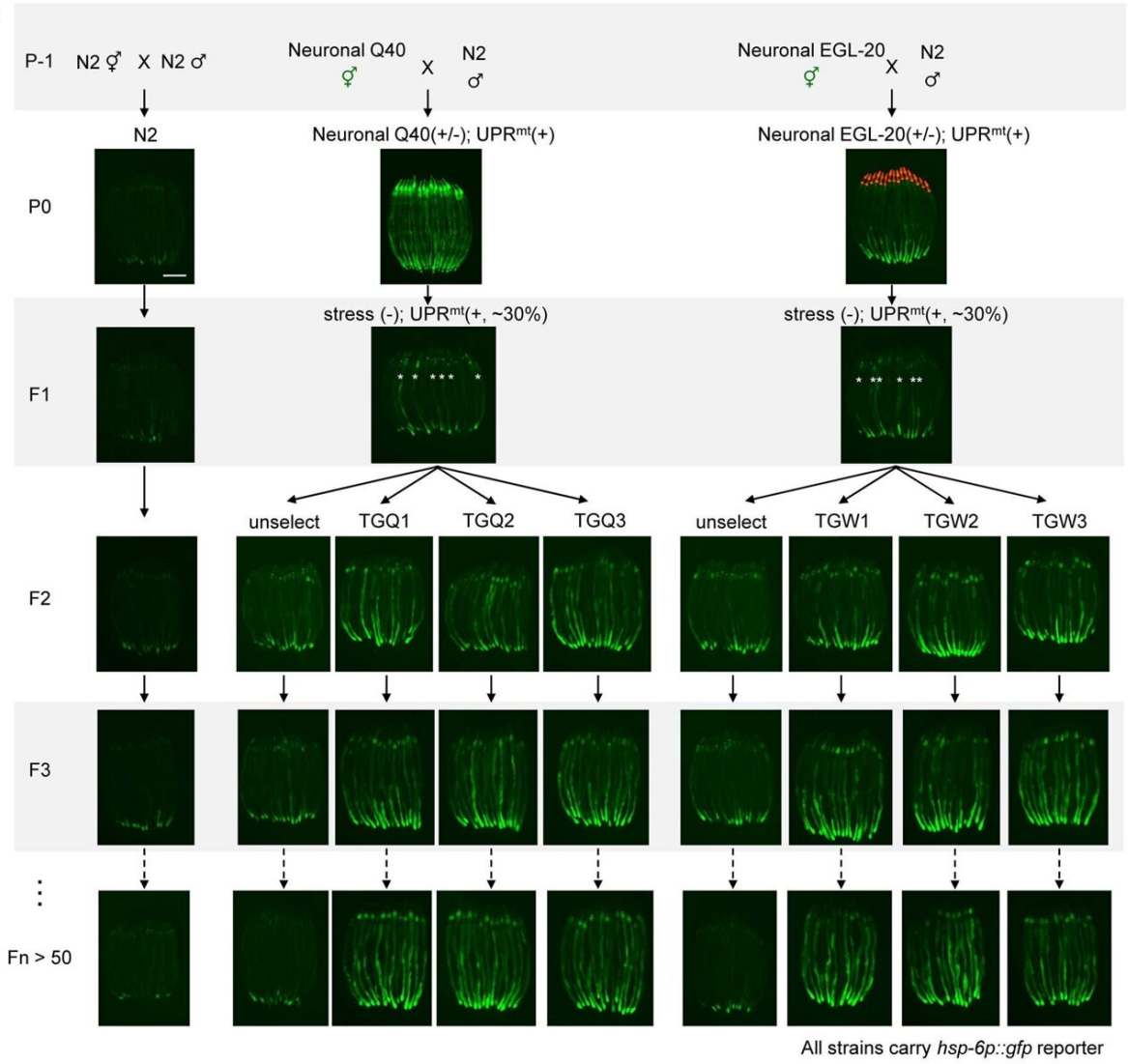
a



b

Generations	WT	*rgef-1p::Q40::YFP* (Neuronal Q40)				*rgef-1p::egl-20* (Neuronal Wnt)			
F1	5% (n=40)		27.5% (n=80)				31.5% (n=95)		
		unselect	TGQ1	TGQ2	TGQ3	unselect	TGW1	TGW2	TGW3
F2	2.5% (n=40)	18% (n=50)	55.5% (n=36)	40% (n=40)	42.8% (n=42)	19.3% (n=52)	53.3% (n=45)	54.3% (n=35)	56.3% (n=32)
F3	5% (n=40)	10% (n=36)	84.4% (n=45)	69.8% (n=43)	70% (n=40)	20% (n=40)	78.9% (n=38)	85.7% (n=35)	87.8% (n=41)
F4	0% (n=40)	4.76% (n=42)	86.5% (n=37)	67.4% (n=43)	66.7% (n=45)	5% (n=40)	90.1% (n=44)	62.2% (n=37)	86.8% (n=38)
F5	0% (n=40)	0% (n=40)	85% (n=40)	77.7% (n=45)	70% (n=40)	0% (n=38)	82.9% (n=35)	85.7% (n=42)	90% (n=40)
F6	5% (n=40)	0% (n=35)	90.5% (n=42)	95% (n=40)	88.4% (n=43)	0% (n=41)	91.3% (n=46)	86.4% (n=44)	85% (n=40)
F7	0% (n=40)		78.9% (n=38)	89.7% (n=39)	90% (n=40)		85.4% (n=41)	85% (n=40)	88.9% (n=36)
F8	5% (n=40)		88.9% (n=45)	90.9% (n=44)	92.7% (n=38)		90% (n=40)	92.3% (n=39)	81.4% (n=43)
F9	0% (n=40)		87.5% (n=32)	91.4% (n=35)	78.0% (n=41)		81.4% (n=43)	75% (n=40)	87.0% (n=46)
F10	0% (n=40)		88.9% (n=45)	90% (n=40)	78.9% (n=38)		81.1% (n=37)	78.6% (n=42)	88.9% (n=45)
F11-50	0-5%		70-90%	70-90%	70-90%		70-90%	70-90%	70-90%

The penetrance of the UPRmt induction in each generation.

Fig. 1: Representative fluorescence visualization of the transgenerational induction of the UPRmt across multiple generations. a, Fluorescence visualization of the hsp-6p::gfp reporter in descendant animals generated from crosses between animals with neuronal mitochondrial stresses and wild-type animals. The schematic design of the experiment is presented in Fig. 1a. Worms with neuronal expression of Q40 or Wnt were crossed with WT males to generate the P0 animals with the expression of neuronal Q40 or Wnt. Then, P0 worms were allowed to produce F1 offspring through self-fertilization. 20%–30% of the F1 animals without expression of neuronal Q40 or Wnt still exhibited the strong induction of hsp-6p::gfp (indicated with white stars). We followed three independent lines with strong hsp-6p::gfp expression and one line that was not selected for the hsp-6p::gfp expression (randomly maintained) from each cross for over 50 generations. Worms with hsp-6p::gfp fluorescence over one-third of the intestine were considered to show the strong induction of the UPRmt. Scale bar, 250 μm. b, Percentage of worms showing the strong UPRmt induction in each generation as shown in a. Credit: DOI: 10.1038/s41556-021-00724-8

