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Inherited predisposition to malignant mesothelioma: germline *BAP1* mutations and beyond

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Abstract. – Malignant mesothelioma (MM) is a rare aggressive neoplasm arising from mesothelial lining of body cavities, most commonly pleura and peritoneum. It is characterised by a poor prognosis and limited treatment options. A universally recognised risk factor for the development of MM is exposure to asbestos. However, evidence supporting a genetic susceptibility to the development of MM has been accumulating during the last decades. Intensive research for the identification of MM susceptibility genes has led to the discovery of *BAP1* and to the definition of the so-called "*BAP1*-related tumour predisposition syndrome". Patients carrying germline *BAP1* mutations have an increased risk for the early development of tumours, including MMs, uveal melanomas, cutaneous melanocytic lesions, clear cell renal cell carcinomas and basal cell carcinomas. Furthermore, pathogenic variants in tumour suppressor genes with a role in DNA repair have been recently described in families with clustered MM cases. These genetic alterations seem to confer exaggerate sensitivity to asbestos carcinogenic effect and, arguably, increased response to specific chemotherapeutic strategies. While the translational significance of *BAP1* alterations is explored in the research field, the identification of families carrying germline *BAP1* mutations is mandatory to start appropriate surveillance programs and guarantee the best clinical management to these patients.

Key Words:
Mesothelioma, *BAP1*, *BAP1*-related tumour predisposition syndrome.

Introduction

Malignant mesothelioma (MM) is a rare but highly lethal tumour derived from mesothelial cells. MM has traditionally been considered an occupational disease due to its strong association with exposure to asbestos, a group of naturally occurring minerals extensively used in the construction industry[1]. Despite many countries having banned asbestos in recent years, the incidence of MM has kept increasing worldwide[2]. This trend is partially explained by the long latency period (30-50 years) between exposure to asbestos and the development of the neoplasm[3]. The existence of other types of minerals with still unknown pathogenetic properties may also contribute[4]. Exposure to mineral carcinogens, however, is not the only risk factor for MM. It is clearly established that genetic factors play a fundamental role in determining individual susceptibility and modulating response to environmental factors[5]. In fact, only a minority of highly asbestos-exposed individuals develop MM[4] in absence of any dose-response relationship[6]. Furthermore, it was early noticed that cases of MM tend to cluster in some families, suggesting the existence of hereditary factors conferring exaggerated vulnerability to asbestos[7]. To date, still little is known about the genomic landscape of MM and the inherited predisposition to this malignancy. The present review will focus on the current knowledge about genetic alterations in sporadic MM, the definition of familial MM, its

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clinical, pathological and molecular peculiarities, and their supposed therapeutic and translational implications.

Epidemiology, Pathogenesis, Clinical and Pathological Features of MM

MM arises from the mesothelial layer of serous membranes, including pleura, peritoneum, pericardium and tunica vaginalis of the testis, covering body cavities. Mesothelial cells derive from the embryonic mesoderm. They express both mesenchymal and epithelial markers and form a protective monolayer with an important role in the regulation of inflammation, wound healing and antigen presentation. The pleura is the most frequently site for MM, accounting for 80-90% of all cases, followed by the peritoneum (10-15% of all cases). The incidence of MM greatly varies according to geographic areas, but it is generally higher among male patients, affected approximately 4 times more than females.

A universally-recognised causative agent for the development of MM is exposure to a group of mineral fibres collectively referred to as 'asbestos'. The roles of other factors, such as exposure to Simian Virus 40 (SV40)[8] or radiations, is still controversial. In the past, asbestos products have been widely exploited in construction and other industries for their appealing physical properties[1]. In the last decades, since its recognition as the main etiological agent for MM, asbestos has been banned in more developed countries. However, it is still used in several emerging countries, often without adequate measures for worker safety. Asbestos-related carcinogenesis requires a long latency period (30-50 years)[3]. As a result, the incidence of MM has dramatically increased in the last twenty years[2] in the industrialized countries and it is expected to peak around 2020-2025.

The most recent incidence data available for the USA, published by the Surveillance, Epidemiology and End Results (SEER) of the National Cancer Institute (NCI), report an incidence rate of 0,8/100.000 for the period 2014-2018, with a median age at diagnosis of 74 years[9].

MM is usually diagnosed in advanced stage, when radical surgery is not achievable and only few and poorly efficient systemic treatment options are available. Clinical presentation is usually subtle, with non-specific symptoms and signs. These include fatigue, chest pain, dyspnea and cough for pleural mesothelioma; abdominal pain, abdominal distension and anorexia for peritoneal mesothelioma.

Three main histological subtypes are recognized: epithelioid, sarcomatoid and biphasic.

Epithelioid MMs constitute approximately 60% of all cases; sarcomatoid MMs are less common, accounting for approximately 20% of all. Biphasic MMs are characterised by a combination of both epithelioid and sarcomatoid histologies. Survival is associated with histological subtype[10,11]: a pure epithelioid histology correlates with the longest survival while patients with sarcomatoid histology have the worst survival.

Currently, combination chemotherapy consisting of pemetrexed plus cisplatin remains the only established treatment for advanced MM. Other approaches, including immune checkpoint inhibithors and targeted therapies have failed to show brilliant results. Innovative treatment strategies, such as vaccines and adoptive T-cell therapy, are still under investigation.

