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Inverted DNA turns quiet developmental gene into a potent driver of t-cell lymphoma

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A gene crucial for embryonic development can quickly become a potent cancer promoter in adult mice after a genetic misalignment, according to researchers from Fox Chase Cancer Center, causing white blood cells to become cancerous spontaneously.

In the March 1 issue of the journal Cancer Research, the researchers detail how a gene called Dlx5 works cooperatively with a known oncogene, Akt2, to drive cancer in mice. The protein that Dlx5 encodes could be a target for drugs to slow the growth of lymphomas and other cancers in humans, they say.

“A chromosomal inversion essentially flips a segment of DNA, placing the Dlx5 gene next to an enhancer in a neighboring gene, which in turn activates a number of other nearby genes,” says lead investigator Joseph Testa, Ph.D., a cancer geneticist at Fox Chase. “The result is like placing a V8 engine on a Flexible Flyer – something is going to go fast and without much control.”

According to Testa, Dlx5 is basically a good gene that starts to do bad things when it moves into a dangerous neighborhood. Dxl5 is part of the homeobox family of genes, which direct the timing of events in the physical development of a growing fetus, such as when to sprout a limb, for example. In adults, such genes are almost entirely inactive.

Unfortunately, in white blood cells, such as T cells, Dlx5 moves to a region of DNA involved in the genetic rearrangement that allows

immune cells to switch genes around in order to create new combinations of proteins to respond to disease threats. This recombination process allows B cells to generate antibodies and T cells to generate T cell receptors, enabling the immune system to recognize an enormous array of foreign bacteria, viruses and parasites.

In a mouse model of T cell lymphoma, the researchers found that mice bred to over-express the Akt2 gene also over-expressed Dlx5. In fact, the researchers found the chromosomal inversion that led to cancer was a feature in the majority of mice studied. One particular line of transgenic mice exhibited the inversion in 15 of 15 tumors they examined. “Genetic recombination is a frequent component of T-cell malignancies, but it is startling to see this same pattern come up repeatedly,” Testa says.

In subsequent cell studies, Testa and his colleagues determined that the combined activation of both Dlx5 and Akt2 could result in increased cell growth and proliferation. While their findings are the first to assert that Dlx5 can be an oncogene, the gene has previously been implicated in a number of human endometrial and lung cancers. Moreover, the DLX5 protein was found in abundant amounts within three out of seven human lymphomas that the Fox Chase researchers examined.

According to Testa, molecules that could bind and inhibit DLX5 could provide a more useful drug for therapeutic development than could molecules that inactivate AKT2.

“The AKT family of proteins is crucial to survival in both cancerous and non-cancerous cells, so AKT2 is a potentially risky target for drug development since blocking AKT2 can also kill healthy cells,” Testa says. “DLX5, however, is not generally active in healthy adult cells, so it represents a much more ‘druggable’ target for inhibition.”

Source: Fox Chase Cancer Center

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