The role of fibronectin in BRAF-mutant thyroid cancer treatment

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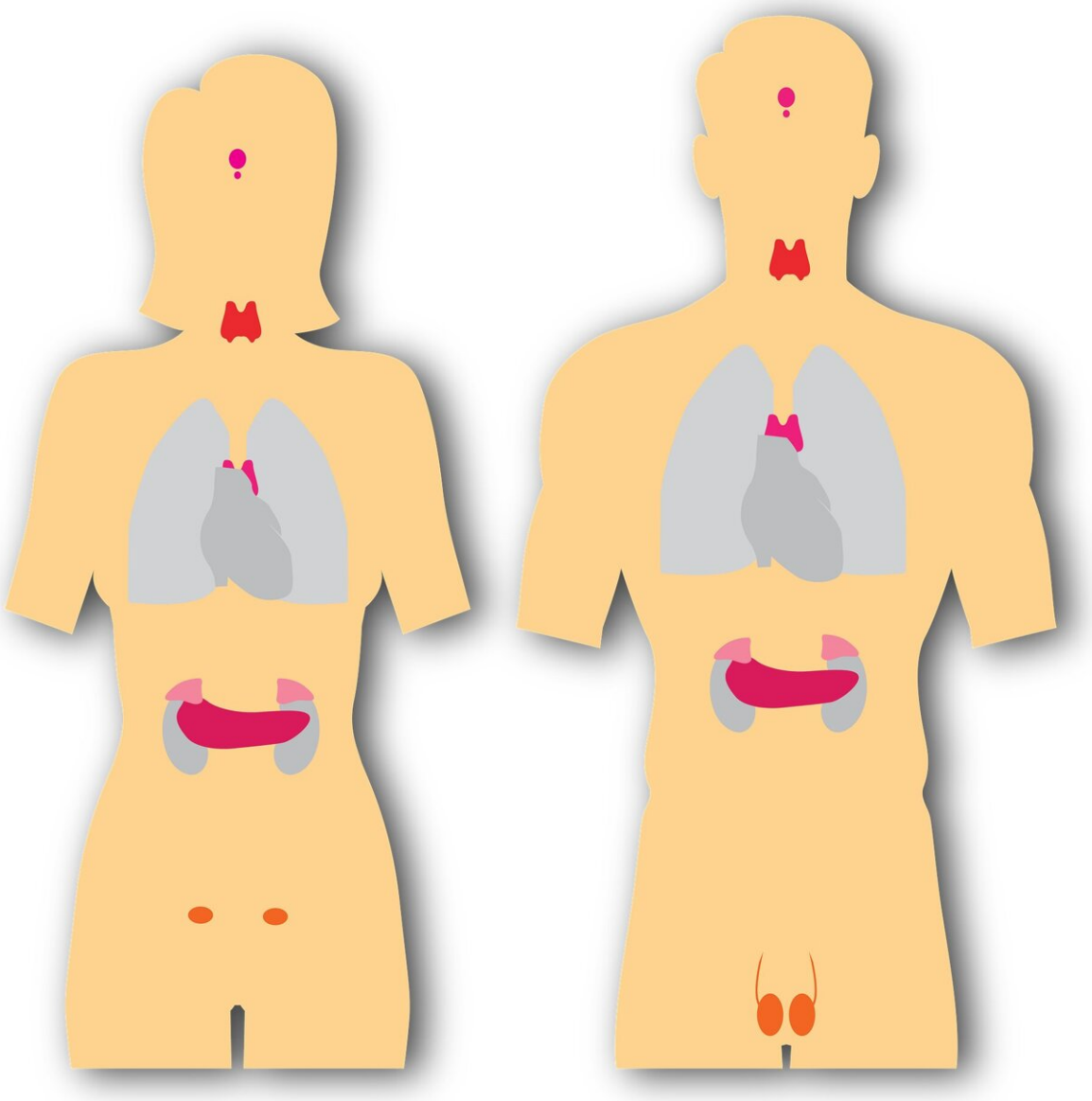

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New research overseen by University of Colorado Cancer Center member Rebecca Schweppe, Ph.D., could lead to improved treatment for people with thyroid cancer characterized by a mutation in the BRAF gene—a mutation also responsible for some types of melanoma, colorectal cancer, leukemia, lymphoma, and ovarian cancer.

The findings were published in September 2023 in the journal *Molecular Cancer Research* and were highlighted by the editor.

"The BRAF mutation is a common mutation in thyroid cancer," Schweppe says. "It has a high prevalence of mutations in two different subtypes—papillary thyroid cancer, or PTC, and anaplastic thyroid cancer, or ATC—and there's a lot of interest in targeting this pathway. Other tumor types, like melanoma and colon cancer, also have a high prevalence of this mutation, but unlike in melanoma, thyroid cancer patients with this BRAF mutation have not responded as well to the medicine that inhibits BRAF activity."

In ATC patients, that medicine is often taken in combination with a drug that targets another member of the BRAF pathway called MEK1/2. Combined BRAF and MEK1/2 inhibition prevents reactivation of the pathway, but tumors tend to return. In PTC patients, meanwhile, there is no effective drug to target BRAF.

The role of fibronectin

Looking for new therapeutic strategies for treating patients with BRAF-mutant thyroid cancer, Hannah Hicks, who recently completed her Ph.D. in the Cancer Biology Graduate Program on the CU Anschutz Medical

Campus, analyzed cell lines and discovered that when thyroid cancer cells resistant to BRAF inhibition are treated with a BRAF inhibitor, a protein called fibronectin is increased, making the cancer cells more invasive, which can ultimately lead to cancer cells spreading throughout the body.

"Early in my graduate studies, we were comparing and contrasting cell lines that are either sensitive or resistant to BRAF inhibitors," Hicks says. "We noticed that in response to BRAF inhibitor treatment, fibronectin increased in resistant cells. After finding that treatment with a BRAF inhibitor or treatment with fibronectin could increase invasion in resistant cell lines, we hypothesized there could be a connection between BRAF inhibitor resistance and fibronectin."

Further research conducted in Schweppe's lab showed that inhibiting a specific protein in the BRAF pathway, ERK1/2, decreases the secretion of fibronectin in the presence of a BRAF inhibitor, and that using BRAF and ERK1/2 inhibitors together resulted in slowed tumor growth and decreased fibronectin secretion.

"Many studies have suggested that robust inhibition of the MAPK pathway is key to avoiding the development of resistance in advanced thyroid cancer patients treated with MAPK inhibitors," Hicks says. "Our work here adds to the mounting evidence that it is important to block multiple nodes of the MAPK pathway to improve outcomes. I hope this research will lead to more studies on the potential use of combination therapies as upfront treatments or salvage therapies to circumvent drug resistance."

More durable treatment

A medicine that inhibits ERK1/2 is currently in clinical trials, Schweppe says, and if it is approved, it could become a powerful new tool to use in

the treatment of BRAF-mutant thyroid cancer that is resistant to the current standard treatment.

"Especially for papillary thyroid cancer patients, who aren't responding to current therapy, would they respond better to this combination?" she says. "Would it be more durable in our anaplastic thyroid cancer patients? It's difficult to fully cure these patients, but this gives us another tool in our toolbox."

More information: Hannah M. Hicks et al, Fibronectin Contributes to a BRAF Inhibitor–driven Invasive Phenotype in Thyroid Cancer through EGR1, Which Can Be Blocked by Inhibition of ERK1/2, *Molecular Cancer Research* (2023). DOI: 10.1158/1541-7786.MCR-22-1031

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