Modern Pathology (2017) 30, 786–787

INSIDE THE USCAP JOURNALS

doi:10.1038/modpathol.2016.28

Malignant melanoma: from cause to cure

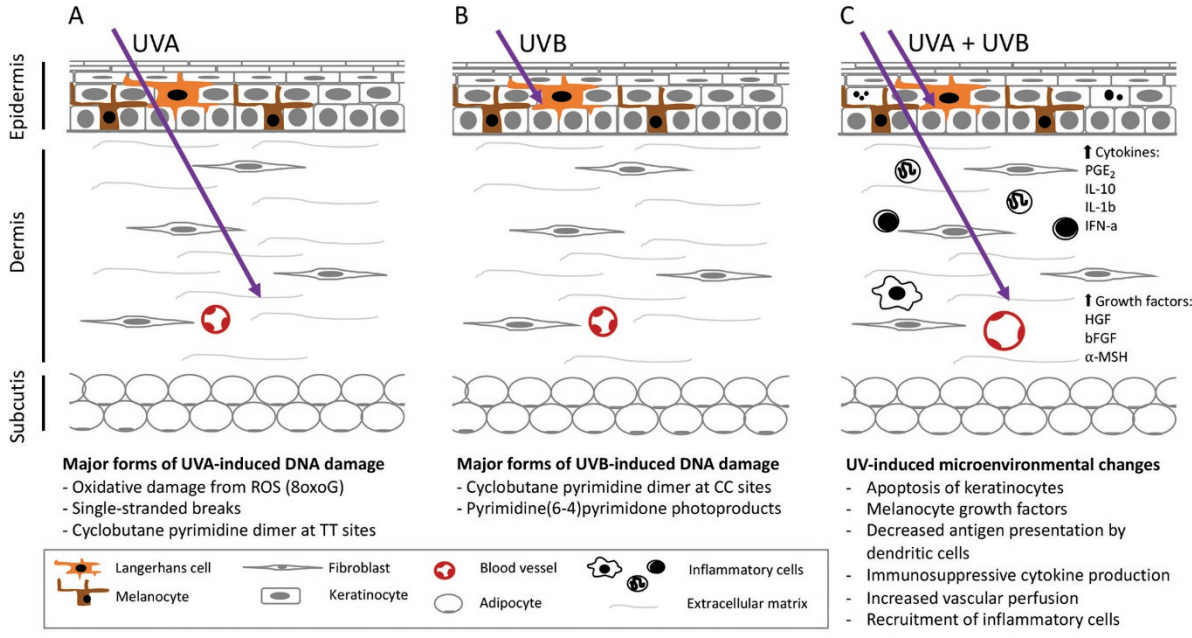
The real voyage of discovery consists not in seeking new landscapes, but in having new eyes.

—Marcel Proust

The second special issue of *Laboratory Investigation* focused on melanoma is testimony not only to the immense interest in the scientific community that emerged when this special issue was conceived but also to the 'new eyes' that are scrutinizing and probing every facet of melanoma virulence in order to hasten both prevention and cure. A cancer that may persist for years before curative excision or lethally metastasize when having little more than the volume of a grain of rice, melanoma is emblematic of the oft-cited 'riddle, wrapped in a mystery, inside an enigma.' But through the questioning new eyes of so many talented and devoted investigators, the mysteries of melanoma causation, virulence, and progression are now beginning to be unraveled.

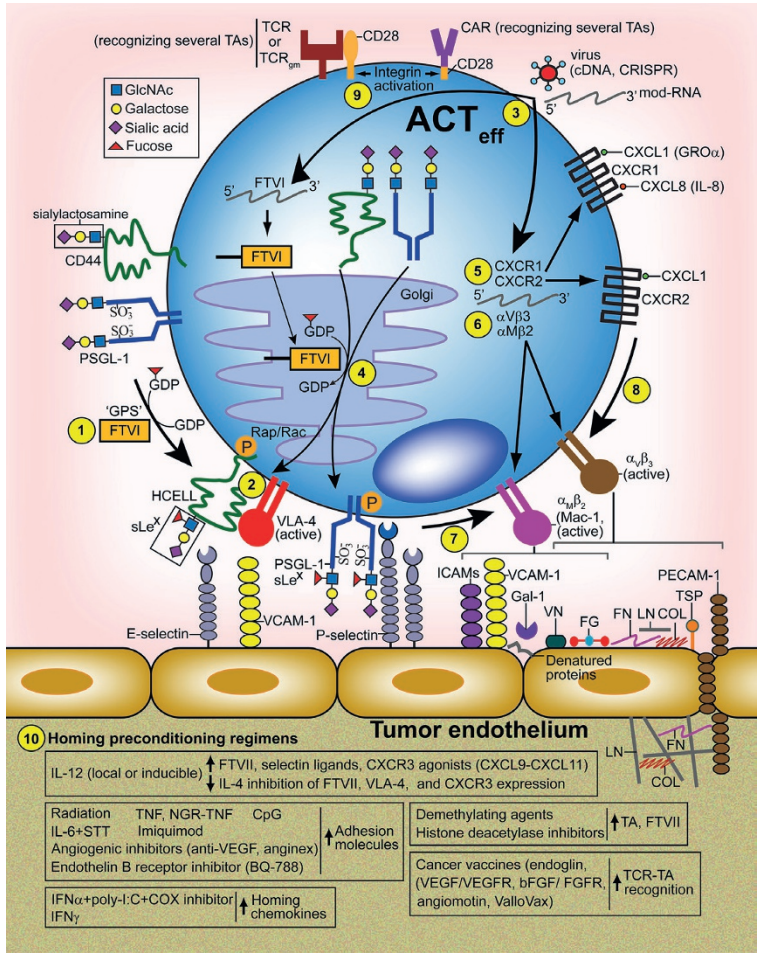
The causes of melanoma are indeed complex. Certainly ultraviolet light (UV) is a primary culprit in the genesis of many lesions, and experimental models of this relationship are therefore critical. In this month's issue of *LI*, Day and colleagues' Mini Review presents the most relevant and timely murine models of UV-induced melanomagenesis in the context of their translational relevance to human disease. Next, the double-edged sword of UV exposure is revealed by Slominski *et al* in an in-depth, scholarly, and timely review of research on one of UV's best-known offspring, vitamin D. Perhaps even more elusive topics are the occurrence and mechanistic understanding of melanoma in sun-protected skin. Merkel and Gerami review the clinicopathologic and molecular underpinnings of this category of lesions, which are not preventable by sunscreens or broad-brimmed hats. The ability to visualize melanoma in the context of both UV-induced and UV-independent pathways is undoubtedly important to investigation directed toward molecular and genomic interception of causative pathways before they gain clinical traction.

