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Review

Molecular Aspects of Melanocytic Dysplastic Nevi

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Melanocytic dysplastic nevi were first described in both patients and their relatives who had one or several cutaneous malignant melanomas. Most of these dysplastic lesions are biologically stable, but some of them have severe histological atypia and can progress further to melanomas. Although several studies have suggested the etiological importance of dysplastic nevi in the development of melanomas, comprehensive reviews of the molecular changes in these dysplastic lesions are still scarce. To remedy this issue, this article analyzes the available molecular information about dysplastic nevi and provides the current state of knowledge regarding the karyotypic abnormalities of the melanoma/dysplastic nevus trait and the involvement of allelic loss, tumor suppressor genes, mismatch repair proteins, microsatellite instability, oncogenes, extracellular matrix proteins, and growth factors in the genesis of these lesions. These studies suggest that although some of these lesions represent "genetic dead-ends," others represent intermediate lesional steps in the melanoma tumorigenesis pathway. ***(J Mol Diagn 2002, 4:71–80)***

Although the concept of the melanocytic dysplastic nevus as a risk factor for cutaneous malignant melanomas (CMMs) was introduced only recently, these lesions were observed long ago[1] (Figure 1). In 1978, Clark et al[2] published the first report to advance melanocytic dysplastic nevi (MDN) as a separate pathological entity. In 1980, Greene and colleagues[3–5] applied the term "dysplastic nevus," as the lesions have clinically, architecturally, and cytologically atypical features. These moles are categorized into sporadic and familial dysplastic nevi.[6,7] The presence of MDN is associated with almost 100% and 60% of familial and sporadic CMMs, respectively.[8–11]

Over the last decade, most of the relevant molecular analyses have focused on CMMs rather than on MDN. The underlying reasons include the relatively large size of CMMs, their direct lethal outcome and the feasibility of propagating and establishing corresponding CMM cell lines. In contrast, due to their relatively small size, variable criteria for histological diagnosis, controversial terminology, and difficulty in establishing *in vitro* cultures, MDN have hardly been studied. The limited studies on these lesions reported some genetic changes and suggested that evolution of some MDN may result in CMMs. Although genetic changes in CMMs have been analyzed in several review articles, reviews about these changes in MDN have remained scarce. To remedy this gap in the literature, this review seeks to examine genetic alterations in MDN.

Genetic Alterations in MDN

The genesis of MDN seems to be a complex process that involves poorly understood phenotypic and genotypic alterations. These alterations include loss of tumor suppressor genes (TSGs) and alterations of oncogenes, housekeeping genes, growth factors, and extracellular matrix proteins. Two models are currently proposed to explain the genesis of MDN. The first one considers that MDN arise by inactivation of one allele of melanoma suppressor genes, while the subsequent loss of the second allele leads to malignant transformation of the dysplastic nevic cells.[12] The second model relies on the presence of at least two genes working independently. Therefore, alterations of one of them cause dysplasia in the melanocytes while the other results in malignant transformation.[13] Both models rely on the "two-hit" hypothesis, suggesting that two genetic events are required for inactivation of TSGs. In familial forms of cancer, one mutation is believed to be germline and the other somatic, whereas in sporadic cancers, both mutations are somatic.[14]

Genetic alterations accompany and drive the evolution of neoplasms and their subsequent progression to more

