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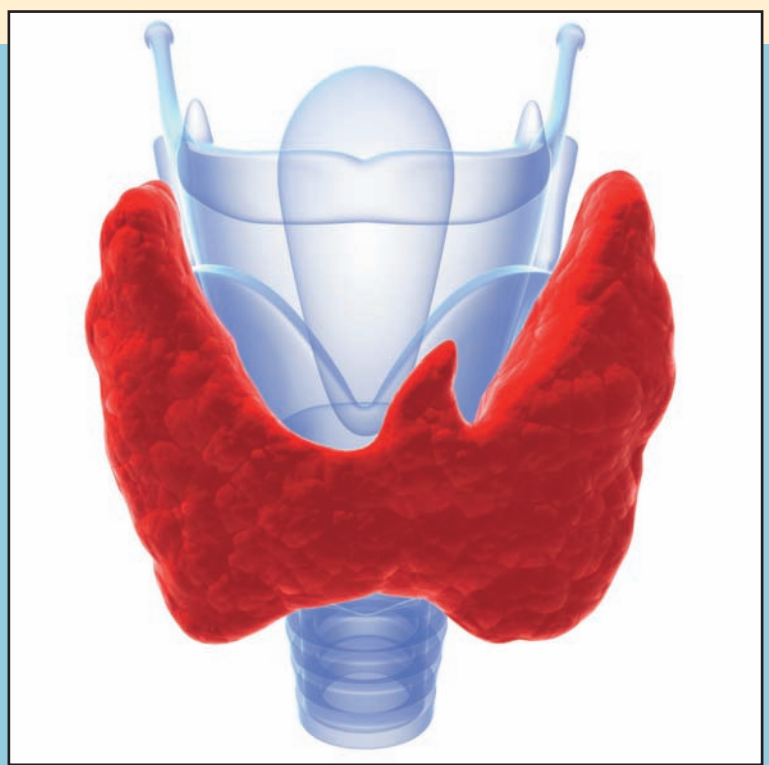


#2 in a Series

FOCUS:

Thyroid Cancer

Treatment & Research Updates

[INSIDE]

MicroRNA Found to Regulate Thyroid Cancer Traits

BY RABIYA S. TUMA, PHD

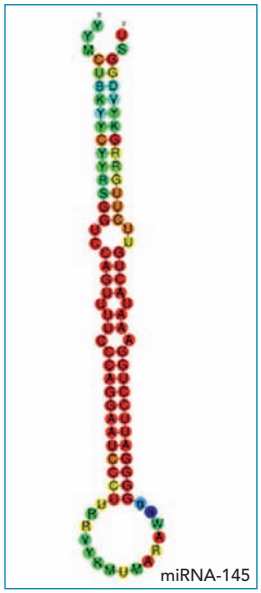
WASHINGTON—MicroRNAs are key regulators in numerous types of cancer, with some serving as tumor suppressors. Now, investigators from the National Cancer Institute report that miRNA-145 is significantly down regulated in both papillary and anaplastic thyroid cancers. According to a study presented at the American Association for Cancer Research Annual Meeting (***Abstract 3098***), restoring the expression in various models reduces cell proliferation, as well as migration and invasion.

> The finding that miR-145 is significantly down regulated in both differentiated and undifferentiated tumors is particularly interesting, because down regulation of miR-145 has been linked to poor outcomes in lung and colon cancers.

To identify miRNAs that might be important in thyroid cancer, Myriem Boufraqech, PhD, a postdoctoral fellow in the Center for Cancer Research at NCI, and colleagues performed miRNA profiling experiments in normal, benign, and malignant thyroid cells. It was found that miR-145 was significantly down regulated in differentiated and undifferentiated tumors, relative to the controls.

The finding is particularly interesting, Boufraqech said, because down regulation of miR-145 has been linked previously to poor outcomes in both lung and colon cancer.

When the team re-expressed miR-145 in thyroid cancer cell lines, they saw a variety of biochemical changes that correlate with a decline in growth and aggressiveness, including an increase in p21 expression and a decrease in CDC25c expression.


miRNA-145

"It looks like every time you overexpress the miRNA in cell lines, you decrease the proliferation," she told *OT*.

Additionally, overexpression of miR-145 led to a reduction in signaling through the PI3K pathway, which is one of the most dysregulated signaling pathways in thyroid cancer.

The investigators also found that miR-145 expression influenced expression of a key differentiation marker, the sodium/iodide symporter (NIS), which is responsible for iodine uptake in thyroid cells, and healthy thyroid cells express a lot of it. Aggressive thyroid cancer and undifferentiated tumors, however, often lack NIS expression, making the patients refractory to I^{125} treatment.

The investigators found that in normal stem cells, NIS was highly expressed, but when the researchers blocked miR-145 expression, NIS expression also dropped dramatically. Conversely, when the team overexpressed the microRNA in thyroid cancer cells, it decreased the amount of a dedifferentiation marker, CD44. Together, the data suggest that miR-145 influences whether a cell is differentiated or not, Boufraqech said.

Working with a mouse model of metastasis, the researchers also saw that miR-145 expression influenced the invasiveness of invasive thyroid cancer cells. When the microRNA in anaplastic thyroid cancer cells was overexpressed and injected into the tail vein of mice, the cells formed primary tumors in the animal's legs, just like the cells that lack miR-145 expression. However, the cancer cells that lacked miR-145 expression gave rise to metastases in the lung, whereas those that overexpress the microRNA do not.

The next step, Boufraqech said, is to find a way to deliver the microRNA to tumors in mouse models. "We will try to start some in vivo experiments using nanoparticles and see if we can really deliver this miRNA to the tumor. Before talking about any clinical trials, we need to see if there is any technology able to deliver this to the tumor."

Asked for their opinion for this article, several translational researchers declined to comment more specifically, saying that the research was still too early to speculate about the clinical significance, but they agreed that the work was interesting and that it should be followed up.

Coming in Future Issues:

- Sorafenib Stalls Growth of Treatment-Related Differentiated Thyroid Cancer: First Active Drug in Four Decades
- Thyroid Cancers Show Intrinsic Resistance to BRAF Inhibitor, with Suggestion that Added Lapatinib Can Block Mechanism
- Debate Continues About Role of Prophylactic Central-Neck Dissection in Papillary Thyroid Cancer
- Thyroid Cancer Survival Rates High After Chernobyl Despite Lag in Care