

## Biological mechanisms of aging

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### ABSTRACT

As human life expectancy is prolonged, age-related diseases are thriving. Aging is a complex multifactorial process of molecular and cellular decline that affects tissue function over time, rendering organisms frail and susceptible to disease and death. Over the last decades, a growing body of scientific literature across different biological models, ranging from yeast, worms, flies, and mice to primates, humans and other long-lived animals, has contributed greatly towards identifying conserved biological mechanisms that ward off structural and functional deterioration within living systems. Collectively, these data offer powerful insights into healthy aging and longevity. For example, molecular integrity of the genome, telomere length, epigenetic landscape stability, and protein homeostasis are all features linked to “youthful” states. These molecular hallmarks underlie cellular functions associated with aging like mitochondrial fitness, nutrient sensing, efficient intercellular communication, stem cell renewal, and regenerative capacity in tissues. At present, calorie restriction remains the most robust strategy for extending health

and lifespan in most biological models tested. Thus, pathways that mediate the beneficial effects of calorie restriction by integrating metabolic signals to aging processes have received major attention, such as insulin/insulin growth factor-1, sirtuins, mammalian target of rapamycin, and 5' adenosine monophosphate-activated protein kinase. Consequently, small-molecule targets of these pathways have emerged in the impetuous search for calorie restriction mimetics, of which resveratrol, metformin, and rapamycin are the most extensively studied. A comprehensive understanding of the molecular and cellular mechanisms that underlie age-related deterioration and repair, and how these pathways interconnect, remains a major challenge for uncovering interventions to slow human aging while extending molecular and physiological youthfulness, vitality, and health.