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New strategic approach against bowel cancer

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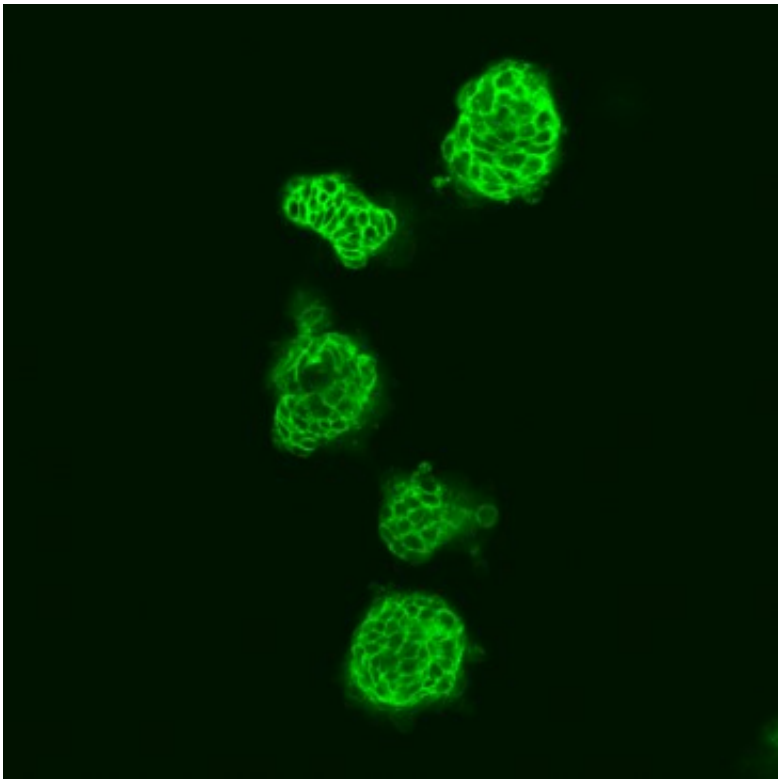

Cells of the colorectal cancer cell line Colo-205 grown in 3D tissue culture. Following treatment with the B-Raf inhibitor PLX4720, these cells form compact spheroids with high levels of the cell adhesion molecule E-cadherin (green staining). Credit: Ricarda Herr/AG Brummer

Colorectal carcinoma is the most frequent type of bowel cancer and the second most common tumour disease among men and women in Germany. So-called microsatellite stable colorectal cancer with mutations in the BRAF gene represents a particularly aggressive form.

The BRAF gene produces the enzyme B-Raf, which plays a critical role in controlling cell division. A team of researchers from Freiburg and Stuttgart including the Freiburg biologists Dr. Ricarda Herr and Dr. Tilman Brummer analysed the effect of B-Raf inhibitors on the behaviour of colorectal cancer cells in three-dimensional tissue culture. Their findings show that B-Raf inhibitors cause the cancer cells to differentiate into cells that are characterised by more mature features and specialised to fulfil a specific function. Importantly, more differentiated cells often display a less aggressive behaviour. Hence, combination strategies, which are currently in clinical trials and involve B-Raf inhibitors, might be able to prevent the cancer from spreading to other parts of the body.

The researchers published their findings in the journal *Cancer Research*.

Usually, B-Raf is regulated by the signalling network in our cells. This tight control ensures that B-Raf is only activated under particular circumstances. Mutations in the BRAF gene lead to the production of a mutant protein that is no longer controlled and always active. A cell that has acquired such a mutation is switched into the cell division mode, multiplies constantly and has initiated a sequence of events ultimately leading to cancer. There are several drugs that predominantly inhibit the mutant B-Raf. They specifically target the cell division mode in the tumour cells, while largely sparing healthy cells. These drugs have become a standard therapy for BRAF mutant metastatic melanoma, a kind of skin cancer. However, very little was known about how these drugs act on other types of cancer such as BRAF mutant colorectal cancer for which only very limited therapeutic options are available.

To gain more insight on this, Brummer, Herr and their team used a three-dimensional tissue culture. This experimental system recapitulates many biological processes more reliably than conventional in vitro methods. As expected, the cell division rate of these cells was strongly reduced by

B-Raf inhibitors. Importantly, the researchers identified a novel aspect of B-Raf inhibitors by showing that they not only reduce the division rate of cancer cells, but also induce their differentiation into cells with more mature features. Vice versa, when the mutant B-Raf was introduced into colorectal cancer cells lacking the BRAF mutation, a more undifferentiated cell type was observed. This points to an aggressive tumour, which is often undifferentiated and has a greater risk to metastasize. Initial experiments in cell culture showed that B-Raf inhibitors reduce the migratory and invasive behaviour of cancer cells, two important prerequisites for metastasis. Brummer's team attributes this less aggressive behaviour to the observation that drug treated colorectal cancer cells increasingly produce cell-cell adhesion molecules. These molecules are located at the cell surface and glue neighbouring cells together, thereby preventing cancer cells from breaking away from the primary tumour and to initiate metastasis.

First small clinical trials in colorectal cancer patients suggested that B-Raf inhibitors as single agents might not be as effective in blocking cell division in this disease as it is observed in melanoma. Nevertheless, the findings published by Brummer's team suggest that a combination of B-Raf inhibitors with other therapeutics might be more potent. This concept will be further pursued by follow-up studies.

Brummer is leading a research group at the Institute of Molecular Medicine and Cell Research of the University of Freiburg. He is also a member of the Cluster of Excellence BIOSS Centre for Biological Signalling Studies and a principal investigator within the Collaborative Research Centre 850 at the University of Freiburg. Herr is a postdoctoral researcher in Brummer's laboratory.

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