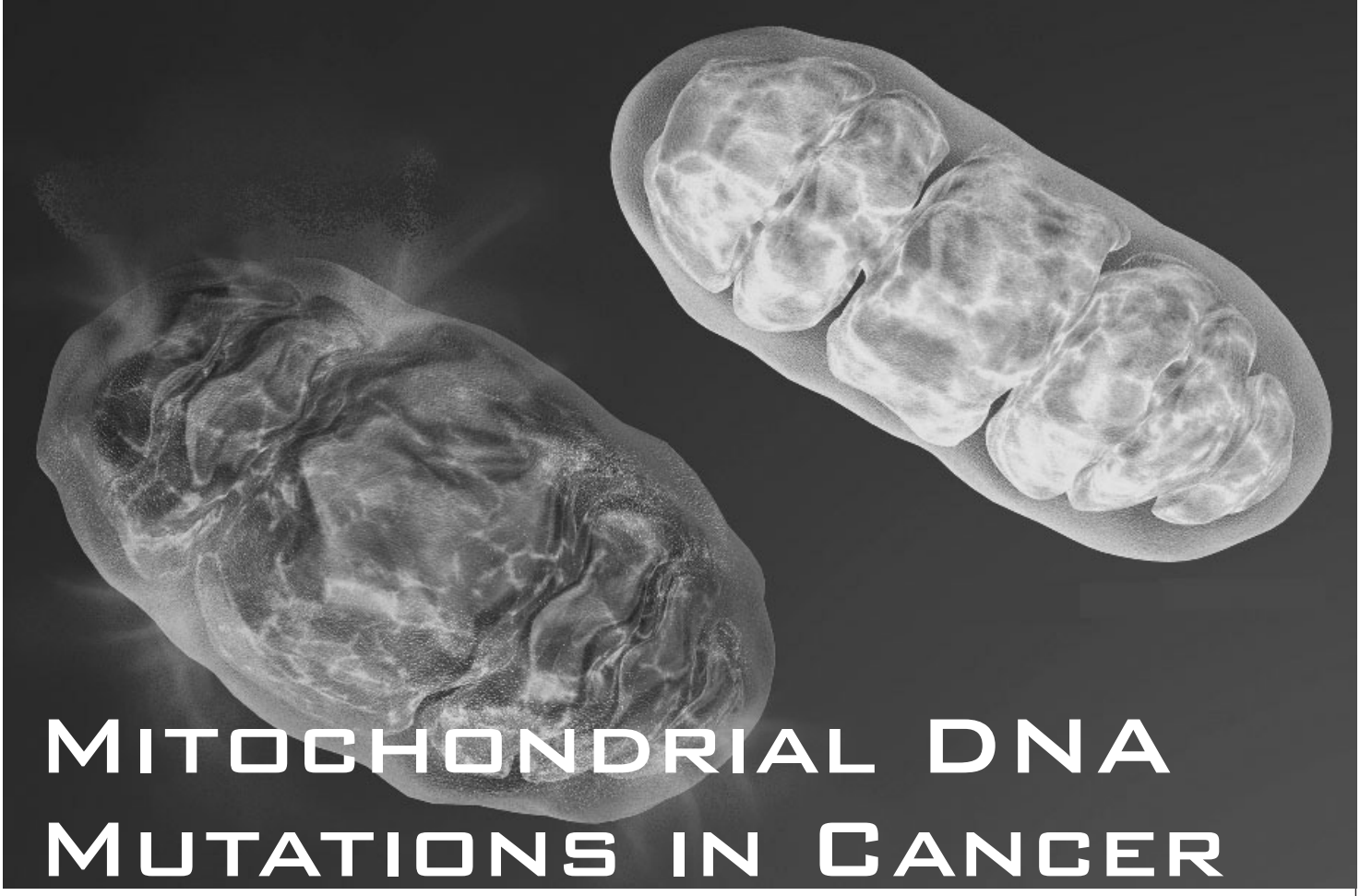

Mitochondrial DNA Mutations in Cancer

Insight or Oversight?

