Study sets framework for precision surveillance of colorectal cancer

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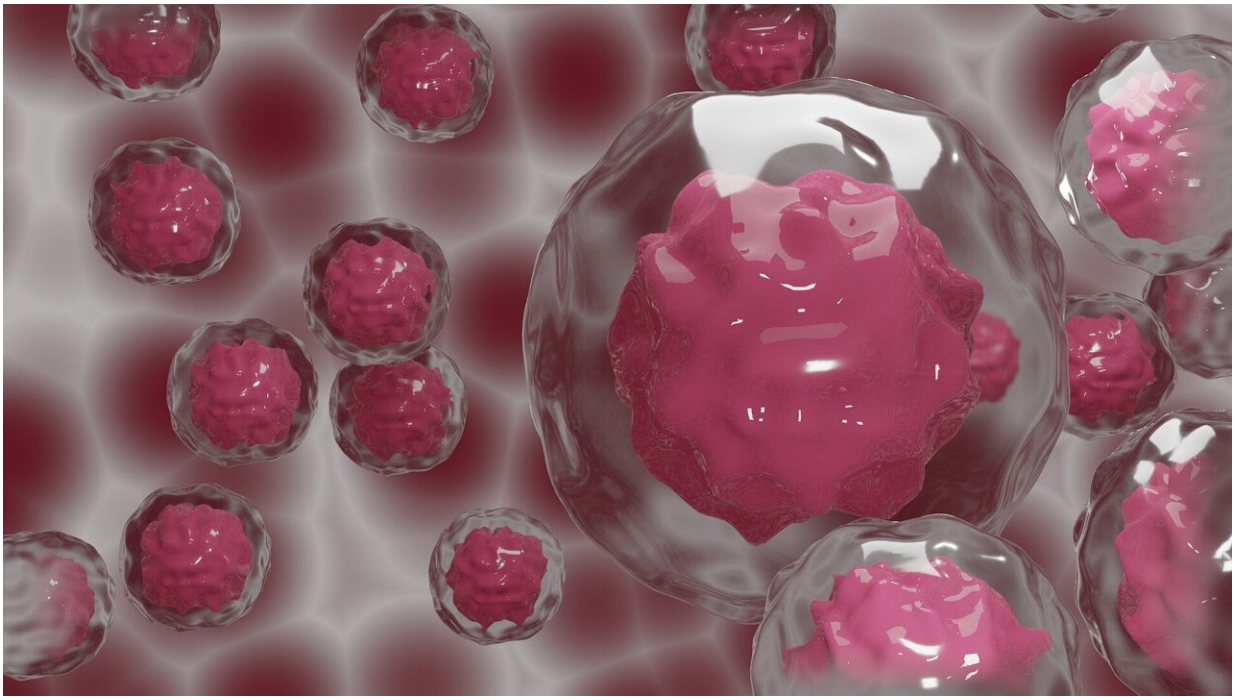

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A team of Vanderbilt researchers has revealed some of the mechanisms by which polyps develop into colorectal cancer, setting the framework for improved surveillance for the cancer utilizing precision medicine.

Their study, published Dec. 14 in *Cell*, describes findings from a single-cell transcriptomic and imaging atlas of the two most common colorectal

polyps found in humans: conventional adenomas and serrated polyps. They determined that adenomas arise from expansion of stem cells that are driven by activation of WNT signaling, which contributes to the development of cancer, while serrated polyps derive into cancer through a different process called gastric metaplasia. The finding about metaplasia, an abnormal change of cells into cells that are non-native to the tissue, was surprising, the researchers said.

"Cellular plasticity through metaplasia is now recognized as a key pathway in cancer initiation, and there were pioneering contributions to this area by investigators here at Vanderbilt," said Ken Lau, PhD, associate professor of Cell and Developmental Biology, one of the study's corresponding authors. "We now have provided evidence of this process and its downstream consequences in one of the largest single-cell transcriptomic studies of human participants from a single center to date."

The researchers did an integrative analysis of 128 datasets of tissue samples from 62 tumors. They performed single-cell RNA sequencing, multiplex immunofluorescence and multiplex immunohistochemistry on the samples, which were collected from diverse sex, racial and age groups.

The cells from serrated polyps did not exhibit WNT pathway activation nor a stem cell signature. Moreover, the researchers observed that these cells had highly expressed genes not normally found in the colon, leading them to hypothesize that metaplasia plays a role in how serrated polyps become cancerous. The researchers observed in the serrated-specific cells highly expressed genes not normally found in the colon but are expressed in the stomach, including MUC5AC, AQP5, TACSTD2 (TROP2), TFF2, MUC17 and MSLN.

"We propose a new paradigm in which damage to the proximal colon,

possibly from microbiota, initiates a metaplastic cascade that may eventually select for survival/proliferative pathways, such as activating mutations in BRAF," the researchers wrote in the paper.

Bob Chen, a Vanderbilt University graduate student, and Cherie' Scurrah, PhD, are the paper's co-first authors.

The study provided a number of other findings of clinical significance. For instance, sessile serrated lesions can be challenging to identify, and the study suggest biomarkers that may confirm their diagnosis. The study revealed much about the mechanisms of sessile serrated lesions in regulating the tumor immune landscape.

"The findings in our atlas lay the foundation for opening novel strategies for interception of cancer progression, including better surveillance protocols, chemoprevention and pre-biotic and pro-biotic therapies" said Martha Shrubsole, PhD, research professor in the Division of Epidemiology, and a corresponding author.

The Vanderbilt research was supported by the Human Tumor Atlas Network grant from the Cancer Moonshot initiative of the National Cancer Institute and other funding from the National Cancer Institute, the Congressionally Directed Medical Research Program of the U.S. Department of Defense, Cancer UK, Janssen, and the Nicholas Tierney GI Cancer Memorial Fund.

"This massive effort is only made possible through the close collaboration of a multidisciplinary team, integrating expertise from the Vanderbilt University Basic Sciences, the Vanderbilt University Medical Center Epithelial Biology Center, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center," said Robert Coffey, Jr., MD, Ingram Professor of Cancer Research, professor of Medicine and Cell and Developmental Biology, and a corresponding author.

More information: Bob Chen et al, Differential pre-malignant programs and microenvironment chart distinct paths to malignancy in human colorectal polyps, *Cell* (2021). DOI: 10.1016/j.cell.2021.11.031