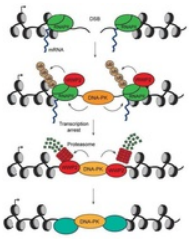
Scientific news

DNA damage: towards a better understanding of the repair process



WWP2 recruitment scheme

May 2, 2019

Among the various damages that DNA can suffer, double-stranded breaks are the most dangerous and lethal. In this study, researchers from Evi Soutoglou's team, including Tibor Pankotai, at the IGBMC (CNRS/Inserm/Université de Strasbourg) in collaboration with the University of Leiden in the Netherlands, described the mechanisms that block the expression of genetic information when DNA is damaged. They highlighted the key role of an enzyme, ubiquitin ligase WWP2, in this process. These results are published on the 2 May in the journal Genes & Development.

Different types of DNA damage constantly attack the integrity of our genome. Double-stranded DNA breaks are the most dangerous, as they can lead to chromosomal translocations and cancers. To avoid this, the cells have developed several mechanisms to detect, report and repair this damage.

Consequences of these damages on transcription, one of the first steps of gene expression leading to protein synthesis, are not well understood. During this process, the DNA is "read" (transcribed) by an enzyme (RNA polymerase II), which then produces a strand of RNA that will then serve as a carrier for the production of a specific protein. In a previous study, Evi Soutoglou's team had shown that a break in the DNA molecule causes RNA polymerase II to dissociate from the DNA molecule and leads to complete transcription failure. In particular, they had shown the key role of DNA-dependent protein kinase (DNAPK).

In this study, Evi Soutoglou's team, including Tibor Pankotai, in collaboration with the University of Leiden, go even further as they identified an enzyme, the ubiquitin ligase WWP2, as an essential mediator in stopping transcription when encountering a double-strand break. The presence of a double-strand DNA break at a transcribing gene blocks transcription in a DNAPK dependent manner. This is because DNAPK recruits the enzyme WWP2 to the DNA lesion, which adds ubiqitin proteins at the RNA polymerase II. The proteasome, a large enzyme complex, recognizes this ubiquitination and then degrades RNA polymerase II, promoting complete transcription arrest. The removal of RNA polymerase II not only prevents the appearance of mutations, but also leaves the field clear for the DNA repair machinery to be further stabilized at the chromatin surrounding a double stand break.

This study provides a better understanding of how the mechanisms that cause transcription to stop are essential for effective DNA repair and for maintaining the integrity of our cells.

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