IN ATOPIC DERMATITIS,

EPISODIC CONTROL MAY NOT GET TO THE CORE OF THE PROBLEM

UNDERLYING, PERSISTENT INFLAMMATION IS A CAUSE OF LESIONS AND ITCH, THE PRIMARY SIGNS AND SYMPTOMS OF ATOPIC DERMATITIS[1-3]

Addressing the source of this inflammation may be key to keeping current and future disease signs and symptoms, including itch, at bay.[1,2]

Some patients may need strategies that manage the overall disease course of atopic dermatitis, instead of reacting only to episodic flares on the superficial layers.[4]

A proactive approach is warranted for management of the persistent inflammatory process, which, even if subclinical, is always present.[5]

SANOFI GENZYME

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REVIEW ARTICLE

Dysplastic/Clark naevus in the era of molecular pathology

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ABSTRACT

Dysplastic naevus has been a controversial entity since its first description by Clark in 1978. Despite a recent paradigm shift from the initially proposed notion that dysplastic naevus is a precursor to melanoma, its management has been increasingly more aggressive in the last decade. The latter is due to an unresolved uncertainty regarding its biological nature which necessitates further clarification. Recent molecular genetics, epigenetic and transcriptomic discoveries have revealed that a subset of dysplastic naevi exhibits a genomic profile which is intermediate between that of benign naevus and melanoma. This group of lesions often shows somatic mutations in non-*V600E BRAF*, *NRAS* and *TERT* and hemizygous deletion of *CDKN2A* gene as well as upregulation of genes involved in proliferation, cell adhesion and migration, and epidermal and follicular keratinocyte-related genes. These new genomic insights suggest that a proportion of dysplastic naevi have a greater propensity to evolve to melanoma; however, the clinical and histopathological features of this proposed intermediate category are still to be elucidated by further research.

Key words: *BRAF*, *CDNK2A*, Clark naevus, common melanocytic naevus, dysplastic naevus, gene expression profile, melanoma, *NRAS*, *TERT*.

INTRODUCTION

In the emerging era of molecular pathology, our knowledge of mechanisms involved in initiation and evolution of melanocytic neoplasms is expanding. We are rapidly learning about the dynamic alterations occurring at the molecular level during the development of melanocytic naevi and their progression to melanoma. Atypical or so-called 'dysplastic' naevus has been a subject of debate since its initial description in 1978[1] with no definite resolution after decades of controversy. There has been much uncertainty about its biological nature and substantial inter-observer variability in the morphological classification and grading of dysplastic naevus due to the lack of minimum well-established diagnostic criteria. A recent survey has revealed that American dermatologists increasingly believe that patients with dysplastic naevus have additional risk of developing melanoma, and they perform significantly more re-excision of moderately and severely dysplastic naevus with positive margins in 2015 (67% and 98%, respectively) versus 2001 (28% and 67%, respectively).[2] In 2015, up to 49% of dermatologists re-excise severely dysplastic naevi with negative margin and 10% of them perform re-excision for moderately dysplastic naevi.[2] A similar survey conducted in Australia in 2017 showed that 49% and 81% of dermatologists would re-excise a mildly and a moderately dysplastic naevus with positive margin, respectively.[3] If a severely dysplastic naevus involved margins, 62% of Australian dermatologists would aim for a re-excision for complete removal of the lesion, and 37% would choose a 5-mm clinical clearance.[3] These surveys highlight a trend towards a more aggressive management of dysplastic naevus in recent years; however, there is still little evidence to justify this approach.

This manuscript represents a comprehensive review of the latest molecular genomic discoveries on dysplastic naevus in comparison with those on banal naevus and melanoma in an attempt to shed light on the biological nature of this controversial entity.

HISTORICAL PERSPECTIVES

Dysplastic naevus was first described by Clark and colleagues in 1978 in six melanoma-prone families who also had multiple clinically atypical naevi.[1] Subsequently, it has

