

Cytoplasmic NAD⁺ regulates mitochondrial calcium in *C. elegans*

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Introduction

Mitochondrial calcium homeostasis is essential for a plethora of cellular activities. Compromised mitochondrial calcium homeostasis leads to mitochondrial dysfunction, which may contribute to pathological conditions, ranging from diabetes to neurodegeneration. Whereas the molecular machineries controlling mitochondrial calcium influx and efflux have been identified, the regulatory mechanisms for maintaining mitochondrial calcium handling are less defined. We have studied the regulatory mechanism of *in vivo* mitochondrial calcium handling in the simple nematode worm *C. elegans*, which enables spatiotemporally quantifiable mitochondrial calcium monitor at intact organismal level. In this study we show how mitochondrial calcium transient responses to disrupted metabolic signaling and delineate a functional crosstalk between NAD⁺ availability and mitochondrial calcium handling.

Figure 1. Mitochondrial Ca²⁺ uptake by RyR-MCU axis

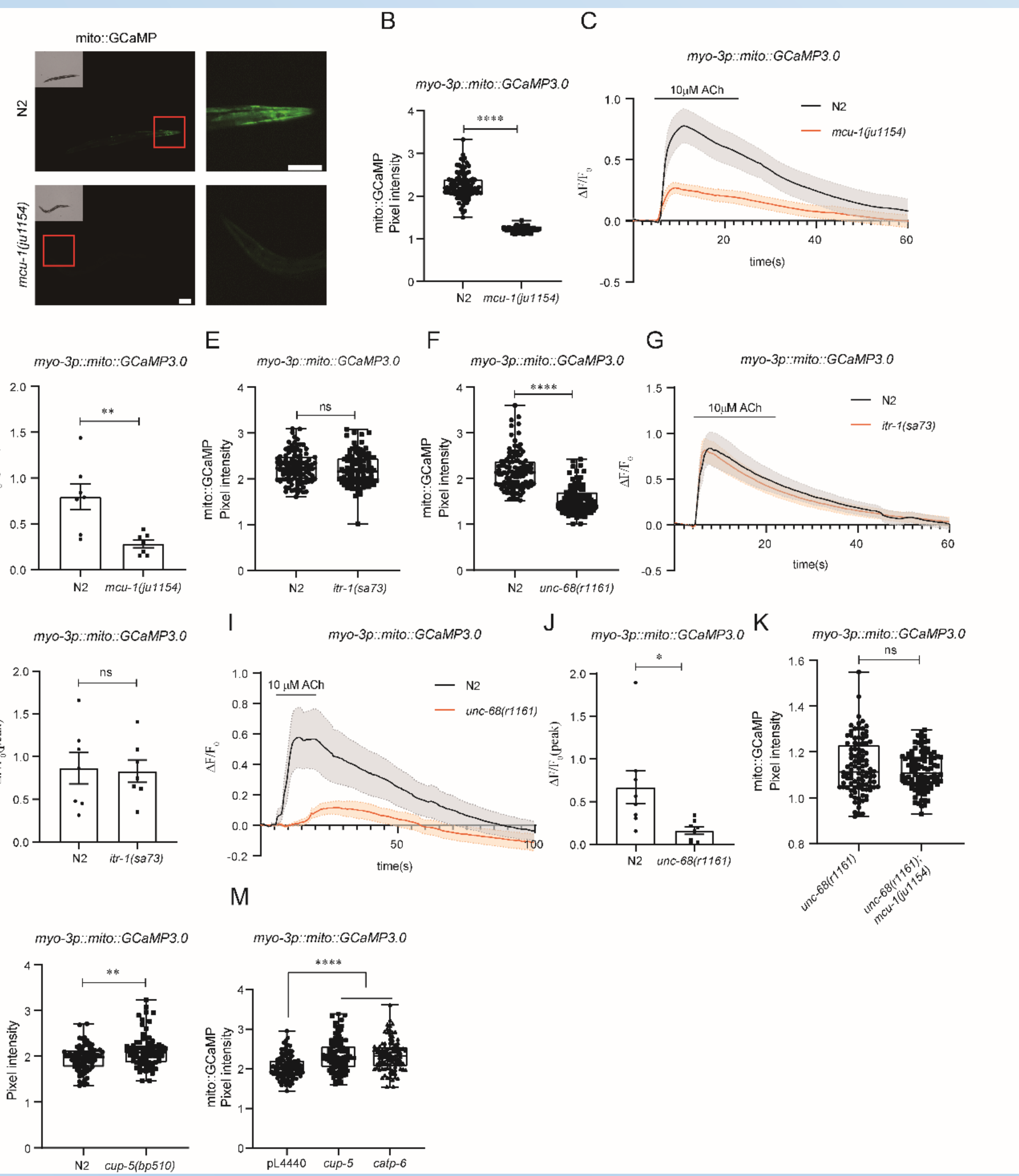


Figure 2. Mitochondrial Ca²⁺ responses upon RNAi screening

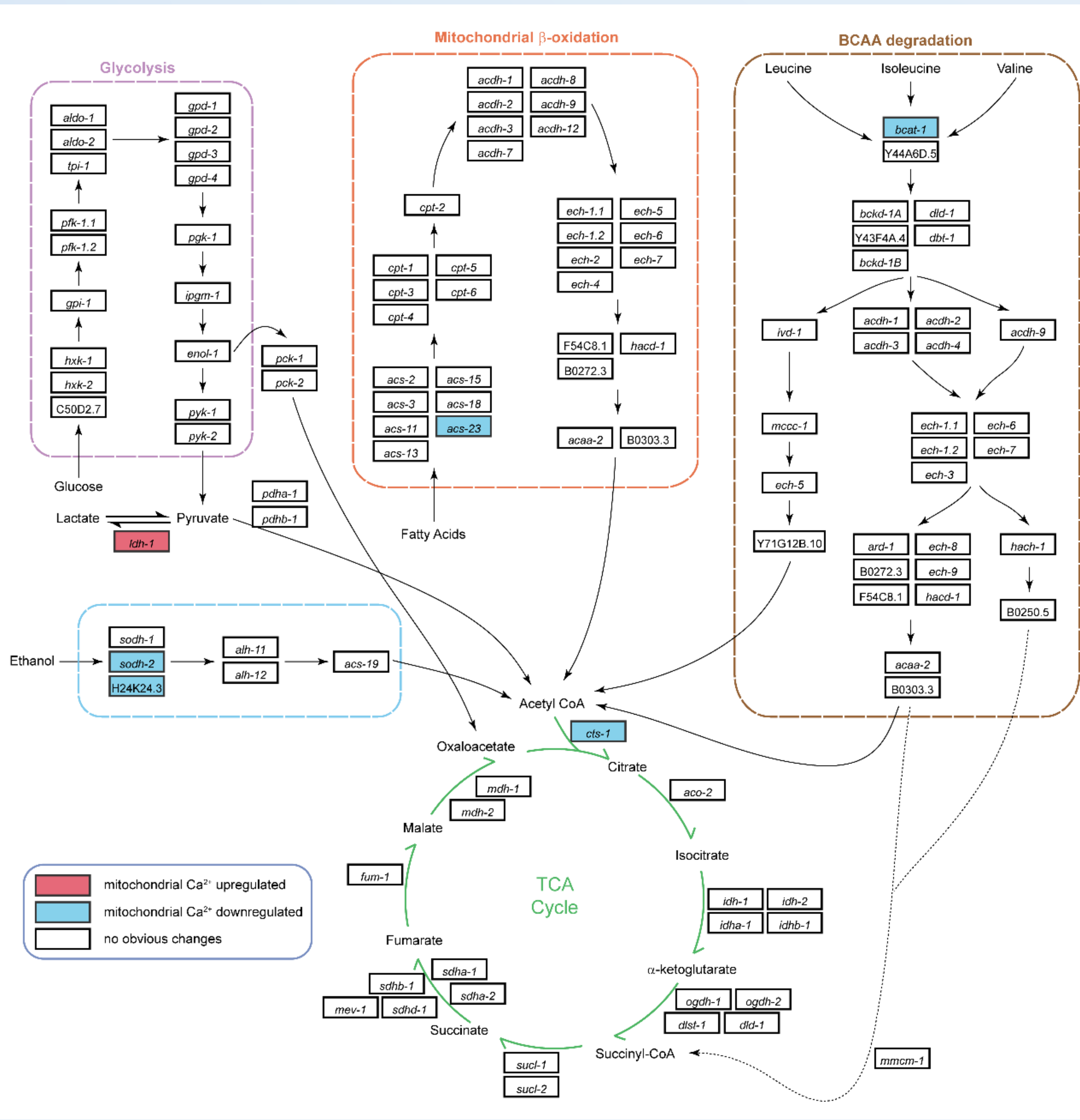


