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Melanoma Resistance: A Bright Future for Academicians and a Challenge for Patient Advocates

See also pages 504 and 520

"The only true wisdom is in knowing you know nothing."

Socrates

In this issue of *Mayo Clinic Proceedings*, 2 complementary papers review recent advances in the contemporary therapy of melanoma[1] and provide a speculative synthesis[2] on the similarities between the mechanism protecting the fetus from an immune response by the mother and the evasion of host responses by metastatic melanoma. The first of these articles, by Shah and Dronca,[1] predicts a bright future for academicians and clinicians who will be responsible for evaluating and clinically applying multiple new strategies proposed to treat this devastating disease. That treatment will likely involve a flurry of new molecules and treatment modalities that are currently being developed.[1] These novel patient- and tumor-specific therapies are expected to target the hallmark features of cancer that promote cancer formation and progression (Table).[3] The second article, by Enninga et al,[2] discusses multiple mechanisms used by the placenta to protect itself and the fetus from the mother's immune attack. Mechanisms similar to these can potentially be used by metastatic melanoma to evade the host response and immunotherapy.[2] The multiplicity of potential mechanisms listed[2] will secure the academic future for years to come as we attempt to resolve new methods for targeting immune modulation as a treatment for patients with melanoma.

Unfortunately, the immediate future is not so bright for these patients because currently available or developing treatment strategies are able to prolong life for only a few months before the disease relapses, leading to death. Any modest improvements in overall survival typically occur during periods in which the therapies, which are very expensive, produce toxic adverse effects.[1,4-6] Tumor progression often occurs because of the evolution of melanoma biology, which, in turn, produces multiple resistant mechanisms that hinder the efficacy of both new and older therapies. The resistance mechanisms include, but are not limited to, preexisting or developing intratumor heterogeneity, alterations in tumor microenvironment, and the ability of tumor to generate an immunosuppressive environment. At a genetic level, the tumor may develop intrinsic resistance to proto-oncogene B-Raf (BRAF) gene inhibitors, develop additional BRAF or neuroblastoma RAS viral oncogene homolog mutations, and misregulate downstream mitogen-activated protein kinase kinases, beta-type platelet-derived growth factor—phosphatidylinositide 3-kinase/AKT or epidermal growth factor receptor—SRC family kinase—signal transducer and activator of transcription 3 pathways, or other growth factor (Figure), cytokine, and metabolic pathways.[1,2,6-8] The issues raised in both papers[1,2] are extremely important and deserve further consideration, as discussed herein.

Immune-Based Therapy Has Its Limitations Owing to the Tumor's Ability to Generate an Immunosuppressive Environment

Complementary to the information reported by Enninga et al,[2] one should realize that melanoma cells in or without cooperation from the stroma can produce a large spectrum of immunosuppressant agents, such as immunosuppressive growth factors, cytokines, proopiomelanocortin (POMC) peptides (including adrenocorticotropin hormone [ACTH], α-melanocyte-stimulating hormone (α-MSH) and β-endorphin[9]), glucocorticoids,[10] and lymphotoxic intermediates of melanogenesis (defined later herein).[11,12]

TABLE. Strategies for Melanoma Persistence and Progression Are Targets of Therapy[a,b]

Hallmark of melanoma	Target—agent (examples)
Sustaining proliferative signaling	BRAF—vemurafenib, dabrafenib
	MEK—trametinib
	C-KIT—imatanib
	Receptor kinases—nilotinib, lapatinib
	NMPRTase—APO866
Evading growth suppressors	Not defined yet
Activating invasion and metastasis	Not defined yet
Enabling replicative immortality	hTERT—BIBR1532 or nucleoside analogues
Inducing angiogenesis	VEGF—bevacizumab, ranibizumab
Resisting cell death	Not defined yet
Escape from immune surveillance/immune destruction	CTLA-4—ipilimumab
	PD-1—MK3475 or nivolumab
Other mechanisms of immunosuppression, including systemic immunosuppression	Not defined yet
Altered melanogenic activity[c]	Tyrosinase inhibitors, melatonin
Tumor promoting inflammation	Not defined yet
Genome instability and mutation	Not defined yet
Regulating cellular energetics	Mitochondria respiration—oligomycin
	Proteosomes—bortezomib

[a]BRAF = proto-oncogene B-Raf; CTLA-4 = cytotoxic T-lymphocyte antigen 4; hTERT = human telomerase reverse transcriptase; MEK = mitogen-activated protein kinase; NMPRTase = nicotinamide phosphoribosyltransferase; PD-1/PD-L1 = programed cell death protein/PD-ligand; VEGF = vascular endothelial growth factor.

