A miR boost enables acute leukemia cells to mature

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Dr. Ramiro Garzon is a hematologist-oncologist at the Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute. Credit: Ohio State University

A new study by Ohio State University cancer researchers shows that boosting the level of a molecule called miR-29b in acute myeloid leukemia (AML) cells can reverse gene changes that trap the cells in an immature, fast growing state of development.

The study discovered how the miR reactivates silenced genes, which enables the leukemic cells to differentiate and mature, important steps that precede their death. The findings suggest that miR-29b could be a potent treatment for AML.

The molecule blocks the action of three enzymes, all of which add small

chemical units called methyl groups to genes. The addition of the units locks genes down tight and takes them out of action.

By blocking the enzymes, the miR removes the methyl groups from genes, a process called demethylation, which then reactivates them.

The study is reported online in the journal *Blood*.

"We show that miR-29b is a powerful demethylating agent and provides a rationale for developing this molecule as a possible drug for the treatment of AML, alone or in combination with other agents," says first author Dr. Ramiro Garzon, a hematologist-oncologist and assistant professor of internal medicine at the Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute.

Garzon notes that the miR might prove to be more potent than current demethylating agents, which block only one of the three enzymes inhibited by miR-29b. "The action of miR-29b is more complete," he says.

Earlier research by the same investigators using lung cancer cells showed that miR-29b targets two enzymes, DNMT3A and DNMT3B, that both add the chemical units (methyl groups) to genes.

When the researchers raised the level of miR-29b in leukemic cells, the amount of a third enzyme, called DNMT1, fell.

"We discovered that this miR blocks DNMT1 also, but indirectly," Garzon says.

The miR, it turns out, targets another protein - called Sp1 - that boosts production of the DNMT1 protein.

Thus, low levels of the miR may result in lots of Sp1 protein and of DNMT1, which busily adds the chemical units that silences genes. High levels of the miR, on the other hand, may keep the amount of Sp1 low, so there is little DNMT1 and much less gene silencing.

"Our paper explains why this miR is a powerful demethylating agent," Garzon says. "It shows that putting this miR back into leukemia cell lines and leukemia cells from patients causes a drop in global DNA methylation and reactivates protective tumor suppressor genes, which allows the cells to differentiate and mature."

Source: Ohio State University Medical Center