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Review

Prioritizing therapeutic targets using patient-derived xenograft models

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ABSTRACT

Effective systemic treatment of cancer relies on the delivery of agents with optimal therapeutic potential. The molecular age of medicine has provided genomic tools that can identify a large number of potential therapeutic targets in individual patients, heralding the promise of personalized treatment. However, determining which potential targets actually drive tumor growth and should be prioritized for therapy is challenging. Indeed, reliable molecular matches of target and therapeutic agent have been stringently validated in the clinic for only a small number of targets. Patient-derived xenografts (PDXs) are tumor models developed in immunocompromised mice using tumor procured directly from the patient. As patient surrogates, PDX models represent a powerful tool for addressing individualized therapy. Challenges include humanizing the immune system of PDX models and ensuring high quality molecular annotation, in order to maximize insights for the clinic. Importantly, PDX can be sampled repeatedly and in parallel, to reveal clonal evolution, which may predict mechanisms of drug resistance and inform therapeutic strategy design.

Contents

Abbreviation: WT, wildtype

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1. Introduction: identification of therapeutic targets in the clinical setting

Through our improved understanding of cancer biology, identification of molecular drivers of cancer growth, and the development of targeted therapeutics, we have an increased ability to deliver treatment matched to a patient's cancer. The reality, however, is that for the majority of patients, this approach is still beyond their reach. The process of personalized medicine focuses on treating a patient as an individual, rather than as a representative member of a group of patients with similar histological designation, as has been the historical mechanism for assigning treatment [1]. However, this approach entails significant challenges in terms of logistics and identification of the best model systems in which to validate the utility of personalized therapies. The use of patient-derived xenografts (PDXs), or human tissue transplanted into immune-deficient mice without any intervening *in vitro* culture step, provides powerful models in which to determine the efficacy of therapies targeted to specific molecular aberrations [2].

In the past five decades of cancer therapeutic discoveries, the way in which a cancer case has been described and matched to treatment has focused on the organ in which the cancer was thought to have arisen [1], the histopathologic appearance of the cancer tissue and draining lymph nodes and the staining of between one and ten protein markers present on or in the cancer cell. Indeed, apart from a number of molecular tests involving the analysis of one or two genes, such as the routine use of *in situ* hybridization analysis to determine amplification of the *HER2* gene in breast cancer [3] or DNA sequencing to determine mutations in *KRAS* in lung cancer or colorectal cancer [4]; or *BRAF* in melanoma or colorectal cancer [5], histopathology and immunohistochemistry underpin the majority of treatment decisions for many for many patients today.

We are currently in the middle of the most extraordinary technological revolution [6], which has led us from the mammoth task of proposing to sequence the first human genome, predicted to take 15 years and cost three billion USD, to the current availability of whole genome sequencing (WGS), of an entire genome (or a cancer genome) in only a few days, for the cost of around one thousand USD. Indeed, genomic technologies, such as high-throughput sequencing of DNA, RNA (RNASeq), microRNA and the epigenome, now provide the first systematic approaches to discover the genes and cellular pathways underlying disease [6]. Although these technologies provide a tremendous opportunity, being able to read individual base pairs and compare them with a reference sequence does not tell us what we urgently need to know: who will get cancer, what type and when and how should that cancer best be treated? There is hope, however, that companion technologies that allow us to determine gene expression and epigenetic marks, or silencing or accessibility of the genome, will enhance our ability to interpret gene sequence variations.

Thanks to exponential improvements in the speed and depth of DNA sequencing, next-generation sequencing (NGS) can analyze entire human genomes in days, at a reassuring read depth [7]. Sequencing a cancer genome is more complex than a germline genome, due to the variety of complex aberrations found in cancer, including multiple gene copies, structural changes, epigenomic changes and intra-tumoral genetic heterogeneity [7]. This complexity necessitates greater read depth, or coverage (how many times a specific region has been sequenced by unique reads with a different start/end site/read length), with a median coverage of 50× (excluding duplicate reads), rather than the 30× generally accepted for standard germline genomes. Criteria for ensuring quality NGS data and interpretations are being addressed by the Next-generation Sequencing Standardization of Clinical Testing (Nex-StoCT) workgroup [8] and the College of American Pathologists [9].

Many diagnostic cancer samples are preserved in formalin fixed paraffin embedded (FFPE) tissue blocks, containing fragmented or cross-linked DNA, with few whole genomes reported from FFPE samples to date. It has been suggested that if cancer tissue is not preserved appropriately (for example, snap frozen in addition to formalin fixed), this could constitute willful destruction of evidence, necessitating that clear practice guidelines are generated to describe acceptable standard of care around tissue preservation for treatment-focused testing [1]. In response to this practical problem, new approaches are being developed to ensure optimal use of FFPE sections, such that sufficient information may be obtainable [10].

The availability of NGS has resulted in datasets ripe for interrogation and new insights. Companies are racing to provide panel tests, which interrogate hundreds of cancer genes, each gene included because it has been proven or hypothesized to be a cancer-causing or cancer-driving gene. This includes panels such as the Foundation Medicine T5a test [11]. If a potentially actionable aberration is detected by sequencing, for example, a mutation which is known or predicted to cause a non-functional (tumor suppressor) or activated (onco)-gene, then a recommendation may be made regarding the utility of a targeted therapy which may impact on that gene, or its associated pathway. The level of evidence underlying such a recommendation is variable [12]. Access to the right drug may be problematic and the chance or durability of response in that tumor type usually unknown. How should we validate potential actionable aberrations to aid in clinical trial design and choice of treatments for patients?

2. What constitutes an actionable aberration?

2.1. Human tumor cohort association studies

The molecular analysis of human tumors has the potential to unlock a series of molecular alerts or flags that may be predictive of drug response or resistance. In this setting, an actionable aberration is a molecular flag, which is underpinned by variable levels of evidence to suggest that a therapy targeting this aberration could be effective [12]. To date, molecular interrogation of cancer specimens has varied from analysis of expression of single genes or proteins by *in situ* hybridization or immunohistochemistry, or DNA sequencing of single genes (e.g., *KRAS* in lung cancer or colorectal cancer [4]; or *BRAF* in melanoma or colorectal cancer [5]) through to DNA sequencing of up to several hundreds of genes (such as the Foundation One T5a test [11]). Analysis of the whole exome or whole genome is available but the interpretation is problematic and these are not approved to guide treatment, outside research studies.