The impact of the parental experiences has been observed to extend over multiple generations in various organisms. It is therefore of significant scientific interest to determine what environmental and physical conditions could induce transgenerational effects.

In a study published in *Nature Cell Biology*, Dr. Tian Ye's group from the Institute of Genetics and Developmental Biology of the Chinese Academy of Sciences revealed that neuronal mitochondrial stress signals can be transmitted to the mitochondria in the germline to potentially promote the maternal inheritance of elevated mtDNA levels across many generations in a Wnt signaling-dependent manner.

The researchers described a discovery from a serendipitous observation

that neuronal mitochondrial stresses elicit a global induction of the UPRmt that can be transmitted to offspring for multiple generations (>50) in Caenorhabditis elegans even after the original stress signal has been gone.

The transgenerational induction of UPRmt was caused by the elevated mtDNA inherited maternally, which disturbed the balance between mitochondrial oxidative phosphorylation subunits encoded by the mtDNA and the nuclear DNA to induce mitochondrial proteostasis stress. Wnt signaling is required for the propagation of elevated mtDNA levels across generations via transgenerational regulation of the mtDNA polymerase polg-1.

The transgenerational inheritance of the elevated mtDNA levels and the UPRmt enable their descendants to live longer and confer increased stress tolerance. However, there is clearly a cost of transgenerational UPRmt, animals with these transgenerational effects take a longer time to sexually mature and will produce less progeny. The presence of such a trade-off implies a fitness cost of inheritance of elevated mtDNA levels if stress conditions are not experienced in the near future.

This study showed a novel transgenerational inheritance of mitochondrial stress response, revealed the unexpected role of mtDNA content in transgenerational effects, and extended the understanding of Wnt signaling in the transmission of neuronal mitochondrial stress signals even across generations. It will be interesting to further investigate the interaction of Wnt signaling and the mtDNA copy numbers in the multigenerational plasticity related to mitochondrial physiology.

More information: Qian Zhang et al, The memory of neuronal mitochondrial stress is inherited transgenerationally via elevated mitochondrial DNA levels, *Nature Cell Biology* (2021). DOI:

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