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Scientists can predict in the lab whether a drug will be effective for individual colorectal tumours

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Colorectal carcinomas arise in different forms, so all treatments do not work for all patients. OncoTrack, a public-private consortium supported by the Innovative Medicines Initiative Joint Undertaking, has conducted one of Europe's largest collaborative academic-industry research projects to develop and assess novel approaches for identification of new markers for colon cancer. Scientists from the OncoTrack Consortium, including researchers from the Max Planck Institute for Molecular Genetics in Berlin and the Institute's spin-off Alacris Theranostocs, have analysed tumour samples from patients with this type of cancer in a preclinical study. In particular, the scientists looked for biomarkers, i.e. molecules that are typical of the different tumour sub-groups and provide valuable information for diagnosis and potential treatment. Among other things, the research team discovered molecules that can predict the effectiveness of two drugs commonly used to treat this disease: Cetuximab, which inhibits the receptor for the epidermal growth factor (EGFR), and the chemotherapy drug 5FU.

Bowel cancer is the third most common form of cancer in the world and 95 percent of cases are colorectal carcinomas. At an advanced stage they are one of the most common causes of death, as only some patients respond to drug treatment. The experts do not know all the precise reasons for this, but this much is clear: "Colorectal carcinomas are a very heterogeneous group of cancers, and because of this the effectiveness of the available drugs varies," explains Marie-Laure Yaspo, a researcher at

the Max Planck Institute for Molecular Genetics in Berlin and lead author of the recently published study. "Although we already know about molecular sub-groups, we do not yet fully understand the causal relationships between those molecular patterns and their response to treatment." However, to be able to predict a tumour's response to certain drugs more accurately, scientists require detailed information about the molecular profiles of the patient and their tumour.

Medical scientists working at the Charité University Hospital in Berlin and University Hospital Graz collected tumour samples from over 100 colorectal cancer patients at different stages of the disease for their study.

These tumours were then grown in tissue culture systems, as well as in special mouse strains, and subsequently treated with a range of medicaments. Through this, the scientists were able to better understand the relationships between the molecular pattern and the response of the tumour to drugs. "The number of tumours analyzed in this way using matched tumour models exceeds all previous studies by far," says Yaspo.

RNA molecules for identifying tumour type RNA

The scientists identified the genetic composition of the tumours and analysed their so-called transcriptome, namely the set of all RNA molecules synthesized in a given tissue. Based on this analysis, they were able to produce a definite molecular fingerprint for all of the tumours. Yaspo and her colleagues at EPO-Berlin and at Eli Lilly-Madrid then tested how the tumours responded to different drugs and in this way correlated the tumour fingerprints with their response to the different clinical compounds.

If a group of tumours could be successfully treated using a drug, the scientists looked for typical biomarkers for this tumour type. Up to now,

doctors have decided for and against the use of a drug directed against the EGF receptor mainly based on gene mutations. However, the mutation status alone is not specific enough. The knowledge of additional biomarkers could help to improve the individual treatment of cancers.

Selection of most suitable therapy

The consortium team identified two such biomarkers, which predict whether either the EGFR inhibitors Cetuximab or the chemotherapy 5FU could trigger a successful response in colorectal cancer. "Through our analyses we learned a lot about the type of colorectal cancer that responds to these drugs. This means that rather than relying on the mutation status alone, we now have much more information on which to base decisions about treatment," explains Yaspo. The scientists now know the molecular profile of the tumours, which are more likely to be successfully treated with these drugs.

"This pre-clinical analysis comparing tumours and their models provided us with the most detailed data on colorectal carcinomas available to date," says Yaspo. "Based on these findings it will be possible to develop diagnostic tools that will provide better predictions of the effectiveness of drugs. This means that in the future it may be possible to treat colorectal cancer patients more individually based on the type of tumour they have."

More information: Moritz Schütte et al. Molecular dissection of colorectal cancer in pre-clinical models identifies biomarkers predicting sensitivity to EGFR inhibitors, *Nature Communications* (2017). DOI: 10.1038/ncomms14262

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