

DNA DAMAGE IN AGING CELLS

A high-fat diet, and in particular a ketogenic diet, can rescue symptoms in animal models of Cockayne syndrome, an accelerated aging disorder caused by defects in DNA repair, suggesting that genome instability introduces metabolic alterations that occur in the aging process. Accumulation of damaged DNA leads to activation of poly-ADP-ribose polymerase 1 (PARP1). As a consequence, levels of NAD⁺, a cofactor in glycolysis, and acetyl-CoA, an alternative to lactate as the outcome of glycolysis, decline, as does the activity of mammalian sirtuin SIRT1, which normally metabolizes NAD⁺ to drive the deacetylation of proteins such as histones and transcription factors. Pharmacological inhibition of PARP1, restoration of NAD⁺ levels, increases in ketone levels, and activation of SIRT1 have all shown promise in attenuating age-related decline.