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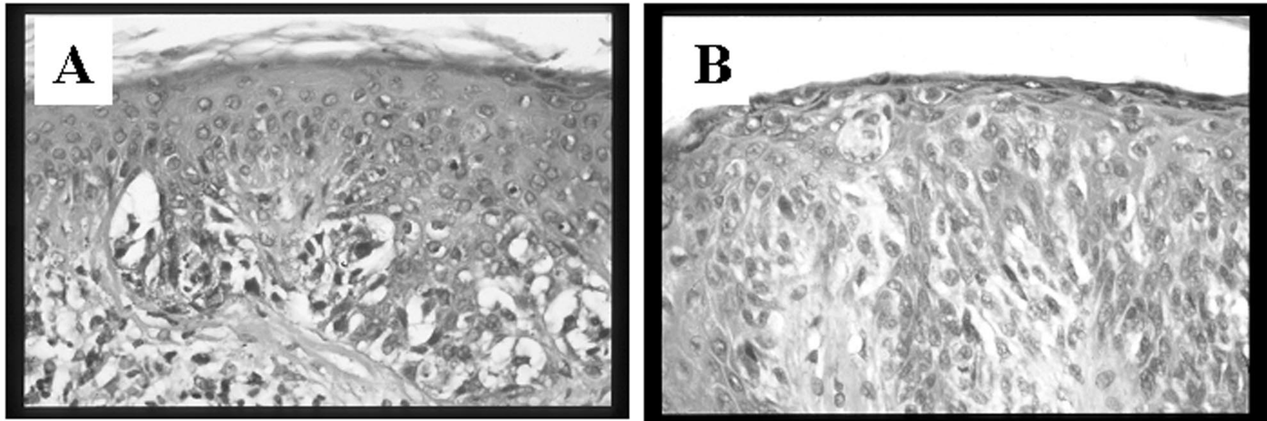

Figure 1. Histological appearance of melanocytic dysplastic nevus (**A**) and cutaneous malignant melanoma (**B**).

malignant phenotypes. These alterations may either provide new potential for aggressive behavior of the tumor cells, such as by activation of oncogenes and alterations of housekeeping genes, or may release the tumor cells from regulatory effects through the loss of TSGs. We subdivided these genetic alterations into: karyotypic changes in CMM/MDN trait; allelic loss; alterations of tumor suppressor genes; alterations of mismatch repair protein expression; microsatellite instability; alterations of oncogenes; alterations of the extracellular proteins; and alterations of cytokines and growth factors.

Karyotypic Alterations

Chromosome 1p and CMM/MDN Trait

Linkage analysis studies mapped a susceptibility locus for CMM/MDN to chromosome 1p near the rhesus blood group locus (Rh). Subsequent linkage analysis studies supported a role for 1p but also excluded many candidate regions around this locus.[15,16] In 1989, a CMM/MDN locus was mapped to chromosome 1p36 by Bale et al.[17] To determine the site of this locus, Bale and colleagues evaluated 99 relatives and 26 spouses in six families with CMM/MDN predisposition using 26 polymorphic markers on the 1p region. They analyzed the cosegregation of the CMM/MDN trait and mapped the trait susceptibility locus to be between an anonymous DNA marker (D1S47) and the gene locus for pronatrodilatin (PND) at the 1p36 region.[17] The failure of subsequent studies from 1989 to 1991[12,18] to confirm linkage between a CMM/MDN locus and the 1p region may have been due to diagnostic, clinical, and genetic heterogeneity.[19,20].

In 1992, Goldstein et al[12,18,19,21–23] incorporated the previous linkage analyses and performed three linkage analyses to examine the relationship between CMM/MDN and D1S47, PND, and D1S160 markers in several families. They demonstrated that the CMM/MDN susceptibility locus is located at 1p36 and linked to the D1S47 marker.[19] They also showed strong evidence for genetic heterogeneity in these lesions. In 1996, Goldstein and colleagues[20] simultaneously examined the 1p36 and 9p21 regions using two-trait-locus, two-marker-locus linkage analysis. Their work suggested the presence of two susceptibility loci at these regions, with the 1p locus contributing to both CMM and CMM/MDN and a 9p locus contributing mostly to CMM alone.

Chromosome 9p and CMM/MDN Trait

In 1991, Fountain et al and Petty et al[24,25] presented papers at the eighth International Congress of Human Genetics proposing chromosome 9p as a possible location of melanoma susceptibility genes. In 1992, further support for this proposal came from the work of Nancarrow et al,[21] who carried out genetic linkage analysis in Australian kindreds with CMMs. This group found two major gaps in the exclusion map, located at 9p22 cen and 9q12-q32, as well as smaller regions at each telomere. Simultaneously, Cannon-Albright et al[26] examined eleven extended kindreds with 82 cases of CMMs using genetic markers for the 9p22–21 region. They assigned the susceptibility locus to 9p13-p22 and addressed the possibility that the locus functions as a tumor suppressor gene.[27] In 1993, Nancarrow et al[28] confirmed these findings by examining linkage analysis in 26 Australian CMMs families for IFNA and D9S126 markers in the 9p region. Subsequently, Goldstein et al[29] performed linkage analysis on 13 families previously investigated for linkage to chromosome 1p.[16,21,22,28] They used IFNA/D9S126 markers and reported significant evidence for linkage to IFNA. In contrast, they found no evidence for linkage between CMM alone or CMM/MDN and D9S126.

