Study finds known lung cancer oncogenes ALK and ROS1 also drive colorectal cancer

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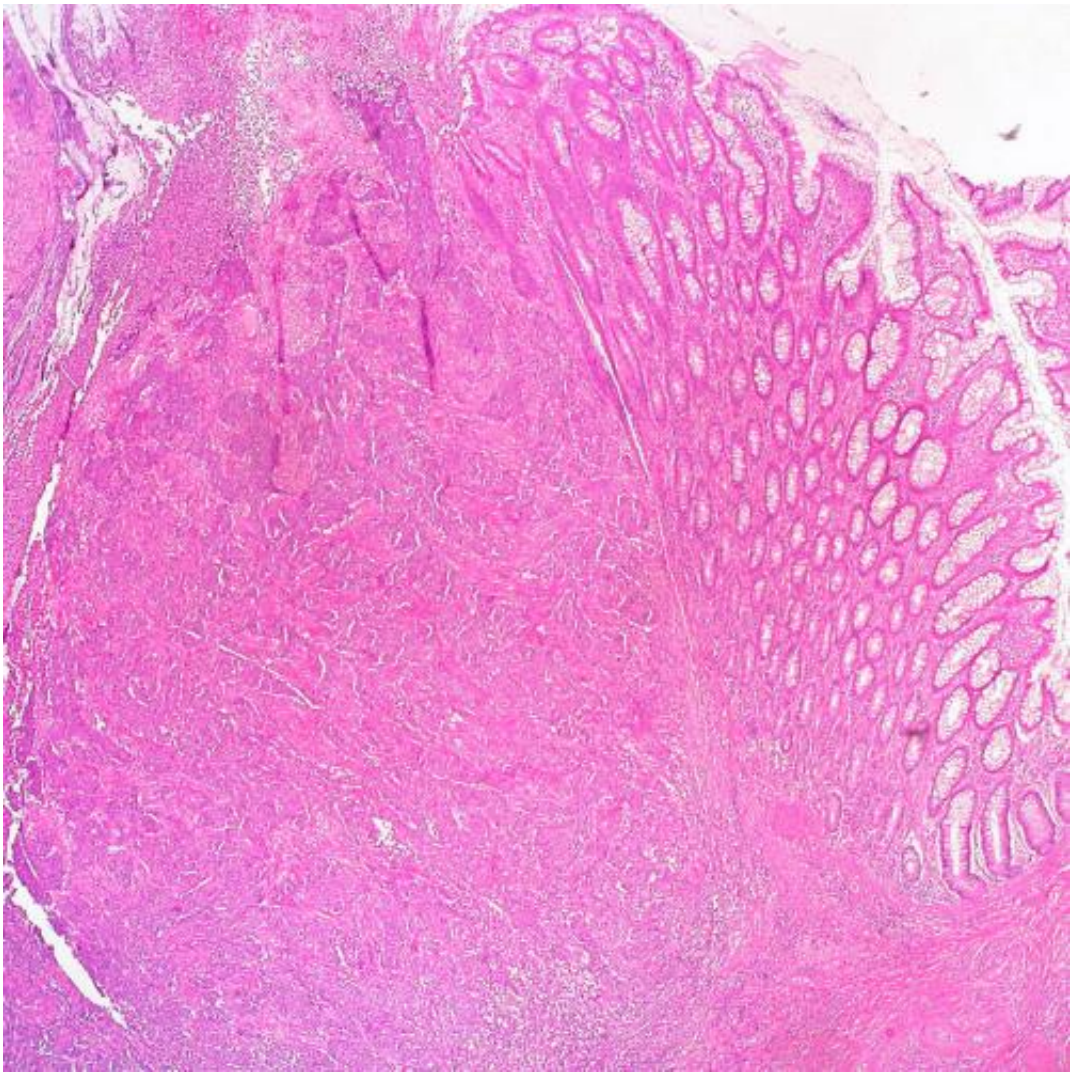

Colorectal cancer cells like these may develop from some of the same gene alterations found in subsets of lung cancer. Credit: Flickr/Euthman

A University of Colorado Cancer Center study published online ahead of print in the journal *Molecular Cancer Research* shows that ALK and ROS1 gene rearrangements known to drive subsets of lung cancer are also present in some colorectal cancers. These results imply that drugs used to target ALK and ROS1 in lung cancer may also have applications in this subset of colorectal cancer patients.

"When you have known oncogenes that are already targeted by FDA-approved drugs, it just made sense to look for these oncogenes in other cancers," says Marileila Varella Garcia, PhD, investigator at the CU Cancer Center and professor at the CU School of Medicine.

"By rethinking the way we understand cancers – as their genetic mutations and not just as the sites where they live in the body – we see that a therapy that targets a specific mutation may show benefit in treating any other cancer that shares the same mutation," says Dara Aisner, MD, PhD, investigator at the CU Cancer Center and molecular pathologist at the CU School of Medicine.

In this study, Garcia, Aisner and colleagues used the technique known as fluorescence in situ hybridization (FISH) to test for the oncogenic gene rearrangements in 236 tumor samples of colorectal cancer collected from patients enrolled in a large, Australian clinical trial. The work found one patient carrying the ALK rearrangement, confirming previous findings, and demonstrated the first finding of ROS1 as an oncogenic driver of colorectal cancer – in this case found in 2 of the 236 tumor samples.

"Even though the percentage of colorectal cancer patients with these gene rearrangements is small, the benefit to these few patients could be dramatic. It's worth the work. It's worth following this line of reasoning to its conclusion to see if colorectal cancer patients will also benefit from drugs proved effective in lung cancer," says Robert C. Doebele, MD,

PhD, investigator at the CU Cancer Center and assistant professor at the CU School of Medicine.

Surprisingly, these gene alterations tended to co-exist in colorectal tumors along with other molecular alterations –tumors that were positive for ALK rearrangements were also positive for another well-defined molecular alternation known as KRAS; ROS1 mutations occurred in one specimen along with the known, oncogenic mutation, BRAF.

"Conventional wisdom is that one molecular driver alteration exists throughout all tumor cells in a specimen, and that it's mutually exclusive of other alterations. We found that neither of those axioms held true – some tumor regions had different alterations, and even more surprisingly, in some regions both alterations were seen. These findings show that you can find more than one alteration in a single specimen, and that not all cells within a single tumor are necessarily driven by the same oncogene," Aisner says.

The group writes that "identification of ALK and ROS1 oncogenes may open new therapeutic options for CRC," specifically with the class of drugs known as tyrosine-kinase inhibitors (TKIs) shown to "turn off" ALK and ROS1 gene mutations thereby killing or slowing the growth of cancer cells. For example, the drug crizotinib was approved by the FDA in 2011 to treat ALK-positive lung cancer, and this drug or others that are in development to treat ALK+ and ROS1+ cancers may have similar benefit in CRC.

"This is a case in which we have all the background science – we know that when ALK and ROS1 improperly fuse with other genes, the result can be oncogenic. We have drugs that target these oncogenes. And we even have tests to determine who has the gene rearrangements and so should benefit from these drugs. The important piece missing was finding these oncogenes in other cancers, and now we've filled in that

piece in colorectal cancer," Aisner says.

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