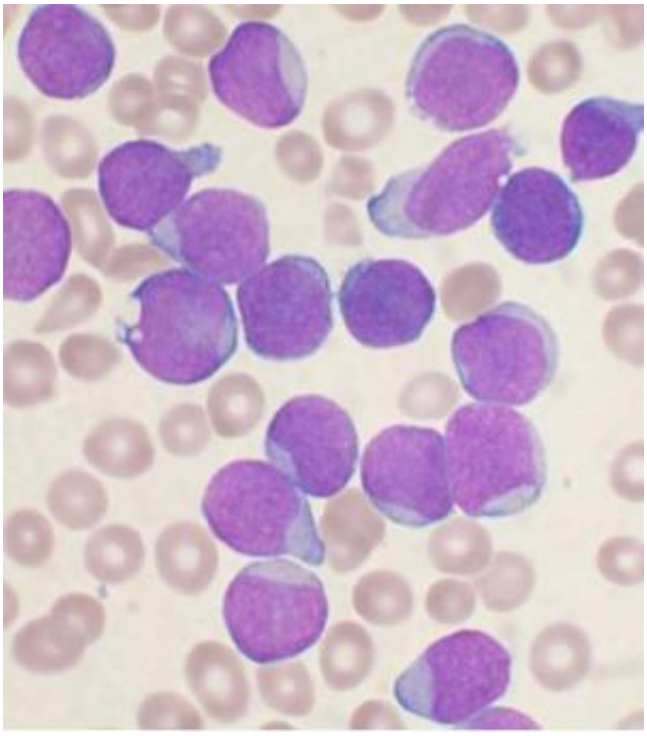
MedicalXpress

Leukemia study reveals role of RNA binding protein in driving cancer

March 14 2016



A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A study of gene expression in leukemia cells has identified an RNA binding protein that plays an important role in driving the development of cancer. The protein is normally active in fetal tissue and switched off in adults, but it is reactivated in some cancer cells. This expression pattern makes it an attractive target for cancer-fighting drugs, because

blocking its activity is unlikely to cause serious side effects.

The new study, published March 14 in the *Journal of Clinical Investigation*, focused on a particularly aggressive form of B-cell acute lymphoblastic leukemia (B-ALL), the most prevalent type of leukemia in children and young adults. A team led by scientists at UC Santa Cruz and UCLA found an overabundance of the RNA binding protein known as IGF2BP3 in the cancer cells of this subset of B-ALL patients.

"This protein, IFG2BP3, has been correlated with many types of malignancies and with the worst prognoses," said coauthor Jeremy Sanford, associate professor of molecular, cell, and developmental biology at UC Santa Cruz. "What is exciting about this study is that it goes beyond correlation and shows causation, because we demonstrated for the first time that aberrant expression of this protein is sufficient to induce pathology."

The researchers identified genes that are directly regulated by this RNA binding protein, and many of them turn out to be oncogenes that have already been implicated in cancer. In particular, the protein enhances the expression of a well-characterized oncogene called MYC, which in turn regulates a large number of genes involved in cell proliferation.

Compared to other proteins involved in regulating gene activity, RNA binding proteins have not been well studied. When a gene is turned on or "expressed," an RNA copy is made of the gene's DNA sequence, and the genetic code carried by this "messenger RNA" is then translated into a protein that carries out some cellular function. Many factors are involved in controlling which genes get transcribed into messenger RNA and when, but RNA binding proteins interact with the messenger RNA itself to regulate gene expression after transcription has occurred. Scientists are only beginning to unravel the complexity of this post-transcriptional regulation of gene expression.

In the case of IGF2BP3 and B-cell leukemia, the overall effect of the RNA binding protein is to promote the proliferation of B cells by shifting the expression of a large number of genes, Sanford said.

Leukemia starts in the "hematopoietic" stem cells in the bone marrow that give rise to all the different kinds of mature blood cells. A variety of genetic alterations can cause abnormal white blood cells to proliferate and crowd out the normal blood cells. Sanford's collaborator at UCLA, Dinesh Rao, was studying B-ALL cases involving chromosomal rearrangements of the mixed lineage leukemia (MLL) gene, which accounts for about 5 percent of B-ALL cases and is associated with poor prognosis and increased risk of early relapse after treatment.

After Rao's lab identified IGF2BP3 as one of the top dysregulated genes in these cases, they began working with Sanford's lab to figure out which genes were being directly regulated by IGF2BP3. Sanford and Rao have been friends since they were undergraduates, and Rao knew that Sanford's lab was among the few using a technique that can capture RNA molecules bound to a particular protein. Called individual nucleotide resolution crosslinking immunoprecipitation (iCLIP), the technique enabled Sanford's lab to identify IGF2BP3 binding sites in several hundred RNA transcripts in two B-ALL cell lines. They also showed that IGF2BP3 enhanced the expression of MYC and other oncogenes in hematopoietic stem cells.

Studying its effects in mice, the researchers found that overexpression of IGF2BP3 in the bone marrow leads to proliferation of hematopoietic stem cells and B cell progenitors, reproducing some features of MLL-rearranged B-ALL.

"Understanding its mechanism of action is important for thinking about therapeutics that might interfere with the action of this protein in disease," Sanford said. "One possibility is an RNA-based therapeutic

that could sequester the protein and keep it from binding to RNA transcripts. That would be a way to influence the expression of many genes involved in the proliferation of cancer cells."

Provided by University of California - Santa Cruz