GNA11-mutated and BAP1-negative Melanomas Ex Blue Naevi: A Particularly Aggressive Entity

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The molecular mechanisms involved in the development and progression of various subtypes of melanoma have been studied widely. In melanomas that lack *BRAF*-, *NRAS*- or c-*KIT*- activating mutations, found in common subtypes of skin melanoma, driver mutations were identified in *GNAQ* and *GNA11* genes coding G proteins in uveal melanomas and in the rare skin melanomas associated with blue naevi or mimicking cellular blue naevi, so-called "melanoma ex blue naevi" (MEBN) (1–6). Whereas the loss of p16 protein (coded by the *CDKN2A* gene) tumour suppressor function is a major molecular event in the progression of most skin melanomas, the loss of function of another tumour suppressor BAP1 protein is a key molecular event in the progression of uveal melanomas and in their metastatic evolution (3, 7). BAP1 loss was further shown to be implicated in many tumour subtypes in cases of sporadic tumours, but also in the novel field of an inherited *BAP1* germline mutation cancer predisposition syndrome including, notably, uveal and cutaneous melanomas and epithelioid atypical Spitz tumours (8). In addition, BAP1 loss has recently been reported to be a frequent molecular event in the progression of MEBN, emphasizing that uveal melanomas and MEBN share some molecular features (2).

The aim of this paper is to highlight the particular aggressive behaviour of *GNA11*-mutated MEBN, with a *BAP1* loss of expression and/or deletion. This particular profile could be a key factor in determining the risk of metastatic evolution of these rare melanomas.

GNAQ/GNA11 MUTATIONS, CHROMOSOMAL ABERRATIONS AND LOSS OF BAP1

Chan et al. (1) searched for chromosomal copy number variations and *GNAQ/GNA11* mutations in the spectrum of cellular blue naevi, atypical cellular blue naevi and MEBN. They found that the more atypical/malignant the tumours were, the more chromosomal aberrations were present. Notably, they reported 2/8 melanomas having the specific *GNA11Q209L* mutation and losses of chromosomes 3 including the *BAP1* locus (with no loss in the 2 *GNAQ*-mutated melanomas), but they did not study BAP1 expression.

The loss of *BAP1* has recently emerged as a key molecular mechanism in the progression of MEBN. Costa et al. (2) reported a file of 11 MEBN. Eight cases were *GNA11Q209L*-mutated, with 5 cases presenting a loss of BAP1 expression in the melanoma cells. In 4 of these 5 cases, an adjacent benign blue naevus counterpart was seen with preserved BAP1 expression. Loss of *BAP1* has also been reported by Shain et al. (3) to be involved in the progression of a *GNA11Q209L*-mutated blue naevus to melanoma. The loss of *BAP1* was linked to a homozygous deletion of the 3p21.1 locus in the melanoma counterpart. This chromosomal loss was also observed in 2 cases of *GNA11*-mutated and BAP1-negative MEBN reported by Costa et al. (1) (chromosome 3 deletion, 1 3p deletion) and in 2 *GNA11*- and *GNAQ*-wild type tumours lacking BAP1 expression (2). Dai et al. (9) also reported a case of a *GNA11*-mutated and BAP1-negative MEBN. Other authors reported some MEBN with *GNA11* mutations without data about BAP1 expression and a case of BAP1-negative MEBN of the scalp with no data about *GNAQ/GNA11* (4, 10, 11). The loss of BAP1 expression in the progression to MEBN emphasizes the reported tumour suppressor function of BAP1 (12).

ASSOCIATION WITH SCALP AND UVEAL LOCATIONS

From a clinical viewpoint, many of the *GNA11*-mutated MEBN with loss of expression and/or deletion of *BAP1* arose in the scalp (2/2 cases in Chan et al. (1), 4/5 cases in Costa et al. (2), 1/1 case in Dai et al. (9)). The 3 cases of *GNA11*-mutated melanomas reported by Yilmaz et al. (4) and Patel et al. (10) also arose in the scalp with no data about *BAP1*. Besides *GNA11*, its paralogue *GNAQ* is mutated more frequently in benign blue naevi (approximately 55% of blue naevi are *GNAQ*-mutated vs 7% *GNA11*-mutated) than in MEBN and less associated with *BAP1* loss (1/11 cases in Costa et al. without *BAP1* loss, 2/8 cases in Chan et al. without chromosome 3 deletion, 2/10 tumours in Yilmaz et al.) (1, 2, 4, 13). Moreover, the predilection for the scalp is less evident for *GNAQ*-mutated MEBN (2 of the 5 tumours) (1, 2, 4). *GNA11*-mutated melanomas are also classically described in uveal melanomas and reported in the melanomas and melanocytomas of the central nervous system (5, 6, 13). In the uvea, the spatial distribution of *GNAQ*- and *GNA11*-mutated melanomas also varies, with a predominance of *GNA11*-mutated tumours in the cilio-choroidal region compared with the choroid area (6). Predilection sites of *GNA11*-mutated melanomas ask for a potential link with the embryological origin of the cells involved in these rare tumours.

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METASTATIC POTENTIAL

Besides the predisposition to uveal melanomas in *BAP1* germline mutation syndrome, it is worth emphasizing that the loss of *BAP1* also predisposes to metastatic evolution of uveal melanomas (5, 8). This is also true in the study by Costa et al. about MEBN because 3 of the 5 malignant *GNA11*-mutated tumours lacking BAP1 expression had a metastatic evolution (no follow-up data for one patient, short follow-up of only 6 months for one patient). On the contrary, none of the *GNA11*-mutated BAP1-positive melanomas had a metastatic evolution (2). In the study by Chan et al., the 2 *GNA11*-mutated melanomas with loss of chromosome 3 also had a metastatic evolution and another case, without data about *GNAQ* or *GNA11* mutations, but also presenting a 3p21.1 deletion (*BAP1* locus) had a fatal outcome (1). None of the *GNAQ*-mutated melanomas reported by Costa et al. (1 case), Chan et al. (2 cases) or Yilmaz et al. (2 cases) had a metastatic evolution (1, 2, 4). The *BAP1*-negative MEBN with unknown *GNA11/GNAQ* status reported by Yeh et al. (11) did not have a metastatic evolution, whereas the BAP1-negative *GNA11*-mutated MEBN reported by Dai et al. (9) had a fatal outcome and the *GNA11*-mutated melanoma reported by Patel et al. (10) also had a metastatic evolution (no data about *BAP1*). Thus, BAP1-negative *GNA11*-mutated MEBN are more aggressive tumours in comparison with the tumours lacking this molecular combination. Beyond the prognostic implications, taking into account the high degree of similarities between these cutaneous and uveal aggressive subtypes of melanomas, it can be hypothesized that the new therapeutic strategies developed to treat patients with *GNA11*-mutated and BAP1-negative metastatic uveal melanomas could also allow treatment of patients with metastatic melanomas of cutaneous origin who have this similar *GNA11*-mutated BAP1-negative molecular profile (14).

CONCLUSION

Recognizing BAP1-related melanomas and/or epithelioid atypical Spitzoid tumours lacking BAP1 expression (so-called "BAPomas") […] syndrome, BAP1 loss in a malignant melanoma with clinical, histopathological and molecular (i.e. GNAQ/GNA11 mutations) features of MEBN could also be of prognostic relevance. Taking into account the diagnostic and prognostic interest of BAP1 loss in melanocytic tumours, pathologists and clinicians are encouraged to search for BAP1 loss of expression using immunohistochemistry in suspected cases.

The authors declare no conflicts of interest.

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