Scientists resolve how chromosomal mix-ups lead to tumors

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(Medical Xpress) -- A new study by scientists from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), part of the National Institutes of Health, resolves longstanding questions about the origin of recurrent chromosomal rearrangements — known as translocations — that drive lymphomas and leukemias in humans. Translocations occur when broken strands of DNA from one chromosome are erroneously joined with those of another chromosome, thus deregulating genetic information and leading to cell transformation. Sometimes chromosomal rearrangements can be beneficial, in that they enable the immune system to respond to a vast number of microorganisms and viruses. However, translocations can result in tumors. The study was reported in the journal *Nature*.

Specific chromosomal translocations driving human cancer have been known since 1960, when scientists in Philadelphia (Peter Nowell and David Hungerford) first visualized one such lesion in patients suffering from chronic myeloid leukemia, an aggressive form of cancer in the blood. The origin of such malignant rearrangements, however, has been unclear. At least three theories have been put forward to explain their etiology:

- Translocations between two genes are driven primarily by how frequently the genes interact in the nucleus of tumor precursor cells.
- Translocating genes undergo DNA damage more frequently than

non-translocating genes.
- All genes in the genome have about an equal chance of translocating with one another, but certain translocations are particularly selected because they drive cell transformation.

In the new study, NIAMS scientists used cutting-edge technologies to explore the three theories. Using immune cells known as B cells, they found that the frequency of DNA damage was directly proportional to the frequency of translocation. Intriguingly, the researchers found that an enzyme, called AID, damages approximately 150 genes in the B cell genome, thus making them susceptible to translocations. Among the targeted genes, many have been previously shown to be translocated in human cancer. Further study also revealed that, in the absence of AID, gene proximity or interaction frequency was the driving force behind translocations.

The new results not only clarify the origin of tumor-inducing translocations, but they also suggest that finding ways to stop AID could potentially prevent the development of many human cancers.

More information: Ofir Hakim et al. DNA damage defines sites of recurrent chromosomal translocations in B lymphocytes. *Nature* DOI: 10.1038/nature10909 [Epub ahead of print]

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