discovered was clk-1(e2519) with longer embryonic and postembryonic development, and increased lifespan, as well as the periods of the defecation, swimming and pumping cycles. Disrupted timing of several developmental and behavioral processes in the mutant led to a hypothesis that the clk-1 gene is a component of some biological clock.[30] In fact, the clk-1 gene encodes an enzyme involved in the synthesis of ubiquinone (coenzyme Q, CoQ), a mitochondrial electron carrier molecule necessary for respiration. It is noteworthy that transgenic expression of mouse clk-1 homologue in *C. elegans* completely rescued the slowed rhythmic behaviors of clk-1 nematode mutants and reverted their extended lifespan to a level comparable with that of the wild-type control.[31]

Since this initial seminal discovery, it has been found that disruption of several components of the mitochondrial respiratory chain or its assembly factors, as well as low doses of mitochondrial toxins (such as rotenone and antimycin A) can increase the lifespan in *C. elegans* (see ref. 17 for a review). In *D. melanogaster*, alterations in mitochondrial functions caused by overexpression of mtDNA polymerase and uncoupling protein 3 or knockdown of cytochrome c oxidase[32–34] decreased lifespan, whereas elevated expression of heat shock protein 22 and uncoupling proteins 1 and 2 [35–37] increased lifespan. In mice, knockouts of the cytochrome c oxidase assembly factor Surf1 [38] or of clk-1 orthologues,[39,40] as well as the reduced expression of mitochondrial ribosomal protein S5 [41], have all been reported to prolong life.

Overall, at present, the accepted consensus is that a moderate lowering of functioning of mitochondria and, consequently, a moderate decrease in mROS production is the major factor contributing to the lifespan increase in animals, whereas its strong lowering shortens lifespan (see ref. 42 for a review). The observations of increased lifespan caused by disruption of mitochondrial functions can be explained in terms of mitohormesis: mildly increased mROS generation may cause an adaptive response that triggers a stress resistance increase that eventually causes long-term lowering of oxidative stress.[43] Another (and simpler) explanation of the same paradox is an assumption that mROS are intermediates of the aging program.[44,45]

9.3 The Link Between Oxidative Stress and Aging

The key role of free radicals in aging was first proposed by Harman in 1956;[46] he also suggested that free radicals arise as by-products of respiration,[46] and that mROS-generating mitochondria might serve as a biologic clock that determines the rate of aging[47,48] (see also ref. 49–51 for excellent reviews on the role of mROS in the pathophysiology of aging).

The modern version of free radical theory of aging suggests that senescence is not only caused by direct ROS-induced damage to DNA, proteins, lipids and other cellular components, but, mainly, is a consequence of the imbalance in cellular ROS signaling (see ref. 52–55 for recent reviews). In particular, mROS play a central role in the regulation of programmed cell death and other vital processes in organisms ranging from single-cell eukaryotes to humans.