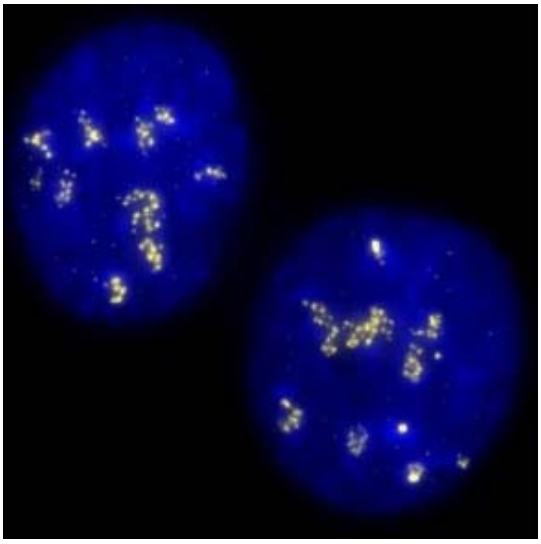

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Depuis 80 ans, nos connaissances bâtissent de nouveaux mondes

The choreography of ribosomal DNA: its mobility allows its repair

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Scientific results Biochemistry-structural biology

Double-strand breaks in DNA are among the most toxic lesions for the cell because they are often the cause of cancer. The genes being transcribed are more prone to undergo this type of lesion, without the repair processes of these breaks being understood. By studying the most actively transcribed region of our genome, ribosomal DNA, researchers are shedding light on its particular mechanism of repair. These results are published in the journal *Genes & Development* .

Our DNA undergoes many external aggressions that lead to damage that threatens the integrity of the genome. Among these damages, double-strand breaks in DNA are considered to be the most toxic lesions for the cell because they can lead to chromosomal mutations and rearrangements, events that cause cancer. In contrast to lesions caused by external attacks, recent work indicates that the threats are also internal to the cell, caused by its normal metabolic activity, resulting in double-strand breaks preferentially localized in genes whose transcription is active. The repair of these so-called "active" genes nevertheless remains a subject that has not been studied much.

The researchers therefore focused on repairing the most transcribed region of our genome: ribosomal DNA, which encodes the ribosome structure RNAs within a particular compartment of the nucleus of the cells, the nucleolus. In addition to being "hypertranscribed", ribosomal DNA is composed of repeated DNA units, which poses a real threat to the integrity of the genome because the slightest imbalance (variation in the number of repetitions or their rearrangements) could endangering cellular homeostasis, especially through abnormal production of ribosomes that synthesize proteins, essential for any cell function. It can also be noted that instability of ribosomal DNA has already been associated with cancer and premature aging.

In order to understand the repair mechanisms of ribosomal DNA, the researchers used a cell model (DIvA) allowing the induction of double-strand breaks at known positions in the human genome, and in particular in DNA. ribosome. They showed that double-strand breaks within ribosomal DNA caused its transcription to stop, in a manner dependent on architectural chromosome proteins (the cohesins) and a complex repressing gene expression via epigenetic modifications (called HUSH). Contrary to what has been proposed, stopping transcription is not sufficient to promote the observed movement of damaged ribosomal DNA out of the nucleolus. The researchers have shown that this mobility also requires the formation of single-stranded DNA (resection), extensively, thus allowing a repair of breaks by the mechanism of homologous recombination.

This study also shows that invaginations of the nuclear envelope frequently affect the nucleolus and that the mobility of ribosomal DNA to the outside of the nucleolus repairing it would be an active process involving nuclear and cytoplasmic skeleton proteins.

These results are a first step in identifying proteins that protect ribosomal DNA against genomic instability.