Figure 3. NAD⁺ regulates mitochondrial calcium handling

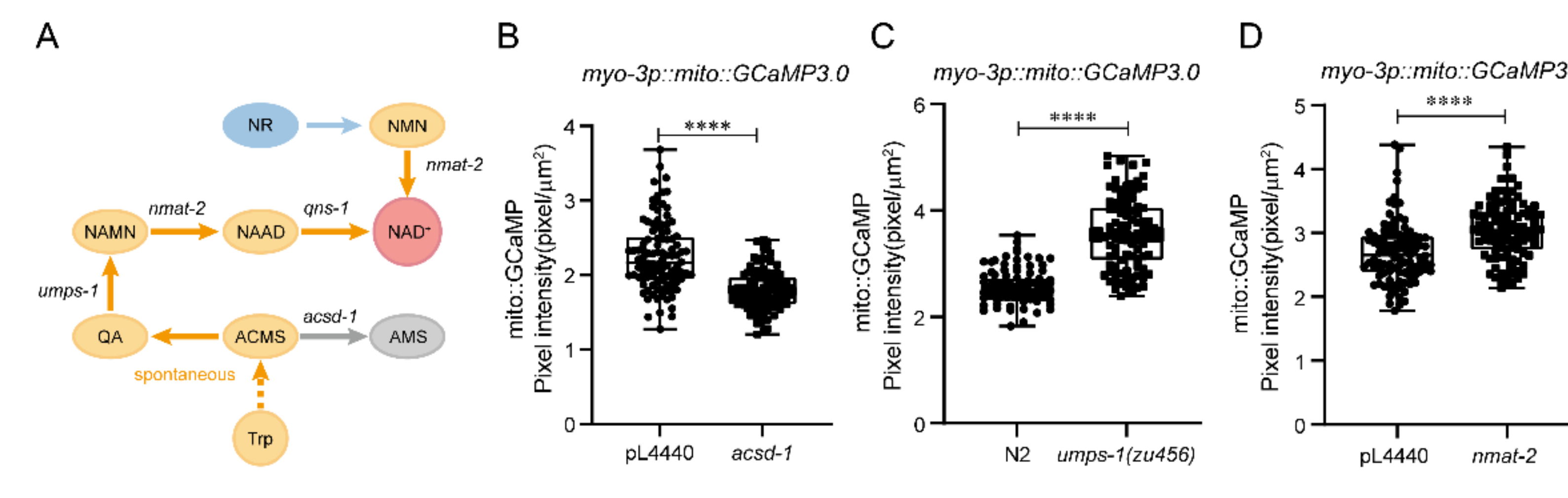
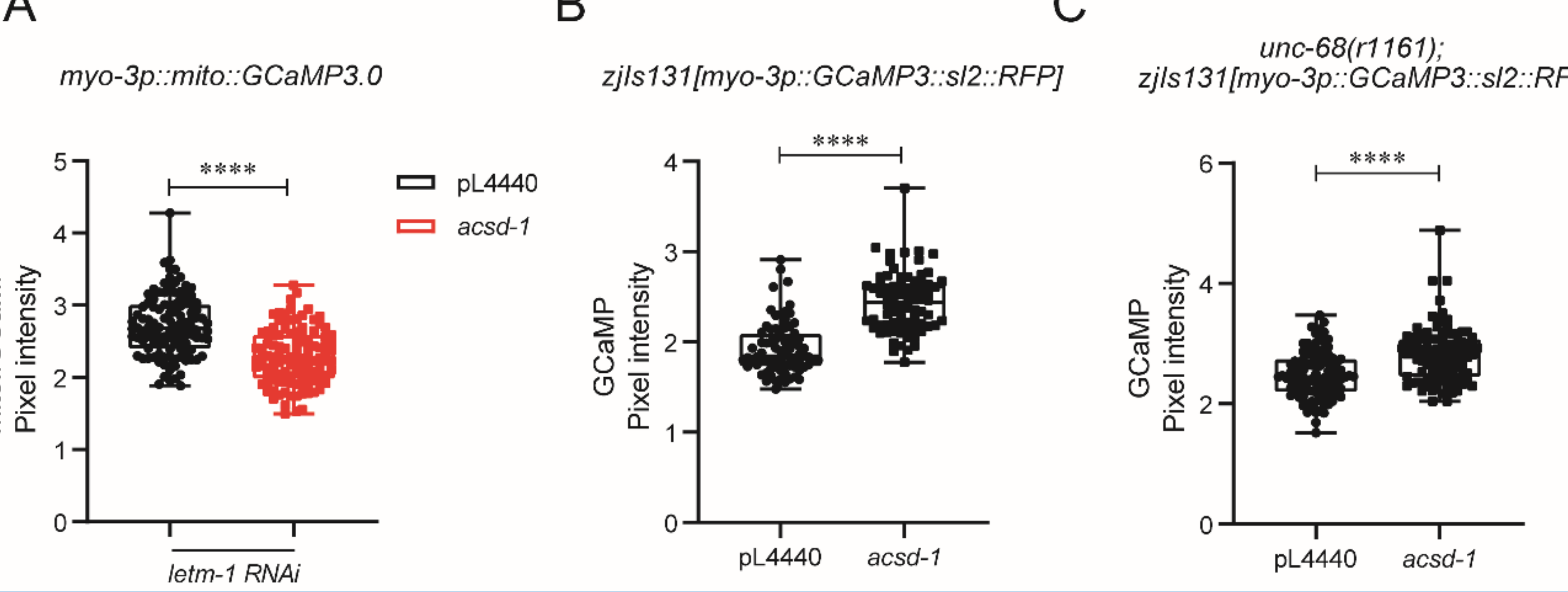


Figure 4. Increased NAD⁺ enhances cytosolic calcium



Conclusion

Metabolite sensing is fundamental for cell health. Multiple metabolite-sensing pathways have been established to govern mitochondria-related processes. By contrast, how mitochondria per se sense metabolites fluctuation and modulate their functionality is unclear. We here show mitochondrial calcium handling is shaped by cellular NAD⁺ and regulates energy production by tuning mitochondrial biomass.