Cell type switch helps colon cancer evade treatment, study suggests

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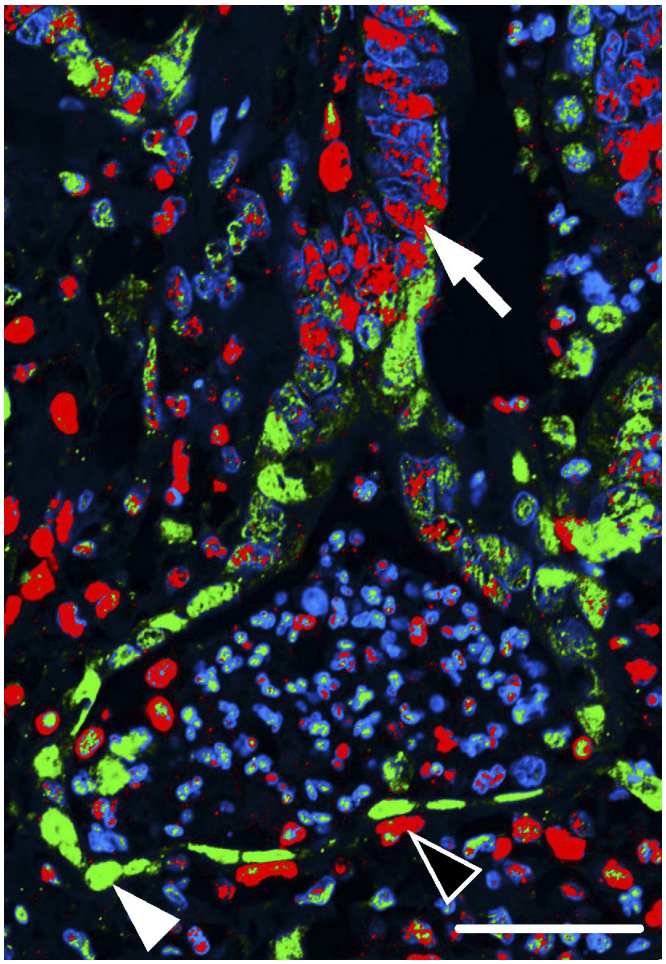


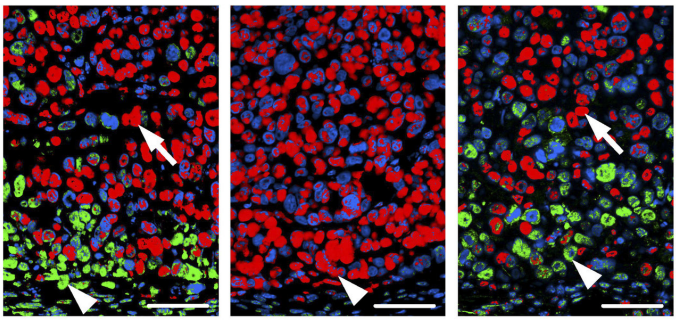
Human colon cancers contain two populations of cancer cells, one at the tumor edge in which the MAPK pathway is highly active (indicated by green staining and the white arrowhead), and one in the center of tumor in which the NOTCH pathway is activated (indicated by red staining and the white arrow). Credit: Schmidt et al., 2018

Researchers in Germany have discovered that colon cancers are often resistant to existing drug treatments because they are composed of two different cell types that can replace each other when one cell type is killed. The study, which will be published May 16 in the *Journal of Experimental Medicine*, suggests that combination therapies targeting both cell types at once may be more effective at treating colorectal cancer, the third highest cause of cancer-related death in the United States.

Early-stage colon cancers can be surgically removed but later stages of the disease require more targeted treatments, including therapies designed to block the MAPK signaling pathway that promotes colon cancer progression. "However, targeting MAPK signaling has limited effects and usually prolongs patient survival by only a few months. We therefore urgently need radical improvements in targeted therapy for patients with colorectal cancer," says Professor David Horst of the Charité University Hospital in Berlin, Germany.

One potential alternative is to target the NOTCH signaling pathway, which is also thought to drive colon cancer progression even though, in bladder cancer, it suppresses MAPK signaling. But initial trials of NOTCH pathway inhibit ors have so far yielded disappointing results.

Horst and colleagues examined over 300 patient samples and found that the NOTCH pathway wasn't activated in all colon cancer cells. Cells in the middle of tumors showed signs of active NOTCH signaling but reduced MAPK activity. This population of cells appeared to be highly proliferative. Cells at the edges of colon cancers, in contrast, showed high levels of MAPK signaling but little NOTCH pathway activity. This population of cells was less proliferative but appeared to be undergoing the initial stages of metastasis, in which colon cancer cells invade and spread to other tissues.



Human colon cancer cells injected into mice form tumors (left) consisting of both MAPK-active cells (green) and NOTCH-active cells (red). Treatment with the MAPK inhibitor selumetinib results in tumors consisting of NOTCH-active cells only (center), but after treatment is stopped, the NOTCH-active cells give rise to new MAPK-active cells, restoring the tumors' original composition (right). Credit: Schmidt et al., 2018

These two different cell types could also be seen in the tumors formed by human colon cancer cells injected into mice. The tumors quickly lost their MAPK-active cells when the researchers treated these mice with the MAPK pathway inhibitor selumetinib, but the number of NOTCH-active cells increased so that there was minimal disruption to the tumors' overall growth. And, after stopping selumetinib treatment, some of these NOTCH-active cells gave rise to new MAPK-active cells at the tumor edge.

In contrast, treatment with the NOTCH pathway inhibitor dibenzazepine eliminated NOTCH-active cells from tumors but the population of MAPK-active cells expanded and gave rise to new NOTCH-active cells once dibenzazepine treatment was discontinued.

"This suggests that colon cancers may evade targeted treatment against MAPK or NOTCH signaling by a reversible shift in the predominating pathway activity," says Horst. "However, when combining both therapies to target both cell populations, we found strong repressive effects on tumor cell proliferation and increased cell death, resulting in slower tumor growth and prolonged survival times compared to either treatment alone."

Horst and colleagues note that targeting the NOTCH pathway alone may even be detrimental to colon cancer patients, if it results in an increased number of MAPK-active cells poised to undergo metastasis.

"Our data support a new concept for cancer therapy that advocates specific and simultaneous targeting of several different tumor cell subpopulations to strongly improve therapy response," Horst says. "Further preclinical and clinical trials may therefore reveal if combined MAPK and NOTCH inhibition, in addition to established chemotherapeutic protocols, can improve therapy response in patients with colorectal cancer."

More information: Schmidt et al., 2018. *J. Exp. Med*. jem.rupress.org/cgi/doi/10.1084/jem.20171455

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