Identifying the mitochondrial DNA mutations that cause cancer

Mutations that affect the mitochondrial DNA may play a key role in cancers. However, the exact mutations that are involved in cancer are still unknown. Dr Fatimata Mbaye and collaborators, from the University of Dakar in Senegal examined the sequences of two regions of the mitochondrial genome to identify and compare the mutations occurring in different cancers. Understanding the relationship between mitochondrial mutations and their roles in cancer could eventually lead to mitochondrial DNA being used as an oncological biomarker to diagnose cancer at earlier stages.

THE POWERHOUSE OF THE CELL
Mitochondria are organelles that are known as the powerhouses of the cell. They generate most of the chemical energy needed to power all the biochemical reactions that happen in the cell. This chemical energy is stored in small molecules called adenosine triphosphate (ATP).

When a source of energy such as carbohydrates (sugars and fibre), fats or proteins enters the cell, it is brought into mitochondria and converted through a succession of reactions called the Krebs cycle (or citric acid cycle). Products of the Krebs cycle are then used in a second metabolic pathway named oxidative phosphorylation. It is through oxidative phosphorylation that ATP, the universal energy currency in cells, is generated.

Reactive oxygen species (ROS) are side products of oxidative phosphorylation. ROS play diverse roles that are beneficial to the body. They are essential in the cardiovascular and immune systems, for example. However, ROS can also be toxic: they possess an unpaired electron which makes them highly reactive and thus able to damage proteins, lipids and nucleic acids (such as DNA) contained in the cell. The body therefore requires a balance in its ROS levels as an excess will lead to oxidative stress while a level that is too low will lead to reductive stresses that can cause pathologies ranging from cardiomyopathy to cancer.

MITOCHONDRIAL DNA
Beside their characteristic role as the powerhouse of the cell, mitochondria have another specificity: they are the only part outside the nucleus where DNA can be found. While the nuclear genome is linear, mitochondrial DNA is a small circular chromosome. Each cell contains numerous mitochondria and each mitochondrion contains dozens of copies of its mitochondrial genome. This means that a cell can contain thousands of copies of its mitochondrial genome, while it contains two copies of its nuclear genome.

The mitochondrial genome is small, built of 16,569 nucleotides that encode 13 proteins, whereas the nuclear genome is made of 3.3 billion nucleotides. The 13 proteins encoded by the mitochondrial genome all take part in the oxidative phosphorylation pathway that enables mitochondria to generate energy.

FREQUENT MITOCHONDRIAL MUTATIONS
Mutations occur naturally in every cell. However, the rate of mitochondrial DNA mutation is several times higher than the rate for nuclear DNA. A first explanation is that, in the nucleus, a system called mismatch repair recognises and repairs errors in the DNA sequence; mutations can therefore be reverted. In the mitochondria, this repair system is less efficient. A second explanation is that ROS, which are produced during the oxidative phosphorylation that takes place in the mitochondria, can damage DNA and favour mutations.

Mitochondrial mutations may modify the function of normal oxidative phosphorylation chain and lead to important production of denitrogen reactive oxygen species. This would eventually disrupt the cell. Scientists widely accept today that mitochondria play an important role in the ageing processes of both cells and individuals. Increased accumulation of mitochondrial DNA mutations has been reported in ageing tissues such as brain, skeletal muscle, and fibroblasts and in many pathological conditions including neurologic, metabolic, and age-related disorders.

Mitochondrial mutations have also been frequently observed in human cancers and proposed as important oncological biomarkers. However, the exact mitochondrial mutations that are responsible for the pathogenesis of cancer remain unclear. To shed light on this, Dr Mbaye and her team examine mitochondrial mutations in cancer and focus on two specific regions: the D-Loop region and the MT-CYB gene.

THE D-LOOP REGION
Dr Mbaye and her collaborators focus on the D-Loop region of mitochondrial DNA because this region is crucial for replication and expression of the mitochondrial genome. It contains transcriptional promoters that are essential for gene expression. It also contains the leading-strand origin of replication.
Fatimata Mbaye's research focuses on the genetic mechanisms involved in cancer pathologies.

Behind the Research

**Research Objectives**

Fatimata Mbaye and her collaborators' research explores the genetic mechanisms involved in cancer pathologies.

**Detail**

**Bio**

Fatimata Mbaye has a PhD in Population Genetics. Her research activities focus on the genetic mechanisms involved in cancer pathologies. She is MCA at Cheikh Anta Diop University in Dakar, and teaches courses in bioinformatics.

Jean-Baptiste Lamy (PharmD, PhD) is a senior lecturer at University Paris 13 in the LIMICS laboratory. He teaches bioinformatics and medical informatics. His main research interests are information and knowledge visualisation, knowledge representation, drug knowledge and clinical decision support. He designed innovative visual approaches such as the patented VCM medical iconic language, and rainbow boxes.

Mboucké Sembene is a CAMES titular professor of exceptional class at the University Cheikh Anta Diop of Dakar and head of the GENESPOP team. His research focuses on genetic characterisation of animal resources, cancer genetics and genetic identification of crop pests and stocks.

**Personal Response**

What sparked your interest in mitochondrial DNA?

"The Genetics and Population Management team to which I belong and which is headed by Professor Mboucké Sembene is interested in the implication of mutations in the mitochondrial genome due to the lack of genetic studies carried out in the field of cancerology in Senegal."

**References**