Published in final edited form as:

Exp Dermatol. 2015 April ; 24(4): 258–259. doi:10.1111/exd.12618.

The role of melanin pigment in melanoma

Radomir M. Slominski[1], **Michal A. Zmijewski**[2], and **Andrzej T. Slominski**[3,4,5]

[1]Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

[2]Department of Histology, Medical University of Gdansk, Gdansk, Poland

[3]Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

[4]Department of Dermatology, University of Alabama, Birmingham, AL

[5]Center for Adult Cancer Research, University of Tennessee Health Science Center, Memphis, TN, USA

Keywords

melanin; melanocytes; melanoma; melanosomes; metastatic phenotype

Commentary

The synthesis of melanin, a multistep and highly regulated pathway, represents a major differentiated function of normal and malignant melanocytes (reviewed in Refs 1,2). Although the main function of melanin is to protect against UV-induced damage, melanin pigment can also regulate epidermal homeostasis and thus can affect melanoma behaviour (3–7).

Recently, Sarna et al. (8) started to test a hypothesis that melanin pigment can affect the behaviour of melanoma cells *in vitro*. The authors had shown that the presence of melanin pigment affected the elastic properties of the cells as well as the transmigration abilities with the inhibitory effects being mechanical in nature. They had proposed that cell elasticity may play a key role in the efficiency of melanoma cells spread *in vivo* and expect that their findings can contribute to the better understanding of the process of metastasis of malignant melanoma.

We agree with the authors that the mechanical (physical) effect of loading of melanoma cells with melanin granules can attenuate the movement of malignant melanocytes towards the metastatic path. This would be expected for stage 1 melanomas that are localized in the epidermis and dermis. However, other parameters such as cell proliferation, changes in cell

Correspondence: Andrzej T. Slominski, MD, PhD, Department of Pathology, 930 Madison Avenue, RM525, Memphis, TN 38163, USA, Tel.: (901) 448-3741, Fax: (901) 448-6979, aslominski@uthsc.edu.

Conflict of interests

The authors have declared no conflicting interests.

cytoskeleton and motility need to be further investigated. It must be noted that SKMEL-188 cells, as well as the Bomirski Ab and AbC1 melanoma cells, when cultured in media supplemented with L-tyrosine, not only undergo rapid melanization within 3–5 days, but the induction of melanogenesis is accompanied by the dramatic changes in cyto-architecture such as round morphology of heavily pigmented cells (1). Also, the SKMEL-188 cells can easily detach from the substratum, which is in contrast to the amelanotic cells cultured in Ham's F10 medium (reviewed in Refs 1,3,5). Thus, the future challenge in this area is to define biophysical nature and mechanism leading to decreased adhesiveness of pigmented cells, defining changes in the cytoskeleton and establishing at which phase of cell cycle are cells with changed pigmentation level and attendant cyto-morphology.

Recent studies on the induction of melanogenesis in amelanotic human and hamster melanoma cell lines had demonstrated dramatic changes in the metabolic status of the cells and their behaviour both on biochemical and on molecular levels, which were accompanied with dramatic increases of HIF-1α expression in nuclear fractions isolated from pigmented cells (5). Based on the data presented (5) as well as information on the role of melanin and melanogenesis in melanocytic activity reviewed in Refs (1,3), some modifications to the original hypothesis that melanogenesis and melanin pigment can regulate melanocyte and neighbouring cells' behaviour (7) were presented that include a complex and reciprocal interactions that are context dependent and are nonlinear in nature with multitude of regulatory pathways/factors operating as outlined in Fig. 1.

Concerning the work by Sarna et al. (8), we fully agree with the authors that melanin pigmentation is an important marker, which should represent a part of synoptic reporting of melanomas by pathologists. Such report would identify melanogenesis-related proteins (MRP) as a target for immunotherapy; however, it would also include the limitations defined by action of intermediates of melanogenesis and its final product melanin pigment on the outcome of any type of therapy (1,5,6,9). Also, recent clinicopathological analyses demonstrated that high pigmentation level is inversely correlated with overall survival time (OST) and disease-free survival time (DFS) in patients with stages III and IV melanomas (10). As discussed in the corresponding papers (1,5–7,10), pathologically deregulated melanogenesis can shorten the OST and DFS of patients with melanoma through different mechanisms. Thus, melanin pigment and melanogenic apparatus can play an important role in the natural history of melanoma serving as a double edge sword (Fig. 2): protecting the melanocytes against UVR and oxidative stress, but at times accelerating melanoma's progression and attenuating the effects of current pharmacological treatment aimed at handling this devastating disease.

