PERSPECTIVE

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Melanoma Management

No one should die of melanoma: a vision or impossible mission?

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Practice points

- There has been a significant rise in the incidence of thin melanomas, while the incidence of thick melanomas has remained relatively stable.
- This divergent trend may be explained by a dermal origin for thick, fast-growing melanomas, making current screening efforts in order to improve their early detection impossible.
- Cutaneous melanoma can be collected into three main histogenetic groups with peculiar epidemiological, morphological and molecular characteristics.
- The traditional unifying model of melanoma progression suggests that all melanomas derive from malignant transformed epidermal melanocytes.
- The traditional model of melanoma progression does not plausibly explain some of the striking differences between the nodular and superficial spreading melanoma subtypes.
- An alternative model of melanomagenesis suggests that nodular melanoma, superficial melanoma and lentigo maligna derive from melanocytes located in the dermis, epidermis and hair follicles, respectively.
- Melanocyte specification, maturation and migration from the neural crest is a progressive process following a defined direction.
- Human skin at birth contains cells with different melanocyte specifications at different levels of the skin, including the dermis, epidermis and the hair follicles.
- Recent insights into clinical morphology, including histopathology and reflectance confocal microscopy, support the notion of an intradermal origin of nodular melanoma.
- Recent data from molecular research support the notion that nodular melanoma is a distinct entity.
- A dermal origin of melanoma implies that current screening strategies are insufficient to enable early diagnosis.

SUMMARY While the incidence of early-stage melanoma has dramatically increased over the past decades, the incidence and mortality rates of thick melanomas have remained relatively stable during the same period. A number of alternative theories have been postulated in order to explain these divergent trends between thin and thick melanomas, among which is the question of whether nodular melanoma may originate in the dermis. This concept has gained support from recent improvements in the understanding of the origin of melanocytes and the morphological and molecular diversity of melanoma. A dermal origin would plausibly explain why efforts at improving the early detection of melanoma largely fail, as it implies an initially intradermal growth that is hidden from our eyes until clinical signs and symptoms become only secondarily apparent. In light of this, at the current stage, the vision that no one should die of melanoma is an impossible mission.

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Background

• Trends in melanoma epidemiology

Melanoma incidence has dramatically increased over the past decades, which has led to a call for this phenomenon to be labeled a 'melanoma epidemic'. However, the significant rise in incidence is mainly observed only for early-stage melanomas, while the incidence and mortality rates of thick melanomas have remained relatively stable over the same period [1–6].

Although some believe that the epidemic of thin melanomas is the result of improved screening and surveillance, allowing for an earlier diagnosis of melanoma, this explanation largely fails to explain the stable incidence and mortality rates of thick melanomas. In fact, if screening has resulted in an earlier detection of all melanomas, the incidence and mortality of thick melanomas should, after an initial increase, subsequently decrease. However, this is not the trend that has been observed [2,5,6].

• Theories to explain the melanoma epidemiology

Accordingly, a number of alternative theories have been postulated in order to explain the divergent trends between thin and thick melanomas. Among these are the rising detection of biologically indolent melanomas that would never have affected overall survival, shifts among histopathologists towards overdiagnosis of melanoma, medicolegal issues, length time bias and the provocative question as to whether thick, fast-growing melanomas originate in the dermis and, as a consequence, their initial proliferation is hidden from our eyes, making current efforts to improve the early diagnosis of melanoma into an impossible mission [1,2,7–10].

Melanoma classification

It must be admitted that the term 'cutaneous melanoma' encompasses a heterogeneous subset of malignant melanocytic proliferations that differ significantly with respect to their epidemiology, morphology, growth dynamics, genetics and potential to metastasize [11–13]. Even though the classification of cutaneous melanoma is an evolving science and, as a result, different schemes are applied for the classification of melanoma, cutaneous melanomas can be assigned into three main groups.

• Slow-growing melanoma

Slow- or very-slow-growing melanomas (classically referred to as superficial spreading or lentiginous types) show the strongest increase in incidence across time and are associated with intermittent sun exposure, a high nevus count and *BRAF* mutations. This melanoma subtype is clinically characterized by the classical ABCDE criteria (A: asymmetry; B: border irregularity; C: color variegations; D: diameter >5 mm; and E: evolution over time) and, upon dermoscopy, commonly reveals pigmented patterns, such as a network and regression [13–15]. Regression is a histopathological feature due to fibrosis and melanophages, which appears dermoscopically as white structureless areas with gray dots or gray hue.