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been recognised that morphologically similar lesions can occur sporadically in individuals without familial predisposition for melanoma.[4] Dysplastic naevus is clinically characterised by atypical features including larger size (usually > 5 mm), asymmetry, border irregularities and heterogeneous pigmentation.[5] While variable histopathological criteria for diagnosis of dysplastic naevus have been proposed by several groups and health institutions, most of which using a combination of architectural and cytologic atypia together with stromal alterations,[5] the minimum diagnostic features have never been established. On the other hand, the proposed microscopic criteria show some overlap with those of early melanomas.[6] Owing to these overlapping morphological features and the uncertainty of biological significance of the spectrum of atypia observed in dysplastic naevus, there is significant inter-observer variability and lack of precision and consistency in diagnosis and specifically grading of dysplasia amongst pathologists.[5,7,8] In addition, anecdotally there is a higher rate of seeking a second opinion and using descriptive diagnoses as well as a tendency to over-diagnose lesions such as melanocytic naevus with mild architectural disorder, recurrent/traumatised naevi or naevi of the special sites as 'dysplastic' by less experienced pathologists to the extent that ironically at some practices and in some studies, dysplastic naevus is reported more commonly than 'common' melanocytic naevus.[5]

There has been a large volume of publications in late 70s and early 80s advocating for a premalignant nature of dysplastic naevus in both familial and sporadic setting.[4,9–12] Simultaneously and later on, some authorities have expressed strong contradictory views and believed that dysplastic naevus is entirely benign and simply a variant of common melanocytic naevus regardless of the scale of histopathological atypia[13–15]; however, there has been no robust evidence to back up one or the other side of the argument. At the present time, after years of debate, there is an overall agreement amongst most experts that a high naevus count and presence of large dysplastic naevi[16] in a given individual are associated with an increased risk of melanoma up to 15-fold, although the probability of a single dysplastic naevus to progress to melanoma is either similar or slightly higher than that of a common melanocytic naevus.[7,17]

MOLECULAR PROFILE OF DYSPLASTIC NAEVUS IS DISTINCT FROM BANAL NAEVUS AND MELANOMA

It has become apparent from recent molecular genomic and transcriptomic studies that dysplastic naevi exhibit a range of molecular alterations, which is intermediate between those observed in banal naevi and those seen in melanoma. It has been shown previously that a proportion of patients with familial dysplastic naevus harbour germline mutations in tumour suppressor genes such as *CDKN2A* and *CDK4*.[18] New studies using high throughput next generation sequencing (NGS) have established that dysplastic naevus harbours a higher burden of mutations compared to congenital and common melanocytic naevus; however, the average mutation frequency in dysplastic naevus is much less than that of melanoma.[19,20]

In a recent seminal paper, Shain and colleagues[21] demonstrated common molecular alterations and evolutionary trajectories of melanocytic neoplasms from melanocytes to melanoma. They observed that there is a subset of morphologically intermediate melanocytic neoplasms, which is highly populated by dysplastic naevus, exhibiting a molecular profile intermediate between that of unequivocally benign naevus and that of malignant melanoma. These lesions showed common molecular alterations such as somatic non-*V600E BRAF*, *NRAS* and *TERT* promoter mutations and hemizygous deletion of chromosome 9p21 where *CDKN2A/p16* gene is located.[22] Furthermore, it has been demonstrated that lesions in this category tend to show additional weakly activating mutations in other genes involved in mitogen-activated protein kinase (MAPK) pathway such as *NF1*, *HRAS*, *MAP2K1* and *GNA11*.[23] These findings suggest that at least a proportion of dysplastic naevi have an intermediate biological potential with a higher propensity to transform to melanoma, pending additional genomic alterations.[21,22] In line with these discoveries, it has been previously shown that some dysplastic naevi exhibit alterations in tumour suppressor genes such as *P53* and chromosomal deletions and loss of heterozygosity in *CDKN2A*, which are commonly seen in melanomas, but are exceedingly rare in benign naevi.[24] In addition, microsatellite instability in chromosomal loci 1p and 9p with MSI low pattern has been found in melanomas and some dysplastic naevi, but not in common melanocytic naevus.[24]

On the other hand, studies on gene expression profile of melanocytic neoplasms have shown upregulation of genes involved in proliferation, cell adhesion and migration as well as overexpression of follicular keratinocyte-related genes including KRT25, TCHH, KRT27 and KRT71, and inflammatory molecules such as S100A8 and S100A7 in dysplastic naevus compared to common melanocytic naevus.[25,26] Similarly, altered expression of cytokines associated with growth and proliferation such as fibroblast growth factor has been detected in dysplastic naevus and melanoma by *in situ* hybridisation.[27] Interestingly, it has been shown that the immune microenvironment of dysplastic naevus is distinct from common melanocytic naevus by higher density of T lymphocytes and antigen-presenting dendritic cells as well as significant upregulation of many immune activators and immune suppressors, implying a much more immunogenic nature.[26] Altered expression of extracellular matrix proteins such as collagen type I, III and IV and fibronectin has been observed in dysplastic naevus by immunohistochemistry.[28] To this end, it has been speculated that the morphological atypia observed in dysplastic naevus may be related to an interaction between melanocytes and their microenvironment and molecular alterations in epidermal/follicular keratinocytes, rather than an intermediate phase of neoplastic progression to melanoma.

