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Understanding the Enemy

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Abstract

In this issue of *Science Translational Medicine*, Tanas and colleagues describe a disease-defining genetic alteration for the vascular cancer epithelioid hemangioendothelioma (EHE). The resulting EHE-associated fusion gene encodes an aberrantly expressed putative transcription factor. This molecular information is the latest in a series of genetic discoveries that aid in cancer diagnosis and may pave the way to targeted therapeutic agents.

In the ancient Chinese text entitled *The Art of War*, author Sun Tzu writes that a key step to achieving victory is to "know thy enemy" (1). One of the challenges in the war on cancer has been in understanding the roots of this complex disease, which represents a multitude of neoplastic illnesses with different underlying genetic alterations. Cancer is commonly defined as a disease of the tissue of origin (for example, cancer of the colon, breast, or lung) and of specific cell types (carcinoma, sarcoma, etc.). Certain cancer subtypes have been classified by immunohistochemical labeling of marker proteins that are differentially present in selected tumors. However, conventional pathological analyses alone often cannot precisely identify the underlying tumor type, nor can they fully predict why individual patients respond to certain therapies or can display markedly different prognoses. Given the high complexity of this disease, one might expect that an intricate understanding of human cancer and, thus, disease management might only be possible when the underlying genetic changes are fully elucidated. A recent flurry of genome-wide sequencing analyses have revealed that tumors possess an underlying wealth of tumor-specific (somatic) genetic alterations that can be useful for improved tumor classification, appropriate therapeutic stratification, and disease monitoring.

In this issue of *Science Translational Medicine*, Tanas and colleagues describe the identification of a novel gene fusion between the *WWTR1* and *CAMTA1* genes in EHE (2). This study elegantly demonstrates that this gene fusion, resulting from a reciprocal t(1;3)(p36;q25) translocation, is present in virtually all EHEs but absent from other vascular neoplasms. This is an important finding because EHEs are difficult to distinguish clinically from other vascular tumors. Using this molecular translocation, the authors provide an immediately useful fluorescence in situ hybridization (FISH) test for accurate identification of EHE.

The *WWTR1/CAMTA1* fusion gene consists of the vascular tissue–specific *WWTR1* promoter and part of the gene that encodes the NH_2 terminus of *WWTR1* (a protein that is highly expressed in endothelial cells), fused in frame to the part of the *CAMTA1* gene that encodes the COOH terminus of the brain-specific *CAMTA1* transcription factor. Although

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the function of the resulting fusion protein is not known, it is likely that the aberrant expression of *CAMTA1* in vascular tissue is crucial to the biology of this disease.

The observations by Tanas and colleagues (2) represent the latest in a series of recent discoveries of genomic alterations identified in human cancers. With the advent of unbiased approaches for massively parallel sequencing of tumor genomes and transcriptomes, a variety of previously unrecognized genes are now emerging as cancer gene "mountains," or recurrently mutated genes in specific tumors (Table 1). One characteristic of these mountains that distinguishes them from common cancer genes, such as *KRAS* or *TP53*, is that they appear to be mutated predominantly in one or a few tumor types.

Analogous to the specificity of the *WWTR1/CAMTA1* rearrangement for EHEs, mutations in the isocitrate dehydrogenase genes *IDH1* and *IDH2* have been found in a significant fraction of gliomas and acute myeloid leukemias (AML) but rarely in cancers of epithelial or other origins (3–5). A similar pattern emerges for many of the genes in Table 1, including *TMPRSS/ERG* rearrangements in prostate cancer (6), mutations in *ARID1A* (which encodes a SWI/SNF transcriptional regulatory protein) in ovarian clear cell carcinoma (7, 8), alterations of the chromatin remodeling genes *DAXX* and *ATRX* genes in pancreatic neuroendocrine tumors (9), mutations in *PBRM1* (which encodes part of the SWI/SNF chromatin-remodeling complex) in clear cell renal cancer (10), and alterations in the histone methyltransferase–encoding *MLL2* gene in medulloblastomas and non-Hodgkin lymphoma (11, 12). The mechanism for this tumor specificity is unknown but may be related to the function of the products of altered genes in cell types that give rise to these tumors, such as high expression of *WWTR1* in endothelial cells or the androgen-regulated spatial proximity of the *TMPRSS* and *ERG* genes in prostate cancer cells (2, 13).

