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Origin of Mouse Melanomas

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In humans, melanomas are found mostly in the epidermis, whereas mouse melanomas are found in the dermis. It is, however, possible to force mouse melanomas to develop more efficiently in the epidermis. The histological location of a melanoma when discovered, whether in the epidermis or dermis, does not necessarily reflect the location of the original cell.

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Melanomas are caused by genetic and/or epigenetic modifications in melanocytes *in vivo*. Such modifications can be observed in biopsies from patients with melanoma, in which the initial transformation occurred many cell divisions earlier. Although the presence of genetic modifications is not in itself evidence of their causal role during melanomagenesis, the generation and use of mutant mice is a powerful approach in testing the direct pathophysiological role of mutations *in vivo*. Melanocytes may grow abnormally in mouse mutants, and some of the proliferating melanocytes may transform into melanoma cells that can metastasize. The relevance of such models to humans is a key issue in elucidating the molecular, cellular, and histological events that occur during melanomagenesis and to test new therapies. Evaluating the relevance of any melanoma model for humans is a difficult task for several reasons, including the variability of melanoma biology in humans, the absence of spontaneous melanomas in mice, and clear differences in the structure of skin in humans and mice.

The number of mouse melanoma models has increased regularly in recent years, and the models that are available have become increasingly sophisticated (for review see Larue and Beermann, 2007, and also see Delmas *et al.*, 2007; Dankort *et al.*, 2009; Dhomen *et al.*, 2009; Damsky *et al.*, 2011; Walker *et al.*, 2011; Rae *et al.*, 2012). All of these mouse melanoma models provide information about the oncogenic function of proteins of interest and are in most cases relevant to human melanoma at the molecular and cellular levels. In this issue, Handoko *et al.* (2012) elegantly illustrate this complexity with two models that are apparently quite similar (Walker *et al.*, 2011; Rae *et al.*, 2012). In both models, KITL is expressed in keratinocytes under the control of the K14 promoter (Kunisada *et al.*, 1998), and Map kinase is activated constitutively. In one, an activated form of Nras ($Nras^{Q61K}$) begins to be expressed during development, and in the other an activated form of Braf ($Braf^{V600E}$) is first expressed after birth.

A major difference between these two mouse melanoma models is that the expansion of the melanoma occurs in the dermis in one and in the epidermis in the other.

> Despite their dermal location, mouse melanomas are likely to be of epidermal origin.

Most human melanomas are thought to be epidermal in origin and to invade the dermis during progression, whereas in mice they are ordinarily dermal in origin. This suggests that the cells responsible for initiating mouse melanoma were of dermal origin. The critical question is whether this is always true, and if so is there evidence to support this concept?

The question at hand is the location of the cell from which mouse melanomas originate. There are few melanocytes in the interfollicular epidermis and dermis of 5-day-old mice. In fact, the largest populations of melanocytes are in hair follicles, which are epidermal appendices, located in hair-covered parts of the body. Mouse melanomas are most likely to arise from hairy parts of the body (mostly from follicular melanocytes), tail (mostly from epidermal melanocytes), and ear pinnae (mostly from dermal melanocytes). Melanomas occur much more frequently in the hairy part of the body than elsewhere. This may reflect differences in the numbers of melanocytes in these parts of the body or in differences in the likelihood of cells in each location to undergo transformation. At this point, we have little objective information about the propensity of cell populations in such locations to undergo transformation. However, it may be argued that most mouse melanomas are derived from the melanocytes that are located in hair follicles, an epidermal appendage. These cells are therefore most likely to be of epidermal origin.

In most cases, the melanomas invade the dermis relatively efficiently. Unfortunately, pathologists analyze tumors only after they have reached a certain size, and, consequently, this happens after a considerable number of tumor cell divisions (and days or weeks) have transpired. Moreover, histopathologic analysis cannot be used to investigate the associated dynamics and landmarks that might suggest epidermal origin. These most certainly would have disappeared by the time.

