FROM MELANOCYTES TO MELANOMA
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THE PROGRESSION TO MALIGNANCY

Edited by

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The normal precursor of malignant melanoma is the melanocyte, a cell of neural crest origin. In their embryological state, neural crest cells are unique in that they dissociate from the notochord on days 10–14 and migrate out, or “metastasize,” to numerous sites of the body as their new “homes.” These cells are known as “argentaffin cells” and include the melanocytes. Of interest is that melanocytes can also accumulate abnormally in clusters as nevi and thereafter reside in the lower stratum of the epithelium just above the level of the dermis (and occasionally in the dermis). The most important function of these melanocytes either singularly or in clusters is to manufacture melanin, a pigmented biopolymer that is distributed throughout the skin to protect the host from the damage of ultraviolet radiation. Indeed, the amount of pigmentation sets the background of racial groups in human beings. It is estimated that the number of melanocytes in the body is relatively constant between different racial groups, although the production of melanin varies dramatically from one race to the other. Melanocytes in lightly colored skin make the least amount of melanin, whereas melanocytes in darker skin make larger amounts of melanin, which provides significantly greater protection against the direct ultraviolet radiation at the equator and its subsequent photocarcinogenesis.

It is in the transformation and mutation of these melanocytes that melanoma cells are derived. Approximately 95% of the time, melanoma can be traced to a pre-existing nevus, but about 5% of the time, the original site may not be determined because melanoma presents as metastatic melanoma. Although melanoma is a potentially incurable disease, especially in its late stage, the overall incidence of melanoma is relatively low compared with other types of cancer. Of special interest is the incidence of cutaneous melanoma, which is dramatically lower in the more heavily pigmented populations, such as blacks and Asians. The mechanisms of melanogenesis have been studied, but are still not fully understood. It is our hope that *From Melanocytes to Melanoma: The Progression to Malignancy* presents all available evidence to date in order to establish a scholarly record of what is known about the progression of changes from melanocytes to melanoma. The intriguing differences between the lighter and darker skinned racial groups with respect to the different incidences of melanoma need to be explained. Patients with xeroderma pigmentosum (XP), a multigenic, multiallelic, autosomal recessive disease, have more than a 1000-fold increased risk of cutaneous melanoma. Thus, XP deserves special attention, since mechanisms responsible for the genesis of melanoma in these patients can be understood and applied to melanoma in general. One important goal of these studies is to understand the molecular mechanisms involved in melanogenesis and in malignant transformation of melanocytes. Potential therapeutic maneuvers may then be developed to either block these steps or use relevant specific molecules of melanogenesis as targets of attack.

*From Melanocytes to Melanoma: The Progression to Malignancy* is divided into three parts, with Part I addressing the basic biology of melanocytes and the molecular mechanisms involved in the development, migration, and differentiation of melanoblasts to melanocytes. Part II is devoted to elucidating processes involved in the transformation of melanocytes to malignant melanoma. Finally, Part III focuses on mechanisms
involved in the further progression of primary melanomas into invasive and metastatic melanomas. We hope that by studying the molecular signals involved in these processes, we will be able to develop model systems by which we can trace the molecular mechanisms involved in the malignant transformation of melanocytes to malignant melanoma. From Melanocytes to Melanoma: The Progression to Malignancy will be a valuable reference for all biologists and basic scientists who are interested in the biology of pigment cells, as well as to pathologists, dermatologists, surgeons, and medical oncologists who are interested in the diagnosis and treatment of melanoma.

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LIST OF COLOR PLATES

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**Color Plate 1.**  
*Fig. 2, Chapter 11:* Field cells in acral melanoma detected by fluorescence *in situ* hybridization. Single basal melanocytes with amplifications of cyclin D1 highlighted by arrowheads. (*See* discussion on p. 203.)

*Fig. 6, Chapter 13:* RB is required to suppress apoptosis in normal melanocytes. (A) Nonpigmented hair shaft of TAT-Cre-treated RB<sup>LoxP/LoxP</sup> hair follicles compared with pigmented RB<sup>LoxP/+</sup> hair shaft. (*See* complete caption on p. 232 and discussion on pp. 231–232.)

**Color Plate 2.**  
*Fig. 7, Chapter 13:* RB is highly abundant in melanoma cells relative to normal melanocytes. (A) Western blot showing expression of RB in normal melanocytes (NM) vs melanoma cell strains from different tumors (1–8). (*See* complete caption on p. 233 and discussion on pp. 232–233.)

*Fig. 4, Chapter 18:* Structural model of the leucine to proline substitution at position 65 of p16 (from ref. 72). The model shows that the proline amino acid (indicated in orange), differently from the leucine (behind the proline), no longer makes hydrogen atoms available to the surface of the protein, possibly affecting the ability of this protein to complex or bind with its ligand. (*See* discussion on p. 336.)

**Color Plate 3.**  
*Fig. 2, Chapter 21:* (A) Noninvasive optical imaging of melanoma xenografts. (*See* complete caption on pp. 406–407 and discussion on p. 406.)

**Color Plate 4.**  
*Fig. 2, Chapter 26:* Detection of melanoma inhibitory activity (MIA) by immunohistochemistry. (*See* complete caption on p. 479 and discussion on p. 478.)

*Fig. 1, Chapter 30:* Diagrammatic representation of vasculogenesis, angiogenesis, and photomicroscopy of tumor cell vasculogenic mimicry. (*See* complete caption on p. 537 and discussion on p. 536.)