• Fast-growing melanoma

Thick, fast-growing melanomas (often referred to as nodular melanomas) show a stable incidence across time and are not associated with sun exposure, a high number of nevi and freckles and *BRAF* mutations [11]. In contrast to slow-growing melanoma, this melanoma subtype often presents clinically as symmetric, pigmented or nonpigmented firm and rapidly growing nodules with well-defined borders. Accordingly, the EFG rule (E: elevation; F: firm on palpation; and G: continuous growth for >1 month) has been proposed for its clinical diagnosis [16]. Dermoscopically, fast-growing melanomas lack recognizable pigmented structures, but have structureless blue and black colors or, in the case of amelanotic melanoma, atypical vascular patterns [17–19].

• Lentigo maligna

Classical lentigo maligna shows an increasing incidence across time and is associated with chronic sun exposure, but not with a high nevus count or *BRAF* mutations. Similarly to slow- or very-slow-growing melanomas, lentigo maligna is typified by a long-lasting *in situ* growth phase. Accordingly, it can acquire a significant, large diameter over time [11,20].

Traditional concepts of melanomagenesis and progression

Regardless of the striking differences between these three main groups of melanoma, many still agree with the traditional unifying model of melanoma progression. This model postulates that all melanomas derive from malignant transformed epidermal melanocytes, which initially proliferate along the basal layer (melanoma *in situ*) before acquiring the ability to

invade into the dermis (invasive melanoma). According to this model, the only determinant defining whether a melanoma will grow rapidly and cause death or not is the time needed by the transformed cells to change their horizontal growth into vertical growth. However, this epidermal origin model of melanoma fails to address why nodular melanoma commonly presents as symmetric, well-defined nodules in the absence of a lateral *in situ* component, why it is commonly amelanotic, why it shows a predilection for the head/neck region, why it grows so much faster than any other subtype and why all of the screening improvements have not affected its early detection. Recent improvements in the understanding of the origin, migration and maturation of melanocytes during embryogenesis, along with novel insights into the morphological diversity of nevi and melanomas using dermoscopy, digital dermoscopic follow-up and reflectance confocal microscopy, have led to an alternative model that suggests that nodular melanomas may originate from malignant transformed melanocytes in the dermis [10].

The making of a melanocyte

• Melanocyte origin

The current understanding is that melanocytes differentiate from the neural crest, which is a transient population of cells that delaminates from the neural tube and migrates extensively throughout the embryo during vertebrate development. Melanocyte specification from neural crest precursors is a progressive process during which initially pluripotent cells become restricted to the melanogenic lineage and adopt the gene expression profile and morphology of melanocytes. This specification process is governed by a variety of signaling molecules and pathways [21].

Once the melanogenic fate has been determined, melanoblasts (i.e., melanocyte precursors) migrate mostly along the dorsolateral pathway into the developing skin, whereby they progressively acquire pigment-producing capabilities (i.e., maturation) and the shape of melanocytes. The sequence of melanoblast migration into the skin therefore follows a timely, well-defined intradermal (6–8th gestational week), intraepithelial (12–13th gestational week), intrafollicular (15–17th gestational week) and cephalocaudal and dorsoventral progression [22].

• Melanocytes in human skin

Remarkably, it has been shown that by the end of gestation, dermal melanocytes have disappeared apart from in three anatomic regions: the head/neck, the dorsal aspects of the extremities and the presacral region, in which cells with markers of melanoblasts reside in the dermis even after completion of the intrafollicular migration stage [22]. Accordingly, the human skin contains melanocytic cells at different stages of migration and maturation at different levels of the skin, including in the dermis. This finding supports the notion that some melanocytic tumors, including intradermal nevi and nodular melanomas, may arise from a proliferation of cells with melanocytic lineage in the dermis [23]. Further support for a dermal origin of nodular melanoma is provided by morphologic studies using histopathology, dermoscopy and reflectance confocal microscopy, which is a noninvasive, *in vivo* diagnostic tool that enables the visualization of the skin at a cellular level [24–26].

