Using Somatic Mutations to Guide Treatment Decisions
Context Matters

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). Cell 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 or treatment 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 in 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 up-regulate 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 sub-populations 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 Bernard5). 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-
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.

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