By Sana Raoof

A "cure for cancer" is perhaps the highest-impact scientific aim of the global research community; nonscientists appreciate its potential, and mathematicians, physicists, engineers, and chemists alike provide interdisciplinary perspectives to bring us closer to a cure.

Although research on cancer development has historically focused on mutations in nuclear DNA, there are now increasing experimental observations to suggest a role of mitochondrial DNA (mtDNA) mutations in tumorigenesis and cancer metastasis (1, 2, 3, 4, 5). In particular, recent experimental studies have established a higher frequency of homoplasmic mtDNA mutations in tumor cells. A mutation is homoplasmic in a group of cells if every mitochondrial chromosome in every cell of that group contains the mutation (1).

"mathematical modeling brought the medical world back into a zone of sobriety"

The percentage of mutations that are homoplasmic and the number, location, and type of homoplasmic mutations have been studied in breast, ovarian, colorectal, pancreatic, gastric, hepatocellular, prostate, lung, renal cell, and other carcinomas, and a map has been constructed linking mutations in specific regions of the mitochondrial genome to specific types of cancer (3, 4, 5)! This finding shook the medical research world at the turn of the 21st century and continues to spark reviews and rebuttals in *Nature* and *Science* even a decade later (2).

A famous experimental demonstration that the metastatic potentials of various cancer cells were modulated by mtDNA mutations in those cells was published in 2000 (1). Transfection of mitochondria between cells of high and low metastatic potential successfully transferred the metastatic potential of those cells—without altering nuclear DNA at all! This observation suggests a causal link between mtDNA mutations and tumor progression, which is of great significance to genetic therapy strategies.

As excitement built in the early 2000s around evidence of homoplasmic mitochondrial DNA mutation in tumor cells, mathematical modeling brought the medical world back into a zone of sobriety. A computational model of mtDNA mutation dynamics showed that random processes are sufficient to explain the high incidence of homoplasmy in carcinomas. These random processes include random mutation, replication, and segregation

of mtDNA molecules (1).

Since cancer-causing mutations confer a replicative advantage to the cell in order for tumors to develop, such mathematical demonstrations that even a neutral mutation can be homoplasmic in a biologically realistic timeframe questions the developing view that homoplasmic mtDNA mutations are actually tied to cancer (1, 6).

So what does this computational model do and how can it deflate the excitement of experimental biologists so drastically? Let's construct our own simplified model to find out!

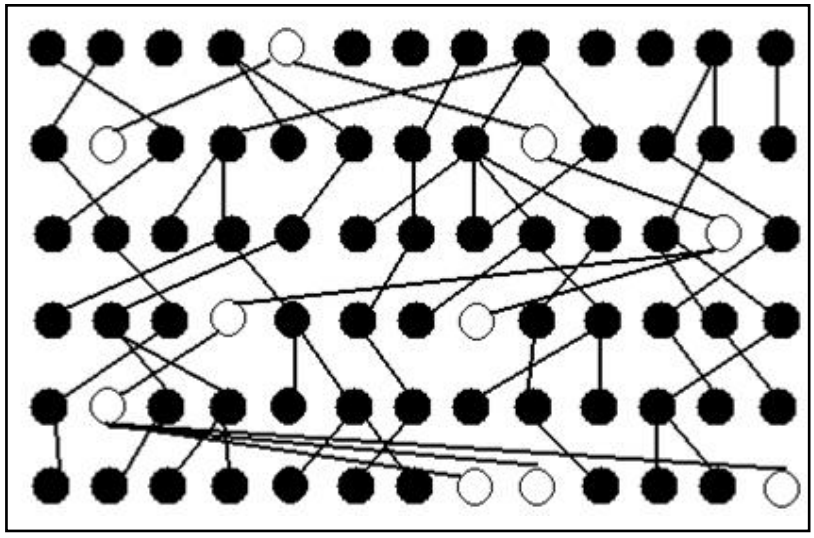

Figure 1. Mitochondrial Level Wright-Fisher Process.

credit: Sana Raoof

Let M and C denote the number of mitochondria/cell and the number of chromosomes/mitochondrion, respectively. In the "average" non-tumor cell, M~50 and C~5. Based on these parameters and our knowledge of mitochondrial genetics, let us construct our own version of the classic Wright-Fisher population dynamics model (Figure 1).