Lessons from clinical morphology

Several lines of evidence prove that both intradermal nevi of the Miescher type and nodular melanomas have a remarkable predilection for the head/neck area [27–32].

• Histopathology

In this context, a study by Dadzie *et al.* is of particular interest, in which the authors reported the presence of clinically unapparent, incidental small nevic aggregates in the dermis of normal skin from pathology specimens obtained from excisions [24]. Notably, these dermal nevic aggregates were most commonly observed in specimens from the head and neck area. It appears possible that both intradermal nevi of the Miescher type and also nodular melanomas may originate from a proliferation of these small dermal aggregates.

• Noninvasive skin imaging techniques

Other intriguing observations have been provided by studies using reflectance confocal microscopy. Segura *et al.* compared the confocal and histopathological findings between nodular melanomas and secondary nodular superficial spreading melanomas [25]. Remarkably, they found only sparse pagetoid spread and a relatively preserved epidermis over nodular melanomas, while nodules arising secondarily in superficial spreading melanoma subtypes were

typified by a marked epidermal disarrangement and abundant pagetoid infiltration.

This observation has been recently confirmed by another confocal study in which the authors investigated the confocal–histopathological correlates in a series of pigmented nodular melanomas that had been dermoscopically characterized only by their blue and black color [26]. Notably, in this study, the authors noticed a significantly thinned epidermis overlying a massive infiltrate of dermal atypical melanocytes. Accordingly, the authors speculate that ulceration in nodular melanomas may appear secondary to the constant epidermal extension and thinning of the upward bulging of rapidly proliferating dermal cells.

Lessons from basic research

Besides these new insights into clinical morphology, recent data from basic research also support the notion that nodular melanoma is a distinct biological entity [33].

• MAPK pathway

Much research has focused on the oncogenic mutations involved in the MAPK pathway (RAS/RAF/MEK/ERK), which has been identified to be a critical growth pathway in melanocytic tumors. Notably, mutually exclusive oncogenic mutations in *NRAS*, BRAF and *HRAS*, as well as those involving the *GNAQ* gene, occur at variable frequencies in both nevi and melanomas and appear to be linked to specific histogenetic and morphological tumor characteristics [34–37].

Oncogenic *BRAF* is the most common mutation among all melanomas, but it occurs at the highest frequency in melanomas of the superficial spreading subtype. By contrast, other types of melanoma, including fast-growing nodular melanomas and blue melanomas (often contradictorily referred to as malignant blue nevi) display mutations in other genes, such as *NRAS* or *GNAQ*, respectively [33,36,37]. Of particular interest in the discussion regarding a dermal origin of nodular melanomas are the findings that large to intermediate congenital nevi and blue nevi, which are widely accepted as originating in the dermis, frequently harbor mutations in *NRAS* and *GNAQ*, respectively [23,38–40].

• Stem cell markers

Of further interest is a study showing that nestin, a neural stem cell marker, was highly expressed among amelanotic and pigmented nodular melanomas (up to 80%), whereas its expression was only seen in a minority of melanomas of the superficial spreading type [41,42].

Conclusion

While it is increasingly being accepted that benign melanocytic proliferations such as intradermal nevi, large to intermediate congenital nevi and blue nevi originate in the dermis, many still do not believe in a dermal origin of melanoma. However, it must be recognized that there are several lines of evidence in support of a dermal origin of nodular melanomas. Although this concept remains speculative, it provides plausible answers to some of the key questions that remain unanswered by the traditional concept of melanomagenesis. For example, the fact that nodular melanomas may derive from not fully developed and matured melanocytes in the dermis could well explain why they are commonly amelanotic, as these cells have not acquired the capability to produce pigment. This also explains why they grow so much faster, as not fully matured cells have a higher proliferative capacity than fully matured dendritic cells. It also explains why nodular melanomas commonly present as symmetric nodules, as they lack any epidermal involvement, and why they are biologically much more aggressive, because they grow in a microenvironment that has a high vascular supply and a lack of proliferation-controlling keratinocytes. Finally, this concept also explains why all efforts at improving the early detection of nodular melanomas have largely failed, as they initially grow while they are hidden from our eyes until the proliferating cells acquire enough volume to give a secondary rise to clinical signs and symptoms.

Future perspective

In light of these findings, the vision that no one should die of melanoma [43] is, at the current stage, an impossible mission.

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