But once a clinical reality, what pathways mediate the extraordinary virulence of primary melanoma? Kawakami and Fisher provide an up-to-date summary of how the 'master transcriptional regulator' of melanocyte lineage—microphthalmia-associated transcription factor—may, depending on its mutational status, be responsible for such diverse phenomena as UV-shielding skin pigmentation,



Major effects of ultraviolet radiation on the skin. Ultraviolet A (UVA) (**a**) and UVB (**b**) penetrate into the skin to different degrees (purple arrows) and cause different types of DNA damage. In addition to DNA damage, UVA/UVB exposure causes a wide variety of changes to the skin microenvironment (**c**). See the paper by Day *et al*, page 698.

syndromic depigmentation, and melanocyte oncogenic transformation. Beyond transcription, the epigenomic milieu adds an extragenomic wrinkle to melanoma aggressiveness, as highlighted by Babapoor and colleagues, who focus on next-generation sequencing of microRNAs important in melanoma invasion and progression. At a structural level, there remains much to learn regarding cell–cell relationships that portend virulence, as emphasized by Barnhill and co-workers, who provide novel insights into the biological and prognostic impact of ocular melanoma cell growth along the abluminal surfaces of blood vessels. These complexities in primary lesions are likely to conspire to facilitate the metastases responsible for most of the clinical morbidity—and ultimately for the mortality that typifies melanoma progression. However, not all cells that stray from the primary site find soil in which to flourish. Our evolving understanding of the 'metastatic niche' is emphasized by Wang and colleagues, who have identified a role for marrow adipocytes in establishing fertile ground for colonization of melanoma metastases to bone. Hsu and colleagues extend their pioneering work by presenting novel findings regarding the means by which melanoma stem cell–like plasticity and formation of the metastatic niche are mediated in part by the Notch3 pathway.



Optimization of culture expansion of adoptively transferred T-effector cells for broad delivery into widespread melanoma metastases. Bioengineering of $CD8^+$ or $CD4^+$ T-effector cells with vastly improved capacity for homing into widespread, metastatic tissues is now possible by combinatorially leveraging and integrating new glycoengineering and genetic engineering technologies with the latest knowledge on immune-cell homing and cancer metastatic circuitries. See the paper by Sackstein *et al*, page 669.

Finally, the immune response remains a mainstay for understanding the cellular and molecular biology of this highly immunogenic tumor. Recent findings in the area of therapy through blockade of immune checkpoints have been encouraging. Our goal is to devise therapies that will induce regression in metastases, but potentially critical knowledge regarding regression in primary melanoma remains incomplete. Aung *et al* address this issue by examining what is currently known regarding the pathogenesis and clinical significance of regression in primary lesions. It is almost a truism that immune ablation of metastases will never be successful unless effector cells can successfully reach their targets. However, this goal is easier to conceive than to accomplish. In a magnum opus dealing with the issue of T-lymphocyte homing with regard to immunotherapy, Sackstein and coauthors present a state-of-the-art review of our understanding of the complex mechanism by which lymphocytes find their way into tumor tissue, with emphasis on therapeutic implications for future translational innovation.

These and many more new eyes will be deconstructing melanoma in 2017 and beyond. Indeed, we appear to be on the cusp of a steepening trajectory of progress in effective prevention of and impactful therapy for melanoma as we leverage and deploy informed approaches to translational investigation. There is much more to investigate—although examination of data, however big, or technology, however high, will not be enough. This is probably attributable to the transcendent reality articulated by Thoreau: 'It's not what you look at that matters, it's what you see.' And in the prevention and cure of one of the most aggressive cancers to which human flesh is heir, seeing may be everything.