PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

How mtDNA mutations cause aging

ArticleInfo		
ArticleID	:	5027
ArticleDOI	:	10.1186/gb-spotlight-20050718-01
ArticleCitationID	:	spotlight-20050718-01
ArticleSequenceNumber	:	90
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2005–7–18 OnlineDate : 2005–7–18
ArticleCopyright	:	BioMed Central Ltd2005
ArticleGrants	:	
ArticleContext	:	130595511

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Mitochondrial DNA mutations appear to lead to aging by induced apoptosis and not by increased production of free radicals that lead to cellular damage as previously thought, scientists report in this week's *Science*. Tomas Prolla at the University of Wisconsin-Madison and colleagues found a rise in mtDNA mutations led to premature aging but not to increased levels of reactive oxygen species.

"The finding of no increased reactive oxygen species is very surprising," Nils-Goran Larsson at Karolinska University Hospital in Stockholm, Sweden, who did not participate in this study, told *The Scientist*. "The hypothesis that reactive oxygen species are important for aging must be reconsidered."

Prolla and colleagues created mice with a version of the mtDNA polymerase gamma that lacked proofreading capacity. These mutants showed premature aging, including hair loss, graying and hunched backs, and had a maximum life span of 460 days compared to more than 850 for wild-type mice. MtDNA sequencing revealed the mtDNA mutation frequency of these mutants was three to eight times that of wild-type.

The researchers measured several markers of oxidative stress, including hydrogen peroxide, protein carbonyls, F2-isoprostanes, and oxidative damage to DNA and RNA, in liver and skeletal muscle. None of these markers showed any sign of increased oxidative stress.

However, when they measured cleaved caspase-3–a marker linked with the mitochondrial pathway of apoptosis–the researchers found that in wild-type mice, levels increased by 50% or more between 5 and 30 months of age. Cleaved caspase-3 levels were also significantly higher in 3-month-old mutant mice compared with wild-type, thus revealing that normal and accelerated aging are linked with apoptosis.

In the mutants, age-related features were most common in tissues undergoing rapid cellular turnover, including loss of intestinal crypts, testicular atrophy associated with spermatogonia depletion, and thymic involution. Using the TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling) assay, which detects apoptotic cells in situ, the researchers found that the intestinal epithelium, thymus, and testis showed significantly more TUNEL positive cells in mutants than in wild-type. This demonstrated that tissues affected by premature aging and undergoing rapid cellular turnover experience greater levels of apoptosis, according to the report.

"We believe that what we see there is that tissues with rapid cell turnover are more susceptible to apoptosis, possibly because there is always the possibility of them developing cancer because of their high proliferation rates," Prolla told *The Scientist*.

Prolla noted that the main mechanism of action of caloric restriction, the only nutritional intervention that retards aging, "was thought to be a suppression of free radical production." Prior research had found that caloric restriction also delayed mtDNA mutation accumulation and reduced mitochondria-linked apoptotic pathways. "So our findings and those of others suggest inhibition of apoptosis may instead be one of the key mechanisms by which caloric restriction retards aging," he said.

George Martin at the University of Washington in Seattle, who did not participate in this study, found it "a nice job. What we'd really like to see now is if enhancing the fidelity of proofreading in mice makes them live longer," he told *The Scientist*.

Martin added future experiments should autopsy mutant mice that die of old age. "Most mice that die of old age develop malignant neoplasms, almost always lymphomas," he said. "So you'd want to know if these mutants died of a similar pathology to see if their mice represent a faithful model of aging."

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