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MicroRNA controls growth in highly aggressive B-cell lymphomas

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A recent study by researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine showed that a microRNA called miR-181a dampens signals from the cancer-driving NFκB protein pathway in the most aggressive large B-cell lymphomas (DLBCL). By reducing NFκB signaling, miR-181a controls tumor cell proliferation and survival and could be the target of novel therapies. The study was published in the journal *Blood*.

"The miR-181a microRNA is one of the first examples of a pathway that deactivates NFκB at multiple levels, functioning as a master regulator," said Izidore S. Lossos, M.D., director of the Lymphoma Program at Sylvester and lead author of the study. "In certain tumors there is no expression of this microRNA, which allows cells to propagate. We believe miR-181a could eventually be used therapeutically."

DLBCL is the most common form of non-Hodgkin lymphoma, affecting more than 100,000 patients in the U.S. Recent genomic advances have allowed researchers and clinicians to subtype DLBCL into two groups: GCB-like and ABC-like. In addition to being more aggressive and deadly, ABC-like lymphomas resist the programmed cell death induced by chemotherapy.

ABC-like DLBCLs are driven, in part, by a hyperactive form of NFκB, which is known to play a significant role in several cancers. In normal B-cells, NFκB gets turned on when necessary and subsequently turned off. However, in ABC-like DLBCL, the pathway is turned on permanently,

leading to rampant growth.

"NFκB one of the most important and most studied pathways in humans," noted Lossos. "In normal cells it can only be activated in response to stimuli. However, in this subset of lymphoma cells, it is constitutively active all the time."

The ABC-like form of DLBCL has another distinction - it has less miR-181a, a critical gene regulator. While messenger RNAs carry instructions to translate genes into proteins, microRNAs perform a very different function: shutting down gene expression post transcriptionally. Previous studies by Lossos' group have shown that DLBCL patients whose tumors contain more miR-181a have better prognoses.

To understand the roles played by miR-181a and NFκB in each type of DLBCL, the team studied both cell lines and human tumor grafts in mice. They found that miR-181a levels were significantly lower in the ABC-like tumors compared to the GCB-like group.

In addition, adding miR-181a to ABC-like cell lines and tumor grafts reduced NFκB activity, diminished tumor growth, and significantly increased animal survival. This ability to reduce NFκB levels may be why the presence of miR-181a is linked to better outcomes for certain DLBCL patients.

In fact, the researchers found miR-181a is a master regulator, turning off a number of genes in the NFκB pathway, including CARD11, a known DLBCL oncogene, and a number of transcription factors (proteins that turn on genes) that drive NFκB signaling.

"We knew that miR181a was biomarker for survival," said Lossos. "This explains the mechanisms behind it."

In addition to providing a better understanding of the NFκB pathway, these results provide hope that miR-181a could be used therapeutically to help patients with ABC-like DLBCL.

"We are trying to develop miR-181a as a potential therapy," said Lossos, "but we are only at the beginning. Much more work needs to be done. It will not be a simple journey, but we are sure it can be done and tested in humans eventually to see that it indeed will improve patients' outcomes."

Provided by University of Miami Miller School of Medicine