SnapShot: Melanoma

Adina Vultur and Meenhard Herlyn
Melanoma Research Center, The Wistar Institute, Philadelphia, PA 19104, USA

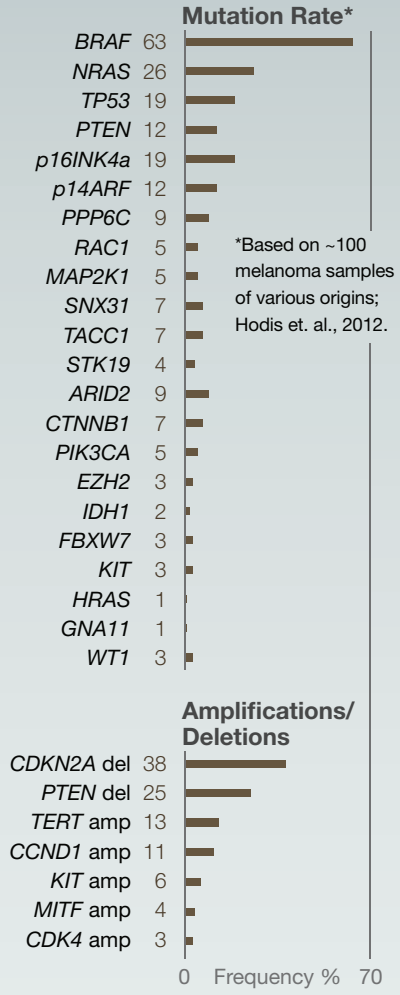
Cancer Cell

INCIDENCE, TYPES, AND ASSOCIATED MUTANT GENES

91.2% Cutaneous
- Chronic sun damage (*KIT, BRAF, NRAS*)
- Non-chronic sun damage (*BRAF, NRAS*)

2.3% Acral (*KIT, BRAF, NRAS*)
1.3% Mucosal (*KIT, NRAS*)
5.2% Ocular/Uveal (*GNAQ, GNA11*)

