New multimodal signature could predict immunotherapy success

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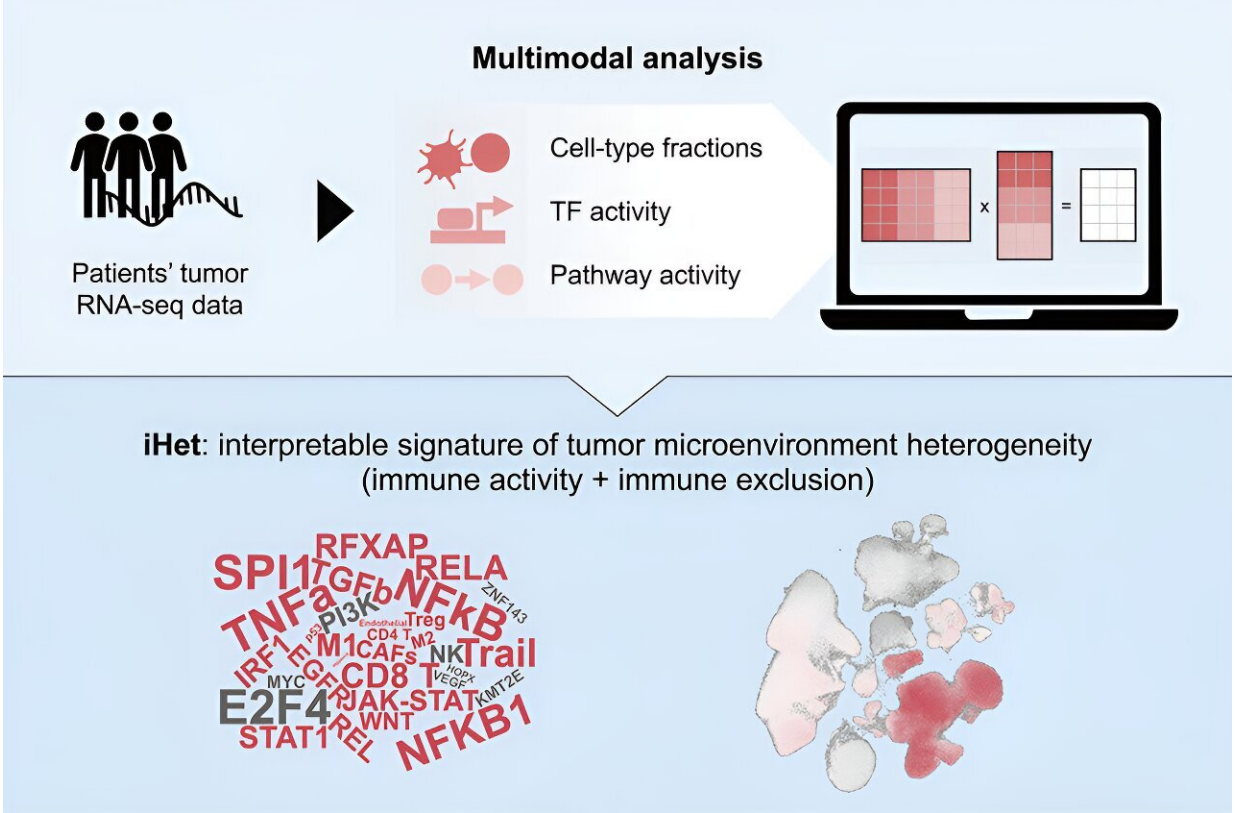

Credit: *iScience* (2024). DOI: 10.1016/j.isci.2024.110529

An international team of researchers led by Francesca Finotello from the Digital Science Center (DiSC) and the Department of Molecular Biology has derived a molecular signature from tumor transcriptomics data that

quantifies the main sources of heterogeneity in the tumor microenvironment.

This innovative signature, which the researchers call iHet, offers deeper insights into patients' responses to immunotherapy and could improve cancer treatments.

"Tumors exhibit a remarkable heterogeneity in their cellular and molecular structure. This diversity makes treatment considerably more difficult," says bioinformatician Francesca Finotello from the Digital Science Center and the Department of Molecular Biology, and lead author of the recently published article in the journal *iScience*.

Together with colleagues from the Medical University of Innsbruck, the Universities of Eindhoven (NL) and Leiden (NL) and University College London, she has developed the iHet signature. This signature is associated with anti-tumor immunity in various types of cancer and makes it possible to precisely predict how well a patient will respond to immunotherapy.

Immunotherapy success

Immunotherapies have become increasingly important in the treatment of cancer in recent years. Instead of attacking cancer cells directly, immunotherapy targets the body's own immune system, supporting it in the fight against cancer. "Unfortunately, it is very difficult to predict whether a patient will respond to immunotherapy or not. This is also due to the heterogeneity of the tumor microenvironment, and this is precisely where we come in," says Finotello.

In the current study, the researchers led by Finotello used a systems biology approach to analyze the heterogeneity of the tumor microenvironment. They analyzed transcriptomic data from lung cancer

samples, specifically non-small cell lung carcinomas, from more than 1,000 patients. Using a special method called multi-omics factor analysis (MOFA), they were able to identify the main sources of heterogeneity in the tumor microenvironment.

"We first derived some interpretable, high-level features from these samples that inform us on which cell types are present and which transcription factors and pathways are active in the tumor microenvironment. We then used MOFA to determine which features vary most within and between tumors and derived the iHet signature.

"By analyzing more than 6,000 patient samples, we were able to show that this signature is also conserved in other types of cancer and is associated with cancer immunity," explains the bioinformatician.

More accurate prediction

A significant aspect of the current work is the improved predictive accuracy of potential treatment success, particularly through the integration of digital pathology data to distinguish in the iHet signature "good" mechanisms—which underlie anti-cancer immune activity—from "bad" mechanisms—i.e., negative feedback mechanisms that arise as a response in the tumor to keep our immune system in check.

"We specifically used digital pathology data to correct for features in the iHet signature that are associated with the exclusion of immune cells from the tumor," explains Finotello.

"An important contribution—in addition to the prediction of patients' clinical outcome—is the interpretability of the signature, which opens the door to more in-depth analyses of the factors that determine the success or failure of immunotherapy and that could be targeted to

improve the clinical efficacy of therapies."

More information: Óscar Lapuente-Santana et al, Multimodal analysis unveils tumor microenvironment heterogeneity linked to immune activity and evasion, *iScience* (2024). DOI: 10.1016/j.isci.2024.110529

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