VIEWPOINT

Using Somatic Mutations to Guide Treatment Decisions
Context Matters

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Mutations and other somatic genomic abnormalities are commonly used to inform treatment decisions. Such molecularly based personalized treatment strategies were until recently limited to an assortment of rare tumor types or molecularly defined subtypes of common cancers. Lately, these strategies have expanded to other tumor types, in particular lung cancer and melanoma. Although the approach to genomic-based treatment decisions has been broadly embraced, provision of a targeted agent to a patient whose cancer harbors the genomic target rarely leads to cure, and sometimes responses are incomplete. Also, opportunity costs for patients and the expenses of ineffective treatments are great; therefore, improvements are needed in the effective clinical use of mutation data. Although patients do benefit from today's approach to interpreting mutation data, we propose that interpretive strategies considering both cellular and genomic context of mutations will provide a more accurate rationale for treatment decisions (**Figure**). Cellular context accounts for histologic etiology and how cell type–specific differences in cellular signaling impact treatment success. Genomic context includes 3 distinct considerations: (1) clonal diversity of cancer cell populations and resulting evolution induced by treatment, (2) the presence of resistance mutations or other genomic features that preclude effective targeting of a mutation 9treatment efficacy barriers), and (3) the driver or activation status of the mutation at the time of treatment.

Cellular Context Matters

Cellular context matters in guiding treatment decisions. The wide range of clinical response to vemurafenib between patients with a melanoma and patients with a colorectal carcinoma with identical *BRAF*^{V600E} mutation is an illustrative example. This large contrast in pharmacologic sensitivity to *BRAF*^{V600E} inhibition is caused by a difference in feedback activation of *EGFR*. Melanoma cells, which express low levels of EGFR, cannot circumvent the growth inhibitory effect of BRAF inhibitors. By contrast, colorectal cells upregulate EGFR in response to BRAF inhibition, resulting in EGFR-driven tumors. Therefore, combinatorial drug therapy of EGFR and BRAF inhibition in *BRAF*^{V600E} mutant colon cancers might be more effective.[1]

Although our understanding of the impact of cell context on the signaling perturbations induced by mutations is growing, too little is known about distinctions between cells from benign and malignant lesions. For example, *BRAF*^{V600E} mutations are detectable in both benign nevi and melanomas. However, in melanomas *BRAF*^{V600E} cooperates with PTEN loss to induce metastasis. Ultimately deciphering the impact of cellular context of mutations found in benign and malignant tumors will also be crucial for optimal cancer treatment strategies.[2]

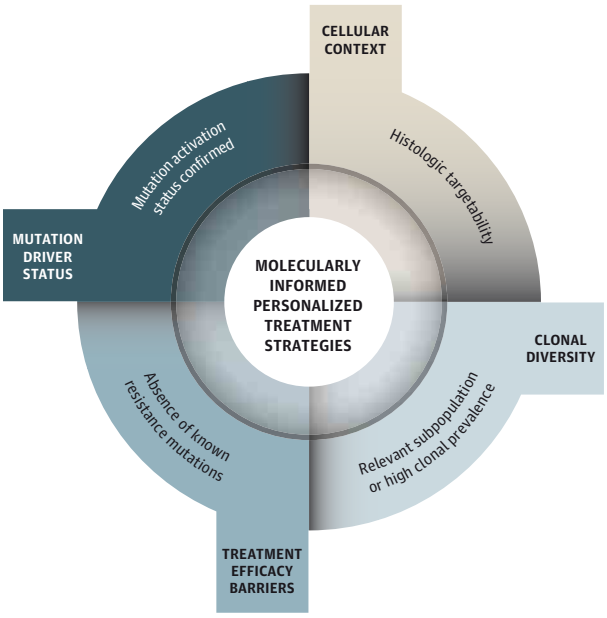
Clonal Diversity

Genetically diverse cell populations within a tumor are related by descent through branched evolutionary patterns. This genealogy, conceptually modeled with a phylogenetic tree, is created through stochastically acquired mutations and subsequent clonal expansion of individual cells. There is a great variation in degree of complexity (clonal diversity) and phylogenetic tree topology between cancers. Cancers with minimal genomic complexity such as small-cell hypercalcemic ovarian carcinomas have a stereotypical diagnostic mutation and few other genomic abnormalities, providing limited scope for divergence.[3] Cancers with more complex genomes such as high-grade serous carcinomas of the ovary show multiple clones, which are related by descent but which show extensive genetic divergence.[4] In such cancers, mutations may be present only in small subpopulations of cells and many are absent in specific, spatially distinct samples. However, initiating mutations such as loss of function *TP53* mutations in high-grade serous ovarian cancers will usually be present in every cell. Knowledge of clonal diversity in a tumor's evolutionary pattern can be important for guiding optimal cancer treatment decisions. For example, early clonal mutations at the root of the phylogeny may be optimal targets from a genomic perspective; however, other considerations such as the type of mutation (activating or truncating) strongly influence target selection.

Treatment Efficacy Barriers Due to Resistance Mutations

Intrinsic or acquired drug resistance due to resistance mutations is a major barrier for effective cancer treatment. A cancer cell can have different escape routes to acquired resistance including (1) acquiring a mutation of the drug target itself, (2) activation of the pathway downstream of the targeted blockade, (3) activation of a parallel pathway, and (4) hyperactivation of the inhibited pathway (reviewed in the article by Bernards[5]). Knowledge and identification of drug targets whose inactivation is only effective after a second mutation (synthetic lethality) may also help to develop combinatorial drug therapy to target multiple driver events or provide pre-

Figure. Consideration of Cellular and Genomic Context of Mutations to Guide Treatment Decisions



Interpretation of mutations, driven by consideration of cellular (beige shade) and genomic (blue shades) context, including (1) clonal diversity, (2) treatment efficacy barriers, and (3) mutation driver status, will be required to optimally deploy cancer genomic data for treatment decisions.

dictive biomarkers to avoid treatment efficacy barriers due to known resistance mutations.[6]

Mutation Activation Status Confirmed?

The first step to determine if a mutation has a functional role in the tumorigenic process would be to distinguish "driver" mutations from "passengers." Another challenge in distinguishing drivers from passengers is that a driver gene contains a driver gene mutation but can also contain multiple passenger gene mutations. Bioinformatics approaches that can predict the impact of mutations on the encoded gene and pathways will be essential for the translation of genomic data into useful clinical applications. So far, most methodologies to predict the functional effect of mutations have relied on the DNA sequence alone. Now that DNA mutation data and gene expression levels are available through collaborative efforts like The Cancer Genome Atlas, some algorithms are taking advantage to identify likely driver mutations by virtue of their effect on messenger RNA expression to predict the functional effect of the mutation (eg, DriverNet).[7] In addition, pathway activation status could be assessed by a variety of proteomic approaches including reverse-phase protein arrays.

Conclusions

Although the identification and use of somatic mutations to inform cancer treatment decisions is now standard of care, the accuracy of clinical decisions may be improved if mutation data are contextualized through consideration of the cellular and genomic milieu in which the mutations are found.

ARTICLE INFORMATION

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