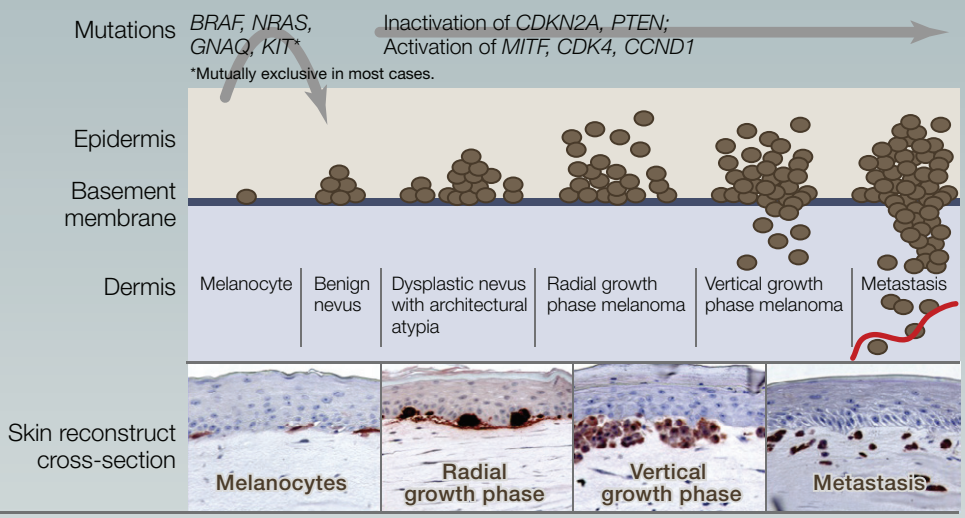
FREQUENT GENETIC ALTERATIONS



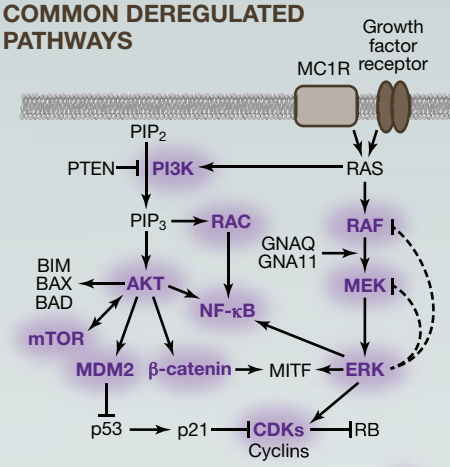
MELANOMA MOUSE MODELS

Chemically-induced carcinogenesis
Transgenics
Patient-derived xenografts (PDX)
Genetically engineered mice (GEMS):
- Tyr-*Nras*^{Q61K};*Cdkn2a*$^{-/-}$
- Tyr-*CreER*^{T2};*Braf*^{CA};*Pten*$^{lox/lox}$
- Tyr-*CreER*^{T2};*Braf*^{CA};*Pten*$^{lox/lox}$;*Ctnnb1*$^{lox\text{-}ex3}$
- Tyr-*CreER*^{T2};*Braf*^{CA};*Cdkn2a*$^{lox/lox}$
- Tyr-*CreER*^{T2};*Kras*^{LSLG12D};*p53*$^{lox/lox}$;*Lkb1*$^{lox/lox}$
- Tyr-*Hras*^{G12V};*Cdkn2a*$^{-/-}$
- Others with *Cdk4*^{R24C}, *p53*$^{lox/lox}$, *Ret*

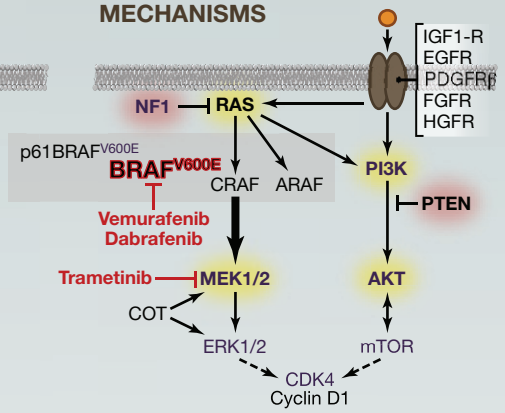
MELANOMA PROGRESSION



COMMON DEREGULATED PATHWAYS

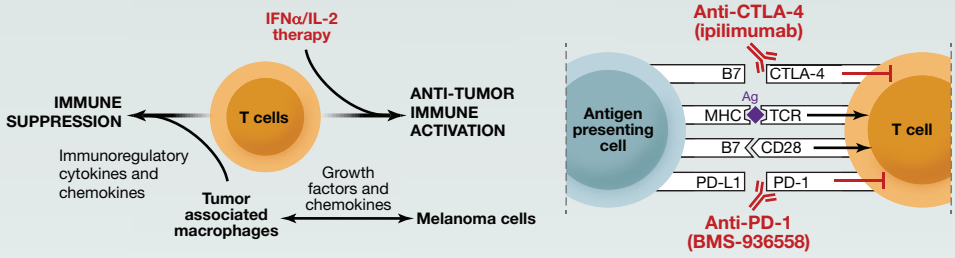


RAF INHIBITOR RESISTANCE MECHANISMS

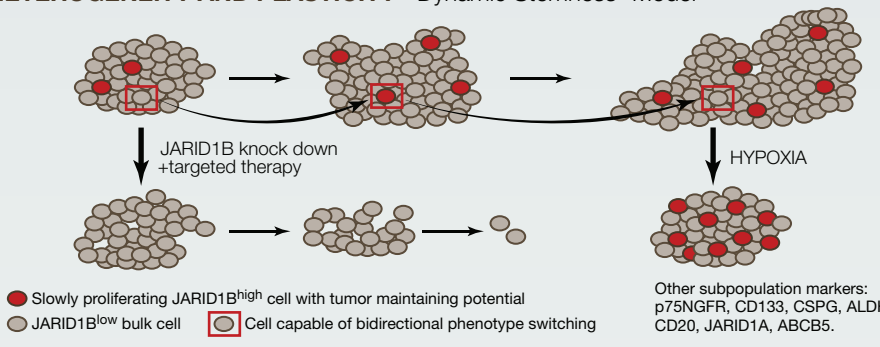


Druggable targets | Therapies approved or approval pending | Activating mutations found | Inactivation

