Novel Anti-aging Small Molecules Greatly Extend Yeast Life Span by Specifically Targeting a Mechanism Linking Lipid Dynamics and Longevity

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The fundamental mechanisms of aging are conserved across phyla. We use the yeast *Saccharomyces cerevisiae* as a model to study the mechanisms of cellular aging in multicellular eukaryotes. Our objective is to establish the mechanisms underlying the essential role of lipid dynamics in regulating longevity. Yeast aging can be slowed down by calorie restriction, a low-calorie dietary regimen that extends life span and delays age-related disorders in a wide spectrum of organisms. We assessed the effect of a calorie restriction diet and numerous mutations extending yeast life span on the spatiotemporal dynamics of the proteomes and lipidomes of organelles involved in lipid metabolism. These organelles include the endoplasmic reticulum (ER), peroxisomes and lipid bodies. We also examined the spatiotemporal dynamics of organellar proteomes and lipidomes in long-lived yeast mutants impaired in various pathways of lipid metabolism and transport. Our findings revealed a mechanism linking longevity and lipid dynamics. In this mechanism, a calorie-rich diet suppresses peroxisomal oxidation of free fatty acids (FFA) that originate from neutral lipids synthesized in the ER and deposited within lipid bodies. The resulting accumulation of arrays of FFA within lipid bodies initiates several negative feedback loops regulating the metabolism of neutral lipids. Due to the action of these negative feedback loops, aging yeast accumulate diacylglycerol (DAG). The buildup of monounsaturated FFA promotes necrotic cell death, whereas the accumulation of DAG triggers a protein kinase C-dependent signal transduction network affecting multiple stress response-related processes. Implementing our understanding of the mechanism linking longevity and lipid dynamics, we developed a life-span assay that was used for a high-throughput screening of extensive compound libraries. We identified five groups of novel anti-aging small molecules that greatly extend yeast longevity by remodelling lipid metabolism in the ER, peroxisomes and lipid bodies and by preventing the age-related, FFA-induced necrotic cell death.