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Most elementary school students know that mitochondria are the powerhouses that supply cells with their energy. But mitochondria contain their own set of genetic instructions completely separate from the rest of a cell's DNA. Now a KU Medical Center researcher and his colleagues at the University of Alabama–Birmingham (UAB) have discovered that mitochondrial DNA might play a role in whether certain people are more susceptible to diseases than others. They have published their work in the August 2013 issue of *Biochemical Journal*.

"A question that has long perplexed scientists," says Danny Welch, Ph.D., founding chair of the University of Kansas Medical Center's Department of Cancer Biology, "is why, of two individuals who are the same age and in the same environment, does only one develop cardiovascular disease or metastatic cancer?"

With just 37 genes, the mitochondrial genome seems so small as to be irrelevant, particularly when compared to the nuclear genome's 30,000 genes. Welch says. "But we think it may well be a co-pilot, in terms of predisposition toward some complex diseases."

Of mice and men

In 2009, while on faculty at the University of Alabama at Birmingham, Welch gave a cancer biology lecture on metastasis and highlighted a series of experiments carried out by his friend Kent Hunter, Ph.D., head of the Metastasis Susceptibility section at the National Cancer Institute in Bethesda, Md.

Hunter had mated a male mouse carrying a breast tumor oncogene (a gene with the potential to

cause cancer) with 60 different strains of female mice. Analyzing the crossbred offspring, he observed that some were prone to metastasis, while in others, the tendency for their induced breast tumors to spread to the lungs was almost stifled.

"Kent's research was percolating through my mind as I taught that class," Welch says. "The point of mentioning it was to raise and discuss the concept of inherited susceptibility. But mitochondria didn't figure in the equation right then."

Shortly afterwards, Welch sat in on a lecture given by his UAB colleague Scott Ballinger, Ph.D., on a different topic: heart disease risk. Ballinger noted that certain cardiovascular problems had been mapped to defects in the mitochondria.

Mitochondrial DNA is maternally inherited, but Welch hadn't spent much time thinking about it. But after some conversations in the hallway, he says, "It hit Scott and me: Kent's data resulted from breeding *one* male mouse with many different females. So could the next generation's varying likelihood of metastasis have come from Mom, through the mitochondria?"

"Like Louis Pasteur once said, 'In the fields of observation chance favors only the prepared mind.' I guess our minds were prepared. Neither of us would have come up with this idea on our own."

Theory testing

Welch and Ballinger set about engineering MNX (pronounced "minx") mice — named for the technique, mitochondrial-nuclear exchange, used to produce these animals. The method allows researchers to determine whether a given trait tracks with the nucleus or the mitochondria. The technique involves pushing a fine needle into a fertilized cell and, applying just the right amount of pressure, removing its nucleus. The step is repeated with a second fertilized cell that displays the *opposite* of the trait of interest; its nuclear is then transferred into the first. The original fertilized cell with its swapped nucleus then blossoms into a viable ball of cells before being implanted into a female mouse that carries the pregnancy to term.

The resulting MNX progeny, Welch explains, contain nuclear and mitochondrial DNA that would not normally be associated. After females from this first MNX generation are mated with males that share their nuclear genome, *their* offspring are the ones in which the traits of interest are actually studied — thereby confirming a trait's maternal heritability or lack thereof.

"It takes impeccably precise hands to maneuver the nucleus out of a cell without contaminating it with mitochondrial DNA," Welch notes. He credits Robert Kesterson, Ph.D., and Larry Johnson of UAB's Transgenic Mouse Facility for mastering this feat of dexterity.

The researchers generated mice with interchanged nuclear and mitochondrial genomes from two strains: C57/BL6 (or simply C57), which is prone to heart disease; and C3H, which is resistant. They

then exposed the mice to various forms of cardiac stress.

"We found that MNX mice with C57 nuclear DNA and a C3H mitochondrial background had different energy metabolism; they were also much less sensitive to conditions capable of inducing heart failure," Welch says. MNX mice created through the opposite exchange, meanwhile, proved more vulnerable to heart failure.

Jessica Fetterman, Ph.D., the paper's first author, found a DNA tweak by which cytochrome oxidase III, a mitochondrial protein central to energy metabolism, differs in C57 and C3H mice. "We speculate that this minute change might alter COIII's shape and, in turn, its enzyme activity in the mitochondria," Welch says.

C57 mice are also far less susceptible to metastatic cancer, even while being prone to heart trouble.

Welch and Ballinger have been tinkering with other MNX mice in additional experiments. Preliminary evidence indicates a reduced metastatic burden, or total tumor mass, in MNX mice with the C57 mitochondrial genome, and further research is underway.

Out of the shadows

"What we're learning here is that instead of unidirectional signaling from the nucleus to the rest of the cell, there's a language of communication involving the mitochondria that hasn't been fully appreciated," Welch says.

Given that it currently takes about one day, at the cost of a few thousand dollars, to sequence the nuclear genome (and the cost is going down), Welch doesn't see why parallel sequencing of, say, a breast cancer patient's mitochondrial genome couldn't be included in the diagnostic toolbox. "We're talking a mere 16,000 mitochondrial versus three billion nuclear base pairs; that's 100,000-fold less DNA to deal with," he says.

Beyond metastasis, several of Welch's peers have also suggested another way that potentially relates energy production in mitochondria to cancer. Perhaps tweaks in the mitochondrial genome similarly influence whether, and how much, a patient suffers from post-chemotherapy fatigue?

"What it all comes down to is a change in perspective," he says. "We've focused on the 800-pound gorilla, ignoring the monkey on its accordion in a corner of the same room. But no longer should anyone trying to do so-called precision medicine draw conclusions based solely on nuclear DNA."

Figuring out how to interpret and use these observations will take some time, Welch says. "But in the immediate future, I think scientists *will* take time to look more closely at what our mitochondria may have to tell us."