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Tissue-specificity in cancer: The rule, not the exception

Cancer driver genes exhibit remarkable tissue-specificity

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We are in the midst of a renaissance in cancer genetics. Over the past several decades, candidate-based targeted sequencing efforts provided a steady stream of information on the genetic drivers for certain cancer types. However, with recent technological advances in DNA sequencing, this stream has become a torrent of unbiased genetic information revealing the frequencies and patterns of point mutations and copy number variations (CNVs) across the entire spectrum of cancers. One of the most important observations from this work is that genetic alterations in bona fide cancer drivers (those genes that, when mutated, promote tumorigenesis) show a remarkable spectrum of tissue specificity: Alterations in certain driver genes appear only in cancers derived from one or a few tissue types (*1*). Only a handful of cancer drivers [such as telomerase reverse transcriptase (*TERT*), *TP53*, the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) locus, and *MYC*] show broad tissue spectrums. Here, we discuss the concept of tissue specificity of genetic alterations in cancer and provide general hypotheses to help explain this biological phenomenon.

Tissue-specific mutational frequencies of both tumor suppressor genes and oncogenes have been observed in sporadic cancers (see the figure). Similarly, individuals with classical inherited cancer predisposition syndromes only develop cancers in certain tissues. Although differences may relate to tissue-specific variation in expression and/or mutability of these genes (in sporadic cancers), it is becoming increasingly clear that the tissue-specificity of oncogenes and tumor suppressor usage is more likely rooted in the underlying biology of tissues (*1*). Understanding how and why distinct genetic alterations promote cancer in one tissue but not another remains an important and enigmatic question in cancer research. Nevertheless, the answer to this conundrum may also hold the key to precision medicine because unlocking the secret of what makes a particular tissue permissive to a specific cancer-causing genetic alteration may also reveal tissue-specific therapeutic vulnerabilities.

Various molecular mechanisms have been invoked to explain the tissue specificity of certain oncogenes and tumor suppressors (*1*, *2*). For example, the estrogen receptor (*ESR1*) gene is highly expressed, and its product controls proliferation and differentiation in the specific organs subject to estrogen-driven cancers, such as ovarian, endometrial, and breast cancer. Alternatively, xeroderma pigmentosum proteins (such as ERCC3 and XPC) are involved in excision repair of DNA damage, and their loss primarily leads to cancers of the skin, an organ that is uniquely exposed to ultraviolet (UV) radiation. Last, each tissue uses a specific regulatory mechanism to promote differentiation and limit stem cell expansion, which can contribute to tumorigenesis. The transcription factor GATA3 is one such example because it regulates breast cell ductal differentiation and its loss is significantly enriched in breast cancers (*3*).

Although these cases are illustrative, there are many more tissue-specific drivers for which the underlying mechanism is not understood. For example, *BRCA1* and *BRCA2* are ubiquitously expressed essential genes, the protein products of which are involved in the homologous recombination DNA repair pathway and are thought to prevent genomic instability, which can generate additional mutations. Nevertheless, inherited *BRCA1*- and *BRCA2*-inactivating mutations predispose largely to breast and ovarian cancer. It is possible that complete BRCA loss of function can only be tolerated in these tissues (*4*), or perhaps the cyclical response to estrogen in these tissues generates a greater need for homologous recombination. Many other prominent cancer genes show broad patterns of gene and protein expression yet restricted patterns of cancer-associated mutation, such as von Hippel Lindau tumor suppressor (*VHL*) in renal cancer; adenomatous polyposis coli (*APC*) in colorectal cancer (CRC); and *KRAS* in cancers of the pancreas, colon, and lung. One tantalizing explanation for these observations is that cells from different developmental lineages differ greatly in their ability to respond to growth-promoting events (*5*). That is, loss-of-function or gain-of-function alterations in specific genes can promote tumorigenesis in some tissues while being ineffectual, or even detrimental, in others.