[b]Based on data from *Cell*[3] and *Nat Rev Clin Oncol*[6] and on http://clinicaltrials.gov.

[c]From *Physiol Rev*[12] and *Endocrine*.[25]

The POMC System. High expression of POMC in melanomas positively correlates with tumor progression.[13,14] Noteworthy, POMC-derived melanocortins are recognized for their immunosuppressive properties, but they also serve as anti-apoptotic, mitogenic, and melanogenic factors in human melanocytes (acting through activation of the MC1 receptor).[12,15] Although the cell's synthesis of melanin is considered a marker of differentiation, intermediates of melanogenesis are highly immunosuppressive or selectively toxic toward immune cells.[11,16] Therefore, pathologic expression of POMC in melanoma can contribute to tumor progression, identifying POMC as a facultative and context-dependent tumor facilitator.

Steroidogenesis and the Hypothalamic-Pituitary-Adrenal Axis. Melanoma cells also have the capability to produce corticosterone and cortisol, a property shared by normal melanocytes and other skin cells (as previously reviewed by Slominski et al[17]). Interestingly, this production can be stimulated by locally expressed corticotropin-releasing factor (CRF) and POMC-derived ACTH (as previously reviewed by Slominski et al[18]). This hypothalamic-pituitary-adrenal (HPA)–like axis operates in the skin to attenuate damage imposed by environmental factors and to prevent autoimmune attack against the skin due to damage-induced exposure of cutaneous antigens.[17,18] The misplaced or deregulated HPA-like organization or its elements can also operate under pathologic conditions, such as melanoma, to generate an immunosuppressive and protumor environment that, in turn, facilitates melanoma growth and progression.[18]

Although the previously mentioned neuroendocrine regulatory pathways are operating on the local, skin, and melanoma levels,[17,18] there also is a strong possibility for concomitant systemic immunosuppressive activity. Specifically, melanoma-derived CRF or CRF-like peptides, interleukin-1, IL-6, tumor necrosis factor α, and ACTH could either activate the pituitary-adrenal axis or directly affect the adrenal cortex, leading to systemic immunosuppression.[9,18] Thus, the factors listed previously herein would affect not only tumor environment but also systemic homeostasis through activation of the central HPA

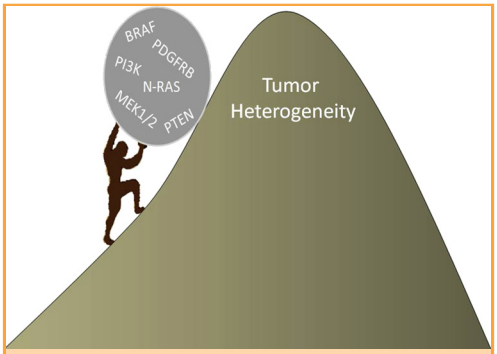

FIGURE. Current approaches to treating metastatic melanoma resemble "Sisyphus work" from Greek mythology. Similar to Sisyphus, it will be problematic to reach the pinnacle where targeted cure is achieved because clonal heterogeneity will overcome the drug effects in most patients with metastatic melanoma. BRAF = proto-oncogene B-Raf; MEK1/2 = mitogen-activated protein kinase kinase 1 or 2; N-RAS = neuroblastoma RAS viral oncogene homolog; PDGFRB = beta-type platelet-derived growth factor; PI3K = phosphatidylinositide 3-kinase; PTEN = phosphatase and tensin homolog.

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