Chromosome 1p and 9p Involvement in CMM/MDN Trait

Despite their contributions, these studies failed to answer a challenging question: is there a single CMM/MDN locus or are there two tightly linked loci, one for CMM and the other for MDN? To address this question, Goldstein and colleagues[20] conducted two-trait-locus, two-marker-locus linkage analysis on 19 CMM/MDN kindreds (previously genotyped for one or more markers on the 9p and

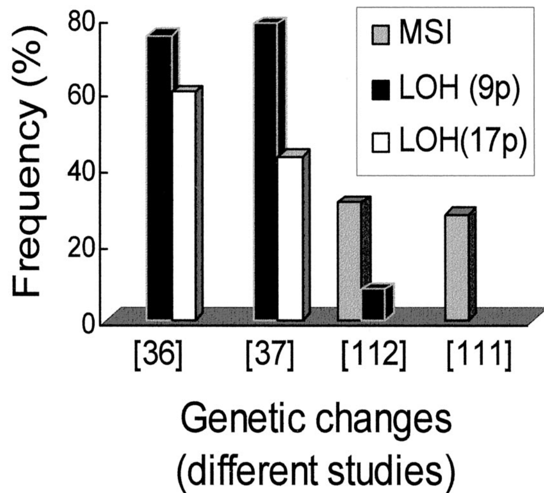

Figure 2. The reported frequency of microsatellite instability (MSI) and loss of heterozygosity (LOH) on several chromosomal arms in melanocytic dysplastic nevi. The **bars** compare the frequency of these genetic changes among the different studies.[36,37,111,112]

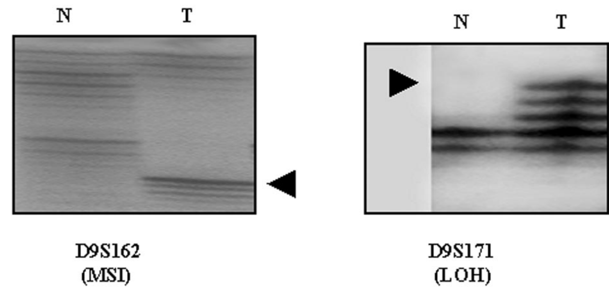

Figure 3. Genetic changes in melanocytic dysplastic nevi. **Left:** Microsatellite instability (MSI), with the **arrowhead** indicating the appearance of a novel band in the tumor (T) DNA as compared to DNA from the normal tissues (N). **Right:** Loss of heterozygosity (LOH) in the tumor DNA, with the **arrowhead** indicating loss of upper allele in the tumor.

1p regions) in 1996. This study suggested that two loci act separately in production of CMM or CMM/MDN, with substantially stronger evidence of CMM linkage to a 9p than to a 1p region. In contrast, another study presented comparable evidence for CMM/MDN linkage to both regions. Nevertheless, it is still possible that the 1p locus contributes to both CMM and CMM/MDN, whereas a 9p locus contributes more to CMM alone.[30]

To summarize, most genetic analysis studies have suggested that CMMs and MDN may be pleiotropic manifestations of alterations of the same susceptibility gene.[31] A subset of kindreds showed evidence of linkage to a 1p region, another subset to a 9p region, and others to both 1p and 9p regions. Furthermore, the assignment of the locus for CMM/MDN to regions (1p and 9p) in the human genome that are usually involved with karyotypic abnormalities in CMMs raised the possibility that chromosomal deletions represent an important event in the evolution of the CMM/MDN trait.[32,33]

Allelic Loss at the 1p, 9p, and 17p Regions

The concept of TSGs implies that every living cell is potentially cancerous, but as long as it has functioning TSGs, it is somehow prevented from fulfilling its malignant potential. The evidence for the presence of tumor suppressor genes can be obtained from loss of heterozygosity (LOH) studies. Loss of heterozygosity can result from chromosomal deletion, mitotic recombination, non-disjunction, or unbalanced translocation.[34,35]

