Accelerated Mitochondrial DNA Mutagenesis May Suppress Tumor Growth

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Mitochondria, the intracellular organelles responsible for energy production in eukaryotic cells, contain their own DNA (mtDNA). In animals, this DNA is the cell's only genetic material stored outside the nucleus, and replication of the mitochondrial genome is independent of the cell cycle and uses different enzymatic machinery.

Human tumors frequently carry clonally expanded mutations in their mtDNA. Some of these mutations, which are the progeny of single mutated mtDNA molecules, may confer a neoplastic advantage on the host cell and contribute to cancer progression. The high prevalence of clonal mutations observed in tumor mtDNA has led to the assumption that the mitochondrial genome in cancer in genetically unstable. However, until now, the fidelity of genomic replication in the mitochondria of cancer cells had not been experimentally tested.

Recently, Dr. Jason Bielas' lab in the Molecular Diagnostics Program of the Public Health Sciences Division was the first to measure the frequency of random single nucleotide substitutions in the mtDNA of cancerous and healthy tissue from 21 colorectal cancer patients using the highly sensitive Random Mutation Capture assay. Unlike clonal mutations, random mutations arise after a clonal population of cells has been established, and are only present in a subset of cells.

The authors have previously demonstrated a >100 fold increase in the frequency of random mutations in the nuclear DNA of human tumors. However, surprisingly, they found that the frequency of mutations in mtDNA was decreased in colorectal cancer tumors relative to adjacent healthy tissue (Figure).

In a series of subsequent experiments aimed at understanding the potential mechanisms involved, the authors demonstrated that the difference in mutation burden is attributable to a >3 fold reduction in C:G to T:A transitions in tumor tissue relative to normal colon. They also showed that tumor tissue is characterized by a shift in glucose metabolism from oxidative phosphorylation to anaerobic glycolysis – a process associated with decreased production of reactive oxygen species in the mitochondrial matrix. Finally, they demonstrated that mutation frequency decreases concomitantly with reduced mitochondrial respiration in both normal and tumor tissue. This result is consistent with the hypothesis that a significant fraction of mtDNA mutagenesis occurs as a result of oxidative

damage, generated as a byproduct of oxidative phosphorylation. It also offers a plausible explanation for the lower frequency of random mutations in colonic tumor cells, particularly C:G to T:A transitions which are associated with oxidative damage.

These findings suggest that, unlike with nuclear DNA, reduced mtDNA genetic diversity does not limit tumor progression; rather, normal mtDNA mutation rates may hinder cancer development. The results of this study therefore raise the possibility that cancer therapies focused on reactivating mitochondrial metabolism in order to increase mtDNA damage and mutation in tumor cells could potentially suppress malignant tumor growth.

Ericson NG, Kulawiec M, Vermlust M, Sheahan K, O'Sullivan J, Salk JJ, Bielas JH. (2012). Decreased mitochondrial DNA mutagenesis in human colorectal cancer. *PLoS Genetics* 8:e1002689.

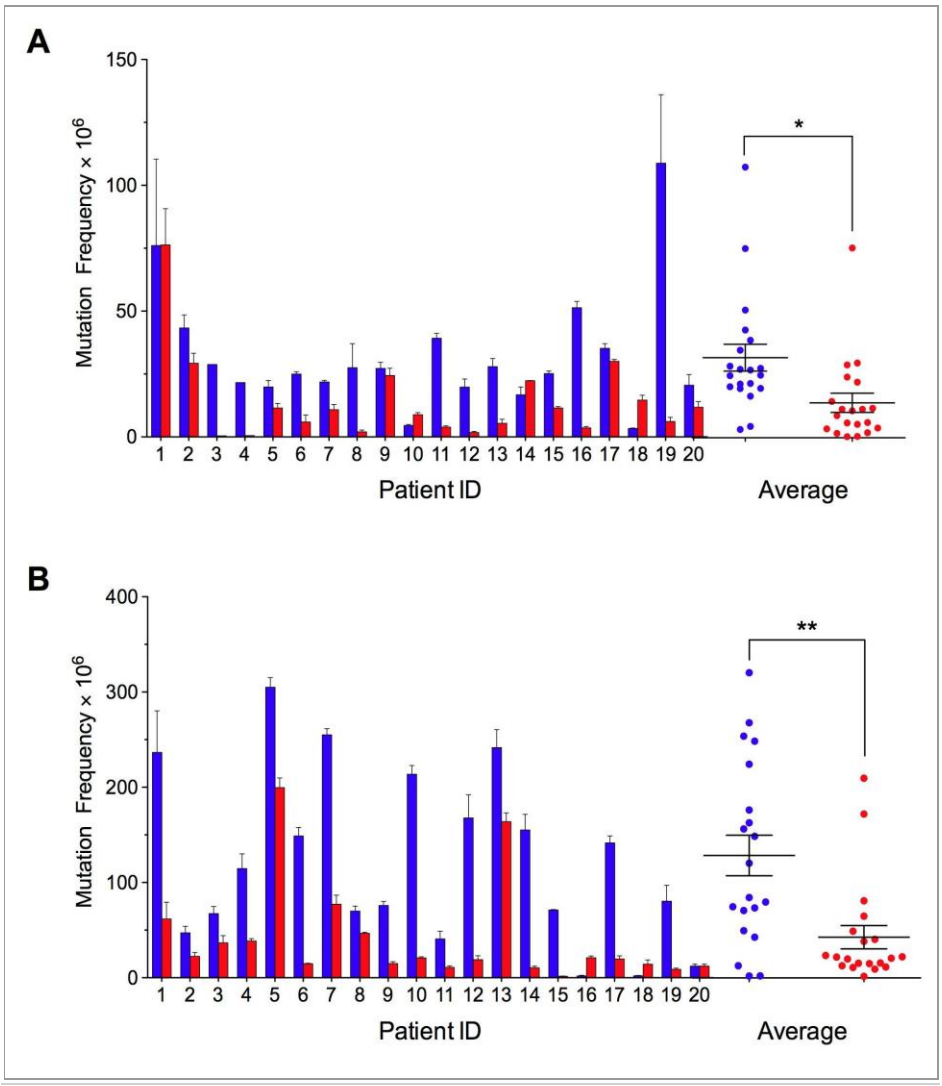

Image provided courtesy of N. Ericson

Figure. Decreased random mitochondrial DNA mutations in colorectal cancer. (A) mutation frequency (± s.e.m.) was determined at Taq1 restriction sites 1215-1218 within the 12S rRNA gene, and (B) at sites 7335-7338 within the COX1 gene, in mitochondrial DNA isolated from patient-matched normal (blue) and carcinoma (red) colorectal tissues.