

Melanocytic Skin Tumors: Genetic Aberrations and Clinicopathological Classification

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Melanocytic tumors are currently classified as *nevi*, considered benign; *melanomas*, considered malignant; and *melanocytomas*, considered borderline tumors [1]. However, recent studies on the genetic aberrations tend to make this classification problematic. In fact, the genomic analysis shows that both nevi and melanomas present mutations activating a certain number of growth-promoting signaling pathways. Tumors labeled as nevi and considered to be benign generally have a single or a small number of pathogenic mutations, often activating the MAP-kinase pathway (*driver mutations*), but no apparent additional genomic alterations. Tumors labeled as melanomas and considered to be malignant may harbor the same driver mutations detected in those labeled nevi, associated with a variable, generally high, number of additional mutations tending to ablate tumor-suppression mechanisms and to activate additional oncogenic pathways, including *CDKN2A*, *PTEN*, *TP53*, and *TERT*-promoter mutations (*promoting mutations*). Tumors histologically regarded as problematic, sometimes termed *melanocytomas* or *MELTUMPs*, harbor the same driver mutations detected in “nevi” and in “melanomas,” but a lower number of promoting mutations than “melanomas” [1-4]. The study of the distribution of pathogenic mutations has suggested they may occur in certain characteristic sequences [1]. The initial event

is often represented by a single mutation, which appears to be different in the different types of lesions: *BRAF* in common nevi; *N-RAS* in some congenital and some acquired nevi; *GNAQ* or *GNA11* in blue nevi; kinase fusions of *ALK*, *BRAF*, *ROS1*, *NTRK1*, *NTRK3*, *MET*, *RET*, or *MAP3K8* in Spitz nevi; and kinase fusion of *NTRK3* in spindle cell nevi of Reed [1,5-15]. Moreover, in some *BRAF*-mutated neoplasms, more specific histological and biological characteristics may be produced by a supervening driver mutation, just as *BAP1* mutation in *BAP1*-inactivated nevus, *CTNNB1* in deep penetrating nevus, and *PRKAR1A* in epithelioid blue nevus/pigmented epithelioid melanocytoma [16-20]. Subsequently, other driver and/or promoting mutations may be progressively acquired, because driver mutations tend to induce an increase of cellular proliferation and, consequently, an increase of the probability that additional mutations occur. These supervened genomic aberrations may be ineffective or capable to alter, lightly or severely, a certain number of cell proliferation control mechanisms. If effective, they may lead to an additional enhancement of cell proliferation and, consequently, to an additional probability that other mutations take place, and so forth [1-4]. Therefore, in any given tumor, the total amount of the acquired mutations produces a certain risk of neoplastic progression, parallel to a certain risk of

unfavorable events (recurrences, local and distant metastases, or death). This dual risk can be considered the *malignant potential* of the tumor, definable as the probability that a certain number of adverse events may occur and directly proportional to the global pathogenic mutational burden. When genetic alterations are small in number, limited to the driver mutation or few more, this potential is low or very low, adverse events are rare or very rare, and, clinically, the tumor appears as benign. When genetic alterations are numerous, including driver and promoting mutations, the malignant potential is high, adverse events are frequent, and, clinically, the tumor appears as malignant. Of course, all intermediate cases may exist, because the malignant potential may theoretically assume every value between a minimum value (>0) and a maximum one ($=100$). The lowest possible value is >0 , because all melanocytic tumors harbor at least 1 genomic alteration affecting the proliferation control mechanisms, and this inevitably implies a certain risk (risk 0 is to be reserved to the healthy skin, in which melanocytes harbor no pathogenic mutations). In sum, there do not seem to exist tumors with no chromosomal aberrations and consequently with no risk (risk = 0) and, at the same time, there seem to exist very few, if any, tumors harboring the *totality* of the possible chromosomal aberrations and, consequently, with the maximum possible risk (risk = 100). Tumors tend to show a certain variable number of pathogenic mutations and consequently may have all possible levels of risk, the malignant potential ranging between >0 and 100.

Sic stantibus rebus, the concept that melanocytic tumors can be only either benign or malignant, comes to be hardly applicable [1] because no tumor has malignant potential =0 and few, if any, have a malignant potential =100. This may produce 2 important conceptual and practical effects on the current clinicopathological classification of melanocytic skin tumors. The first is that the great majority of melanocytic tumors, having a malignant potential of intermediate value, ranging between these extremes, tend to appear as “borderline or intermediate,” between “fully benign” and “fully malignant” tumors. Paradoxically, virtually all melanocytic neoplasms seem to be attributable to an “intermediate” category, currently considered only as a very small and very narrow area, between the much larger categories of *nevi* and *melanomas*. The second is that the categorization of melanocytic tumors into *nevi* and *melanomas* appears simplistic and/or inadequate. In fact, the diagnostic categories of *nevus*, *melanoma*, and *melanocytoma* do not appear as 3 definite tumors with specific clinical, histological, and genetic characteristics, but as 3 large, heterogeneous assemblages of melanocytic tumors. Each of these 3 categories encompasses a mixture of dissimilar tumors, different because they have different driver events and, therefore, different pathogeneses and different clinicopathological features. In each of these 3 categories,

the only common denominators are that “nevi” harbor a single mutation or few more, producing a minimal malignant potential, the amount of which, however, can be different in the different histological types of nevus; “melanomas” show a variable, relatively high, number of additional promoting mutations, producing a high malignant potential, the amount of which, however, can be different in the different histological types of melanomas; “melanocytomas” harbor a relatively small number of additional promoting mutations, producing a relatively low malignant potential, the amount of which, however, can be different in the different histological types of melanocytomas. In short, rather than specific diagnoses, the current diagnostic categories *nevus*, *melanoma*, and *melanocytoma* emerge as generic terms encompassing a great number of heterogeneous unrelated tumors, different in their genetic profiles, in their clinical and histological morphology, and in their malignant potential.

Conclusions

Genetic studies suggest that the current classification of melanocytic tumors needs to be critically reevaluated and opportunely updated. In particular, 2 points seem to be put forward by genomic analyses and considered: (1) melanocytic neoplasms sharing the same driver mutations, and consequently having the same pathogenesis, show strong clinicopathological similarities and may constitute a single class of neoplasms or a unique neoplasm; and (2) the malignant potential of every single neoplasm could be potentially estimable, by matching the pathogenic mutational burden with the follow-up data of the patients.

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