Colorectal cancer: lipids can predict treatment efficacy

A UNIGE team has identified lipid signatures associated with chemotherapy-resistant cells, paving the way for new treatment strategies

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Illustrative image, generated by artificial intelligence, showing chronic exposure to FOLFOXIRI (top), which induces significant lipidomic alterations in colorectal cancer cells (bottom).

High resolution pictures

Colorectal cancer, the second most common cause of cancer-related death, affects almost 2 million people worldwide every year. It is mainly treated with chemotherapy, but its effectiveness decreases over time due to the progressive resistance of tumor cells. A team from the University of Geneva (UNIGE) has identified specific alterations in certain lipids in cancer cells resistant to chemotherapy. These lipid signatures could serve as prognostic markers for understanding resistance to treatment and pave the way for personalized, targeted strategies to restore drug sensitivity. This work is published in the *International Journal of Molecular Sciences*.

Every year, almost 2 million people are diagnosed with colorectal cancer worldwide. By 2040, this number could exceed 3 million, which could increase the number of deaths from 700,000 to 1.6 million. This poor prognosis results from the disease often being discovered late, as symptoms do not appear immediately.

Its treatment, at an advanced stage, is mainly based on a combination of chemotherapies called FOLFOXIRI. It has significant side effects, and its effectiveness varies greatly from one individual to another. Above all, cells that make up tumors gradually become insensitive to it, eventually developing resistance. Preventing or overcoming this process is one of the major challenges in oncology research.

A lipid "signature"

The team led by Prof. Patrycja Nowak-Sliwinska, Associate Professor in the School of Pharmaceutical Sciences at the UNIGE Faculty of Science, has carried out several research projects on this issue. After developing drug combinations (2022) that could potentially "bypass" this resistance, and then artificial tumors to test the effectiveness of treatments (2023), the team demonstrated that cancer cells that have become resistant to FOLFOXIRI display specific changes in certain lipids.

"The identification of altered lipid species could serve as potential prognostic markers of chemotherapy resistance. Additionally, understanding these changes may help to develop new treatment strategies to overcome this resistance, and may play a crucial role in restoring drug sensitivity," explains Dr. George M. Ramzy, Research and Teaching Fellow in the School of Pharmaceutical Sciences at the UNIGE Faculty of Science, and first author of the study.

To achieve these promising results, Prof. Nowak-Sliwinska's team collaborated with the group headed by Serge Rudaz, Full Professor in the School of Pharmaceutical Sciences. Four cancer cell lines from four patients were studied, each with a different genetic profile. In the laboratory, some of these cells were exposed to FOLFOXIRI for up to 60 weeks, the time required for them to develop resistance to the treatment, as observed in clinical settings. Another part of the sample was left untreated. "We then analyzed and compared the lipid profile, known as the "lipidome", of the cancer cells that were resistant to this chemotherapy with those that had not received any treatment," explains Prof. Patrycja Nowak-Sliwinska, who led the study.

Using an "in-house" algorithm

"Untargeted lipid profiling was performed using liquid chromatography coupled with high-resolution mass spectrometry to distinguish between the different lipid subspecies," explains Dr. Isabel Meister, Research and Teaching Fellow in the School of Pharmaceutical Sciences at the UNIGE Faculty of Science and co-author of the study.

For data analysis and interpretation of the different lipid alterations, the team used a specially designed algorithm to differentiate common and specific variations between the lipidomes of cells sensitive and resistant to FOLFOXIRI. "The high dimensionality of the data and the various sources of variability in the lipidomic signatures were efficiently handled using an approach that combines experimental design and factor analysis," explains Dr Julien Boccard, Senior Lecturer in the School of Pharmaceutical Sciences at the UNIGE Faculty of Science.

Inter-individual variation

In a first cell line, this method revealed that resistance was associated with an increase in triglycerides and cholesterol esters. In the other three lines, it was associated with an increase in phospholipids. "These differences can be explained by the different genetic profiles of each individual. Every patient is different. This explains the variability in the effectiveness of treatments, and therefore the importance of a personalized approach" explains George M. Ramzy.

While these results pave the way for personalized treatment strategies or treatments aimed at restoring sensitivity to chemotherapy, they are not yet applicable in clinical settings. Before taking this step, they will have to be tested directly on freshly isolated tumor samples, rather than laboratory cell lines.

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DOI: 10.3390/ijms26031169