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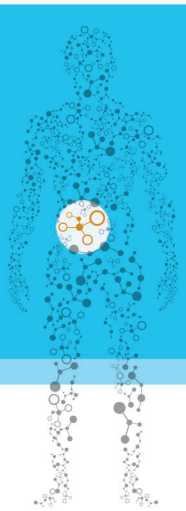

METABOLOMICS EXPANDS THE PRECISION ONCOLOGY TOOLBOX

Precision oncology has a variety of definitions. In the simplest terms, it is an approach that identifies and targets the molecular drivers of cancer cells and matches patients to therapeutic treatments that specifically block those drivers.

Because cancer is a genomic disease, genomic profiling is an undeniably important tool for precision oncology. It was central to identifying the molecular drivers of BRAF in melanoma and ALK in non-small cell lung cancer, for example.

Genomics, however, is frequently insufficient for identifying tumor-specific targets and delineating responders to targeted therapies. In fact, an assessment of the clinical utility of genomic and proteomic data across tumor types concluded that molecular data only slightly improved clinical predictions over and above standard clinical variables.[1]

This is because most cancers are the product of a cocktail of mutated genes operating collectively toward initiation, progression and maintenance. Separating the key oncogenic driver mutations from the less significant or passenger mutations is a major challenge.

What's more, many tumors demonstrate a plasticity/redundancy of signaling pathways that can be "re-routed" around a therapeutic blockage point to preserve key oncogenic functions (the use of BRAF inhibitors in metastatic melanoma is a prime example). This has led to the emergence of treatment resistance in targeted, genomic-focused therapeutics and forced clinicians to use multiple cancer therapeutics in combination in an effort to "short circuit" these alternate routes.

Metabolomics can help answer critical questions.

What pathways/biomarkers will delineate response?

- Profiling reaches beyond overexpression or mutational status of an a priori driver or target gene to ensure "the right patient"

What is the basis of drug response?

- Determine the basis of sensitivity and resistance to define new targets and treatment strategies
- Understand pathways that drive efficacy beyond the primary target

Is my preclinical model predictive of clinical outcome?

- Validate key translatable features from model
- Design/refine model to reflect key tumor features and cancer genetics
- Find the best fit to the human indication

What are the molecular details driving cancer?

- New targets
- New strategies for combinations

Downstream Targeting to Improve Outcomes

To address these challenges, many researchers and oncologists have begun to advocate targeting signaling pathways further "downstream," where the signaling message directs molecular phenotype.

Metabolism is a particularly alluring target because it is far downstream of genetic mutations, post-translational modifications and epigenetic alterations. It also sits very close to the tumor's molecular phenotype; many tumors rely heavily on metabolic changes in order to grow, expand or divide. As such, one common outcome of altered cancer cell signaling pathways is the reprogramming of metabolism.

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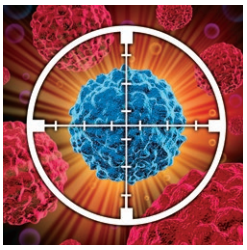
Tracking metabolite changes improves understanding of tumor metabolic reprograming and can offer insight into which genetic changes are critical for driving the cancer phenotype. This type of reverse engineering is particularly useful when trying to understand and treat a tumor with a high level of heterogeneity or a high number of mutations.

Metabolic pathways may also be a strong candidate for therapeutic targeting in cancer treatments. Many successful chemotherapeutics already target metabolic pathways, either directly or through their impact on oncogenic signaling pathways.

More precise and personalized treatments targeting specific metabolic pathways may lead to better results with fewer side-effects. And, by taking away the opportunity for upstream redundancy to circumvent targeted therapies, metabolism-targeting therapeutics might also reduce the chance of emergent resistance.

Defining Metabolic Targets in Tumors with Metabolomics



Metabolomics is a key tool for understanding both the genomic drivers of cancer and the metabolic changes they produce.

Metabolon has been involved in numerous research projects to better define the metabolic reprogramming strategies employed by tumor cells. For example, work done in Celeste Simon's lab at the University of Pennsylvania could lead to a precision oncology strategy for clear cell renal cell carcinoma (ccRCC).[2]

ccRCC is the most common form of kidney cancer. Although VHL mutations occur in over 90% of ccRCC tumors, deletion of VHL in the mouse does not produce a consistent effect, suggesting that additional mechanisms are involved. To identify these mechanisms, investigators used a systems approach including metabolomics to profile primary ccRCC tumors.

They determined that the gluconeogenic enzyme, fructose-1,6-bisphosphatase 1 (FBP1), was uniformly depleted in over 600 ccRCC tumors and associated with poor prognosis. Metabolomic data also pointed to a clear rationale for why—Warburg characteristics and accompanying pentose phosphate pathway flux.

The identification of this single metabolic feature across all ccRCCs demonstrates how metabolomics can often cut through the genomic and tumor heterogeneity to reveal common themes and suggest new targets or biomarkers.

Advancing Precision Oncology

Since the discovery of oncogenes and the subsequent success of targeted drug therapies, the quest to find the next key targeted therapy and associated companion diagnostics has been in full gear—fueling an aggressive effort in precision oncology. Metabolism may hold the answer.

We are already starting to see drugs directed toward metabolic targets entering into clinical trials. Metabolon has contributed to some of this work at biopharmaceutical companies, including Cornerstone Pharmaceuticals.[3] Results from its Phase 1 trial of metabolic targeting in subjects with hematological malignancies were recently published and showed striking results: the compound, an α-ketoglutarate and pyruvate dehydrogenase inhibitor, was well tolerated (a frequent concern regarding metabolic targets) and resulted in close to a 30% response rate, with one complete response to the drug.[4] It remains to be seen whether this success will translate to larger cohorts, but additional Phase 1 and Phase 2 trials of CPI-613 are ongoing.

As dramatic breakthroughs in precision medicine continue and new therapies such as immunotherapy add to the clinical oncologist's knowledge and armamentarium, we expect that exploration of the metabolic basis of tumors will yield additional, vital information. Metabolomics will play a key role in that research and may soon expand the tools available to advance precision medicine for cancer.

Supporting References

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2. Li, B., et al. "Fructose-1, 6-bisphosphatase opposes renal carcinoma progression." *Nature* **513**: 251-255, 2014.
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4. Pardee, Timothy S., et al. "A Phase I Study of the First-in-Class Antimitochondrial Metabolism Agent, CPI-613, in Patients with Advanced Hematologic Malignancies." *Clinical Cancer Research* **20.20** (2014): 5255-5264.

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