In MDN, few studies have examined the presence of LOH at the 1p, 9p, and 17p regions using polymerase chain reaction-based microsatellite assays (Figures 2 and 3).[36–38] Previous studies indicated a close link between the sites of LOH and the location of TSGs.[39,40] Interestingly, the TSGs at these chromosomal regions are commonly involved in a wide variety of tumors.[41–46] It is unknown if these TSGs belong to the class of general TSGs that can be inactivated by various mechanisms in a variety of tumors.[45,47] Although the allelic loss in MDN was much lower than that in CMMs, it was still similar in pattern. Therefore, it is conceivable that LOH at these (1p36 and 9p22–21) regions does play an early role in CMMs tumorigenesis. These observations may support the existence of a biological continuum between some MDN and CMMs[48,49] and reinforce the need to follow up these dysplastic lesions.

Loss of Tumor Suppressor Genes

TSGs are genes which, when deleted, inactivated, or expressed at a reduced level contribute to carcinogenesis. So far, three TSGs have been examined in MDN, including *p16/CDKN2A, TP53*, and *Melastatin* genes.

p16/CDKN2A *Gene (Cyclin Dependent Kinase Inhibitor 2A)*

p16 (MTS1/multiple tumor suppressor 1) is a putative TSG[50,51] located at 9p21 region and encoding for a $p16^{INK4a}$ protein or INK4a (inhibitor for kinase 4a).[52–54] This protein inhibits the activity of the cyclin D1-CDK4 complex. This complex phosphorylates the retinoblastoma (Rb) protein and therefore allows progression of the cells through the G1 cell cycle checkpoint. Therefore, p16 protein works as a TSG by exerting negative regulation of cell growth.[52] *p16* is commonly deleted and mutated in a variety of neoplasms, such as bladder tumors, esophageal cancer[44–46] and CMMs, and in lymphoblastoid cell lines derived from patients with dysplastic nevus syndrome.[45]

In MDN, mutational analysis of *p16* revealed contrasting results. Therefore, while some groups asserted the absence of these mutations,[55] others acknowledged the presence of point mutations in these dysplastic lesions.[36] *p16* mutations were not of the type commonly involved in CMMs, raising the possibility that they could represent artifacts of polymerase chain reaction.[54]

On the immunohistochemical level, p16 protein was expressed in nearly all MDN at levels similar to those in benign nevi.[56–58] Keller-Melchior et al[58] reported a uniform labeling pattern in almost 86% and 59% of the cells of MDN and CMMs, respectively. Whether p16/INK4a

alterations play an important role in the evolution of MDN and development of CMMs is still unclear.

TP53 *gene*

TP53 is a stress response gene, located at the 17p13.1 region, that encodes a 53-kd oncosuppressive nuclear protein with an M_r of 53,000.[59–66] Its main functions include maintenance of genomic stability and induction of apoptosis in response to DNA damage.[67–69] Loss of these functions leads to increased genomic instability and gene amplification and change in DNA ploidy.[70,71] A combination of these alterations is associated with transformation *in vitro* and development of neoplasms *in vivo*.[72,73] This critical role of p53 in tumorigenesis is evidenced by the fact that *TP53* is involved in more than 50% of human malignancies.[72,74,75]

Several methods have been used to detect p53 gene alterations in MDN, including single stranded conformation polymorphism of exons 5 through 8 (the hot spots for mutations).[76] In MDN, the frequency of *TP53* gene mutations is much lower (~0% to 18%) than that in CMMs. These mutations include the presence of C:G to T:A transition-type mutations related to UV irradiation[36] and silent mutations.[77,78] Of note, most *TP53* mutation-positive nevi were found in patients who previously had cutaneous moles and a family and/or personal history of CMMs.[78] It is still unclear whether the presence of these mutations in MDN implies that *TP53* gene mutations play a role early in the evolution of CMMs.[36]