The overall genetic, epigenetic and transcriptomic findings in melanocytic naevus and its histopathological

variants appear to be largely distinct from dysplastic naevus; however, there are some subtle similarities. Based on gene expression studies, melanocyte-related genes such as TRPM, TYR and MLANA are similarly upregulated in both dysplastic naevus and common naevus; however, there are some significant differences, specifically in the expression of epidermal and follicular keratinocyte-related genes; and dysplastic naevi can be separated from common naevi based on transcriptomic assays.[26] Common naevi show a lower mutational burden and often harbour somatic mutations in *BRAF V600E* gene (approximately 80%)[29,30] in contrast to *BRAF non-V600E* mutations recently observed in dysplastic naevus.[21] Genomic alterations in well-recognised histopathological subtypes of melanocytic naevi are also different from those of dysplastic naevus. For example, naevi with spitzoid morphology, which may occasionally show overlapping histopathological features with dysplastic naevus,[31] exhibit distinct molecular alterations including kinase (ALK, BRAF, RET, NTRK1, ROS1, MET and PRKCA) fusions; bi-allelic BAP1 inactivation; and *HRAS* mutations with or without gain of chromosome 11p.[32] Other morphologic variants of naevi such as blue naevi and deep penetrating naevi show initiating mutations in *GNAQ/GNA11*[33] and combined mutations in *BRAF* and *CTNNB1* or *APC* genes, respectively.[34] In addition, it has been shown that inactivation of BAP1 protein in blue naevi will result in an intermediate neoplasm with a higher risk of transformation to melanoma.[35] Similarly, deep penetrating naevus can transform to melanoma by acquiring additional mutations in genes such as *P53*, *TERT* and *CDKN2A*.[34]

While there are some overlapping molecular genomic findings between dysplastic naevus and melanoma, the latter shows much more extensive and complex molecular alterations due to accumulative genomic damage. Melanomas show a high mutation burden (often > 100 mutations per sample); however, similar to dysplastic naevus, somatic mutations in melanoma frequently exhibit a UV signature.[36] Significantly, mutated genes in melanomas include *BRAF* in up to 52% of melanomas (of which 75% being *BRAF pV600E* mutations), followed by *NRAS* (28%) and *NF1* (14%).[36] Melanomas often show concurrent multiple strong MAPK-activating mutations and amplification of genes involved in this pathway, resulting in significant increase in gene dosage and ramp-up of the pathway signalling.[23] Other less frequent somatic mutations occur in genes such as *CDKN2A*, *P53*, *PTEN*, *RAC1*, *MAP2K1*, *PPP6C*, *ARID1A/B* & *ARID2*, *IDH1*, *RB1*, *DDX3X*, *MRPS3* and *RPS2*.[36] Similar to intermediate lesions, melanomas show frequent somatic mutations in *TERT* promoter; however, *TERT* amplification and overexpression are much more common in melanomas compared to intermediate melanocytic neoplasms.[23] Melanomas often show frequent copy number variations such as deletion of *CDKN2A* and *PTEN* and focused amplification of *MDM2* and *YAP* genes as well as complex structural rearrangements,[37,38] which do not feature in dysplastic naevi, except for isolated hemizygous loss of *CDKN2A* in a subset of cases. Transcriptomic studies have shown some similarities between dysplastic naevus and melanoma such as upregulation of genes involved in immune signalling and regulation, epithelial keratin and neuronal development as well as cell adhesion, migration and extracellular matrix production[26,37]; however, in melanoma there is overexpression of genes such as PRAME,[39] CCL8, MAGEA3 and MAGEA6 and genes involved in pigmentation, negative regulation of apoptosis and metabolic processes which is not typically seen in dysplastic naevus.[25,26]

ROLE OF SUN EXPOSURE

Somatic mutations in dysplastic naevus are frequently related to excessive sun exposure and UV radiation.[40] Recent studies have confirmed that most additional genomic mutations necessary for malignant progression of intermediate melanocytic neoplasms are somatic point mutations with C to T or CC to TT nucleotide substitutions.[19,21] This mutational pattern, which is known as UV signature, highlights the significance of sun exposure in acquiring mutations in tumour suppressor genes such as *PTEN*, *P53* and *P16*, and malignant transformation. These findings suggest that a special attention should be given to the clinical assessment and follow-up of dysplastic naevi in sun-exposed body areas. It also signifies the role of sun protection in prevention of melanoma in individuals with high number of dysplastic naevi.