When a strong chemoattractant, such as KITL, is present in the epidermis, melanoma-initiating cells are expected to migrate superficially and to proliferate in a manner that leads to a ''pseudo'' superficial spreading melanoma. This is the case for Arf−/− ::Tyr-$Nras^{Q61K}$:: K14-Kitl. The melanoma-initiating cells are subjected to two major influences. KITL, which functions as a chemoattractant for melanocytes (and melanocyte

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stem cells) during melanocyte development and after birth, has an influence, provided that KIT is present on the surface of the tumor cells. The second influence results from the induction of the Map kinase pathway, via NRAS in this case, which is known to induce proliferation. In an NRAS-mutant (dominant-active) background, the balance between attraction and proliferation results in both attraction in the epidermis and subsequent proliferation. The melanoma-initiating cells then migrate out from the hair follicle, being attracted to KITL, and proliferate between keratinocytes in the epidermis.

In the presence of a strong chemoattractant and a very strong oncogene leading to massive proliferation, as for $BRAF^{V600E}$::K14-Kitl, the cells proliferate *in situ* in the follicle and rapidly invade the dermis. In a BRAF background, the balance between attraction and proliferation leads to proliferation *in situ* without migration toward the upper layers of the skin and with destruction of the basal layer separating the hair follicle and the dermis. This might be associated with a decrease in KIT levels in the presence of $BRAF^{V600E}$ or with other mechanisms.

Most melanocytes are located in hair follicles, and the transformation of dermal or epidermal (interfollicular or follicular) cells is, presumably, stochastic. As such, mouse melanomas are much more likely to arise from the epidermis than from the dermis. Thus, despite their dermal location, mouse melanomas are likely to be of epidermal origin, and this should not be forgotten when interpreting the results of studies using mouse melanoma models.

CONFLICT OF INTEREST

The author states no conflict of interest.

REFERENCES

Damsky WE, Curley DP, Santhanakrishnan M, Rosenbaum LE, Platt JT, Gould Rothberg BE *et al.* (2011) Beta-catenin signaling controls metastasis in Braf-activated pten-deficient melanomas. *Cancer Cell* 20:741–54

Dankort D, Curley DP, Cartlidge RA, Nelson B, Karnezis AN, Damsky WE Jr. *et al.* (2009) Braf(V600E) cooperates with Pten loss to induce metastatic melanoma. *Nat Genet* 41:544–52

Delmas V, Beermann F, Martinozzi S, Carreira S, Ackermann J, Kumasaka M *et al.* (2007) Beta-catenin induces immortalization of melanocytes by suppressing p16INK4a expression and cooperates with N-Ras in melanoma development. *Genes Dev* 21:2923–35

Dhomen N, Reis-Filho JS, da Rocha Dias S, Hayward R, Savage K, Delmas V *et al.* (2009) Oncogenic Braf induces melanocyte senescence and melanoma in mice. *Cancer Cell* 15:294–303

Handoko HY, Box NF, Walker GJ (2012) Modelling epidermal melanoma in mice: moving into new realms but with unexpected complexities. *J Invest Dermatol* 132:2299–302

Kunisada T, Yoshida H, Yamazaki H, Miyamoto A, Hemmi H, Nishimura E *et al.* (1998) Transgene expression of steel factor in the basal layer of epidermis promotes survival, proliferation, differentiation and migration of melanocyte precursors. *Development* 125:2915–23

Larue L, Beermann F (2007) Cutaneous melanoma in genetically modified animals. *Pigment Cell Res* 20:485–97

Rae J, Viros A, Hayward R, Bennett DC, Dhomen N, Longley BJ *et al.* (2012) (V600E)Braf::Tyr-CreERT2::K14-Kitl mice do not develop superficial spreading-like melanoma: keratinocyte Kit ligand is insufficient to "translocate" (V600E)Braf-driven melanoma to the epidermis. *J Invest Dermatol* 132:488–91

Walker GJ, Soyer HP, Handoko HY, Ferguson B, Kunisada T, Khosrotehrani K *et al.* (2011) Superficial spreading-like melanoma in Arf(-/-)::Tyr-Nras(Q61K)::K14-Kitl mice: keratinocyte Kit ligand expression sufficient to "translocate" melanomas from dermis to epidermis. *J Invest Dermatol* 131:1384–7