NATIONAL PRESS RELEASE I PARIS I 30 APRIL 2015

How does a mobile DNA sequence find its target?

To understand how transposable elements[1] shape genomes, where they are maintained over generations, it is vital to discover the mechanisms behind their targeted integration. Researchers from the Laboratoire Pathologie et Virologie Moléculaire (CNRS/Inserm/Université Paris Diderot)[2], in collaboration with researchers from CEA[3] and a US laboratory[4], have identified an interaction between two proteins that is essential for the integration of a transposable element into a specific area of the yeast genome. These results, published on 1 May 2015 in the journal *Science*, emphasize the role of these mobile DNA sequences in the evolution and adaptation of organisms, and their potential value for gene therapy.

Transposable elements are DNA sequences capable of moving within genomes. They represent a significant proportion of the genome and play an important role in its evolution. By integrating into the DNA, these elements can contribute to genome plasticity and the emergence of new cellular functions. Conversely, they can also cause mutations that endanger cell survival. Their integration usually occurs in specific gene-poor regions, where it is least harmful. The mechanisms that make this targeted integration possible are still poorly understood.

The authors of this study focused on the Ty1 retrotransposon[5] of the yeast *Saccharomyces cerevisiae* to examine how the integration site is determined. Ty1 integrates itself into a region that is small compared to the scale of the genome, and is positioned upstream of specific genes, all transcribed by the RNA polymerase III (Pol III) enzyme complex. Using Pol III as bait, the researchers found that one of the proteins of this complex, which is known as AC40, interacts with the protein encoded by Ty1, allowing retrotransposon integration. Further analyses showed that this interaction is essential for the targeted integration of the transposable element. Indeed, in cells containing a protein from another yeast species that is functionally similar to AC40, but does not interact with Ty1, the retrotransposon was always inserted efficiently into the genome but very rarely into its usual target sites.

[1] A transposable element is a DNA sequence capable of moving independently in a genome. Such mobile sequences are present in all living organisms and are considered powerful drivers of evolution and biodiversity.

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[5] A retrotransposon is a particular type of transposable element, capable of replicating itself in a "copy and paste"-like method. It is thus able to multiply and invade a genome. This replication involves an RNA intermediate. Retrotransposons have some similarities with retroviruses.

The study therefore found a mechanism by which a mobile DNA sequence finds its target. It also revealed which regions of the genome the sequence was integrated into in the absence of this control mechanism. The retrotransposon inserts preferentially into areas at the ends of chromosomes. These areas contain gene families that are non-essential in normal conditions, but nonetheless necessary for yeast to adapt to environmental changes. Furthermore, the expression of RNA polymerase III, which determines the targeted insertion of Ty1, is dependent on environmental conditions. These results therefore support the hypothesis that the mobility of transposable elements, often activated in response to environmental stress, promotes reorganization of the genome, allowing yeasts to adapt to environmental changes and thus improving their survival.

Beyond the progress in basic research, clarifying the Ty1 integration mechanism is also beneficial for gene therapy, which uses vectors derived from retroviruses to transfer genes into cells. Like retroviruses, these vectors are often integrated into gene-rich regions where they can have mutagenic effects. The properties of transposable elements like Ty1 could be used to reduce the impact of gene transfer vectors by directing their integration to safer areas of the genome.

Bibliography

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