The specificity of these gene alterations has provided new opportunities for cancer diagnosis and prognosis (Fig. 1). For example, the discovery of alterations in *IDH* genes has provided a specific marker to distinguish between primary and secondary glioblastomas (5). The precise genetic alterations can be detected by direct sequencing of tumor tissue DNA at several regions of the *IDH* gene sequence that constitute mutational hotspots. Sequence analysis of such selectively mutated genes is also useful in classifying visibly indistinguishable tumor subtypes that have different clinical outcomes. For example, *IDH* mutations have been shown to represent an independent prognostic marker for improved survival in patients with gliomas (3, 5). Similarly, mutations in *ATRX* or *DAXX* identify a subset of pancreatic neuroendocrine patients with improved clinical outcomes (9). Surprisingly, the same gene may have different effects in different tumor types, as mutations in *IDH* and in the *DNA* methyltransferase–encoding *DNMT3A* gene have been reported to be indicators of worse prognosis in patients with AML (14, 15).

In addition to identifying tumor subtypes with different courses of natural progression, tumor-specific alterations may be useful in stratifying patients for specific therapies. In some cases, the proteins encoded by the altered genes provide direct therapeutic targets. the classic example of such rational therapeutic targeting is the protein kinase inhibitor imatinib (Gleevec) and its use in CML patients with the *BCR/ABL* translocation. More recently, lung cancers and neuroblastomas that contain alterations in the *ALK* tyrosine kinase provide an exciting use for new protein kinase inhibitors such as crizotinib (16–22). Mutations in *IDH* genes have spurred efforts to identify compounds that inhibit its newly acquired metabolic function (23, 24). Alterations in *BRAF* genes have led to the development of various targeted compounds that block the aberrant protein kinase activity of the encoded mutated signaling protein; the most recent of these drugs, vemurafenib, has shown dramatic clinical effects in patients with melanoma—the tumor type in which this gene is most frequently mutated (25, 26). Importantly, the effect of such targeted inhibition is efficacious only in

tumor cells that express the genetically altered version of the target gene. Given the high expression of the *WWTR1/CAMTA1* fusion gene in EHEs, it is conceivable that this gene could serve as a useful therapeutic target if the fusion gene is required for continued proliferation of EHEs and the targeting compounds are specific for the altered cells.

Because they are not present in normal cells, somatic alterations should be highly specific for tumor cells and, thus, have the potential to serve as biomarkers for tumor detection and monitoring. Mutation-associated biomarkers also could be useful for monitoring tumor response to specific therapies, detection of residual disease after surgery, and long-term clinical management. For example, quantitative reverse transcription–polymerase chain reaction (qRT-PCR) measurement of *BCR/ABL* mRNA transcripts has provided a sensitive method for determining the response, at the molecular level, to imatinib therapy in CML patients (27). More broadly generalizable approaches have been developed recently with the use of cancer-specific gene-sequence alterations (28) and genomic rearrangements (29, 30). Tumor-specific recurrent rearrangements, such as the *WWTR1/CAMTA1* translocation in EHEs, may be particularly useful as biomarkers because these genetic disruptions can be detected with a direct PCR-based test that analyzes the DNA sequence across the rearranged fusion gene junction.

Although understanding the complexity of cancer provides new avenues for clinical intervention, a number of challenges must be met before such approaches can be made clinically practicable. First is the transfer of high-throughput genomic analyses from the research laboratory to clinical evaluation of individual patient samples. Although such mutational analyses can be performed on a gene-by-gene basis in clinical labs (including the newly described FISH analysis of the *WWTR1/CAMTA1* translocation), it is now possible to routinely analyze the entire genomic landscape of each patient's cancer (31). Although this proposition may seem daunting, technology has reached the point at which a large number of individual gene tests could be performed more efficiently through the simultaneous analysis of all protein-coding genes. Such assays take full advantage of new DNA sequencing technologies; however, substantial effort is required to make such large-scale tests affordable, timely, and integrated in routine care.

Perhaps more important, the immense amount of data obtained by such tumor sequencing needs to be carefully analyzed to extract bona fide somatic alterations and to interpret the results of these molecular events from a biological and a clinical perspective. Using genomic sequencing information for tumor diagnosis, therapeutic decision making, and clinical monitoring will require a new generation of appropriately trained scientists and physicians who can incorporate the ever-changing connections between genetic alterations and novel therapies into clinical practice. Much remains to be done, but with such molecular tools, we are on the verge of understanding the complexity of human tumors in individual patients. Once the enemy is known, writes Sun Tzu, "a thousand battles, a thousand victories" (1).

