

Tracking the molecular pathway to mixed-lineage leukemia

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Infants and adults with the blood cancer mixed-lineage leukemia (MLL) typically have a poor prognosis, and most infants die before their first birthdays. Although there are varying causes of MLL, most cases are caused by a fusion of two genes, the MLL and the AF4 genes.

When the MLL gene is fused to the AF4 gene, a potent cancer-causing oncogene is created. Although researchers have known that the MLL-AF4 protein produced by this genetic fusion causes leukemia, they had not been able to determine precisely how this oncogene disrupted cells' normal protein production.

To pinpoint the oncogene's activities, Matthew Guenther, a postdoctoral researcher in Whitehead Member Richard Young's lab, used a technique called ChIP-seq (chromatin immunoprecipitation with DNA sequencing) to map where the MLL-AF4 protein interacts with a cell's genome. He found that in cancer cells the MLL-AF4 protein binds to at least 169 genes, many of which are overexpressed in leukemia cells and encode hematopoietic stem cell regulators (the genes that initiate blood cell production).

It seems that when the MLL-AF4 protein interacts with these genes, it forces them into a hyperactive state, with disastrous consequences.

"The MLL-AF4 fusion protein is somehow targeted to a set of genes that essentially hijacks the blood stem cell machinery and makes that cell become cancerous, basically a younger-looking cell that is dividing much

more than it should," says Guenther.

Looking closer at the MLL-AF4 protein-bound genes, Guenther noticed that these genes display strange patterns of chromatin proteins. In the cell, DNA is wrapped around chromatin proteins for dual purposes: to safely package DNA for cell division and to control gene expression (epigenetics). Changes in chromatin structures can affect normal gene expression, and other studies have linked chromatin misregulation to cancer and to leukemia disease progression. In MLL patients, it seems the MLL-AF4 protein alters the normal chromatin state of the hematopoietic stem cell regulators.

Guenther's findings may take scientists one step closer to a treatment for this deadly disease.

"We think we've figured out a key piece of how this leukemia works," says Young. "If we understand the molecular pathway for how the MLL-AF4 protein interacts with genes, it gives us a set of new target genes that might be used for drug development."

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