New technique identifies first events in tumor development

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A novel technique that enables scientists to measure and document tumor-inducing changes in DNA is providing new insight into the earliest events involved in the formation of leukemias, lymphomas and sarcomas, and could potentially lead to the discovery of ways to stop those events.

Developed by a team of researchers at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Cancer Institute (NCI), both parts of the National Institutes of Health, and The Rockefeller University, the technology focuses on chromosomal rearrangements known as translocations. Translocations occur when a broken strand of DNA from one chromosome is erroneously joined with that of another chromosome. Sometimes these irregularities can be beneficial in that they enable the immune system to respond to a vast number of microorganisms and viruses. However, translocations can also result in tumors.

The findings are reported in the Sept. 30 issue of the journal *Cell*.

Translocations can take place during the course of normal cell division, when each chromosome " a single strand of DNA containing many genes " is copied verbatim to provide genetic information for the daughter cells . Sometimes, during this process, byproducts of normal metabolism or other factors can cause breaks in the DNA.

"The cell expresses specific enzymes whose primary purpose is to repair

such lesions effectively, but when the enzymes mistakenly join pieces of two different chromosomes, the cell's genetic information is changed," said Rafael C. Casellas, Ph.D., senior investigator in the Genomics and Immunity Section at the NIAMS, who led the research team along with Michel C. Nussenzweig, M.D., Ph.D., from Rockefeller.

Casellas likens the phenomenon to breaking two sentences and then rejoining them incorrectly. For example, "The boy completed his homework." and "The dog went to the vet." might become "The dog completed his homework." or "The boy went to the vet." When a cell gets nonsensical information such as this, it can become deregulated and even malignant.

Scientists have known since the 1960s that recurrent translocations play a critical role in cancer. What was unclear was how these genetic abnormalities are created, since very few of them were studied, and only within the context of tumors, said Casellas. To better understand the nature of these tumor-inducing rearrangements, the authors had to create a system to visualize their appearance in normal, non-transformed cells.

The system the teams created involved introducing enzymes that recognize and cause damage at a particular sequence in the DNA into cells from mice, thereby constructing a genome where a unique site is broken continuously. The group then used a technique called polymerase chain reaction — which allows scientists to quickly amplify short sequences of DNA — to check all the sites in the genome that would get translocated to this particular break. Using this technique, they were able to examine more than 180,000 chromosomal rearrangements from 400 million white blood cells, called B cells.

Based on this large data set, the scientists were able to make several important observations about the translocation process. They learned that most of the translocations involve gene domains, rather than the space on

the DNA between the genes. They also found that most translocations target active genes, with a clear bias for the beginning of the gene, as opposed to its middle or end. The team also showed that a particular enzyme that normally creates DNA breaks in B cells dramatically increases the incidence of translocations during the immune response. This feature explains the long-standing observation that more than 95 percent of human lymphomas and leukemias are of B cell origin.

"This knowledge is allowing us to understand how tumors are initiated," said Casellas. "It is the kind of information that in the near future, might help us prevent the development of cancer."

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