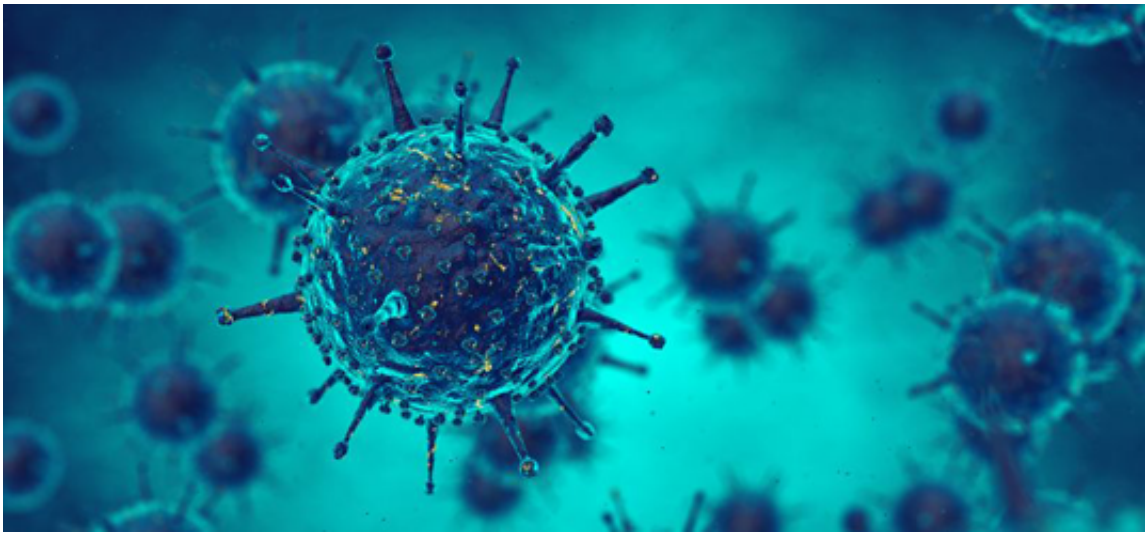
Protein silences endogenous retroviral genomes integrated in cellular DNA

May 27 2015



Artist's impression of the structure of a retroviral particle. Credit: nobeastsofierce / fotolia.com

An LMU team has uncovered a new role for the protein Atrx, which is involved in various aspects of gene expression. The new work shows that the protein is also involved in silencing endogenous retroviral genomes integrated in cellular DNA.

In any given mammalian cell, much of the genome is inactive at any given time. Indeed, many genes are subject to long-term inactivation in virtually all cells, and to this class belong the so-called retrotransposons. Retrotransposons represent the now more or less degenerate genomes of

retroviruses, which infiltrated the germline at some point in evolution, were integrated into the host's genome and have since been passed down for many generations. Some of these alien sequences have become 'domesticated' in the meantime, and have taken on regulatory functions for nearby cellular genes. Others must be permanently inactivated, because their expression would otherwise have deleterious consequences for gene regulation and the stability of the genome as a whole, and so disrupt the normal development of the organism. How integrated retrotransposons are effectively silenced in cells is not entirely understood. Professor Gunnar Schotta and his research group at LMU's Adolf Butenandt Institute have now identified a previously unknown role for the protein Atrx in this context. Their findings appear in the journal *EMBO reports*.

Gene sequences can be silenced by making them inaccessible to enzymes required for gene expression. Often this occurs by condensing the DNA into a tightly folded form of chromatin called heterochromatin, primarily by specific modification of proteins called histones around which the genomic DNA is wrapped. The significance of such "heterochromatinization" is revealed by the fact that defects in this mechanism of gene silencing can lead to serious illness. "More than 50% of mammalian genomes consists of silenced sequences," Schotta explains. He and his colleagues have now shown that the protein Atrx plays a central role in inducing the formation of heterochromatin. "Atrx has already been implicated in the pathogenesis of neurodegenerative conditions and various forms of cancer. We have now pinpointed a new function of the protein, which may help to explain its involvement in these diseases," says Schotta.

Loss of Atrx compromises silencing

The new work was carried out in a mouse model system, and focused on a specific class of endogenous retroviruses called IAP retrotransposons.

Using molecular genetic techniques, the LMU team first analyzed which segments of the viral genomes are essential for them to be recognized as foreign and mark them for silencing. "We discovered that the silencing process is always initiated from a defined region of the retroviral DNA, and propagates until it encompasses the whole viral genome," says Schotta. The LMU researchers then went on to identify the cellular proteins that were involved in the silencing process itself: "We systematically tested various components that interact with chromatin for their ability to induce the formation of heterochromatin," says Schotta.

In addition to the previously identified factors Setdb1 (a histone methyltransferase), which modifies histones in such a way that they induce silencing, and Trim28, which mediates the interaction between Setdb1 and chromatin, the molecular genetic screens revealed a previously unknown function for Atrx, which appears to have multiple roles in the modification of chromatin. "Atrx is clearly also required for the silencing of retroviral sequences, because we found that it has a crucial role in the assembly of densely packed heterochromatin. In cells that lack Atrx, the rate of inactivation of viral sequences is reduced, and the whole process takes longer," Schotta explains, adding that efficient silencing of such sequences is essential for the well-being of cells.

Defects in Atrx function have previously been linked to neurodegenerative illnesses. Thus, individuals that produce a defective form of Atrx display an array of symptoms, including mental retardation, referred as the ATR-X syndrome. "But it is not yet clear how loss of functional ATRX results in the characteristic features of the condition," says Schotta. "We believe that the new findings regarding the function of the mouse Atrx also hold for the corresponding protein in humans. It is therefore conceivable that defects in the silencing of endogenous viral genomes could contribute to the development of ATR-X syndrome." At all events, the new results point to new approaches to the investigation of pathologies that are linked to mutations in Atrx.

More information: "Atrx promotes heterochromatin formation at retrotransposons." *EMBO reports* (2015) embr.201439937. DOI: 10.15252/embr.201439937

Provided by Ludwig Maximilian University of Munich