In MDN, immunohistochemistry has been used to detect alterations in p53 protein expression. This method can detect the altered p53 protein with an increased half-life.[76] Accumulation of p53 protein in MDN has been reported by a few groups.[79–82] However, in most of these reports, the overall frequency of p53 immunoreactivity was much lower (~5% to 15%) when compared to CMMs.[83] Similarly, the p53 staining in these lesions was heterogeneous, with a considerably reduced percentage of positively stained cells (less than 1%) when compared to CMMs.[83,84] These observations raise two notions: the difference in p53 protein expression between MDN and CMMs might be related to the differences in their biological behavior and the rare p53 positivity in MDN may merely reflect cell cycle fluctuations of p53 protein at the checkpoints, not underlying *TP53* gene defects.[79,85–87]

Melastatin

Located at 15q13-q14 regions, *Melastatin* is a novel suppressor of metastasis gene identified in murine and human CMMs cells. The expression of this melanocyte-specific gene is down-regulated with CMM progression and is inversely related to tumor thickness. In MDN, *in situ* hybridization revealed diffuse *Melastatin* mRNA expression, although the exact role of this molecule is still unknown.[88–90]

Alterations of Mismatch Repair Protein Expression

The mismatch repair (MMR) system is responsible for the repair of mismatched bases during DNA replication.[91] In humans, its enzymatic components include *hMSH2* (*MutS homolog 2*), *hMLH1* (*MutL homolog 1*), *hPMS1* and *hPMS2* (*human postmeiotic segregation 1 and 2*), and *GTBP* (*GT binding protein*).[92–94] These genes are located on 2p16, 3p21–23, 2q31–33, 7p22, and 2p16 chromosomal regions, respectively[95,96] and function similarly to TSGs.[97] Therefore, loss of both alleles causes rapid accumulation of mutations, altered expression of the corresponding MMR proteins, and microsatellite instability. In some tumors, such as those of the urinary bladder and lung, these alterations have diagnostic and prognostic ramifications.[98–102] In MDN, examination of the expression patterns of the repair proteins using immunoperoxidase-staining methods revealed that the vast majority of MDN had strong immunopositivity (Figure 4).[103] Interestingly, the repair protein expression values in MDN were intermediate between those of benign melanocytic nevi and CMMs. In this respect, these findings are consistent with the hypothesis of Clark et al[48,103] that MDN represent intermediate lesions in the evolution of CMMs.

Microsatellite Instability

Microsatellites are sequences made up of single sequence motifs no more than six bases long that are arranged in a head-to-tail manner. These sequences are repetitively scattered throughout the human genome with the most common class being in the form of $(CA)_n$.[104] The variation in microsatellite pattern length between tumorous and matching non-tumorous tissues is referred to as microsatellite instability (MSI), and the tumors demonstrating this phenomenon are labeled as tumors with MSI (Figure 2).[104–106] According to the level of instability, tumors with MSI were categorized into two groups: MSI-H and MSI-L (for high and low instability). The group with instability at >30% of tested markers (ie, MSI-H pattern), such as human non-polyposis colorectal cancer (HNPCC),[107] was found to have mutations in MMR genes.[92,108,109] The other group of tumors, with instability at <30% of tested markers (ie, MSI-L pattern), arises through unknown mechanisms.[107,110]

In MDN, MSI-L pattern was found at the 1p and 9p regions (Figures 2 and 3).[111,112] These chromosomal regions are well known for their karyotypic abnormalities in CMMs and harbor significant cancer genes such as *p16* (9p22–21), *p73*, and *p58* (1p36).[113] The incidence of MSI was statistically significant in MDN as compared to benign melanocytic nevi, and there was a statistically significant difference in the prevalence of MSI between both MDN with severe and moderate atypia when compared to those with mild atypia. The finding of MSI-L pattern in MDN suggests that MSI is acquired early during CMMs development and supports the notion that some MDN represent an early stage of this process. The presence of MSI-L in these lesions may be explained by:

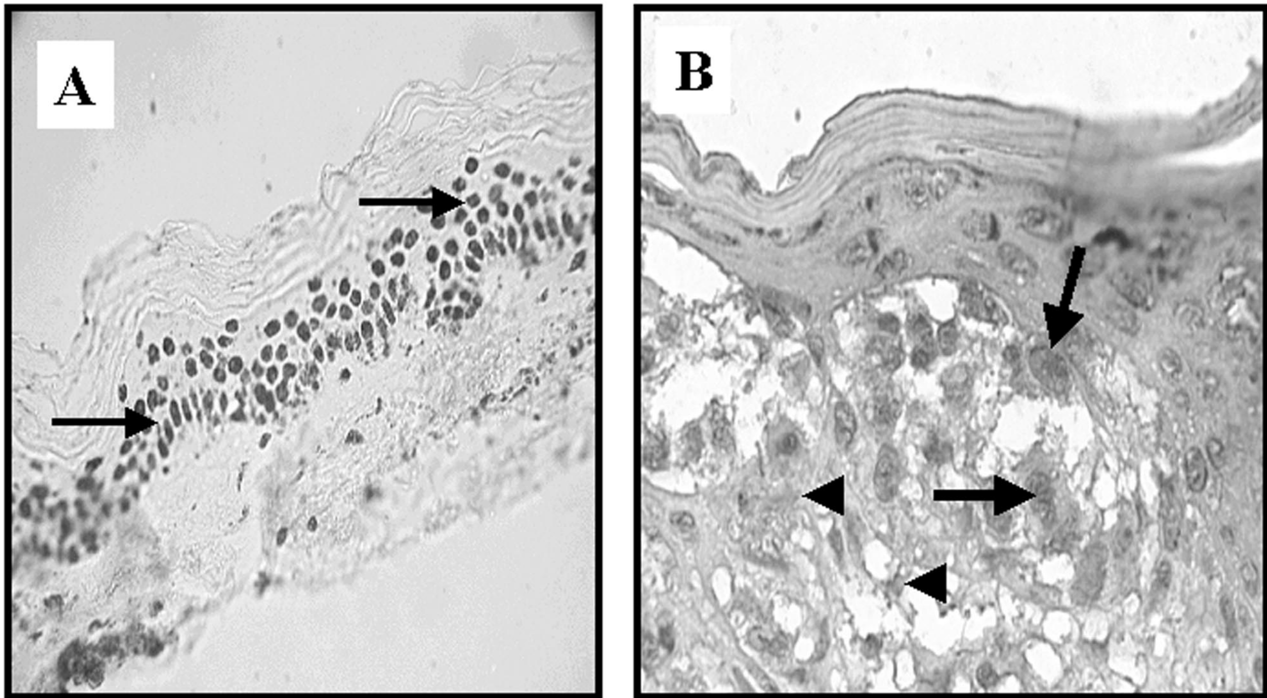

Figure 4. Immunohistochemical staining of MMR proteins in melanocytic dysplastic nevi (MDN). **A:** hMLH1 expression in the normal epidermis. Note the nuclear expression pattern (**arrow**): **B:** hMSH2 expression in MDN. Positively (**arrow**) and negatively (**arrowhead**) stained cells are observed in both MDN and CMM.

the variable expression of MMR genes with weakly penetrant mutations and attenuated phenotype;[114] inherent intrinsic instability of these loci; and the inactivation of non-MMR genes or additional MMR genes other than those encountered in HNPCC, such as the *hMSH6* gene.[111,115,116]

Oncogenes

Proto-oncogenes have critical roles in the regulation of both cell growth and differentiation and after alteration can confer a malignant potential and become oncogenes.[117] So far, few studies have examined the role of oncogenes, such as *ras* and *myc,* in the pathogenesis of MDN. The *ras* family of proto-oncogenes encodes small GTP-binding proteins involved in intracellular signal transduction of mitogenic signals arising from activation of growth factor receptors.[54] Although mutations of *ras* genes are relatively common (5% to 24%) in CMMs,[118,119] they are only occasionally found in MDN. It is still unclear if the infrequent *ras* mutations in MDN indicate involvement of this gene in the initiation or progression of these atypical lesions.[120]

The *myc* oncogene is a cellular proto-oncogene that codes for a nuclear phosphoprotein. Its functions include regulation of G0/G1 cell cycle transition and control of cellular differentiation. myc overexpression has been reported in a variety of tumors.[121–123] In CMMs, high c-*myc* expression has been found in primary and metastatic tumors.[122] Using interphase fluorescence *in situ* hybridization, Kraehn et al reported c-*myc* gain in relation to the centromere 8-copy number in advanced CMMs and the absence of a similar gain in nevi.[123]