In conclusion, melanogenesis and melanin pigment affect the behaviour of normal and malignant melanocytes with potential implications in the therapy and diagnosis of melanoma.

Acknowledgements

RMS, MAZ and AST analysed data and wrote the paper. Writing of this commentary was supported in part by grants from NIH/NIAMS (2R06AR052190, 1 R21 AR066505-01A1 and 1R01AR056666 to AS).

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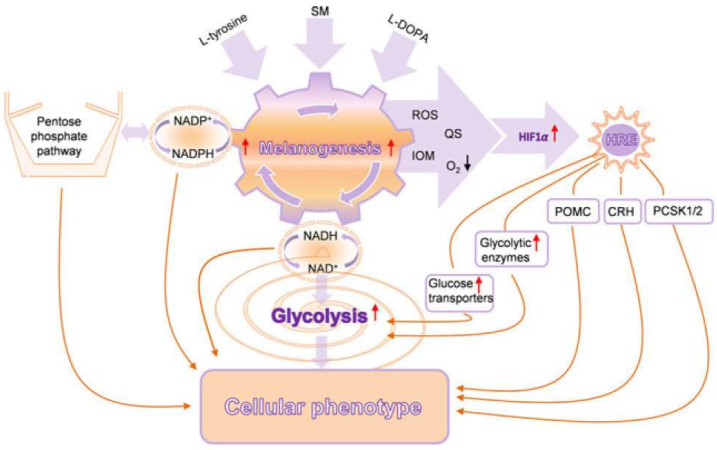

Figure 1.

Complex interactions between melanogenesis and cellular metabolism in melanoma cells. SM, stimulators of melanogenesis; ROS, reactive oxygen species; QS, quinones and semiquinones; IOM, intermediates of melanogenesis; POMC, proopiomelanocortin; CRH, corticotropin-releasing hormone; PCSK1/2, proprotein convertase subtilisin/kexin types 1 and 2. The figure is reprinted from (7) with the permission from the publisher.

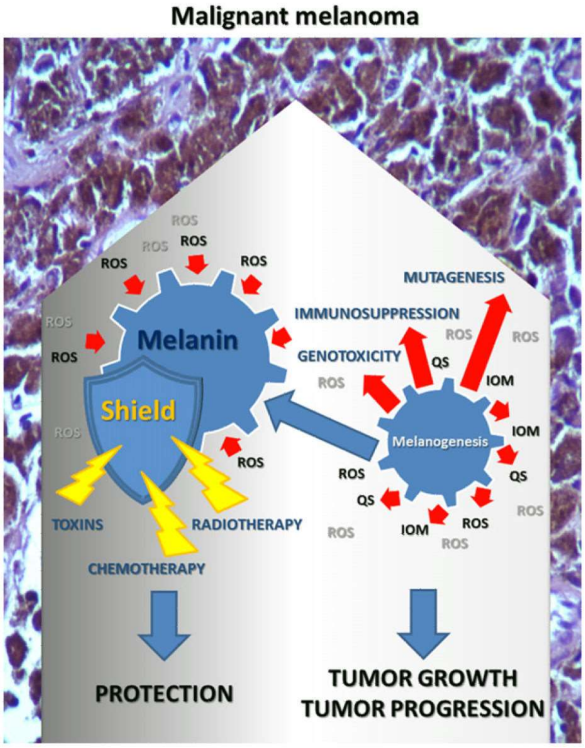

Figure 2.

Melanin and melanogenesis are a two-edged sword. Melanin acting as a radiation protector and scavenger of cellular toxins will protect normal melanocytes against noxious insults, but will attenuate effectiveness of radiation or chemotherapy (1,6). Furthermore, because of immunosuppressive, genotoxic and mutagenic properties, melanogenesis can enhance tumor growth or induce tumor progression (1,3,6,10).