IMMUNOLOGY



HETEROGENEITY AND PLASTICITY "Dynamic Stemness" Model



 DOI http://dx.doi.org/10.1016/j.ccr.2013.05.001 See online version for legend and references.

SnapShot: Melanoma

Adina Vultur and Meenhard Herlyn
Melanoma Research Center, The Wistar Institute, Philadelphia, PA 19104, USA

Cancer Cell

Melanoma, the deadliest of skin cancers, is caused by the transformation of melanocytes (pigment-producing cells) that accumulate genetic alterations, leading to abnormal proliferation and dissemination. The American Cancer Society estimates that ~76,690 new cases of melanoma will be diagnosed in the United States in 2013, and the incidence is rising. Predisposition to the disease can be influenced by an individual's genetic background, pigmentation status, and exposure to ultraviolet light (in the case of cutaneous melanoma). Clinically, melanoma lesions can be classified based on location and progression, which range from benign nevi to metastatic melanoma, while tumor-node-metastases (TNM) staging focuses on melanoma thickness, ulceration, lymph node burden, and visceral or nonvisceral metastases. Current classification schemes do not always predict survival or response to therapy; the heterogeneous genetic and molecular processes driving the disease must also be taken into account. Important driver mutations, their frequencies, and their prevalence in subtypes of melanomas are shown in the adjacent figure.

Key Signaling Pathways

The MAPK pathway controls cell proliferation, invasion, migration, and survival. In melanoma, MAPK signaling can be constitutively activated through alterations in membrane receptors or through mutations of *RAS* or *BRAF*. BRAF is mutated in ~60% of melanomas, and 90% of these mutations display a valine to glutamic acid substitution (V600E), causing constitutive kinase activation. Although mutations of PI3K do not occur frequently, the activity of its associated pathway is often increased in melanoma and can have widespread effects on numerous downstream effectors such as AKT, mTOR, NF-κB, p53, and others, all potentially contributing to a more aggressive cancer phenotype. One way to increase PI3K activity is via loss of PTEN through mutation, gene deletion, or promoter methylation. Other important effectors of melanoma include the melanocortin receptor 1 (MC1R), a melanocyte-specific G protein receptor involved in human pigmentation, UV response, and DNA damage; KIT, a tyrosine receptor for the stem cell factor (SCF) that plays a role in melanocyte development and has shown clinical responses to imatinib; GNAQ, which relays signals from G protein-coupled receptors and is commonly found mutated in uveal melanomas as an early genetic event; the microphthalmia-associated transcription factor (MITF); MDM2 or MDM4; and others.

BRAF Mutant Melanomas: Therapeutic Response and Resistance

Targeted therapies against mutant BRAF have shown efficacy in the clinic and are well tolerated. Vemurafenib, for example, has shown overall response rates of ~50% and median progression-free survival of 5–7 months in clinical trials. Despite these encouraging results, resistance occurs in most patients. Documented mechanisms of BRAF inhibitor resistance include reactivation of the MAPK pathway by CRAF, ARAF, the p61BRAF(V600E) splice variant, mutational activation of *NRAS* or *MEK*, loss of the tumor suppressor NF1, and activation of compensatory pathways such as the PI3K network via enhanced receptor tyrosine kinase signaling (particularly through the PDGFRβ, IGF1-R, FGFR, HGFR, and EGFR). Data are also emerging with regards to the importance of metabolism in modulating drug response. Therapeutic strategies involving the combination of BRAF inhibitors with other targeted agents are currently underway to improve patient outcomes. In addition, a new study suggests that alternative treatment schedules may delay the emergence of drug resistance.