We begin our model in a cell with 50 mitochondria, each with five chromosomes. One chromosome in one mitochondrion is initially designated as mutant. At each timestep, a new generation of mitochondria is generated as follows: every mitochondrion in generation t+1 is randomly assigned a parent mitochondrion from generation t. Therefore, mitochondria in generation t may have multiple offspring or none at all. A chromosome is randomly selected from a parent mitochondrion to "replicate" and enter its daughter mitochondrion. This process occurs five times per daughter mitochondrion, so that each daughter mitochondrion contains 5 chromsomes. This simulation is run until the mutant achieves homoplasmy (250 chromosomes in the cell are mutants) or is extinct. The dynamics of this model are summarized in Figure 1.

Let us think back to the experimental researcher's conclusion regarding mitochondrial DNA homoplasmy in tumor cells. In order to comment on this conclusion, our model must tell us how long it takes for a mutation to become homoplasmic and how frequently this event occurs. So what does this simple model say after being simulated 250,000 times? Homoplasmy occurs in 1/MC of the cases and with an average fixation time of 100= 2M generations. Considering that the average lifespan of a stem cell is 200 - 600 generations, this fixation time is very realistic, implying that random processes can account for the homoplasmy of even neutral mutants! This delivers quite a damaging blow to experimentalists who consider homoplasmy of mitochondrial mutants to be extremely significant and causally-linked to cancer progression. Our simple model, although incredibly rudimentary and based on many simplifications, does approximate the published mathematical models which find equivalent results regarding the arbitrariness of mitochondrial homoplasmy.

> "active researchers are racing and collaborating for a unifying theory of cancer genetics"

But what does all this mean? Since when can mathematics discount experimental observations? Of course, there can be no real conflict between biophysical truths and mathematical predictions—the inconsistency either lies in our interpretation of biological phenomena regarding mitochondrial homoplasmy (are we jumping to conclusions as the human brain is so quick to do?) or the construction of our computational model (are the model dynamics realistic?), or both! In a subject of such profound impact, active researchers are racing and collaborating for a unifying theory of cancer genetics—reconciling theoretical expectations with experimental findings—a tall order for one of science's greatest open problems. H

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References

1. Coller, Hilary A. et:al. High frequency of homoplasmic mitochondrial DNA mutations in human tumors can be explained without selection." Nature Genetics 28, 147 - 150 (2001).
2. Ishikawa, Kaori et:al. ROS-Generating Mitochondrial DNA Mutations Can Regulate Tumor Cell Metastasis." Science 320 (5876): 661-664
3. Petros, Juan A.et:al. MtDNA mutations increase tumorigenicity in prostate cancer." PNAS 102 no. 3 719-724 (2005).
4. Chatterjee, A. et. al. Mitochondrial DNA mutations in human cancer." Oncogene 25, 4663-4674 (7 August 2006)
5. Gri_ths, J. R. Causes and consequences of hypoxia and acidity in tumour microenvironments." BioEssays 23.3 (2001): 295-96.
6. Nowak, Martin A. Evolutionary Dynamics Exploring the Equations of Life. New York: Belknap, 2006
7. "ADEAR - HTML Templates - November 2005." National Institute on Aging. Web. 16 May 2010. <http://www.nia.nih.gov/Alzheimers/Resources/ProgressReportImages.htm>.