Researchers discover disruptions in signaling pathways that enable colorectal cancer cells to form metastases

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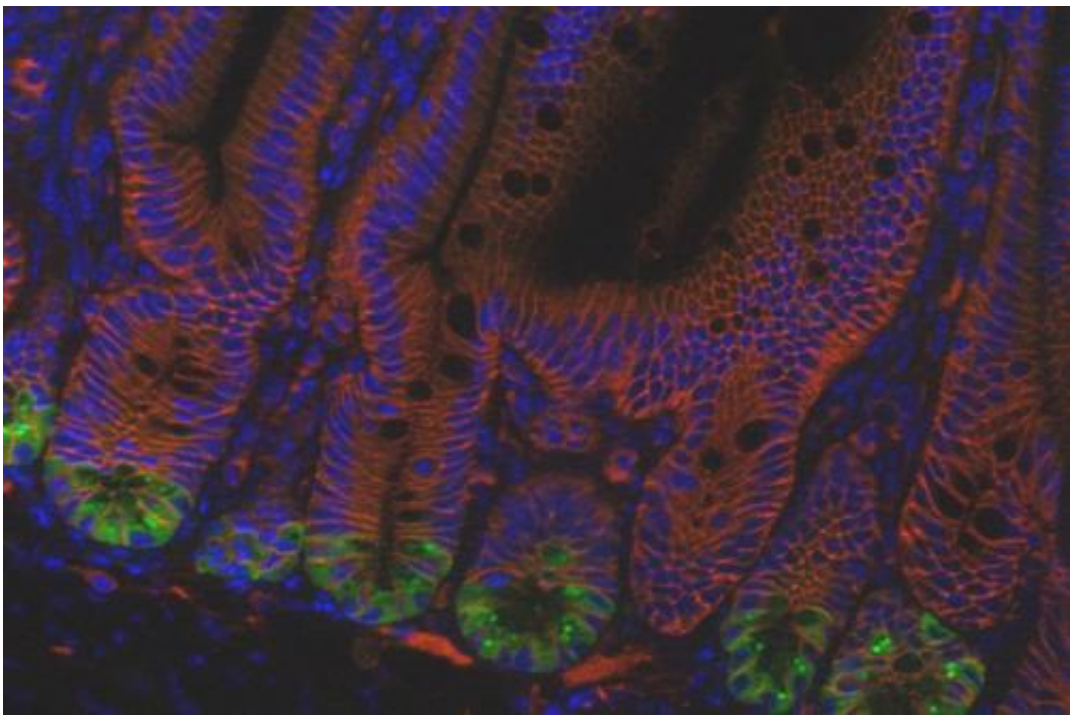

Healthy colorectal tissue is highly structured: Adhesion proteins like e-cadherins (red) hold the cells together, while EPHB receptors dictate where cell types like secretory cells are found in the tissue. Credit: Andreas Hecht

Researchers at the University of Freiburg have found switches that colorectal cancer cells use to migrate away from the primary tumor site and to invade neighboring tissue. This migration is the first step in

metastasis, the process by which the cancer forms secondary tumors in other organs. Prof. Dr. Andreas Hecht and his research group at the Institute of Molecular Medicine of the University of Freiburg published their findings in the journal *Proceedings of the National Academy of Sciences* (*PNAS*).

The researchers hope to develop new diagnostic and therapeutic approaches for colorectal cancer on the basis of the newly discovered signaling events. Hecht is a member of the Cluster of Excellence BIOSS Centre for Biological Signalling Studies as well as the collaborative research center "Control of Cell Motility in Morphogenesis, Cancer Invasion, and Metastasis."

Colorectal cancer is one of the most common forms of cancer worldwide. Principally, tumors in the intestine can be removed and initially the disease poses a limited threat. This changes dramatically when the tumor cells begin to spread beyond the gut and migrate via blood vessels into further tissues to form metastases. These secondary tumors are often difficult to find and to remove and can lead to organ failure or even death. In order to prevent a tumor from forming these dangerous metastases, it is necessary to understand how cancer cells manage to break the chains that hold normal cells in place in the body.

Proteins on the surface of healthy intestinal cells, so-called ephrin receptors, are responsible for instructing specific cell types like secretory cells or stem cells which position to occupy in the tissue. They perform this task when activated through contact with adjacent cells. The ephrin receptors thereby inform cells about their neighborhood: Depending on whether the neighborhood suits the cell, it stays or moves on. In cancer cells, it is known that ephrin receptors control a signaling pathway that prevents the cells from going astray. In order to break free from the primary tumor cell mass, the tumor cells shut down the production of the receptors, particularly that of the proteins EPHB2 and EPHB3. How

they do this was previously unclear.

The researchers found DNA regions in the ephrin receptor genes that regulate the amount of EPHB2 and EPHB3 on cells. These so-called enhancers are switched off in intestinal tumor cells that form metastases. One of the causes is an error in regulatory networks of tumor cells involving the protein Notch. The researchers also showed that the Notch signaling pathway is deactivated in tumors that have a poor prognosis. Determining whether the Notch signaling pathway and EPHB regulation are intact provides an indication as to how dangerous the tumor might be and could thus help doctors to make a more precise diagnosis.

More information: S. Jägle, K.Rönsch, S. Timme, H. Andrlová, M. Bertrand, M. Jäger, A.. Proske, M. Schrempp, A. Yousaf, T. Michoel, R. Zeiser, M. Werner, S. Lassmann, and A. Hecht; Silencing of the EPHB3 tumor-suppressor gene in human colorectal cancer through decommissioning of a transcriptional enhancer *PNAS* 2014 ; March 18, 2014, DOI: 10.1073/pnas.1314523111

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