Alterations of the Extracellular Proteins

The extracellular matrix (ECM) represents a network of proteins that can interact with tumor cells and thereby modulate their proliferation and migration.[124] In CMMs, the expression of these molecules gradually increases with the progression of the tumor. Morphologically, MDN are characterized by the presence of peculiar stromal reactions, ie, fibroplasia.[5] On the molecular level, altered expression of ECM proteins (interstitial collagens type I, III, and VI, tenascin, and fibronectin) was found in the stroma surrounding dysplastic nevic cells, suggesting that alteration of these molecules may create a suitable microenvironment for the progression of these lesions.[125–130]

Alterations of Cytokines and Growth Factors

Cytokines are a group of polypeptides that has modulatory actions on the growth and proliferation of cells. Over the last decade, several lines of evidence have suggested that these substances are critical for the uncontrolled growth of tumor cells *in vitro* and potentially have the same effect *in vivo*.[131,132] *In vitro* experiments have established the role of these peptides in the abnormal growth of CMMs.[133] Basic fibroblast growth factor (bFGF) is a 17.5-kd-polypeptide autocrine growth factor. It is

Table 1. Molecular Changes in MDN

Genetic changes	Chromosomal regions	References
Karyotypic alterations	1p and 9p	60, 67, 75, 76
Allelic loss	1p, 9p and 17p	79, 80, 81, 152
Loss of tumor suppressor genes		
TP53 gene	17p.13	79, 80, 101
p16/CDKN2A gene	9p22-21	80, 92, 93
Melastatin	15q13-q14	131, 132, 133
Alterations of MMR protein expression		54
Microsatellite Instability	1p32-36 and 9p22-21	53, 152
Oncogenes		
ras gene	19q13.3-qter	158, 159
myc gene	8q24, 12q24.13	161, 162, 163
Alterations of the extracellular proteins		
Interstitial collagens type I, III, and VI	17q21, 2q31, 21q22	166, 167, 168, 169
Tenascin and fibronectin	6p21.3, 2q34	165, 169, 170
Alterations of growth factors		
Basic fibroblast growth factor (bFGF)	4q25-27	171, 172

produced by several tissues and is involved in angiogenesis and mutagenesis.[134,135] *In vitro*, it is produced by CMMs cell lines[136] but not by normal melanocytes.[137] In MDN, bFGF was found to be differentially expressed; however, its exact role in these dysplastic lesions is still unknown.[132]

Conclusions

In the multi-step melanoma tumorigenesis pathway that culminates with the metastatic phase, early steps appear to involve mutations of the melanocytes of the MDN. A review of the changes involved in the pathogenesis of MDN (Table 1) reveals four key points: the molecular changes in MDN are complex and involve allelic loss, MSI, and alterations of TSGs, MMR proteins, oncogenes, ECM proteins, and some growth factors; some of these genetic alterations are shared between MDN and CMMs, suggesting that some MDN represent intermediate steps or sequential phases in CMM tumorigenesis; the association of some MDN with CMMs may reflect pleiotropic and divergent manifestations of these genetic changes rather than sequential phases in multi-step melanoma tumorigenesis; and although significant information is accumulating about molecular changes in CMMs, little is available about MDN. Therefore, our understanding of the genetic changes in MDN is limited, and much work is needed to expand it. Finally, the sense of confidence afforded by histological evaluation of the melanocytic lesions and especially CMMs, "the fully developed tumor among the melanocytic lesions," is short-lived, and conclusively predicting their biology is beyond the scope of light microscopy and immunohistochemical or molecular markers available to date. In the face of these inadequacies, unfolding studies regarding gene expression profiling in CMMs, a strategy that can establish the expression of thousands of individual genes in the tissue sample, seem to have promising investigative, diagnostic, and prognostic ramifications. In this sense, expression profiling in CMMs can separate these tumors into distinct subsets and relate these subsets to definitive stages in the course of melanocytic transformation.[138–140]

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