MedicalXpress

A new mechanism that contributes to the evolution of cancer

January 31 2013

Cancer arises from the accumulation of mutations and structural changes in chromosomes, which in some cases give rise to combinations that favour the growth or expansion of the disease. In this context, chromosomes tend to lose or duplicate entire regions, although, the mechanisms that initiate these chromosomal abnormalities are not fully understood.

A study published this week in the journal *Cell*, in which researchers from the Spanish National Cancer Research Centre (CNIO) participated, demonstrates a new mechanism that explains how these changes originate in the chromosomes of tumour cells.

The work, led by André Nussenzweig's group at the National Cancer Institute (NCI, USA), with the participation of CNIO researcher Óscar Fernández-Capetillo, shows that collisions between the machinery responsible for duplicating the DNA and for transferring this genomic information to the RNA for protein synthesis—a phenomenon known as transcription—are the cause of a very high proportion of the chromosomal alterations found in tumours.

Until now, it was believed that the majority of these problems originated in areas of the genome that were difficult to duplicate and which, therefore, required the completion of the entire S phase of the cell cycle; a stage in which cells duplicate their DNA. Due to this episode, these regions were especially exposed to breaks or aberrations.

The current study reveals that other areas of the genome also exist—those that replicate quickly early in S phase—that are prone to breakages. In particular, the researchers demonstrate that this occurs when these DNA regions that replicate, have surrounding genes that are being actively copied to RNA.

"In these cases, the collision between the two machineries, the duplication machine and the transcription machine, can be responsible for generating chromosomal alterations that are deadly for cells," says Fernández-Capetillo.

This study moves us a step closer to understanding the mechanisms that explain the chromosomal alterations in tumour cells most common in tumours. "This new mechanism can even explain up to 50% of the abnormalities associated with some types of leukaemia," says Fernández-Capetillo.

Furthermore, this work defines a new class of genomic fragile sites that might contribute to our understanding of the changes that took place in the genome throughout evolution.

More information: Identification of Early Replicating Fragile Sites that Contribute to Genome Instability. Cell (2013). doi: 10.1016/j.cell.2013.01.006

Provided by Centro Nacional de Investigaciones Oncologicas (CNIO)