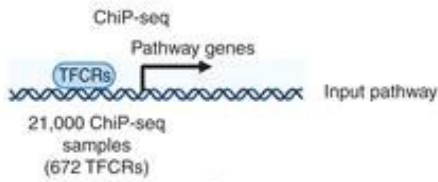


Big data and AI meet cancer research

March 23 2023, by Michele W. Sequeira

A

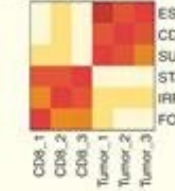
Regulator module
Identify regulator of an input pathway



TFCR's potential to regulate the input pathway

Immune module
Identify immunomodulatory TFCRs preferentially active in cancer cells

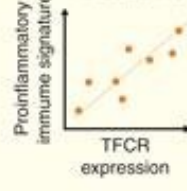
Single cell transcriptome & chromatin



TFCR's preferential activity

Active in cancer cells Active in CD8⁺T cells

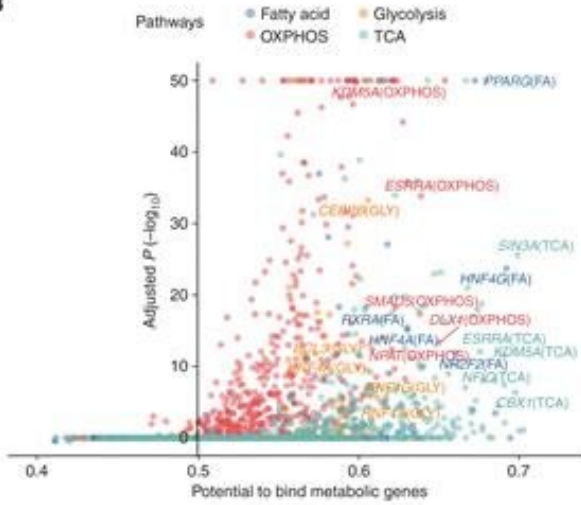
Bulk tumor transcriptome



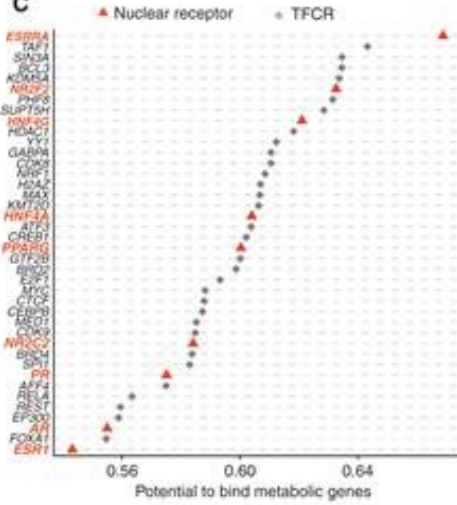
TFCR's immunomodulatory potential

Immuno-stimulatory Immuno-suppressive

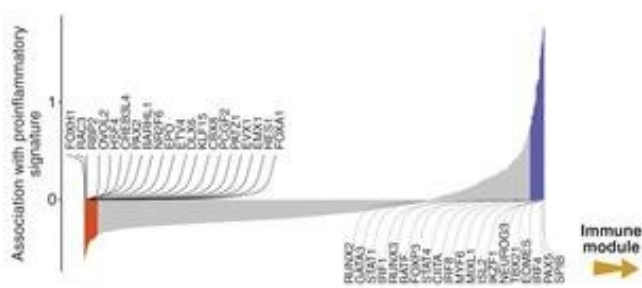
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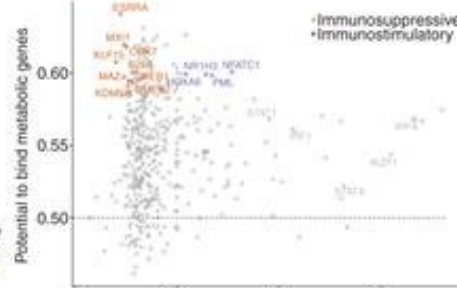
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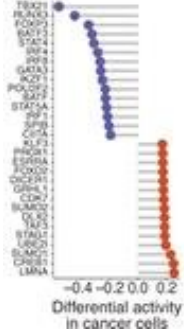
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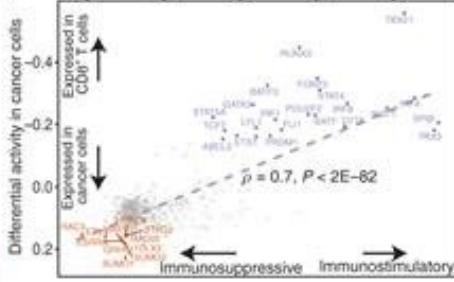
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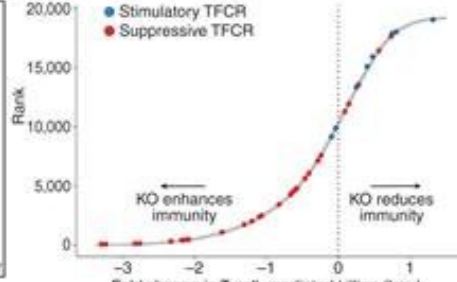
E



