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Trajectories of premalignancy during the journey from melanocyte to melanoma

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Summary

A stepwise progression from melanocytic precursors to cutaneous melanoma is a well-established model, based on decades of careful observation and morphological analysis. The steps identified are benign melanocytic naevus, dysplastic naevus, 'radial growth phase' melanoma (including melanoma *in situ*) and 'vertical growth phase' melanoma (also termed tumourigenic melanoma). Recent genomic data have refined the understanding of the steps of melanoma development and their relationship to one another. These data support the existence of dysplastic naevi as distinct lesions; suggest the importance of clonal dynamics in the precursor steps of melanoma; and confirm the carcinogenic role of ultraviolet radiation throughout early melanoma development and progression. In this review, the steps of melanoma development and progression are summarised and discussed in the context of recent genomic studies. This new understanding of melanoma pathogenesis that has been facilitated through careful correlation of morphological and molecular features will allow the identification and development of robust biomarkers to assist in more accurate diagnosis and prognostication of melanocytic tumours.

Key words: Melanoma; pathology; naevus; diagnosis; tumour progression; carcinogenesis.

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INTRODUCTION

Melanocytic neoplasms are both common lesions in clinical practice and a frequent source of diagnostic difficulty for the general surgical pathologist. While unequivocally benign and malignant lesions pose little diagnostic challenge, there exists a spectrum of morphological changes that are borderline or atypical which span the range of appearances between these two extremes. Such cases are frequently difficult to classify with poor interobserver reproducibility of pathological diagnosis. Prior work has suggested that the spectrum of morphologically intermediate melanocytic lesions represent different stages of development in melanoma progression from benign precursors to malignancy.[1–4] As such, a deeper understanding of these precursor lesions may allow more accurate classification and prognostication of difficult to classify melanocytic neoplasms.

Recently developed next-generation sequencing technology has permitted the analysis of substantial portions of the genomes of melanoma precursors. The recent work by Shain *et al.*[5] has provided a wealth of genomic data with which to derive models of progression in cutaneous melanocytic neoplasia. As such, the understanding of melanoma evolution and the relationship of melanoma to precursor lesions has become clearer, and there may, in time, be opportunities to utilise genomic data to assist pathologists' clinical practice when they encounter difficult melanocytic lesions.

In this review, we summarise recent studies evaluating the genomics of melanoma evolution as well as the role of ultraviolet radiation in melanoma pathogenesis.

BRIEF HISTORY OF THE 'CLASSIC' STEPWISE NAEVUS-TO-MELANOMA PROGRESSION PARADIGM

A link between naevi and melanoma has been suspected since at least 1857, when William Norris noted a relationship between the development of melanoma and increased numbers of moles in patients. This relationship consists of two aspects: firstly that an elevated number of naevi is a risk factor for the development of melanoma *de novo*, and secondly that certain naevi, being spatially contiguous with melanoma, are the lesions from which some melanomas originate.

A number of studies have noted that some melanomas arise in association with pre-existing naevi (Fig. 1). A recent meta-analysis of 25 such studies[6] reported that approximately 30% of melanomas have an adjacent naevus. This is strong circumstantial evidence that a proportion of melanomas develop from recognisable precursor melanocytic naevi, and presented an opportunity for dissecting the genomic steps of progression, as discussed in detail below.

More than a century after Norris reported his seminal observations, the concept of a stepwise progression from benign naevus to invasive melanoma in specific lesions was proposed by the eminent US pathologist Wallace Clark and others.[1,7] In Clark's model (summarised in Table 1), there are six clinically and histologically defined steps to melanoma: (1) the common melanocytic naevus; (2) melanocytic naevus with lentiginous hyperplasia (aberrant differentiation); (3) melanocytic naevus with aberrant differentiation and nuclear atypia (melanocytic dysplasia, or dysplastic melanocytic naevus); (4) the radial growth phase of

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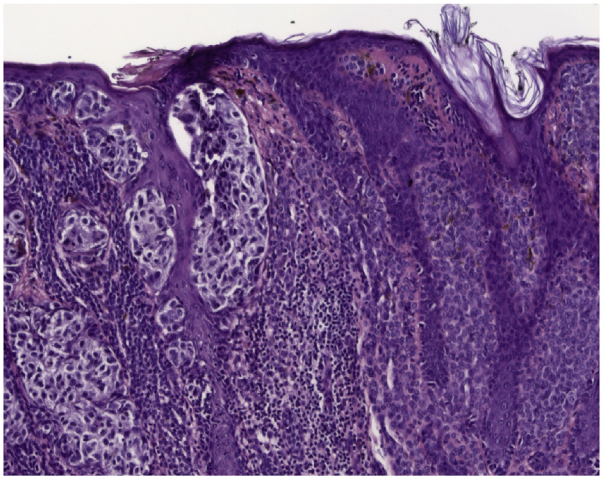

