Up Close and Personal: The Challenges of Precision Medicine in Melanoma

Keiran S. M. Smalley, Jeffrey S. Weber

The review by Griewank and colleagues (1) in this issue of the Journal gives a timely overview of the recent developments in genomics that have led to major advances in targeted therapy for melanoma. The authors describe how genomic analysis, including deep sequencing and comparative genomic hybridization, has led to the identification of many of the genetic alterations that drive melanoma initiation and progression. Although many genomic platforms have contributed to our understanding of melanoma biology, some have proven more useful than others. Techniques such as comparative genomic hybridization and fluorescence in situ hybridization have proven utility in differentiating suspicious skin lesions such as blue nevi or spitzoid lesions from invasive melanomas (2) but little impact in the diagnosis of advanced melanoma. In their central argument, the authors surmise that most of the known and important genetic variants in melanoma will have been discovered within the next few years. Although this is likely to be true, a number of major obstacles remain in the path to improved targeted therapy for melanoma patients. Here we describe what we perceive to be the major impediments to improved targeted therapies for melanoma and propose strategies to overcome them.

Massively parallel sequencing has given us the tools to genetically characterize hundreds if not thousands of melanomas rapidly and cheaply, yet important information on kinetic changes as tumors progress over time from in situ melanoma to primary to nodal metastasis to metastasis to subsequent metastasis are lacking (3,4). These sorts of studies would allow a filtering of the data on the hundreds of single nucleotide variants found in melanoma, many of which are ultraviolet damage–related C-T transitions and are not drivers of malignancy (3,4). A more pressing issue is determining how the many thousands of genetic changes found in a typical cutaneous melanoma interact to drive melanoma development. This will be especially important in melanomas that are BRAF/NRAS wild-type because sequencing studies to date have failed to identify any major oncogenic drivers in this subgroup (3,4). It seems likely that many of the genetic changes identified so far occur in common, overlapping pathways—perhaps defining a core set of processes that drive the oncogenic transformation of melanocytes. How these mutations interact and cooperate to drive the key signaling pathways required for melanomagenesis remains a major gap in our knowledge. In particular, it seems likely that the high mutational rate seen in a typical ultraviolet-induced melanoma conveys a substantial level of functional redundancy in signaling that may contribute to the high rates of treatment failure seen following targeted therapy treatment.

A major impediment to achieving successful personalized therapy in melanoma is the paucity of actionable genetic changes that have been discovered. The ability to catalog single nucleotide variants in melanoma has greatly outstripped our ability to develop drugs that target molecules encoded by potential mutated driver genes. Drugs that target phospho-inositol 3 kinase, TORC 1–2, fibroblast growth factor receptor, ERBB3, protein-kinase C, c-MET, Aurora kinase, and Akt are well along in development but could interact with only a small proportion of the potential targets in melanoma (5). In silico and cell-based screening of the huge number of available antitumor compounds using current genomic data would seem critical for expanding the repertoire of drugs for melanoma and would facilitate the next step in drug development. Kinases and G-protein coupled receptors are highly tractable for the development of pharmacological inhibitors but only represent a minor fraction of the genetic changes identified in melanoma. Some of the most important potential targets in melanoma are GTPases or small G-proteins, such as NRAS, Rac, GNAQ, and GNA11, all of which are difficult targets for drug development (6). Thus far, attempts to target the downstream pathways activated through these small G-proteins have proven disappointing.

Griewank and colleagues (1) point out the potential pitfall associated with known intratumoral heterogeneity for melanoma genetic changes. Biopsying every melanoma metastasis for genetic analysis would be impractical. The development of single circulating cell and circulating plasma DNA genomics may predict progression of disease, allow early assessment of drug resistance, and could offer a comprehensive analysis of the genomic alterations in different metastases, allowing a better choice of treatments for individual patients (7). New insights into epigenetic regulation of melanoma cells may help shed light on how nongenetic heterogeneity emerges and should provide clues as to pharmacological strategies to limit therapeutic escape after drug treatment.

On a clinical level, the major issue that clinicians grapple with is how to overcome resistance to BRAF, NRAS, and KIT inhibition. High response rates with inhibitors of those drivers have translated into prolonged survival in patients with metastatic melanoma, yet progression-free survival is modest at 3 to 6 months, and virtually no patients will remain on treatment and/or be without progression at 5 years (8). A major effort to explore every facet of resistance to targeted therapy in melanoma is called for. Although the focus to date has been mostly upon the genetic mediators of drug resistance (such as truncation mutations in BRAF, new NRAS mutations, MEK1/2 mutations) (8), nongenetic means of drug resistance are also likely, including signals that emanate from the host microenvironment (9). These remain poorly described and have not yet been fully captured in the analysis of postrelapse tumor specimens. The time when patients should be placed on single-agent targeted therapy is past, and every BRAF, NRAS, or KIT mutated melanoma patient should be considered for...
or offered access to a trial of multiple targeted drugs. The recent US FDA approval of the combination of dabrafenib and trametinib (10) also suggests that triple combinations to overcome resistance should become the de facto entry point for new trials.

In conclusion, we certainly agree with Griewank et al. (1) that “[t]hese developments in melanoma serve as a model for the implementation of personalized medicine for patients with all cancers.” However, as we indicate herein, much work remains to be done to translate these discoveries into viable and effective treatments to benefit patients with advanced melanoma. It is likely that multiple inhibitors (>3 drugs) used in complex dosing schedules will be required to turn the once-inevitable death sentence of advanced melanoma into a manageable chronic disease.

References

Affiliations of authors: Department of Cutaneous Oncology (KSMS, JSW), Department of Molecular Oncology (KSMS), Melanoma Research Center of Excellence (KSMS, JSW), Moffitt Cancer Center, Tampa, FL.