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Mini chromosomes that strengthen tumors

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Cancers are due to genetic aberrations in certain cells that gain the ability to divide indefinitely. This proliferation of sick cells generates tumors, which gradually invade healthy tissue. Therefore, current therapies essentially seek to destroy cancer cells to stop their proliferation. Through high-throughput genetic sequencing of glioblastoma cells, one of the most deadly brain tumors, a team of geneticists from the University of Geneva's (UNIGE) Faculty of Medicine discovered that some of these mutations are caused by supplemental extrachromosomal DNA fragments, called double minutes, which enable cancer cells to better adapt to their environment and therefore better resist to treatments meant to destroy them. The research details are published today in *Nature Communications*.

Although scientists have known for about twenty years about double minutes, little chromosomal fragments which sometimes appear during cellular division, they have just started to understand their exact function. Due to replication errors, these mini-chromosomes lack centromere, which allows them to replicate extremely rapidly and autonomously. Scientists therefore suspect that they play a role in the development of cancers, diseases that are caused by mutations in genes that control cellular metabolism and development.

Professor Stylianos Antonarakis and his team in the Genetic Medicine and Development Department of UNIGE's Faculty of Medicine, in collaboration with the Geneva University Hospitals' (HUG) Centre of Oncology, identified double minutes in glioblastoma cells with specific oncogenes. To this end, the scientists used advanced methods of

bioinformatics to perform high-throughput genetic sequencing. The researchers then noticed that one of the main genetic mutations responsible for the anarchic development of cancer cells was not found on actual chromosomes, but only on these double minutes, which, given their very fast proliferation, multiplied the impact of this mutation. The researchers had therefore identified an oncogene whose malignancy was amplified by the number of its copies present on each double minute, but which was not present on the chromosomes themselves.

An Intriguing Adaptability in DNA

The Geneva team also discovered that cells can modulate the number of double minutes according to their environment, and especially in response to chemotherapy. To counter the aggression caused by these treatments and ensure its survival, the cell reduces its number of double minutes until they disappear completely. It is thus freed from the oncogenetic mutation that was present in these DNA fragments. But glioblastoma, like most cancers, depends on a combination of several genes. The tumor therefore begins to exploit a new gene in order to keep growing. "Paradoxically, the cell can return to its initial chromosomal state with regards to that specific oncogene, but other oncogenic genes are then activated in the still living cell. The double minutes therefore act as adjustment variables in cancer cells and limit the effects of therapies," explains Sergei Nikolaev, joint lead author of the study.

These mini-chromosomes amplify the harmful effects of oncogenes and give a selective advantage to sick cells compared with healthy cells, as the tumor grows. In fact, their presence has been detected in most very aggressive cancers. "We must absolutely continue our research in order to better understand this phenomenon of DNA adaptation," emphasizes Federico Santoni, joint lead author of this study. "This will allow us to better measure its implications, and perhaps to find more effective therapeutic strategies against the deadliest cancers," he concludes.

Provided by University of Geneva