Fig. 1 Compound naevus adjacent to melanoma. The nests of melanoma cells (right) are strikingly different from the naevocytes (left); however, genomic data support the melanoma cells arising from the naevus.

melanoma (melanoma *in situ* or invasive non-tumourigenic growth); (5) the vertical growth phase of melanoma (invasion that is tumourigenic); (6) metastasis. Somewhat prophetically, specific mutational events were surmised for different steps in this progression model.[1] Furthermore, similarity between a naevus-to-melanoma tumour progression pathway and a colonic adenoma-carcinoma pathway was highlighted by McGovern in 1983.[3] For the purposes of the following discussion, it should be noted that steps 2 and 3 of Clark's model described above correspond to the spectrum of morphological changes observed in dysplastic naevus. Importantly, Clark's stepwise model was linear, with sequential steps having properties superimposed on those of previous steps. Of note however, all morphological intervening steps were not necessary for melanoma development, consistent with Clark's earlier work[8] and numerous other studies mentioned previously,[6] which highlight that melanoma can develop in association with naevus and without recognisable intervening steps. In addition, consistent with clinical observations, in this model melanoma progression is a rare event for most precursor lesions, with the majority of early precursors representing 'dead ends', i.e., never progressing to melanoma.

MUTATION CORRELATES IN NAEVUS-MELANOMA PROGRESSION PATHWAY

Although many of the elements of a stepwise pathway for melanoma pathogenesis had been proposed and accepted for some time, the actual genotypic correlates had not been systematically studied until recently. In their landmark study, Shain *et al.* performed targeted sequencing on melanomas and their adjacent precursor melanocytic lesions.[5] This study confirmed the early acquisition of activating MAPK mutations in *BRAF* and *NRAS*, with *BRAF* V600E being present in the majority of benign naevi and an increased proportion of *BRAF* non-V600E and *NRAS* mutations in so-called 'intermediate' lesions (a term covering the spectrum of dysplastic naevi). Recently described mutations in the *TERT* promoter were found in intermediate lesions and more advanced lesions, but not in benign naevi. Loss of *CDKN2A* (encoding tumour suppressors p16 and $p14^{ARF}$) and mutations in SWI/SNF subunits were confined to early invasive melanoma. Moreover, localised primary melanocytic lesions harboured increased mutation loads with progression, with most mutations matching an ultraviolet (UV) signature, consistent with the role of UV radiation as the main aetiological agent in melanoma pathogenesis.

ULTRAVIOLET RADIATION AS PRIMARY AETIOLOGICAL AGENT IN CUTANEOUS MELANOMA

Multiple lines of evidence support the role of ultraviolet radiation from sunlight as the primary carcinogen responsible for melanoma development, similar to other cutaneous malignancies. Epidemiological studies have built upon the seminal observations of Lancaster, who in 1956[9] documented an inverse correlation between latitude and melanoma incidence and mortality for demographically similar populations.[10] In contrast to most cutaneous malignancies, where risk of development is correlated to lifetime duration of UV exposure, the risk of cutaneous melanoma is more strongly related to the number of episodes of intense UV exposure (i.e., sunburn) before the age of 10.[11,12] Further evidence is provided by the increased incidence of melanoma in people who use tanning beds which are a source of artificial UV light.[13]

Table 1 Summary of the morphological and genomic components of the steps of melanoma progression identified by Clark *et al.*[1]

Step	Lesion	Description	Timing of genomic correlates with timing of acquisition
1	Common acquired melanocytic naevus	Junctional, compound or dermal naevus	BRAF V600E
2	Naevus with lentiginous hyperplasia	Corresponds to dysplastic naevus, with cytological and architectural atypia	BRAF non-V600E[a] NRAS[a]
3	Naevus with lentiginous hyperplasia and nuclear atypia		*TERT* promoter mutations
4	'Radial growth phase'	Melanoma *in situ* or non-tumourigenic nests within dermis	?loss of CDKN2A ?SWI/SNF mutations *TERT* promoter mutations
5	'Vertical growth phase'	Expansile tumourigenic nests within dermis	Loss of CDKN2A SWI/SNF mutations Non-UV mutations Branching subclones
6	Metastatic melanoma	Melanoma cells with autonomous growth in sites distant from the primary	Non-UV mutations Branching subclones

[a] Mutually exclusive mutations.

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