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A defense protein that causes cancer

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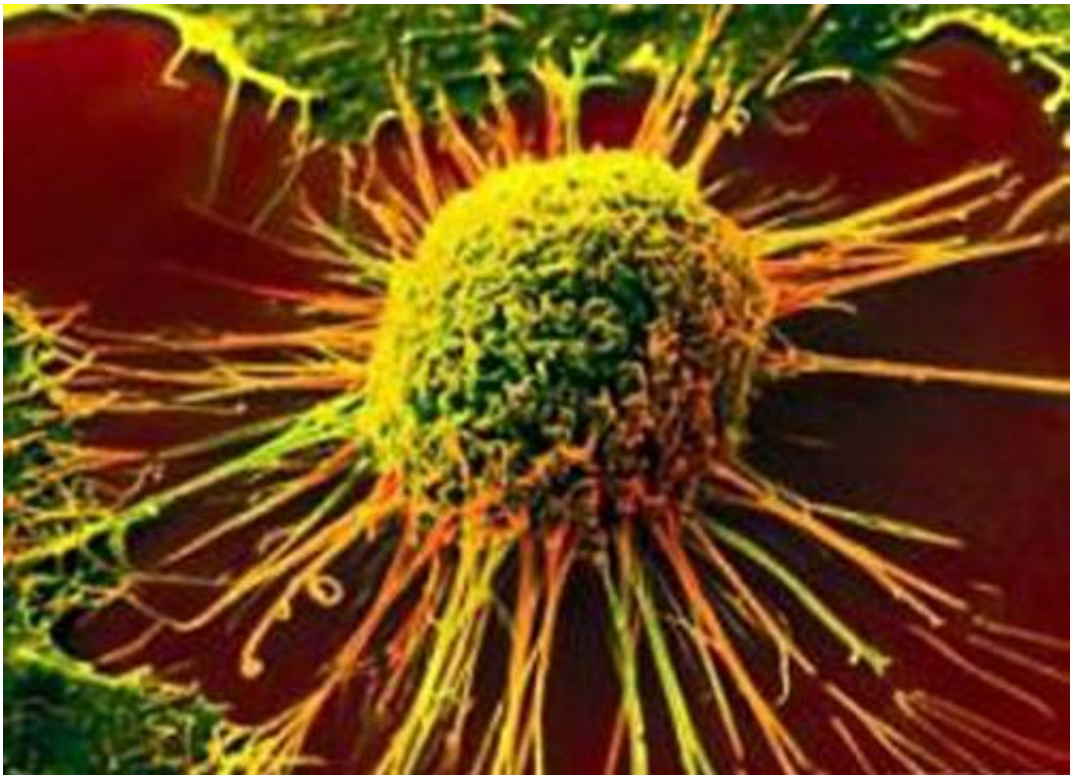

Cancer is caused by the growth of an abnormal cell which harbours DNA mutations, "copy errors" occurring during the DNA replication process. If these errors do take place quite regularly without having any damaging effect on the organism, some of them affect a specific part of the genome and cause the proliferation of the mutant cell, which then invades the organism. A few years ago, scientists have identified an important mutagen which lies in our own cells: APOBEC, a protein that

usually functions as protecting agent against viral infection. Today, a team of Swiss and Russian scientists led by Sergey Nikolaev, geneticist at the University of Geneva (UNIGE), Switzerland, has deciphered how APOBEC takes advantage of a weakness in our DNA replication process to induce mutations in our genome. To be read in *Genome Research*.

APOBEC is a useful, yet dangerous, intrinsic cellular protein. Primarily meant to fight viruses, it has only the power of modifying single-stranded DNA - viral DNA being frequently single-stranded. Our double-stranded human DNA should therefore not be altered. But researchers have observed that mutations induced by APOBEC can be found in many tumorous cells, throughout the genome. How can APOBEC - which can affect only single-stranded DNA - be the cause of so many cancers in human beings? Scientists have already brought the evidence that about 20% of APOBEC mutations originate from an abnormality in the DNA, called "double-stranded breaks" which leaves, for a period of time, a part of DNA in a single-stranded state. It is this particular moment that APOBEC targets to cause multiple mutations. But if this mechanism accounts for 20% of APOBEC-related mutations, it is the mechanism governing the remaining 80% that the scientists at UNIGE and their colleagues in Moscow were able to understand.

The machinery of DNA replication

During the cell division process, the DNA must be replicated according a precise process and timing to produce two identical copies from the original DNA. The replication begins at a specific location. The separation of the two original strands and the synthesis of the new ones then result in a replication fork: the new strands are rebuilt as the fork moves along the chromosome. During DNA replication, the two strands are replicated by different mechanisms which depend on the direction of the replication fork. If one of the two strands is constructed right away, the second one cannot be reconstructed as quickly. As a result, one

strand, the "leading strand", never exists as single-stranded DNA, whereas the other one, the "lagging strand", remains single-stranded for some time.

"Since we knew that APOBEC can only mutate single stranded DNA, we needed to identify in what direction the replication fork was going in order to identify the DNA regions that stay single-stranded for longer period of time, explains Sergey Nikolaev. For the first time ever, we managed to do so in human cells. We were able to identify the direction of the replication fork for about 20% of the genome, and found twice as many mutations on the lagging strand, compared with the leading strand." With this discovery, the scientists brought the evidence that APOBEC, opportunistically, takes advantage of the moment when the lagging strand remains single, therefore weaker.

Mutations that affect our most important genes

DNA replication programme is very conservative: it starts at a well-defined a point of origin. Our most important and well-protected genes replicate early, while some less important genes are replicated later on. Usually, the mutation rate is three times higher in the genome regions that replicate at a later stage.

"We were very surprised to observe that, in APOBEC cancers, the mutation rate is equally distributed in all regions. When APOBEC is involved, mutations occur early during replication, and affect important genes. These mutations tend, therefore, to be more deleterious than other kind of mutations, explains Vladimir Seplyarskiy from the Russian Academy of Sciences and fist author of this study. We do not know why yet, but APOBEC seems to act as a marker of a default in the replication mechanism in the affected cells, opening the door to an opportunistic mutagen. Indeed, the genome regions replicating early should not stay in a single-stranded state long enough for APOBEC to act. It means that

something is going wrong even before APOBEC comes on the scene. " The scientists will continue their research to better understand how tumorous cells replicate their DNA differently from healthy cells.

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