Oncogenes and tumor suppressor genes must function within the framework of the transcriptional and proteomic network that exists in any given tumor cell of origin. These baseline conditions can differ among tissues, thus affecting the "oncogenic output" of the mutation in question. That tissue specificity is likely to be the rule, not the exception, is supported by a series of genetic screens aimed at examining cell proliferation in different cell types by turning on individual genes. Although these experiments showed that the core cell-cycle regulators, such as D-type cyclins and CDK inhibitors, universally affected the proliferation of cells across different tissues, 80 to 90% of the genes that functioned to promote proliferation differed between cell types (*5*). These observations suggest that a profound difference exists in the ability of cells from distinct developmental lineages to respond to different proliferation signals. Notably, tissue-specific oncogenes and tumor suppressors—revealed through genomics analysis of primary cancers—appropriately affected proliferation when overexpressed or ablated, respectively, only in their cognate tissue types in this analysis.

We hypothesize that in many cases, tissue specificity is driven by the preexisting epigenetic landscape across tissues; oncogenes and tumor suppressor genes cannot exert their effects unless the epigenetic state permits a tissue to respond to that particular oncogenic signal in a productive manner. The baseline epigenetic state of a cell is established by its developmental lineage as well as its microenvironment, in which nearby cells signal in a paracrine manner or through cell-cell contact. This epigenetic state consists of the chromatin configuration that dictates which genes are expressed (or not) and which genes have the potential to be activated or repressed in response to stimuli. This in turn also establishes the epi-proteome state, or proteomic circuitry, that determines which signals are capable of being sensed and in what manner a cell can respond. Because different cells of origin (leading to different cancer types) have distinct developmental histories, they have distinct chromatin and proteomic states. Thus, different cell types can respond to a particular stimulus, such as an oncogenic mutation, in the same way, in a completely different way, or not at all. For

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example, activation of a given transcription factor, such as the glucocorticoid receptor, causes a different transcriptional readout depending on the cell type owing to the distinct chromatin state of the cells (*6*). Another example is transforming growth factor–β (TGFβ), which is oncogenic in some settings and tumor-suppressive in others. Thus, the epigenetic state of a cell—defined by its specific chromatin, RNA, and proteomic constitution—ultimately determines how a signal is generated and responded to and therefore dictates which potential cancer drivers will be tumorigenic in different tissues.

Consistent with the idea that the epigenetic state of a cell plays an important role in tumor development, epigenetic regulatory genes themselves are commonly deregulated in human cancer. EZH2, which encodes the catalytic component of the polycomb repressive complex 2 (PRC2), represents a paradigmatic example. The PRC2 complex confers a prominent transcriptional repressive mark [histone 3-Lys^{27} (H3K27) methylation] and plays a central role in gene regulation. Gain-of-function mutations in the *EZH2* gene are oncogenic in lymphomas and melanomas, and *EZH2* is overexpressed in a broad spectrum of solid tumors (*7*). Conversely, loss-of-function defects in *EZH2* and other obligate PRC2 components (SUZ12 and EED) drive the development and/or progression of T cell acute lymphoblastic leukemia (T-ALL), malignant peripheral nerve sheath tumors (MPNSTs), and myeloproliferative disorders (*7*). These observations highlight the concept that each tissue lineage has a distinct preexisting epigenetic state, set forth by a defined pattern of chromatin marks, and that different tissues are susceptible to different oncogenic and/or epigenetic insults. Thus, defects in a vast number of chromatin regulators could profoundly alter the ultimate genetic landscape of a given cancer. Likewise, altering that landscape by using inhibitors of epigenetic regulators could turn a permissive state into a nonpermissive state, presenting therapeutic opportunities.

