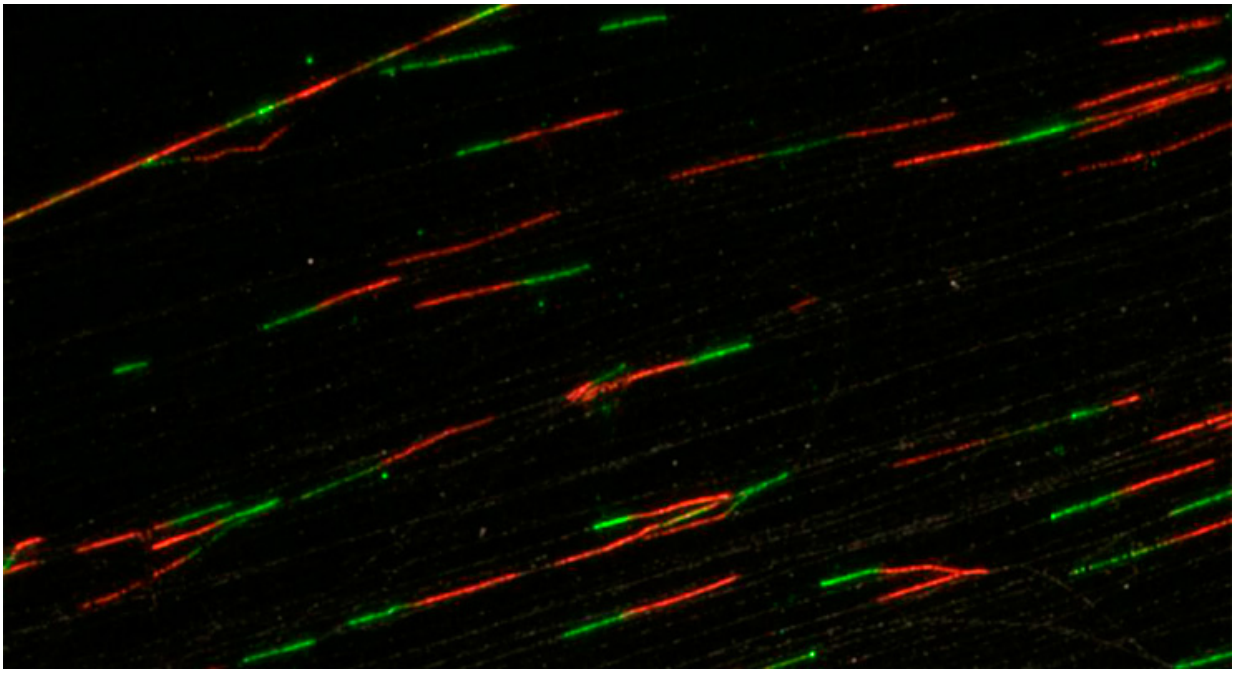
Excessive DNA replication and its potential use against cancer

May 3 2017



DNA molecules undergoing replication. Credit: S. Rodríguez-Acebes, J. Méndez. CNIO

DNA over-replication is a phenomenon that can have devastating consequences for proliferating cells. When parts of the genome are duplicated more than once, cells suffer from 'genomic instability' (alterations to the structure, composition and/or number of chromosomes), and this process gives rise to aberrant cells as those

detected in many carcinomas. The cooperation of two proteins called CDC6 and CDT1 is essential for normal DNA replication but when they are not properly regulated, the genetic material replicates in excess. A paper published in *Cell Reports* by the DNA Replication Group of the Spanish National Cancer Research Centre (CNIO) sets out the fatal consequences of in vivo re-replication for the first time in mammalian organisms.

Genome stability depends, to a great extent, on the accuracy of the DNA replication process. Exposure to UV light or to certain toxic chemicals increase the frequency of errors in the copy that may cause the death or the malignant transformation of the cell. Recent epidemiological studies indicate, for example, that two-thirds of cancerous mutations occur due to replication errors.

"Broadly, there are three things that can go wrong in genome replication," explains Juan Méndez, head of the DNA Replication Group at the CNIO and leader of the study. "There may be too many mutations, the cell may replicate prematurely, without being prepared to do so and, finally, it may replicate too far."

There are control mechanisms throughout all the key points of the process to prevent these situations. Two of these crucial links are the CDC6 and CDT1 proteins, which assemble the replicating machinery responsible for copying the 2 metres of DNA contained in each cell. Once the process is over, these proteins are inhibited biochemically because if they stay active, they can restart the replication process. In unicellular organisms such as yeast, DNA re-replication can lead to gene amplification, a genetic alteration common in cancer cells.

A lethal combination

Méndez and his group have used genetically modified mice to

demonstrate that when CDC6 and CDT1 accumulate at abnormally high levels, DNA re-replication occurs in some cell types, affecting tissue functionality. Animals that overexpress one or another protein do not present replication issues but those with excessive levels of CDC6 and CDT1 do not survive more than two weeks, affected mainly by the loss of progenitor cells required for the regeneration of gastrointestinal tissue.

"Previous cellular studies pointed in the direction that CDT1 deregulation was sufficient to induce over-replication," explains Méndez. However, "in the in vivo studies, we have found that most tissues need the combination of both proteins." What are the implications of this finding? "Cancer cells frequently have a very high basal level of CDC6", says Méndez-, which is related to their high rate of proliferation." Therefore, in these cells, it would be relatively easy to induce re-replication by simply increasing CDT1 levels, which would not affect normal cells.

That is, precisely, what Méndez and his group are working on now. Using drugs to increase the levels of this protein, they are trying to determine whether, in the light of the results obtained so far, lethal DNA re-replication can be induced selectively in cancer cells in order to eliminate them from the body.

More information: Sergio Muñoz et al, In Vivo DNA Re-replication Elicits Lethal Tissue Dysplasias, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.04.032

Provided by Centro Nacional de Investigaciones Oncológicas (CNIO)