



PRESS RELEASE

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Why premature cell division promotes cancers

Researchers at UNIGE have discovered how genes responsible for cell division, when mutated, disrupt the replication process of the genome and promote tumor formation.

The accumulation of mutations in the human genome is at the origin of cancers, as well as the development of resistance to treatments. The *Cyclin E* and *Myc* genes are active in the control of cell division. When they are mutated, for example in response to a carcinogen, these genes induce cells to start replicating their DNA prematurely during the cell cycle. This abnormal cell division causes a tumor to develop. Why is this the case? Biologists from the University of Geneva (UNIGE), Switzerland, show that precocious entry of the genome into the replication phase leads to molecular collisions occurring on the DNA and induces new mutations. These results, published in the journal *Nature*, could be used to develop new therapeutic approaches.

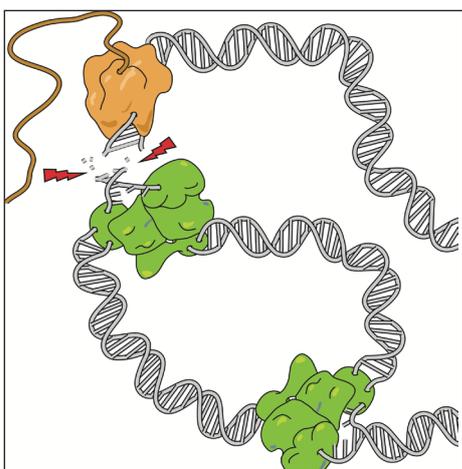
When a cell divides into two daughter cells, it must replicate its entire genome and transcribe part of it to make new proteins. Cell division is notably regulated by specific genes, including the proto-oncogenes *Cyclin E* and *Myc*. Their overexpression or mutation into oncogenes, following exposure of cells to a carcinogen for example, leads to uncontrolled proliferation of cells and promotes the formation of cancer. “We wanted to understand why numerous mutations accumulate in cells with activated oncogenes”, explains Thanos Halazonetis, Professor at the Department of Molecular Biology of the UNIGE Faculty of Science.

Replication must begin between two genes

In order to replicate its entire DNA, that is to say nearly 6.4 billion pairs of nucleotides in just a few hours, the cell organizes the preparation of this process at thousands of sites on each chromosome simultaneously. The position and spacing of these sites, called ‘replication origins’, must be controlled to ensure that replication takes place in a smooth and efficient way.

The UNIGE researchers have developed a method to identify the origins of replication on all chromosomes. This consists of isolating and sequencing the newly synthesized DNA from cells that have just entered the replication phase, in order to map on the genome the sites where replication has begun. This method, specifically developed for human cells, offers high degrees of sensitivity and resolution.

“Initially, the cell identifies all potential replication origins with a molecular marker. We have discovered that in normal cells, the aberrant replication origins are subsequently eliminated. This is the case for those that are located inside a gene, whereas they should be outside the genes so that the integral message of each gene is preserved”, explains Morgane Macheret, a researcher at the Department of Molecular Biology at UNIGE and first author of the article.



The replication (green) and transcription (brown) machineries are simultaneously active on the genes carrying a replication origin, resulting in collisions and DNA breaks.

High definition pictures

When the cells skip steps

The activation of the oncogenes *Cyclin E* or *Myc*, on the other hand, induces the cells to begin replication of their DNA prematurely, without having had time to eliminate all the replication origins present in the genes. “The replication and transcription machineries are therefore active simultaneously on genes carrying a replication origin, which causes conflicts. Our analyses show that these conflicts induce DNA breakdowns, chromosomal rearrangements and, therefore, mutations”, says Thanos Halazonetis.

Do these results explain the genomic instability present in different types of cancers? In order to answer this question, the biologists have studied an array of more than 500'000 chromosomal rearrangements already characterized in a wide range of tumors. “We observed that these chromosomal defects are particularly common in the conflict zones we described. We hope that the discovery of the mechanism that partly or totally explains the genesis of this genomic instability will eventually lead to the development of new therapeutic strategies”, concludes Morgane Macheret.

*Discover the two steps of the preparation of the DNA replication on this short **video**.*

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