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Researchers uncover one force behind the MYC oncogene in many cancers

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DLX5, a gene crucial for embryonic development, promotes cancer by activating the expression of the known oncogene, MYC, according to researchers from Fox Chase Cancer Center. Since the DLX5 gene is inactive in normal adults, it may be an ideal target for future anti-cancer drugs, they reason. Their findings are published in the July 31 edition of the *Journal of Biological Chemistry*, available online now.

Previously the researchers found that a chromosomal inversion - a genetic misalignment, where part of the chromosome containing the DLX5 gene gets flipped around during cell division - cooperates with another known oncogene, AKT2, to drive cancer in mice. In the current paper, the researchers discover that DLX5 binds to and actively promotes the activity of a gene known as MYC, which evidence has demonstrated is a potent factor in numerous cancers, including lymphoma, lung and pancreatic cancer. Their studies were performed in mouse cancer models and in human cell cultures.

"While MYC has a definite role in cancer, MYC also has an important place in the normal functioning of cells, so it may be difficult to target without killing healthy cells," says Joseph Testa, PhD, a Fox Chase professor and co-author of the study. "DLX5, however, is not generally active in healthy adult cells, so it represents a much more 'druggable' target for cancer inhibition."

According to Testa, DLX5 is a member 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.

After their previous studies demonstrated that expression of the protein encoded by the DLX5 gene correlated with that of the MYC gene, Testa and Jinfei Xu, PhD, a research associate in the laboratory, used a luciferase assay - developed from the luciferase enzyme fireflies use to make light - to see exactly where DLX5 protein binds to the promoter region of the MYC gene. They found that there were two sites where DLX5 could bind to the MYC promoter, which is a section of DNA where certain proteins known as transcription factors attach in order to recruit the cellular machinery used to transcribe genes into messenger RNA and then proteins. Studies in both cells and a mouse model for cancer showed that they could promote the expression of MYC by transfecting cells with DNA strands containing DLX5.

Too much DLX5, they found, led to too much MYC. When they knocked out expression of DLX5 in lung cancer cells, it resulted in decreased expression of MYC and reduced cell proliferation. By adding an overabundance of MYC, they found they could turn those cells cancerous again.

From this, Testa and Xu were able to gain a broader understanding of how cancers involving AKT2, DLX5 and MYC might develop. A mutation in AKT2 may act as a "first hit" that makes the inversion on mouse chromosome 6, which contains the DLX5 gene, more likely. When the inversion happens, the cell begins producing the DLX5 protein, a multipurpose transcription factor that normally has a very limited role in adult cells. One of the targets of DLX5 is the MYC gene itself, causing the cells to produce many copies of the MYC oncoprotein.

Normally MYC regulates many functions within the cell, including cell division. With an overabundance of MYC, the cell may reproduce out of

control, accumulating in each generation the further genetic damage that is the hallmark of cancer cells.

Source: Fox Chase Cancer Center (news : web)