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PRESS RELEASE

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Researchers identify a mechanism for the transformation of colon polyps

Researchers from the University of Geneva demonstrate that, in this type of lesion, the rate of progression from a precancerous state to the tumor stage accelerates over time.

The causes underlying the development of certain types of common cancers have not yet been elucidated. In order to better determine the origin and the sequence of events responsible for the onset of colon cancer, the teams led by Thanos Halazonetis and Stylianos Antonarakis, professors at the University of Geneva (UNIGE), Switzerland, have sequenced the DNA of biopsied tissue from colon polyps. The results show that these precancerous lesions have a specific profile called '*mutator*', which is associated with an increased frequency of acquisition of certain mutations. The study, published December 1, 2012 in the journal *Cancer Research*, also designates mutations in three specific genes as being the likely initiators of the progression towards malignancy.

At each cell division, the entirety of our DNA, that is some 6.4 billion base pairs, must be replicated. The enzymes engaged in this task work at a prodigious rate of about 1000 base pairs per minute. This sometimes leads to errors, which are usually corrected by other enzymes. However, the repair mechanisms do not work when there is a defect in the DNA replication process, which is the case for cancer cells.

The genome of human cancer cells is generally unstable. The different forms and causes of this characteristic, which results in a greater susceptibility to acquire mutations, are not all known. "In order to explore the genesis and better understand the sequence of events leading to tumor development, we probed the DNA of precancerous lesions," explains Thanos Halazonetis, Professor at the Departments of Molecular Biology and Biochemistry of the UNIGE's Faculty of Science.

To do this, the team led by the professor sequenced the exome, which is the part of DNA that codes for proteins, from colon polyps sampled from patients. The researchers were thus able to pinpoint mutations in three specific genes, constituting the likely initial cause on the road to malignancy. "These genes, named APC, CTNNB1 and BRAF, all have a vital role in the cell. In particular, they are involved in cell division and adhesion to other cells, as well as various intracellular signaling pathways," explains Sergey Nikolaev, at the Department of Genetic Medicine and Development of the Faculty of Medecine, and first author of the article.

The researchers also compared the DNA of polyps, which most were precancerous, to that of healthy colon tissue. They discovered in the former an abnormally high frequency of mutations called SNS, characterized by the substitution of a single DNA base by another. "These precancerous lesions have a profile called 'mutator' which is associated with an increase in the frequency of acquiring SNS type muta-

tions. During early development of the polyp, the mutation rate in these cells is normal, and then it accelerates over time," says Thanos Halazonetis.

The mutation rate observed in polyps was sometimes 200 times greater than that present in normal cells, which greatly increases their progression towards a cancerous stage. According to the professor, these polyps become cancerous in five to ten years. Thanks to these findings, recommendations for routine biopsies, usually conducted every five years, could henceforth be refined on a case to case basis.

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