CLINICAL TRANSLATION AND PRACTICAL IMPLICATIONS

The aggregate of molecular genomic findings (Fig. 1) indicates that dysplastic naevus is not an obligate precursor for melanoma; however, there is a subset of dysplastic naevi with some molecular alliance with melanoma. This subset may represent an intermediate phase of neoplastic progression from benign to malignant. Alternatively, this group may encompass naevi with some genomic complexities that are biologically stable due to a long-standing

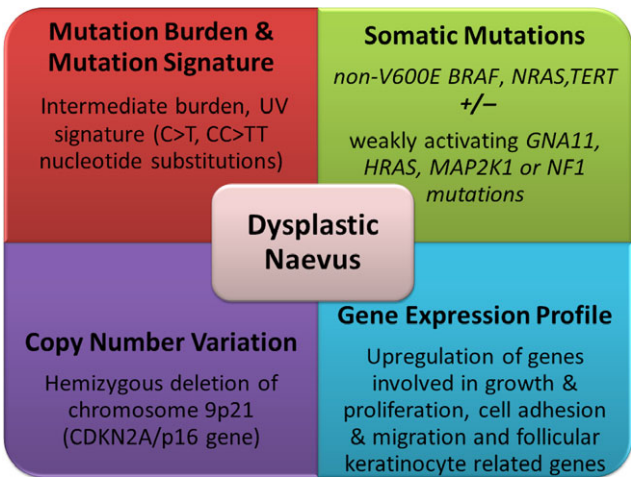

Figure 1 Summary of important molecular genomic alterations observed in the intermediate subset of dysplastic naevus.

balance between proliferation and attritional factors such as oncogene-induced senescence or potent immune surveillance.[22] On the other hand, lesions in this group may be true early melanomas in which the histopathological features of malignancy have not fully evolved at the microscopic level[41]; although, it is extremely difficult to separate them from histopathologically similar lesions without malignant potential. It is not uncommon in practice to observe a fully grown melanoma being associated with a pre-existing dysplastic naevus (Fig. 2). In addition, previous studies have reported remnants of dysplastic naevus in melanoma.[42]

To increase the diagnostic reproducibility and to reflect the intermediate genomic nature of dysplastic naevus, the most recent World Health Organization (WHO) book on classification of skin tumours has introduced a new grading scheme, categorising dysplastic naevus into low-grade (previously moderate) and high-grade (previously severe) dysplasia with abandoning the previously recognised mildly dysplastic category and re-classification of the latter as lentiginous naevus.[43] It also clearly states that based on clinicopathological and genomic aspects, dysplastic naevus represents an intermediate lesion between common acquired naevus and radial growth phase of melanoma.[43] While the latter statement seems to be an over-speculation of the nature of a rather genetically diverse entity, it appears to be correct for a subset of these lesions. Nevertheless, the exact clinical and morphological attributes of this intermediate group are dubious at the current state of knowledge. Therefore, while the clinical management of the majority of dysplastic naevi is rather straightforward, this subset of borderline lesions should be managed cautiously based on a holistic clinicopathological approach. It should be emphasised that both over- and under-treatment of such lesions could result in significant harm and should be avoided. Special attention should be given to atypical naevi in patients with strong personal or familial history of melanoma, naevi rapidly changing in appearance and those in sun-exposed skin areas, and such lesions should be considered for complete excision. However, a proportion of lesions with borderline morphologic features remain diagnostically challenging on routine histopathological examination, and the use of immunohistochemistry may provide some help in such cases. Complete loss of p16 protein expression in lesional melanocytes, assessed by immunohistochemistry, has been suggested as a potentially good marker for supporting a malignant diagnosis.[44] CDKN2A/p16, located on chromosome 9p21, is a tumour suppressor gene that is frequently inactivated in melanomas due to bi-allelic deletion, mutation or silencing of the gene.[44] However, it should be noted that the utility of p16 for diagnostic purposes in melanocytic neoplasms is limited to a fraction of cases/specific scenarios, and the interpretation of staining pattern is subject to some inter-observer variability.[44]