Immunology

Immunotherapy-mediated melanoma regressions have been reported. One strategy involves ipilimumab, a humanized antibody against CTLA-4. CTLA-4 is a key receptor in immunosuppression and blocking CTLA-4 in melanoma patients can stimulate the immune system. Acting in a similar way, the anti-PD-1 antibody has shown favorable and durable responses. Current immunotherapy endeavors also focus on the role of macrophages in promoting tumor growth and immune evasion, indicating that tumor-host interactions could be valid therapeutic targets. Personalized therapies for melanoma patients are likely to benefit from both pharmacological and immunological strategies in the future; however, toxicities will have to be taken into consideration.

Disease Heterogeneity and Plasticity

The heterogeneity of melanoma is not only found among patients and lesions, but also within the tumors themselves. Whereas studies point to the ability of all single melanoma cells to form tumors, evidence suggests that these cells can exist in distinct epigenetic states, display different properties, and are dynamically regulated. For example, JARID1B-^{high} cells are slow cycling, resistant to challenging environments such as hypoxia and drug treatment, and essential for tumor maintenance.

Melanoma Models for Biological and Therapeutic Studies

Resources to conduct melanoma studies include (1) extensive libraries of genetically characterized and distinct human-derived melanoma cell lines, (2) in vitro skin reconstructs that recapitulate human skin architecture, and (3) numerous mouse models that provide insights into melanoma progression, metastasis, and therapy. Exciting new models also include patient-derived xenografts (PDXs) in which primary tumor samples are transplanted from patients directly into animals. PDXs can be used not only to assess responses to therapy, but also to provide avatar models of human cancer for "coclinical" trials.

ACKNOWLEDGMENTS

We thank Drs. S. Somasundaram, M. Perego, C. Krepler, M. Fukunaga-Kalabis, and J. Villanueva for valuable comments.

REFERENCES

Ascierto, P.A., Marincola, F.M., and Ribas, A. (2011). Anti-CTLA4 monoclonal antibodies: the past and the future in clinical application. J. Transl. Med. *9*, 196.

Chang, A.E., Karnell, L.H., and Menck, H.R.; The American College of Surgeons Commission on Cancer and the American Cancer Society (1998). The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. Cancer *83*, 1664–1678.

Das Thakur, M., Salangsang, F., Landman, A.S., Sellers, W.R., Pryer, N.K., Levesque, M.P., Dummer, R., McMahon, M., and Stuart, D.D. (2013). Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature *494*, 251–255.

Hodis, E., Watson, I.R., Kryukov, G.V., Arold, S.T., Imielinski, M., Theurillat, J.P., Nickerson, E., Auclair, D., Li, L., Place, C., et al. (2012). A landscape of driver mutations in melanoma. Cell *150*, 251–263.

Korman, J.B., and Fisher, D.E. (2013). Developing melanoma therapeutics: overview and update. Wiley Interdiscip Rev Syst Biol Med *5*, 257–271.

Quintana, E., Shackleton, M., Sabel, M.S., Fullen, D.R., Johnson, T.M., and Morrison, S.J. (2008). Efficient tumour formation by single human melanoma cells. Nature *456*, 593–598.

Roesch, A., Fukunaga-Kalabis, M., Schmidt, E.C., Zabierowski, S.E., Brafford, P.A., Vultur, A., Basu, D., Gimotty, P., Vogt, T., and Herlyn, M. (2010). A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. Cell *141*, 583–594.

Santiago-Walker, A., Li, L., Haass, N.K., and Herlyn, M. (2009). Melanocytes: from morphology to application. Skin Pharmacol. Physiol. *22*, 114–121.

Vultur, A., Webster, M., Villanueva, J., and Herlyn, D. (2013). Highlights of the 2012 congress of the society for melanoma research, 8-11 November 2012, Hollywood, CA. Melanoma Res. *23*, 237–240.

Whiteman, D.C., Pavan, W.J., and Bastian, B.C. (2011). The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res *24*, 879–897.