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Study finds potential marker of drug response in many cancer types

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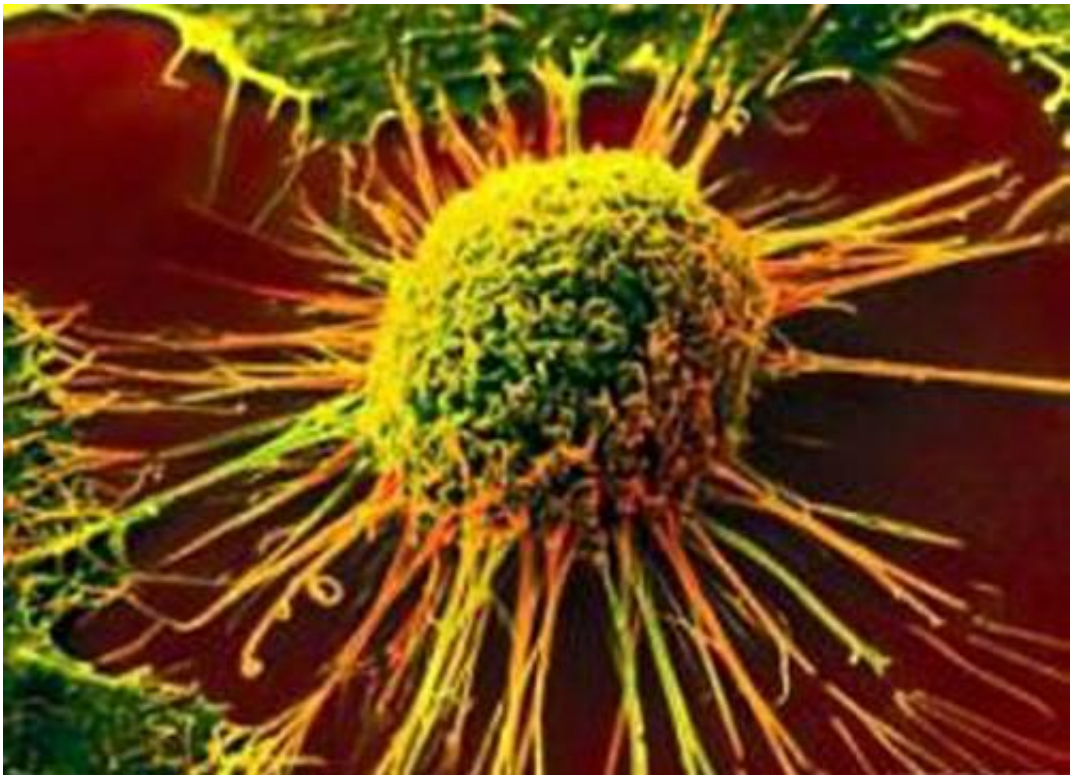

Researchers at the University of Pittsburgh School of Medicine have uncovered a novel genetic mechanism of thyroid cancer, as well as a marker that may predict response to a particular class of drugs, not just in patients with thyroid cancer, but in those with many other types of cancer as well. The new findings were published in *Proceedings of the*

National Academy of Science.

"These results further our understanding of the biology of thyroid cancer . More broadly, they also suggest a potential treatment strategy for many different types of cancer," explained lead study author Yuri Nikiforov, M.D., Ph.D., professor of pathology, vice chair for molecular pathology and director of UPMC's Division of Molecular & Genomic Pathology.

Thyroid cancer is the fastest-growing type of cancer in the U.S., and more than 55,000 people will be newly diagnosed this year. Like many other cancers, thyroid tumors usually result from specific genetic abnormalities. Although previously identified mutations are found in about 90 percent of thyroid cancers, in the remaining cases the culprit is still a mystery.

To identify new genetic abnormalities associated with thyroid cancer, Nikiforov and his team applied a powerful technology called next-generation sequencing to analyze a series of papillary thyroid carcinomas (the most common form of thyroid cancer) that did not contain any of the known mutations.

The researchers found that a significant proportion of these tumors had a complex genetic alteration involving fusion of a gene named THADA to a previously unknown region near a gene called IGF2BP3. The result of this gene fusion was elevated levels of IGF2BP3 protein, an important component of the IGF1R protein signaling pathway that is known to play a role in tumor formation and growth.

"Up until now, we knew that alterations in the THADA gene were associated with thyroid cancer, but we didn't know how this genetic change actually leads to tumor development," explained Nikiforov. "Our study uncovers a new mechanism of thyroid cancer, one that is actually quite common."

The team went on to find that elevated IGF2BP3 also was present in many other types of cancer.

"When we looked at other common cancers, such as those of the lung, pancreas, colon and ovary, we found that 5 to 15 percent of them had elevated levels of IGF2BP3," said Nikiforov.

The team then performed cell culture and animal model experiments that revealed that growth of these tumors could be blocked by IGF1R pathway-inhibiting drugs.

A number of IGF1R inhibitors have been developed and tested in more than 25 clinical trials in the last several years, Nikiforov explained. Unfortunately, these trials failed because only a small subpopulation of patients responded to the drugs, and researchers were not able to determine which tumors would be susceptible to the treatment.

"Our results suggest that we now have a genetic marker – IGF2BP3 – that may be able to tell us who will benefit from these drugs," he said. "What's really exciting is that our study could renew interest in the use of IGF1R inhibitors to treat cancer. We hope that the manufacturers of IGF1R and IGF2 inhibitors will consider initiating clinical trials for these drugs specifically in patients whose tumors show elevated levels of IGF2BP3."

More information: Federica Panebianco et al. fusion is a mechanism of IGF2BP3 activation and IGF1R signaling in thyroid cancer, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1614265114

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