Discoveries in mitochondria open new field of cancer research

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(Medical Xpress) -- Researchers at Virginia Commonwealth University Massey Cancer Center have revealed novel mechanisms in mitochondria that have implications for cancer as well as many other age-related diseases such as Parkinson's disease, heart disease and hypertension. This discovery has pioneered the formation of a whole new field within epigenetics research ripe with possibilities of developing future gene therapies to treat cancer and age-associated diseases.

Shirley M. Taylor, Ph.D., researcher at VCU Massey Cancer Center and associate professor in the VCU Department of Microbiology and Immunology at VCU School of Medicine, was a graduate student when her research helped establish the field of epigenetics (epigenetics refers to the process that controls which genes get expressed in the nucleus of a cell, ultimately determining that cell's biological characteristics). Now decades later, Taylor and her colleagues have further expanded the field of epigenetics into a new area of research they created by discovering enzymes in mitochondria that were previously known to exist only in nuclei.

In mammals, all cells have two distinct genomes, which include all of an organism's hereditary information. One set exists in the nucleus while the other exists in the mitochondrion, the energy generator of the cell.

Published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), Taylor's study found two DNA modifications in the mitochondrial genome: methylated cytosine, known to function in the

nucleus by “silencing” the expression of certain genes; and hydroxymethyl cytosine, which removes the silencing mark imposed by the cytosine methylation.

Together, these modifications act like a genetic on/off switch in a process known as DNA methylation. Taylor’s team also showed that the enzyme responsible for DNA methylation was present in mammalian mitochondria. The presence of these DNA modifications leads the researchers to believe that a system of gene control similar to what occurs in the nucleus is present in mitochondria, functioning to ensure the correct levels of proteins needed for proper energy generation.

“In diseases such as cancer, epigenetic control is lost,” says Taylor. “Genes that should be switched on are switched off and vice versa, leading to uncontrolled growth. Our research indicates that errors in gene expression could be unfolding in mitochondria, possibly contributing to loss of mitochondrial function typical of cancer and a host of other age-related diseases.”

Taylor’s team is currently working to force into mitochondria more of the enzyme responsible for forming the silencing mark, and to identify enzymes responsible for removing it. This should allow the researchers to observe whether these marks impact mitochondrial ability to generate energy. The researchers are also comparing the amount of DNA methylation in diseased cells versus healthy cells to determine whether mitochondrial gene expression plays a role in various diseases.

“Many diseases that afflict the elderly seem to have defects in mitochondrial function,” says Taylor. “We are working to determine whether epigenetic control is a factor contributing to these defects. If so, drugs known to impact gene expression in the nucleus may be useful in reversing damage caused by improper gene expression in mitochondria.”

Taylor collaborated on this study with Richard G. Moran, Ph.D., associate director for basic research at VCU Massey Cancer Center and professor in the Department of Pharmacology and Toxicology at VCU School of Medicine. Other collaborators include doctoral students Lisa S. Shock, Prashant V. Thakkar and Erica J. Peterson from the VCU Department of Microbiology and Immunology. The study was partially funded by the National Cancer Institute and by a pilot project award from Massey.

More information: The full manuscript is available online at www.pnas.org/content/early/201 … 311108.full.pdf+html

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