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Errors made by 'DNA spellchecker' revealed as important cause of cancer

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Cancer is mostly caused by changes in the DNA of our cells that occur over a lifetime rather than inherited traits. Identifying the causes of these mutations is a difficult challenge because many processes can result in a DNA sequence change. Researchers at the Centre for Genomic Regulation (CRG) in Barcelona, Spain, have now identified an important mechanism causing these mutations: mistakes made by a DNA 'spell checker' that repairs damage in the genome.

The researchers identified this process by studying clusters of mutations in more than a thousand tumor genomes, hunting for mutations that occur close together in the same part of the genome, which are highly unlikely to have happened by chance. The goal was to get a better picture of the mutagenic factors that affect human cells and that might cause cancer.

"Clustered mutations are likely to be generated at the same moment in time, so by looking at several neighboring mutations at once, we can gain a better understanding of what has damaged the DNA," says Fran Supek, first author of the study at the CRG. "Like when police study a pattern of recurrent crimes in order to find a serial killer, here, we show that focusing on patterns of clustered mutations and using a large number of cancer genomes, we can identify the culprits that cause mutations in tumors," he explains.

By studying clusters, the scientists identified nine mutational signatures that were evident in more than 1,000 genomes of tumors from various

organs. Their results, published in *Cell*, revealed new major mutation-causing processes, including an unusual case of DNA repair that should normally safeguard the genome from damage, but is sometimes subverted and starts introducing clustered mutations.

"Our work provides information about new biological mechanisms underlying some types of cancers. For example, the main oncogenes involved in melanoma are well known, but it is not known what causes the exact mutations that activate these genes to cause cancer. While many mutations in melanoma are recognized as a direct consequence of UV radiation, the origin of mutations affecting the most important oncogenes is still a mystery. We identified a mechanism that has the capacity to cause these oncogenic, cancer-driving mutations in melanoma," adds Supek.

One of these new mutational processes is highly unusual and most evident in active genes. These regions are usually protected by DNA repair mechanisms—in other words, DNA repair is directed to the places where it is needed most. "Our results suggest that exposure to carcinogens, such as high amounts of alcohol, can shift the balance of the DNA repair machinery from a high-fidelity mode to an error-prone mode, causing the mutation rates to shoot up in the most important bits of the genome," says Ben Lehner, ICREA research professor at the EMBL-CRG Systems Biology Research Unit and principal investigator of this study. "This error-prone repair generates a large number of mutations overall and is likely to be a major mutation source in human cells."

DNA repair is extremely important because our bodies are constantly renewing their cells, which involves copying more than two meters of DNA; errors are inevitably introduced. Moreover, mutagens in the environment, including sunlight and tobacco smoke, damage DNA, and this damage has to be corrected. DNA repair is normally exquisitely

accurate, but some types of damage can only be corrected using lower-fidelity 'spell checkers'. It is the mistakes made by one of these less accurate spell checkers that cause many of the mutations seen in different types of tumors, including liver, colon, stomach, esophagus and lung cancer.

New evidence links high levels of alcohol, sunlight, and smoking to mutations

Alcohol is a well-known contributor to many types of cancer, but the reasons for this are surprisingly unclear. Supek and Lehner's work suggests that one effect of alcohol, when consumed in large amounts, is to increase the use of low-fidelity DNA repair, thereby increasing the mutation rate in the most important regions of the genome. This finding provides a first glimpse into one mechanism by which alcohol may contribute to cancer risk. High exposure to sunlight seems to have a similar consequence.

As another part of the study, the CRG scientists also found that cigarette smoking is associated with several kinds of clustered mutations, further revealing the details of how smoking results in horrific damage to DNA.

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