The Histogenetic Model of Melanoma in the Modern Era of Personalized Medicine

Malignant melanoma (M) can be defined, quite simply, as a malignant neoplasm derived from melanocytes; however, there is great histological and, consequently, clinical variability from case to case (1). In order to try to overcome this intrinsic difficulty, various classification systems have been proposed over the years; as part of this effort, the World Health Organization (WHO) introduced its famous classification about half a century ago (2). Currently, the International Classification of Diseases for Oncology (ICD-O), provided by the WHO International Agency for Research on Cancer (IARC), distinguishes the *in situ* forms from invasive ones, recognizing four main morphological subtypes: nodular M, superficial spreading M, lentigo maligna M, and acral lentiginous M (3). The ICD-O classification includes further morphological codes, such as: balloon cell M, regressing M, amelanotic M, M in junctional nevus, M in precancerous melanosis, desmoplastic M, neurotropic M, mucosal lentiginous M, M in giant pigmented nevus / congenital melanocytic nevus, mixed epithelioid and spindle cell M, epithelioid cell M, spindle cell M (not otherwise specified), spindle cell melanoma (type A), spindle cell M (type B), and malignant blue nevus (3). Alongside a strictly morphological classification, a histogenetic model, based on the concept of tumor progression, has been regaining ground (4,5). In fact, at the onset, M is characterized by a non-tumorigenic radial growth phase (RGP), inside the epidermis (intraepidermal) or within the papillary dermis (microinvasive), which is devoid of metastatic potential and which may be followed, early or late, by a tumorigenic vertical growth phase (VGP), with deeper extension in the dermis or beyond, nodular confluence, mitotic activity, and metastatic capacity (Table 1). The unique exception to this is nodular M, in which either RGP is rapidly overrun by VGP or the tumor arises directly from dermal melanocytes (6). Today, Breslow depth remains the single most important prognostic factor for clinically localized primary M: it allows us to distinguish M as ultra-thin (≤0.5 mm), thin (≤1 mm), thick (>1 mm), or ultra-thick (>6 mm) (7-10). The systematic application of the histogenetic model to Breslow depth allows us to explain the oft-debated question why some thin M behave aggressively: because they possess an early tumorigenic VGP inside them (11). Moreover, any diagnostic report should be also accompanied by further well-known microstaging attributes, such as Clark level, mitotic count, lymphovascular invasion, perineural infiltration, ulceration, satellitosis, tumor infiltrating lymphocytes, and, if available, sentinel lymph node status (12,13). In conclusion, we believe that a renewed histogenetic approach to M diagnosis deserves wide scientific dissemination in order to achieve better clinical management of individual cases in the era of personalized medicine.

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Table 1. The non-tumorigenic radial growth phase encompasses intraepidermal lesions, namely lentigo maligna and in situ melanoma (M), and the microinvasive forms comprising ultra-thin M and the vast majority of thin M. Only a small quota of thin Ms, burdened by an aggressive biological behavior, shows an early tumorigenic vertical growth phase. In contrast, a late tumorigenic vertical growth phase is constantly present in all thick and ultra-thick M.

MELANOMA PROGRESSION MODEL	
NON-TUMORIGENIC RADIAL GROWTH PHASE (RGP)	**TUMORIGENIC VERTICAL GROWTH PHASE (VGP)**
a) Intraepidermal RGP	**a) Early VGP**
b) Microinvasive RGP	**b) Late VGP**

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Received: December 24, 2018

Accepted: November 16, 2020