Preview

The Human Tumor Atlas Network's beginning steps toward the future of collaborative multi-omic discovery

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The Human Tumor Atlas Network is a multi-institutional effort to generate genomic and histologic datasets spanning thousands of patients. Johnson et al., in this issue of *Cell Reports Medicine*, illustrate how disparate data types from a single case can be combined to discover novel therapeutic directions.

In this issue of *Cell Reports Medicine*, Brett Johnson and colleagues, as part of the Human Tumor Atlas Network (HTAN), combine comprehensive single-cell genomic sequencing and histologic imaging to provide a tour-de-force biological narrative of a woman's metastatic breast cancer as it evolves in space and over time.[1] Funded by the Cancer Moonshot initiative, the goal of the HTAN is to provide an efficient means of sharing high-throughput sequencing and imaging data across multiple institutions, with standardized workflows for data collection, processing, and presentation.[2] Distinguishing features of the HTAN database include: (1) serial analyses of tumors and blood ranging from pre-malignancy to metastatic disease, (2) comprehensive clinical annotation of treatment history and clinical response, and (3) a focus on developing spatial methods for integrating single-cell genomic data with histopathologic findings. Much of these data are to be made available for community exploration via the HTAN website and associated biorepositories (https://humantumoratlas.org/).

The investigators provide illustrations of how data from disparate platforms (i.e., "multi-omics") can facilitate discovery of resistance mechanisms relevant to a particular patient. As depicted in Figure 1, they combined whole genome and RNA sequencing over serial tumor specimens to identify a novel therapeutic target in the setting of acquired capecitabine resistance. They identified a focal amplification on chromosome 18 that emerged in a liver metastasis, which had pro-

gressed following capecitabine therapy, resulting in co-amplification of two genes: TYMS, which encodes thymidylate synthase (the therapeutic target of capecitabine), and YES1, a receptor tyrosine kinase oncogene associated with therapeutic resistance in breast cancer.[3] Transcriptional profiling showed that TYMS was upregulated, but not YES1. However, in an emerging liver metastasis that was subsequently biopsied, TYMS and YES1 were again co-amplified, this time with transcriptional upregulation of both TYMS and YES1 (Figure 1). They hypothesized that capecitabine exerted a selective pressure that resulted in DNA amplification and sustained tumor outgrowth driven by YES1 signaling, which could potentially be targeted by the oral tyrosine kinase inhibitor, dasatinib.[4]

A second example comes from multi-modality histologic analysis: multiplex immunohistochemistry was used to quantify cell densities of tumor-infiltrating immune cells, whereas cyclic immunofluorescence and focused ion beam-scanning microscopy was used to visualize tumor-host interactions at subcellular resolution. They identified different mechanisms of immune evasion across space and time: some tumor biopsies contained high levels of suppressive M2-like macrophages, whereas other tumors contained dense neutrophil infiltrates, which can be tumorigenic and secrete immunosuppressive cytokines.[5] One shared feature identified across the 4 tumor biopsies was low expression of programmed death 1 (PD-1) on T cells, suggesting impaired antigen presentation and T cell priming.

They evaluated a variety of mechanisms of impaired antigen presentation. For example, the metastases retained expression of human leukocyte antigen (HLA), and neo-epitope analysis identified plentiful candidate mutated proteins for antigen presentation. At subcellular resolution, they observed abundant filopodia-like tumor cell protrusions associated with macropinosomes. This intriguing feature led them to hypothesize that despite retained antigen presentation machinery and abundant neoantigens, the tumors could circumvent antigen presentation by scavenging and digesting tumor-associated antigens from the local microenvironment.

In the future, the HTAN may evolve as a powerful resource to translate such "n of 1" hypotheses into meaningful clinical benefits for patients. For example, once equipped with a searchable clinical database and hundreds of metastatic breast cancer cases, the HTAN could be used to readily quantify the proportion of capecitabine-treated tumors exhibiting TYMS/YES1 co-amplification and/or transcriptional upregulation. Curated with radiographic and ctDNA outcomes, it would be possible to test whether co-amplification leads to accelerated tumor outgrowth. The HTAN could also promote cross-discipline learning across tumor types: for example, one might use peripheral blood samples of dasatinib-treated chronic myelogenous leukemia patients to investigate whether dasatinib downregulates downstream targets of YES1 *in vivo*.