Development and employment of minimally invasive techniques such as sub-millimetre skin biopsies to obtain genomic material for molecular studies would be of great value in evaluation of clinically difficult lesions.[45] Another promising approach is non-invasive tape stripping of stratum corneum to isolate RNA to evaluate the gene expression profile of suspicious lesions. In a recent study, 312 genes have been identified to be differentially expressed in melanoma, banal naevi and normal skin.[46] This technology was able to discriminate melanomas from naevi, including dysplastic naevi, with a high sensitivity and specificity.[46] The practicality of this test in routine clinical practice has been confirmed by other investigators,[47, 48] who were able to validate a two-gene molecular assay in 398 pigmented lesions, showing 91% sensitivity and 69% specificity in separating benign melanocytic neoplasms from malignant melanoma.[48]

FUTURE RESEARCH OUTLOOK AND CHALLENGES

Further large-scale studies would be the key in decoding histopathological and clinical features of the proposed

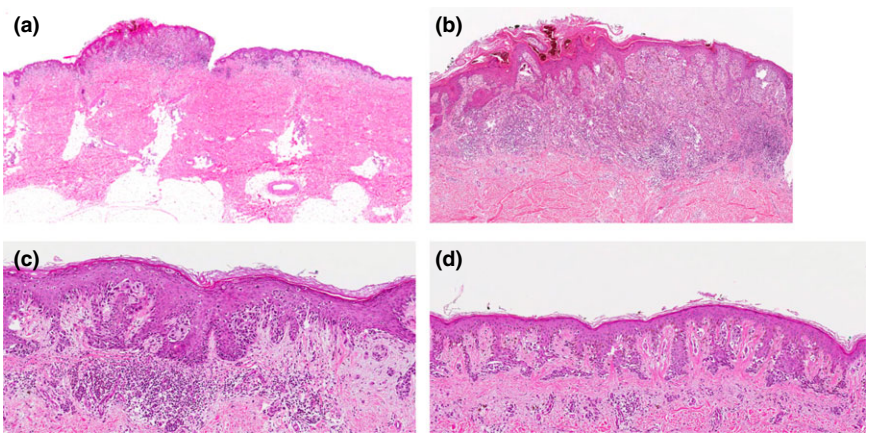

Figure 2 Microscopic images of an invasive malignant melanoma showing; (a) a broad lesion (HE, ×20), (b) with focal dermal invasion (HE, ×40) as well as (c) extensive intraepidermal (*in situ*) growth with pagetoid scatter of melanocytes (HE, ×200); (d) and areas exhibiting morphological features of a pre-existing dysplastic naevus (HE, ×100).

intermediate category of dysplastic naevus. *TERT* promoter mutation is potentially an important biomarker to be further investigated. It has been speculated that *TERT* promoter mutations enable neoplasms to escape involution and acquire further mutations, inducing malignant transformation.[22] In addition, the coexistence of *TERT* with *BRAF* or *NRAS* mutations has been commonly reported in intermediate melanocytic lesions.[22] Therefore, retrospective studies to identify dysplastic naevi with *TERT* promoter mutations in an attempt to further characterise the morphological features and to assess the risk of malignant progression of these lesions with follow-up would be of great interest. Given that the natural history of dysplastic naevus is frequently interrupted by complete excision, which is often curative, undertaking prospective studies is challenging.

The feasibility of a suitable animal model should be considered and further investigated. In recent years, several genetically modified mouse models have been developed to study melanoma and the impact of genomic alterations in intracellular signalling pathways required for growth, proliferation and survival such as activations of RAS-RAF-AKT or disruption of PTEN, CDK4-INK4A-pRB or ARF-p53 pathways.[49] In addition, new chemical protocols have been utilised to induce a spectrum of melanocytic neoplasms in mice, which are morphologically, immunohistochemically and genetically similar to human common melanocytic naevi, dysplastic naevus and melanoma.[50] These novel mouse models can be used to study the progression of naevi and intermediate lesions to melanoma.

CONCLUSION

Emerging molecular genomic and clinical data indicate that dysplastic naevi encompass a heterogeneous group of melanocytic neoplasms. While the majority of dysplastic naevi carry a negligible risk of progression to melanoma individually, a subset of lesions requires more meticulous attention and evaluation based on the overall phenotypic and genotypic features. This subset of dysplastic naevi exhibits genomic alterations, overlapping with those seen in banal naevus and melanoma, suggestive of a true intermediate biological nature. It is critical to define the clinical and histopathological manifestations of this intermediate group and to develop potential biomarkers in future studies to facilitate early detection of these lesions and to avoid under- or over-diagnosis and treatment.

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CONFLICT OF INTEREST

None.

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