Random DNA mix-ups not so random in cancer development

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Researchers at the UC San Diego School of Medicine have pinpointed a mechanism that may help explain how chromosomal translocations - the supposedly random shuffling of large chunks of DNA that frequently lead to cancer - aren't so random after all. They have developed a model of such chromosomal mix-ups in prostate cancer which indicates that the male sex hormone (androgen) receptor unexpectedly plays a key role in driving specific translocations in the development of cancer.

A better understanding of the origin and behavior of such translocations may ultimately lead to ways to both predict and perhaps interfere with their formation, and in turn, cancer development.

Chunru (Ruth) Lin, Liuqing (Luke) Yang and Michael G. Rosenfeld, MD, Howard Hughes Medical Institute investigator and Professor of Medicine at the UC San Diego School of Medicine, headed the basic research study, to be published on line December 3, 2009 in advance of publication in the journal *Cell*.

A series of studies showed that, under certain conditions involving some sort of genetic "stress" - such as cigarette smoke, a toxic chemical exposure or radiation - the androgen receptor can act in concert with several key enzymes and pathways induced by genotoxic stress to unexpectedly direct specific translocations leading to cancer.

"In the future, one goal would be to find tumor-causing translocations in breast and other cancers and develop a chemical library screen to find

compounds that might inhibit these events in cancer formation /behavior," said Rosenfeld.

According to Rosenfeld, chromosome mix-ups are a hallmark of leukemias and lymphomas and, increasingly, other cancers such as more aggressive forms of prostate cancer. Scientists have known that various types of genetic stress can lead to random breaks in DNA and rearrangements in chromosomes, resulting in excessive cell growth and cancer, but the exact mechanisms have been poorly understood.

Evidence from other research teams pointed to the important role of the androgen receptor in the development of translocations in more aggressive forms of prostate cancer. The UC San Diego research team created a tumor translocation model in prostate cancer and found that instead of random DNA breaks, the breaks were in specific chromosomal areas bound by the androgen receptor which directed the pattern of cancer-causing translocations.

Rosenfeld's group identified several mechanisms, some involving specific enzymatic pathways that worked together with the androgen receptor to form specific translocations.

"Our findings suggest that sex steroid receptors - androgen and estrogen receptors - can cause mutations when in the presence of genotoxic stress, and form site-specific chromosomal translocations," Rosenfeld said.

He noted that understanding the molecular mechanisms that underlie tumor translocations and the specific strategies used by normal cells to protect against such rearrangements could provide insights into cancer development and eventually help in the development of new therapeutic approaches.

Source: University of California - San Diego (news : web)