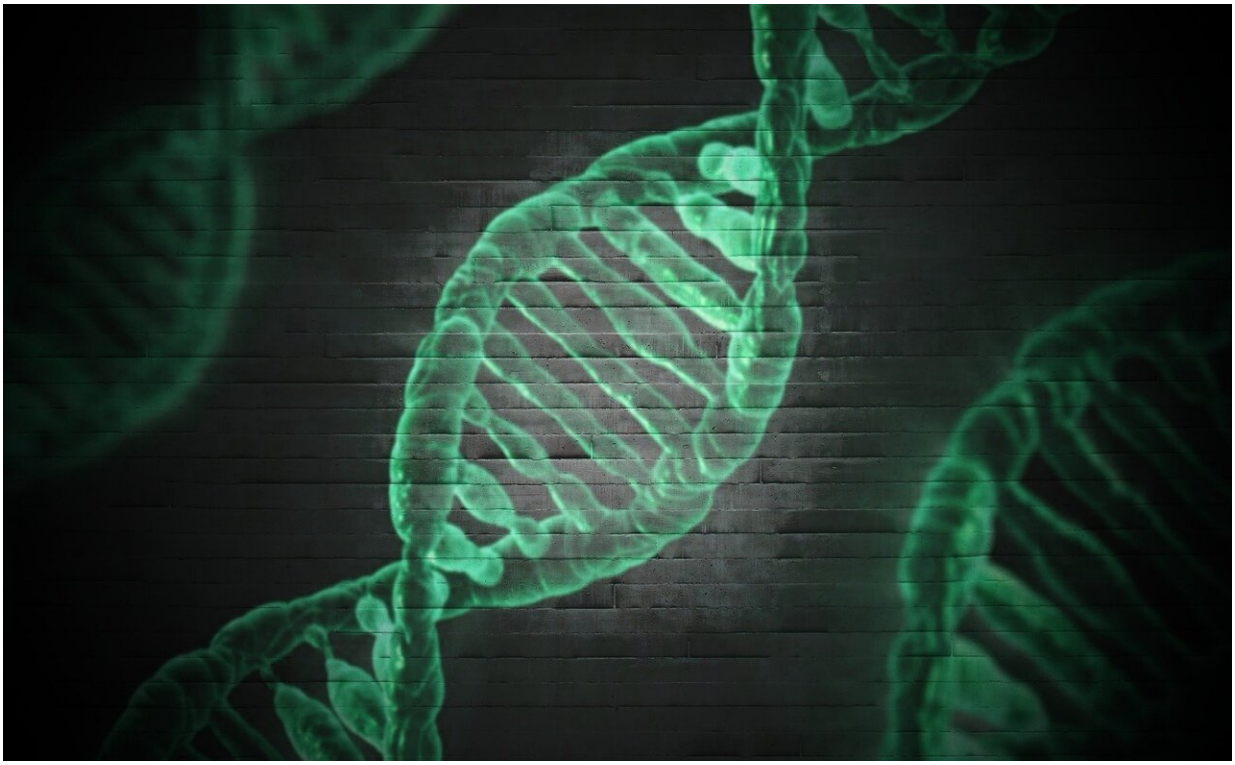
Understanding the origin of genetic instability

October 5 2021



Credit: Pixabay/CC0 Public Domain

Researchers at the Andalusian Molecular Biology and Regenerative Medicine Centre (CABIMER) and the University of Seville have taken another step in the study of genetic instability, as manifested in cancer cells. This has been possible thanks to the identification of the cellular

function of the THO protein complex and the Sen1/Senataxin protein at different stages of the cell division cycle.

A common characteristic of cancer cells is their genetic instability, detectable as a much higher rate of mutations or chromosomal aberrations than in normal cells. Replication stress caused by cellular pathologies or external conditions usually generates genetic instability, which is associated i.a. with conflicts between DNA replication and transcription and with the formation of aberrant structures in DNA, such as DNA-RNA hybrids. The two phenomena, the conflicts and the hybrids, are linked, but the nature of the link is unknown.

The work for Marta San Martin-Alonso's doctoral thesis, carried out at CABIMER and directed by the US Department of Genetics professors Andrés Aguilera and Tatiana García-Muse and published in *Nature Communications*, shows that these hybrids are formed differently depending on the phases of the cell cycle, with specific factors existing in each phase to prevent them, using *Saccahromyces cerevisiae* as a model. These include the THO complex, involved in RNA transcription and processing, which prevents hybrids from forming before DNA replication, or Sen1, the protein homologous to senataxin that is altered in several neurological diseases, which prevents hybrids from forming during replication-transcription collisions. Both proteins are conserved in all eukaryotes. The study not only demonstrates that hybrids can form independently of replication, contrary to the theory defended by some authors, but also opens new expectations to explain the existence of multiple cellular factors that apparently have the same function preventing the accumulation of DNA-RNA hybrids.

Given their role in the origin of genetic instability, a better understanding of the mechanisms of formation and resolution of these structures and the different factors that regulate them may help to better define risk factors in cancer and to identify possible therapeutic targets.

The study was funded by the European Research Council and the Ministry of Science and Innovation, and continues the line of research in which the research group Genomic Instability and Cancer, led by Andrés Aguilera, professor at the US and director of Cabimer, has been working for more than two decades.

More information: Marta San Martin-Alonso et al, Harmful R-loops are prevented via different cell cycle-specific mechanisms, *Nature Communications* (2021). DOI: 10.1038/s41467-021-24737-x

Provided by University of Seville