

Abstract

The leading hypothesis to explain why organisms age suggests that reactive oxygen species (or oxygen free radicals) are primarily to blame for the accumulated cellular damage and physical deterioration characteristic of aging. In humans and other eukaryotes, reactive oxygen species naturally leak from the mitochondrial respiratory chain (MRC), implicating mitochondrial functioning as a key determinant of rates of aging. Indeed, mutations that impair functioning of the mitochondrial respiratory chain are associated with a variety of metabolic and age-related neurodegenerative disorders. The mitochondrial DNA of several natural isolates of the soil nematode *Caenorhabditis briggsae* have been found to harbor varying frequencies of mutant protein-coding gene, *ND5*, the product of which is a central component of Complex I of the MRC and integral to cellular energy metabolism. *ND5* mutations are associated with several human disorders including Parkinson disease. In a series of longitudinal studies, we will characterize the pathogenic effects of this naturally occurring mitochondrial deletion and define the evolutionary forces that may allow the maintenance of such a mutation. Our *C. briggsae* system offers an unprecedented opportunity to understand the interplay between MRC dysfunction, metabolism, reactive oxygen and aging, and the basic biology underlying natural mitochondrial DNA deletion genetics.