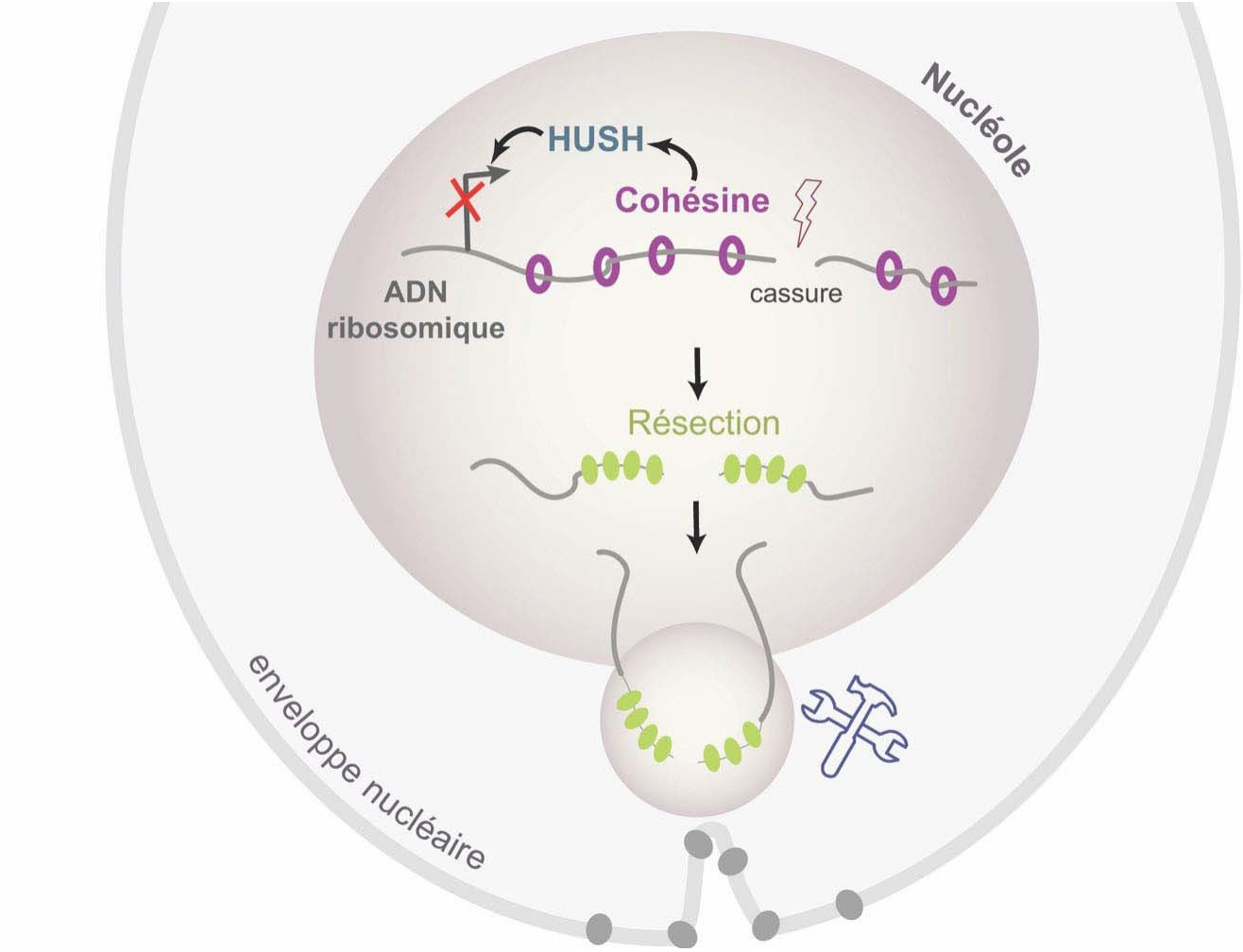

Figure: Double-strand breaks in ribosomal DNA result in repression of transcription via cohesins and the HUSH complex. Then follows the generation of single-stranded DNA (resection) which is a necessary step in the movement of DNA to the periphery of the nucleolus. This movement is presumably an active process involving nuclear envelope proteins linking the nuclear and cytoplasmic skeletons.

To know more:

A cohesin / HUSH- and LINC-dependent DNA ribosomal pathway controls double-strand break repair.
Marnef A, Finoux AL, Arnould C, Guillou E, Daburon V, Rock V,
Mangeat T, PE Mangeot, Ricci EP, Legube G. Genes Dev . 2019 Aug 8.
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