F



H



Identification of immune–metabolic regulators. A, Overall schematic of regulation and immune modules of BipotentR. The regulator module identifies regulators of an input pathway using ChIP-seq data. The immune module identifies TFCRs that show immunostimulatory or immunosuppressive properties in bulk tumor transcriptomes and are preferentially active in cancer cells (using single-cell tumor transcriptomes). B, Output of BipotentR regulator module. Potential and significance of regulators to bind cis-regulatory elements of genes in four energy metabolism pathways. Each dot indicates a regulator, colored by individual pathways. OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle. C, The potential of top predicted master regulators to bind energy metabolism genes. Nuclear receptors are displayed in red. D, TFCRs with positive (or negative) associations with proinflammatory signatures are predicted immunostimulators (purple; or immunosuppressors, orange). E, Top TFCRs predicted to be preferentially active in cancer cells (orange; or CD8⁺ T cells, purple) and their differential activity (estimated from single-cell data). F, Output of BipotentR immune module: combined association with proinflammatory signatures (D, estimate from bulk RNA-seq) and differential activity in cancer cells (E, estimate from single-cell data) are displayed for each TFCR. G, Immune–metabolic regulators identified by BipotentR. Energy regulatory potential (estimated by regulator module) and immune-modulatory potential (estimated by immune module) of TFCRs. Highlighted TFCRs are significant and among the top 15% in both modules. Immunostimulators (purple) and immunosuppressors (orange) are colored. H, Validation of BipotentR-identified targets. Effect of knockout (KO) of target identified by BipotentR on T cell–mediated killing of cancer cells. Credit: *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-22-0244

Many cancer patients undergo treatment with multiple drugs, each of which attacks cancer in a different way, so the combination fights cancer on many fronts. But more drugs mean higher risks of side effects.

"Most [cancer therapy](#) is now a combination treatment," says Avinash (Avi) Sahu, Ph.D., assistant professor at The University of New Mexico Comprehensive Cancer Center. Sahu joined UNM from Harvard and Dana-Farber Cancer Institute. "We wanted to find drugs that could suppress two cancer-causing pathways at the same time."

But instead of spending hours in a lab, Sahu turned to his computer.

Sahu and his research team created two approaches. The first, called BiopotentR, uses publicly available genomic data to find drugs that can attack cancer in multiple ways and identify genes that the drugs target. The second applies [machine learning](#) methods to this information to predict how people will respond to immunotherapy. Their work is published in *Cancer Discovery*.

Machine learning is similar to the way people learn. Just as people learn new things—such as riding a bike or driving a car—through lots of experience, computer-driven machine learning assimilates vast amounts of data and gleans patterns that it can then apply to other tasks.

But cancer research data alone wasn't enough for Sahu and his team to predict how people would respond to a drug. They needed additional biological data that they could then apply to [cancer patients](#) and cancer drug responses. In machine learning terms, they needed to learn from the biological context and apply that knowledge to a cancer context; it's a technique called transfer learning.

Sahu and his team partnered with a company to find a compound that would target the top cancer gene candidate they identified using BiopotentR. In preclinical testing, they confirmed that their predictions were accurate.

But the work can be expanded, Sahu says.

"When tumors have overactive multi-functional drug targets, patients are less likely to respond to immunotherapy," he says. "However, patients with these types of tumors could potentially benefit from a combination of immunotherapy and multi-functional drugs."

The team's work is not limited to just metabolism and immune targets; it can be tailored to explore any two factors to find better multi-purpose drugs. Sahu says this approach thus presents an exciting opportunity for new research in a variety of [cancer](#)-focused projects.

And faster [drug](#) discovery means more accurate personalized medicine.

More information: Avinash Sahu et al, Discovery of Targets for Immune–Metabolic Antitumor Drugs Identifies Estrogen-Related Receptor Alpha, *Cancer Discovery* (2023). [DOI: 10.1158/2159-8290.CD-22-0244](#)

Provided by University of New Mexico Comprehensive Cancer Center

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