

Mutations in cancer often affect the X chromosome

Every cell in a woman's body inactivates one of its two X chromosomes. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) and Heidelberg University have collaborated with international partners to discover that various types of cancer exhibit an abnormally huge number of mutations in the inactive X chromosome. They happen up to four times as frequently as in other chromosomes. The findings, published in the journal "Cell", help scientists understand how mutations accumulate in damaged cells and eventually lead to the development of cancer.

Every case of cancer originates from changes in a person's genetic material (mutations). These usually occur as "somatic mutations" in individual cells during an individual's lifetime, rather than being inherited from a person's parents. "Over time, the original damaged cell accumulates additional mutations, and it is still largely unknown why," says Prof. Roland Eils, who leads bioinformatics departments both at DKFZ and Heidelberg University.

By studying when and where mutations occur the researchers hope to gain insights into the early mechanisms that send cells along a pathway to cancer. The new international study coordinated by Roland Eils has now for the first time analyzed the exact distribution of somatic mutations in the genomes of tumor cells of various types of cancer. Mutations do not affect all regions of the genome to the same extent. It is known, for example, that the number of somatic mutations depends on the sequence of bases making up a gene and the frequency at which it is transcribed into RNA molecules.

In the current study, the researchers analyzed the genome sequences of more than 400 tumors from patients suffering from twelve different types of cancer, including brain cancer in children and adults, leukemias and breast cancer.

The scientists were surprised to find that mutations were extremely frequent in the X chromosome of females, which is responsible for determining sex. In many cancers, this chromosome displayed from two to four times as many mutations as were observed in the other chromosomes. Every cell in a female has two copies of the X chromosome and interestingly the rate was not the same in the two copies. From embryonic development onwards, one of the copies is inactivated in each cell. The higher mutation rate exclusively affects the inactive copy.

This phenomenon was not found in male cancer patients, whose cells carry only one X chromosome, or in inactive X chromosomes of healthy female cells. And in rapidly growing tumors, mutations were found to be particularly frequent in the inactive X chromosome. The researchers also discovered that the build-up of mutations occurs at a very early stage of carcinogenesis.

Prior to each cell division, the DNA in the original cell is duplicated. The inactive X chromosome is always the last to be duplicated. "Our theory is that cells which have accidentally undergone a growth-promoting mutation experience a state of stress caused by the rapid cell division," says Natalie Jäger, first author of the article. "They may not have enough time to repair errors, or they may lack enough of the building blocks necessary to create DNA. These problems mainly affect genomic regions that are duplicated at a late stage such as the inactive X chromosome."

Roland Eils adds: "This finding helps us understand how cellular stress accelerates the fatal process of carcinogenesis and thus contributes to an accumulation of ever more mutations in a cancer cell."

N. Jäger et al: Hypermutation of the inactive X chromosome is a frequent event in cancer. CELL 2013, DOI: 10.1016/j.cell.2013.09.042

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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