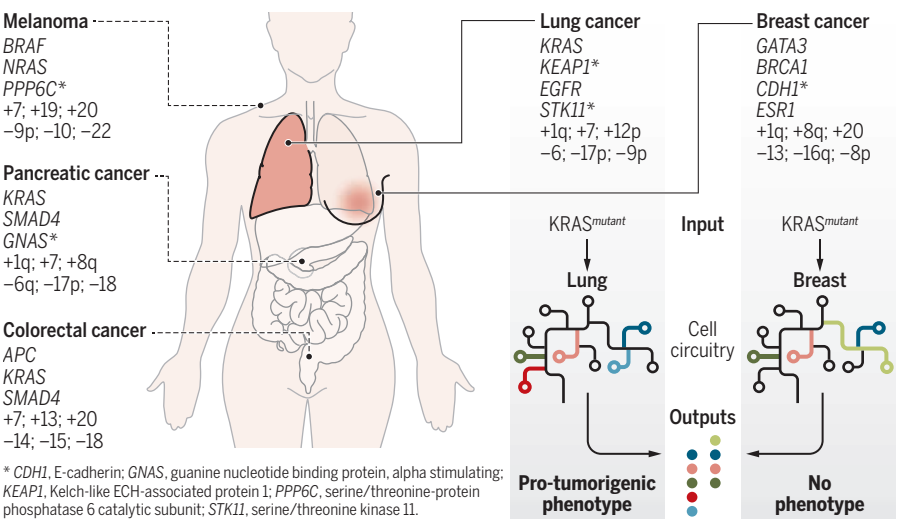
The epigenetic state of a cancer cell also modulates its response to therapies and the evolution of cancers during the acquisition of therapeutic resistance. Indeed, even in cases in which there is a solid rationale for directly inhibiting a druggable oncogene there are clear differences in responses among tissues. For example, RAF inhibition is effective in melanomas that express mutationally activated B-RAF–Val^{600}Glu but has little single-agent efficacy in CRC expressing the same mutant (*8*, *9*). The resistance of CRC is due to epidermal growth factor receptor (EGFR)–mediated feedback onto the mitogen-activated protein kinase (MAPK) pathway in response to RAF inhibition, which does not occur in melanomas because of lack of EGFR expression. Similar tumor-type differences in therapeutic response have been seen for isocitrate dehydrogenase (IDH) inhibition, which shows efficacy in *IDH1*- and *IDH2*-mutant acute myelogenous leukemia (AML), and EGFR inhibition, which is effective in *EGFR*-mutant non–small-cell lung cancer (NSCLC), whereas neither is effective in gliomas with the corresponding mutation (*10*). Clinical trials of a pan-HER kinase inhibitor revealed strong efficacy in cancers of the breast, biliary tract, and cervix, with poorer responses in lung cancer, bladder cancer, and CRC, even though all cancers had a mutation in *ERBB2* (*11*). These observations have important implications for clinical trials solely on the basis of genotype; in the future, genotype-driven trials will need to be of sufficient size to be statistically powered to detect significant variation in response from tissue to tissue.

Epigenetic states are fluid, and this plasticity can allow cancer cells to evolve in response to therapeutic intervention, providing further evidence that epigenetic states define genetic permissivity. For example, retinoblastoma tumor suppressor (*RB1*) mutations are common in small-cell lung cancer but rare in NSCLC. Nevertheless, in some settings NSCLCs expressing mutant EGFR can become resistant to EGFR inhibition by transforming into small-cell lung cancers. These small-cell lung cancers down-regulate *EGFR* expression and acquire mutations in *RB1*, which is commonly mutated in cancers of neuroendocrine origin (*12*).

Although supported by preclinical and clinical studies, tissue specificity remains phenomenological. We need much more mechanistic information to clarify how oncogenes and tumor suppressors exert these tissue-specific effects and how they may affect therapeutic intervention. Although seemingly unconventional, in order to pinpoint the essential biological effects of various cancer drivers, perhaps we need to change our approach and compare the effects of cancer genes in permissive and nonpermissive tissues. A thorough deconstruction of the precise transcriptional, epigenetic, proteomic, and biological responses of different tissues to different cancer-causing alterations should not only lead to important insights about how cancers develop but could ultimately be exploited to identify therapeutic vulnerabilities. ■

Tissue-specific genetic alterations and differential responses

Different human cancers contain a subset of recurring cancer driver gene mutations and chromosome copy number alterations that are specific for, or enriched in, that tumor type. The underlying tissue-specific epigenetic architecture may differentially determine the responsiveness to oncogenic signals and thus the propensity to acquire alterations that lead to cancer.



* *CDH1*, E-cadherin; *GNAS*, guanine nucleotide binding protein, alpha stimulating; *KEAP1*, Kelch-like ECH-associated protein 1; *PPP6C*, serine/threonine-protein phosphatase 6 catalytic subunit; *STK11*, serine/threonine kinase 11.

GRAPHIC: A. KITTERMAN/*SCIENCE*

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