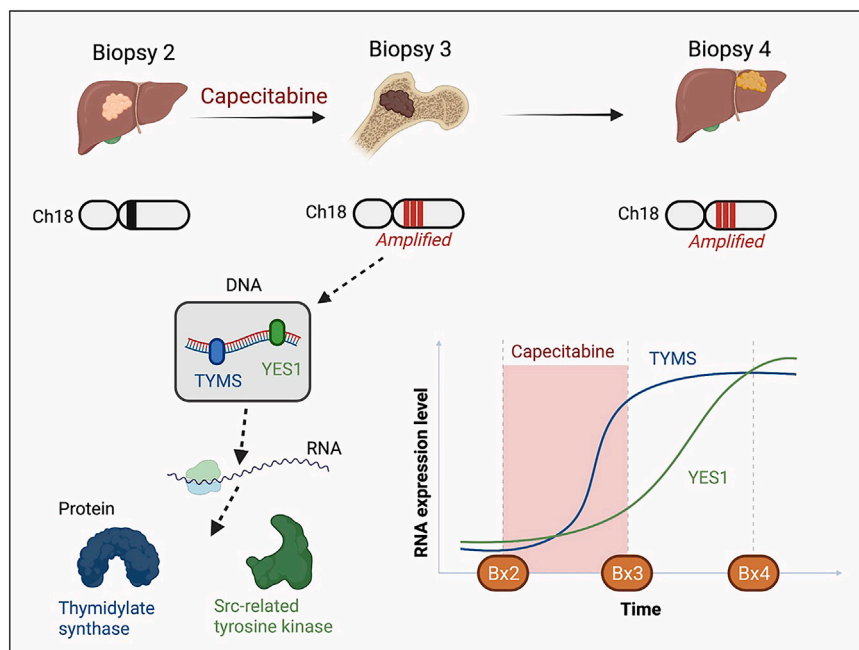In addition to demonstrating the potential of the HTAN, the investigators

Figure 1. Hypothesized mechanism of tumor outgrowth following capecitabine exposure
Combined DNA and RNA transcriptional profiling of serial biopsies (Bx2, Bx3, Bx4) revealed an acquired amplification of a region of chromosome 18 encoding TYMS and YES1. TYMS is the molecular target of capecitabine, and upregulation may confer therapeutic resistance, whereas YES1 is a putatively oncogenic receptor tyrosine kinase. A later biopsy (Bx4) redemonstrated co-amplification, but showed increasing YES1 expression, suggesting a YES1-mediated mechanism of tumor outgrowth.

illustrate another paradigm for accelerated discovery, the Serial Measurements of Molecular and Architectural Responses to Therapy (SMAART) clinical trial.[6–8] The goal of this trial is to utilize multi-omic data to guide therapy for individual patients, with clinical decision-making aided by a multi-disciplinary molecular tumor board. As an early participant of SMAART, the featured patient was treated with precision therapies that are not yet part of the standard-of-care armamentarium for hormone-receptor-positive breast cancer, including novel chemotherapy/immunotherapy combinations, anti-androgen agents (enzalutamide), and dasatinib. Although the clinical benefit of dasatinib cannot be ascertained by a n = 1 experiment, the SMAART trial (and similar initiatives at other institutions) has the potential to generate preliminary clinical and biomarker response data that would be difficult to obtain otherwise.

The experiments featured in this report, while impressive, all follow the conventions of the scientific method, whereby investigators employ prior knowledge (for example, previous reports of TYMS-upre-gulation in capecitabine resistance[9]) to develop a hypothesis and test its validity using the data. Indeed, without such prior knowledge, discovery of the described resistance mechanisms amidst billions of datapoints would be akin to finding a proverbial needle in a haystack. Therefore, as HTAN matures, future discovery will depend increasingly on the statistical learning theory that has defined the "big data" movement.[10] At its core, statistical learning uses computational algorithms to identify novel recurrent patterns (unsupervised learning) and/or predict therapeutic outcomes (supervised learning) from datasets that contain millions or billions of variables per case. Such techniques could identify otherwise obscured genomic and histologic patterns that occur repeatedly across many patients in the setting of capecitabine exposure or could unveil clinical meaning in the seemingly arbitrary spatial orientations of immune cell clusters, tumor cell filaments, and macropinosomes. Because statistical learning methods depend on large numbers of patient cases and cross-disciplinary expertise, to achieve the Can-

cer Moonshot goal of doubling the pace of discovery over the next decade, the HTAN must double down on efforts to make the data as expansive, inclusive, and public as possible.

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