Loss of vacuolar acidity results in iron-sulfur cluster defects and divergent homeostatic Reponses during aging in Saccharomyces cerevisiae

The loss of vacuolar/lysosomal acidity is an early event during aging that has been linked to mitochondrial dysfunction. However, it is unclear how loss of vacuolar acidity results in age-related dysfunction. Through unbiased genetic screens, we determine that increased iron uptake can suppress the mitochondrial respiratory deficiency phenotype of yeast vma mutants, which have lost vacuolar acidity due to genetic disruption of the vacuolar ATPase proton pump. Yeast vma mutants exhibited nuclear localization of Aft1, which turns on the iron regulon in response to iron-sulfur cluster (ISC) deficiency. This led us to find that loss of vacuolar acidity with age in wild-type yeast causes ISC defects and a DNA damage response. Using microfluidics to investigate aging at the single-cell level, we observe grossly divergent trajectories of iron homeostasis within an isogenic and environmentally homogeneous population One subpopulation of cells fails to mount the expected compensatory iron regulon gene expression program, and suffers progressively severe ISC deficiency with little to no activation of the iron regulon. In Contrast other cells show robust iron regulon activity with limited ISC deficiency, which allows extended passage and survival through a period of genomic instability during aging. These divergent trajectories suggest that iron regulation and ISC homeostasis represent a possible target for aging interventions.