

No. 5

February 2, 2017 (AM)

### **DKTK Berlin: The Variety of the Tumor in 3D**

**During its formation, every tumor receives a specific genetic profile, which can be utilized for personalized cancer therapy. But even within one tumor, various regions can develop which have distinct features. By making a three-dimensional tumor model, researchers at the German Cancer Consortium (DKTK) at the Charité Medical University of Berlin, at the Carl Gustav Carus University Hospital in Dresden, and at the Technical University in Munich, were able to show for the first time how cancer-relevant genes in colorectal cancer are amplified in specific tumor regions. The results could help to improve routine molecular diagnostics. The DKTK is made up of the German Cancer Research Center (DKFZ) in Heidelberg as the core location, along with renowned oncology departments of universities in various partner locations across Germany.**

“Cells of one and the same tumor can have very different genetic properties and therefore also respond to therapy quite differently,” explained Christine Sers of the Berlin Charité, the leader of the study published in the science magazine Nature Communications. It was not previously known, just what sort of pattern these genetic differences adhered to.

In order to find that out, the researchers dissected a colon tumor into 68 samples from various tissue regions and analyzed the one hundred most frequently altered genes. Afterwards, they reconstructed the spatial layout of the genetic differences in a three-dimensional model. “Due to the high resolution, it was even possible to discern the genetic differences that were only present in a small percentage of the tumor cells,” emphasized Soulafa Mamlouk, principal author of the study.

Interestingly, the individual tumor regions differed only slightly in the manner and number of coding mutations, but showed highly variable gene copy numbers in numerous genes. The researchers found countless gene copy numbers in the transition area from the outer to the inner tumor region, among them the gene BRCA2, which plays a decisive role in breast cancer. They also found a high number of gene copy gains, such as for the HDAC2 gene, which encodes a central enzyme in gene regulation, in the invasive tumor area – the area which grows into neighboring healthy tissue.

Depending on the stage, the tumors heterogeneity was defined primarily by the gene copy numbers. This became clear when the researchers compared the primary tumor with the various metastases of 27 patients. Genes such as CDX2 and WFDC2, which facilitate metastasis development and tumor growth, were amplified in the metastases, while the tumor suppressor gene SMAD4 had a particularly low gene copy number.

“Our results indicate that tumor progression and therapy behavior are defined by gene amplification and gene deletion,” said Christine Sers. “Tumor cells where entire chromosome sections or whole genes are being amplified, are genetically particularly adaptable and could possibly become resistant to therapy more quickly.” The study also shows, that current biopsies don’t always provide enough information about all tumor features. The results of the researchers could help to create more nuanced profiles and improve current routine diagnostics.

Mamlouk, S. et. al.: DNA copy number changes define spatial patterns of heterogeneity in colorectal cancer. In: Nature Communications (25 January 2017) [Doi:10.1038/ncomms14093](https://doi.org/10.1038/ncomms14093)

Pictures and video for press releases may be downloaded at:

[www.dkfz.de/de/presse/pressemitteilungen/2017/bilder/BRCA2-rotation.jpg](http://www.dkfz.de/de/presse/pressemitteilungen/2017/bilder/BRCA2-rotation.jpg)

[www.dkfz.de/de/presse/pressemitteilungen/2017/bilder/Supplementary-movie.gif](http://www.dkfz.de/de/presse/pressemitteilungen/2017/bilder/Supplementary-movie.gif)

Caption for the picture:

The three-dimensional tumor model shows in which areas the copy number of the gene BRCA2 is changed in the CRC tumor. The researchers found a high gene copy number in the inner tumor area (dark red), while the copy number in some outer areas was barely increased (light red) or remained unchanged (white).

Caption for the video:

Rotating CRC tumor in 3D: Two different gene clusters (green and violet) show a spatially separated pattern of gene amplification in the CRC tumor.

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\* The German Cancer Consortium (DKTK) is a joint long-term initiative involving the German Federal Ministry of Education and Research (BMBF), participating German states and the German Cancer Research Center (DKFZ) and was established as one of six German Health Research Centres (DZGs). As DKTK's core center the DKFZ works together with research institutions and hospitals in Berlin, Dresden, Essen/Düsseldorf, Frankfurt/Mainz, Freiburg, Munich, Heidelberg and Tübingen to create the best possible conditions for clinically oriented cancer research. The consortium promotes interdisciplinary research at the interface between basic research and clinical research, as well as clinical trials for innovative treatments and diagnostic methods. Another key focus of the consortium's work is on developing research platforms to speed up the application of personalized cancer treatments and to improve the diagnosis and prevention of cancer.

More information is available at [www.dktk.org](http://www.dktk.org)

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