activation of cytoprotection pathways can lead to pleiotropic outcomes. In C. elegans, activated SKN-1/NRF2 stemming from defective mitochondrial homeostasis, drives early reproductive senescence in males. The endocrine system integrates physiological systems to maintain homeostasis, in part, by regulating metabolism. Reduced signaling of growth hormone alters the metabolism of methionine, upregulates defense mechanisms and maintains young DNA methylation patterns, all of which lead to lifespan extension in rodents. In the past decade, it has become clear that the anti-diabetic drug metformin also has anti-aging properties. Genetic approaches indicate that the metformin pro-longevity pathway is highly conserved from worm to human and involves reversal of aging-associated nuclear leakage and suppression of mTOR signaling. Homeostasis is maintained at all hierarchical levels (from molecules to organism) and requires constant surveillance throughout the lifespan. As our understanding of the intricacies of this regulation are developed so will our capacity to capitalize on these systems to improve health across the lifespan.

LOSS OF MITOCHONDRIAL AMINO ACID CATABOLISM METABOLISM WITH AGE DRIVES REPRODUCTIVE SENESCENCE
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The contribution of normal cellular metabolism on sperm health and function are not well-defined. Here we show that changes in mitochondrial homeostasis in response to defective mitochondrial proline catabolism has direct roles in maintaining distinct aspects of sperm quality and competitive fitness. Disruption of alh-6, which facilitates the second step of proline catabolism by converting P5C to glutamate, results in premature reproductive senescence, specifically in males. The generation and accumulation of the toxic P5C metabolic intermediate drives oxidative stress, changes in mitochondrial morphology and depletion of energy storing metabolites in sperm, which impair male sperm competitive advantage. Surprisingly the germline phenotypes in response to alh-6 loss are not influenced by diet, as opposed to the somatic homeostasis that can be restored in a diet-dependent manner. Taken together, our results define a role for mitochondrial proline catabolism on sperm function and reveal the importance of mitochondrial homeostasis.

REDUCED GH SIGNALING ENHANCES THE ABILITY OF AN ORGANISM TO RESPOND TO STRESS
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Multiple biological and environmental factors impact the health and life span of an organism. The endocrine system is a highly integrated physiological system in mammals that regulates metabolism, growth, reproduction and the response to stress, among other functions thus ultimately influencing aging and longevity. Reduced signaling of the growth hormone pathway in rodents extends lifespan, in part, by maintaining enhanced defense mechanisms throughout life. Growth hormone appears to regulate oxidative defense and the methionine metabolic pathway via enzymes that, in turn, affect S-adenosylmethionine, glutathione, and detoxification activities. Altered methyltransferase activities may be reflected in maintenance of young DNA methylation patterns also contributing to long life. Together our work and other indicate that GH plays a significant role in an organism’s ability to respond to a variety of cellular stressors by regulating factors that counter oxidative stress, modulating metabolic responsiveness to nutrients and detoxification of endogenous and exogenous compounds.

ANCIENT MECHANISMS BY WHICH METFORMIN PROMOTES HEALTHY AGING
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In addition to its anti-diabetic effects, metformin promotes longevity and reduces aging-associated pathologies. The mechanisms for these effects remain elusive. Through unbiased genetic screening in C. elegans, we have begun to unravel the mysteries of metformin’s beneficial effects. We find that metformin promotes longevity by inhibiting mitochondrial respiratory capacity, which restrains transit of the RagA-RagC GTPase heterodimer through the nuclear pore complex. Nuclear exclusion renders RagC incapable of gaining the GDP-bound state necessary to stimulate mTORC1. Biguanide-induced inactivation of mTORC1 subsequently inhibits growth through transcriptional induction of a previously unstudied metabolic enzyme. This ancient metformin response pathway is conserved from worms to humans. Through unbiased genomics we continue to expand our knowledge of the pro-longevity pathway activated by metformin. We will describe new insights into metformin action and how metformin can be maximally leveraged to promote healthy aging.

TO ADAPT OR NOT TO ADAPT: THE CONSEQUENCES OF AN AGE-DEPENDENT DECLINE IN THE ADAPTIVE HOMEOSTASIS
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Adaptive Homeostasis enables transient modulation of the cellular stress-protective machinery, due to non-damaging signaling molecules or environment, ensuring optimal function in mammalian cells and organisms (nematode worms, fruit flies, and mice), despite ever-changing environments. Non-damaging signaling oxidant exposure triggers increased amount and activity of the 20S-Proteasome and the mitochondrial Lon protease, and a sex-dependent effect: hydrogen peroxide pretreatment causes a female-favored adaptive response, while paraquat induces a male-favored adaptive response. Translational work, with 6- and 21-month C57BL/6 mice, show transient activation of Nrf2-regulated enzymes (HO-1, 20S-Proteasome, GCLC, GCLM) and stress-protective enzymes (Lon, Immunoproteasome) due to short-term, non-toxic exposure to vehicular-derived...