A gene within a gene contributes to the aggressiveness of acute myeloid leukemia

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(Medical Xpress)—A small gene that is embedded in a larger, well-known gene is the true leukemia-promoting force usually attributed to the larger gene, according to a new study by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The findings are published in the journal *Science Signaling*.

The larger host gene is called BAALC (pronounced "Ball C"). The smaller embedded gene is called microRNA-3151 (miR-3151). The study investigated the degree to which each of the genes contributes to the development of acute myeloid leukemia (AML).

"We discovered that the smaller microRNA gene, and not the larger host gene, is the major oncogenic driver of the two molecules in AML," says principal investigator Albert de la Chapelle, MD, PhD, professor of Medicine and the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research.

"When both genes are highly expressed, it means a bad prognosis for patients, but our experiments indicate that it is high expression of miR-3151 that really matters. Overexpression of BAALC alone had only limited cancer-causing activity," he says.

The researchers discovered that miR-3151 promotes the development of

leukemia by blocking a gene called TP53. Normally, TP53 is a central "tumor-suppressor" gene that protects against cancer by causing a cell with serious gene damage to self-destruct. "When miR-3151 blocks TP53 in the tumor cells, it enables the cells to survive, divide and grow faster," says co-senior author Clara D. Bloomfield, MD, Distinguished University Professor and Ohio State University Cancer Scholar.

"We also show that miR-3151 promotes growth in malignant melanoma cells in the same way, suggesting that the molecule might play a role in solid-tumor development," says Bloomfield, who is also senior adviser to the OSUCCC – James and holds the William Greenville Pace III Endowed Chair in Cancer Research.

Last, the researchers show that miR-3151 overexpression may be inhibited by the drug bortezomib, a proteasome inhibitor, suggesting a possible therapy for miR-3151 overexpression.

MicroRNAs are a class of molecules that cells use to help regulate the kinds and amount of proteins they make. "About one-third of the several hundred known human microRNAs are encoded in host genes," says first author Ann-Kathrin Eisfeld, MD, a postdoctoral researcher who works in the laboratory of study co-authors de la Chapelle and Bloomfield.

Specifically, they are located in areas of genes called introns, short stretches of DNA that are not involved in making a protein. "We know very little about how microRNAs located within introns are regulated and how they interact with their host genes," Eisfeld says. "These findings provide an important example of that interaction."

The researchers found, for example, that miR-3151 has the capability to be active on its own, independent of the host gene.

For this study, de la Chapelle, Bloomfield, Eisfeld and their colleagues

used human AML cells, cell lines and an animal model to investigate the overexpression of miR-3151 and BAALC in older patients with cytogenetically normal AML. Key technical findings include:

- MiR-3151 directly targets PT53 and seven other genes in the TP53 pathway;
- Overexpressing miR-3151 promotes AML-cell growth;
- BAALC overexpression enhances that effect while blocking miR-3151 or overexpressing TP53 reverses it;
- miR-3151 alone and in combination with BAALC promotes leukemia development in an animal model.

More information: Paper: stke.sciencemag.org/cgi/conten … /sigtrans;7/321/ra36

Listen here to a *Science Signaling* podcast featuring Eisfeld and de la Chapelle talking about this study.

Provided by Ohio State University Medical Center

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