

Loss of MicroRNA decoy might contribute to development of soft-tissue sarcoma

August 7 2013

Researchers have discovered a novel mechanism responsible for the loss of a critical tumor-suppressor gene in rhabdomyosarcoma and other soft-tissue sarcomas, rare cancers that strike mainly children and often respond poorly to treatment. Their cause is largely unknown.

Knowledge of the mechanism could guide the development of more effective therapies for these malignancies, say researchers who led the study at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

The researchers found that the tumor-suppressor gene called A20 is silenced not by mutation, as in many other cancers, but because a second molecule is lost, a small molecule called microRNA-29 (miR-29). In addition, they found that miR-29 normally protects A20 from destruction. When miR-29 is absent, A20 is degraded. Loss of A20, in turn, leads to a dramatic rise in levels of a protein called NF-kB and to tumor progression.

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

"We do know that NF-kB is a [tumor promoter](#), but we don't know why it is upregulated in many cancers," says principal investigator Denis Guttridge, PhD, professor of [molecular virology](#), immunology and [medical genetics](#) and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

"Our study indicates that it involves a regulatory circuit between NF-kB, miR-29 and the A20 tumor-suppressor gene," Guttridge says. "It also identifies NF-kB as a [therapeutic target](#) in sarcoma and A20 and miR-29 as potential biomarkers for sarcoma."

"We are excited about these findings because they open up new vistas on the role of microRNAs in sarcoma development and provide a rationale for further interrogating this circuitry as a potential target for new treatments," says study pathologist and coauthor O. Hans Iwenofu, MD, FCAP, assistant professor of pathology and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

Soft-tissue sarcomas – cancers of muscle, other soft tissues and bone – make up about 15 percent of pediatric cancer cases. In 2013, about 11,400 cases of sarcoma are expected in the United States, and about 4,400 Americans are expected to die from the malignancy.

For this study, Guttridge, Iwenofu and their colleagues used human tumor samples, cell lines and animal models. Key technical findings include:

- miR-29 and A20 expression are abnormally low in sarcomas;
- The A20 gene showed little evidence of mutation;
- Restoring miR-29 levels in sarcoma cells caused A20 levels to rise;
- miR-29 normally binds with a protein called HuR; when miR-29 is absent, HuR binds with A20, leading to the degradation of A20;
- When miR-29 binds with HuR, it acts as a decoy and protects A20 from HuR-mediated degradation.

"The loss of the A20 tumor-suppressor gene because the microRNA decoy is absent may represent another mechanism to explain why NF-kB

is constitutively active in sarcoma cancers," Guttridge says.

More information: [stke.sciencemag.org/cgi/content ...
/sigtrans;6/286/ra63](https://stke.sciencemag.org/cgi/content/full/sigtrans;6/286/ra63)

Provided by Ohio State University Medical Center

Citation: Loss of MicroRNA decoy might contribute to development of soft-tissue sarcoma (2013, August 7) retrieved 19 April 2024 from <https://medicalxpress.com/news/2013-08-loss-micrna-decoy-contribute-soft-tissue.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--