Structure of a molecular copy machine: How mitochondrial genes are transcribed

September 26 2011

Mitochondria are compartments within cells and have their own DNA. The key protein required for the expression of the genetic information in this DNA is the mitochondrial RNA polymerase enzyme. Its three-dimensional structure has now been determined in atomic detail.

The mitochondria are the cell's power stations. In animal cells, they supply energy in usable form by converting nutrients into the universal energy currency of the cell, adenosine triphosphate (ATP). Mitochondria possess their own DNA, and are inherited via the maternal line. The mitochondrial DNA codes for a small number of proteins that are essential for energy production in the organelle. The first step in the decoding of this genetic information is the synthesis, or transcription, of RNA copies of the DNA by the enzyme mitochondrial RNA polymerase. The RNA molecules are then used to program protein synthesis. However, exactly how the mitochondrial RNA polymerase actually works has not been clear, as its structure was unknown – until now.

Biochemist Professor Patrick Cramer, Director of the Gene Center at LMU, in collaboration with Professor Dmitry Temiakov of the University of Medicine and Dentistry of New Jersey (USA), has now determined the architecture of this molecular copy machine. "With the help of a synchrotron as a source of radiation and using the method of X-ray diffraction, we were able to determine the first three-dimensional structure of a human polymerase, the mitochondrial RNA polymerase, in atomic detail," Cramer explains.

Interestingly, the structure shows a certain resemblance to those of the RNA polymerases found in so-called phages. Phages are viruses that specifically attack bacteria and can insert their genomes into those of their bacterial hosts. It is now generally accepted that mitochondria evolved from free-living bacteria that were engulfed by the progenitor of today's animal cells at an early stage in evolution. The similarities observed between the RNA polymerases of mitochondria and phages provide new insights into the evolution of the organelle and its genome. It appears that, in the course of evolution, a phage polymerase gene developed the ability to transcribe the genes in the mitochondrial DNA.

The structure also provides several hints as to how this molecular copy machine functions. "In particular, the structure explains why two other protein factors are necessary to enable the RNA polymerase to bind at the right site on the DNA, and to transcribe the genetic information from this location," says Cramer. The new results represent a significant first step in understanding the function and regulation of the human mitochondrial genome. And this is not just of academic interest: Some drugs used to treat viral infections, such as hepatitis C, have major side-effects, apparently because they inhibit not only the viral polymerase, but also the mitochondrial RNA polymerase of the host cell. The researchers now hope that their new data can help in the design of antiviral drugs that are better tolerated.

More information: Structure of human mitochondrial RNA polymerase, R. Ringel, M. Sologub, Y.I. Morozov, D. Litonin, P. Cramer, D. Temiakov, *Nature* online 25.09.2011. DOI: 10.1038/nature10435

Provided by Ludwig-Maximilians-Universitat Munchen