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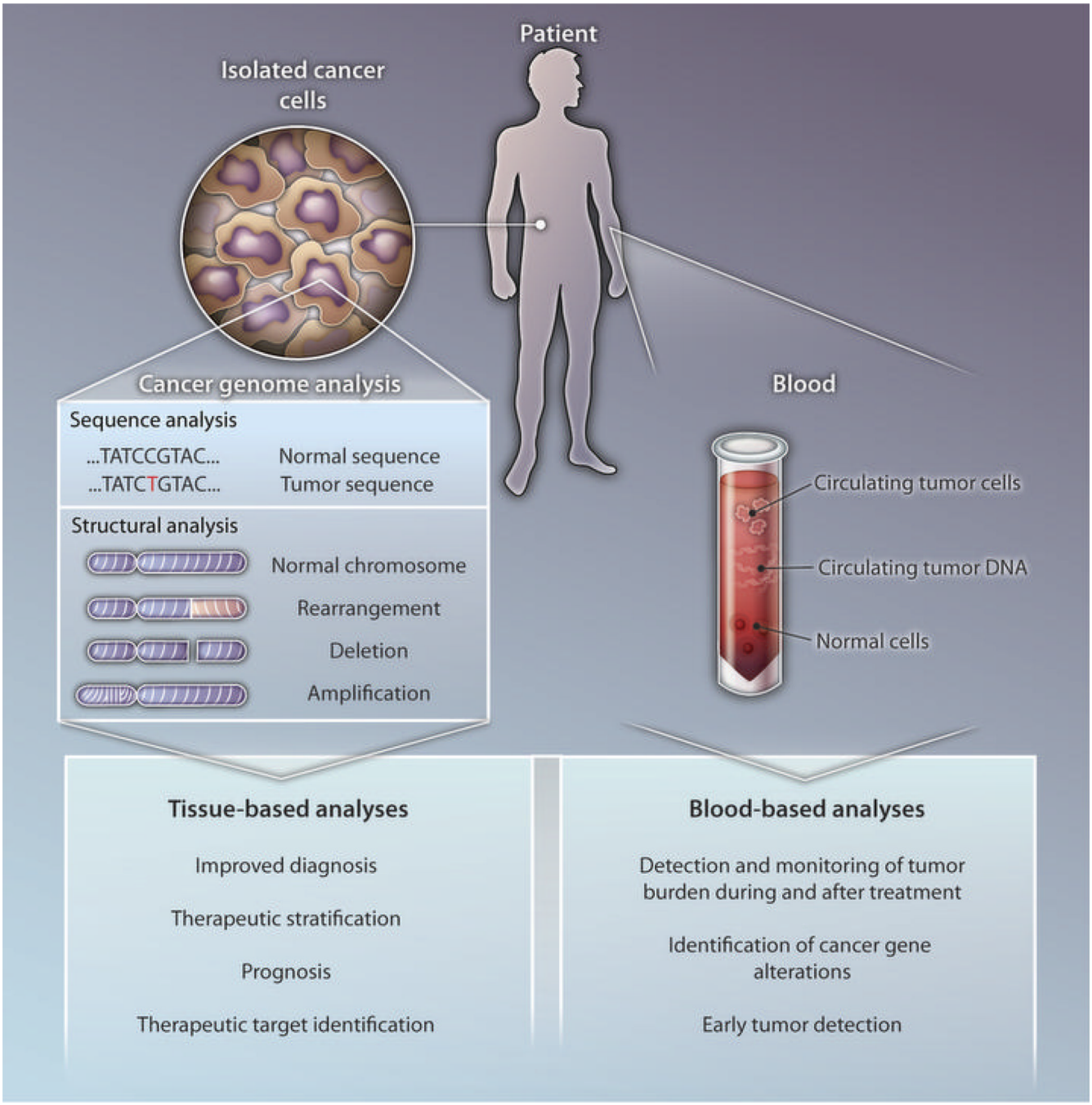

Fig. 1. Combating cancer

Approaches for translating cancer-genome analyses to patient care.

Table 1

Cancer gene mountains identified through unbiased approaches.

Altered gene	Tumors with specific gene alterations	References
ALK	Lung cancer, neuroblastoma	(16–21)
ARID1A	Ovarian clear cell carcinoma, endometrioid tumors	(7, 8)
ATRX	Pancreatic neuroendocrine tumors	(9)
DAXX	Pancreatic neuroendocrine tumors	(9)
DNMT3A	Acute myeloid leukemia	(14)
FOXL2	Ovarian granulosa cell tumors	(32)
IDH1	Gliomas, acute myeloid leukemia	(3–5)
IDH2	Gliomas, acute myeloid leukemia	(3–5)
MLL2	Medulloblastoma, non-Hodgkin lymphoma	(11, 12)
NOTCH1	Head and neck cancer, chronic lymphocytic leukemia	(33–35)
PBRM1	Clear cell renal cancer	(10)
PPP2R1A	Ovarian clear cell carcinoma, uterine carcinoma	(7, 36)
TMPRSS/ERG	Prostate cancer	(6)
WWTR1/CAMTA1	Epithelioid hemangioendothelioma	(2)