The Genetic Landscape of Sporadic MM

The genomic landscape of MM stands out for the abundance of chromosomal aberrations, with copy number losses and/or gains involving most chromosomes and an overall low mutation burden. In the past years, pivotal studies based on whole genome sequencing of MM have also identified recurrent somatic alterations in a set of tumour suppressor genes, with a role in cell cycle progression, DNA repair or regulation of inflammatory response[12,13]. The most prevalent somatic mutations in MM involve, in order of frequency, the following genes: BRCA-1 associated protein 1 (BAP1), neurofibromin 2 (NF2), encoding merlin, and cyclin-dependent kinase inhibitor 2A (CDKN2A), encoding $p16^{INK4A}$ and $p14^{ARF}$.

A detailed overview about the genetics of sporadic mesothelioma is beyond the scope of the present work. Herein, we will focus on *BAP1*. In fact, the presence of germline mutations in *BAP1* has been associated to a specific tumour predisposition syndrome accounting for a proportion of familial MM cases[14-17].

From the Very Beginning: the 'Cappadocia Epidemic'

The first observations in favour of a genetic risk factor for MM date back to more than 50 years ago. In the Seventies, a group of researchers led by professor Baris from the Department of Chest Disease of University of Ankara, Turkey, started autonomous on-field investigation in central Anatolia. Their aim was to study the epidemiology of asbestos-related diseases

in a Turkish region rich in asbestos mines and asbestos workers[18]. During their explorations, they identified a group of three closely proximal Cappadocian villages where mesothelioma incidence was about 1000 times higher than in the rest of the region. Moreover, it showed an equal, 1:1 distribution between men and women and between pleural and peritoneal cases[19]. At that time, in those villages, over 50% of deaths could be attributed to mesothelioma[20]. Levels of asbestos and erionite, another carcinogenic fibrous mineral, were present at high concentrations in the buildings of the area. However, they did not exceed those observed in surrounding villages and could not explain such dramatic epidemiological anomalies[21]. Thanks to the combined efforts of professor Baris crew and Dr. M. Carbone and collaborators from United States, it was ascertained that susceptibility to MM among the population experiencing the mesothelioma 'epidemic' seemed to be inherited as an autosomal-dominant character[22]. After years and years of tireless research, a mesothelioma susceptibility gene was finally identified in 2011. That gene was *BAPI*[23]. Amusingly, *BAP1* mutations could account for only a minority of familial mesothelioma cases spotted in various countries all over the world; in particular, *BAP1* germline alterations failed to be demonstrated in the Cappadocian mesotheliomas, raising the possibility of other, still undiscovered, germline mutations underlying the inherited predisposition to MM[24]. Apart from its rare germline variants, *BAP1* mutations are currently recognised as the most frequent genetic alterations in sporadic MMs, followed by alterations in neurofibromin 2 (NF2) and cyclin-dependent kinase inhibitor 2A (CDKN2A) genes[25]. They have been associated with younger age at onset, epithelioid histological subtype and improved prognosis[26-30].

BAP1 Gene and Protein Function

The *BAP1* gene (BRCA1-associated protein 1) is located on the short arm of chromosome 3 (3p21.1). Identified and firstly described in 1998, it encodes a 729 amino acid-deubiquitinating hydrolase with nuclear localization[29] with multiple functional domains and binding partners. It cooperates in the regulation of many cellular processes such as DNA repair, cellular differentiation, proliferation and cell-cycle progression, acting as a tumour suppressor[30].

BAP1 loss of function has been observed in many sporadic tumours and can be promptly detected by immunohistochemistry on formalin-fixed and paraffin-embedded tissues (Figure 1-2). It usually derives from chromosomal deletions involving its locus on chromosome 3, a recurrent event in numerous human malignancies such as renal cell carcinoma, non-small cell lung cancer and breast carcinoma. However, inactivating mutations of various types, including insertions, deletions, frameshift and base substitutions may also account for BAP1 loss of function. No mutational hotspot has been currently identified for the *BAP1* gene. Regardless of its specific type, all pathogenetically relevant mutations of *BAP1* cause the impairment of the deubiqinating activity or loss of the nuclear localization sequences of the protein.

Germline BAP1 Mutations and Familial Mm: The "BAP1-Related Tumour Predispotion Syndrome"

Germline mutations of *BAP1* are inherited in an autosomal dominant pattern with high, albeit incomplete, penetrance[31]. They underlie the so-called, recently described, "*BAP1*-related tumour predisposition syndrome" (OMIM #614327). According to the Knudson 'two-hit' hypothesis, affected individuals inherit a non-functioning copy of the gene while the second allele is inactivated later during their lifetime. Patients have an increased risk for the early development of tumours such as, in decreasing order of frequency, uveal melanomas, MMs, atypical Spitz tumours/cutaneous melanomas, clear cell renal cell carcinomas and basal cell carcinomas[32,33].

Other neoplasms which have been proposed as part of the spectrum of *BAP1*-related syndrome are breast and ovarian carcinomas, cholangiocarcinomas, lung adenocarcinomas, meningiomas, neuroendocrine carcinomas and some soft tissue tumours (fibrous histiocytomas and undifferentiated pleomorphic sarcomas). However, further investigation is needed to sharply define the full phenotype of the syndrome[34,35].

The most recent and comprehensive review on the topic counted 181 different families worldwide carrying *BAP1* variants, encompassing 140 unique pathogenetic variants[36]. Nonetheless, these numbers are expected to steadily increase in the next future. In fact, according to the results of studies performed on large exome-sequencing databases, *BAP1* syndrome is likely underrecognized and underreported, being actually much more frequent than initially thought[37].

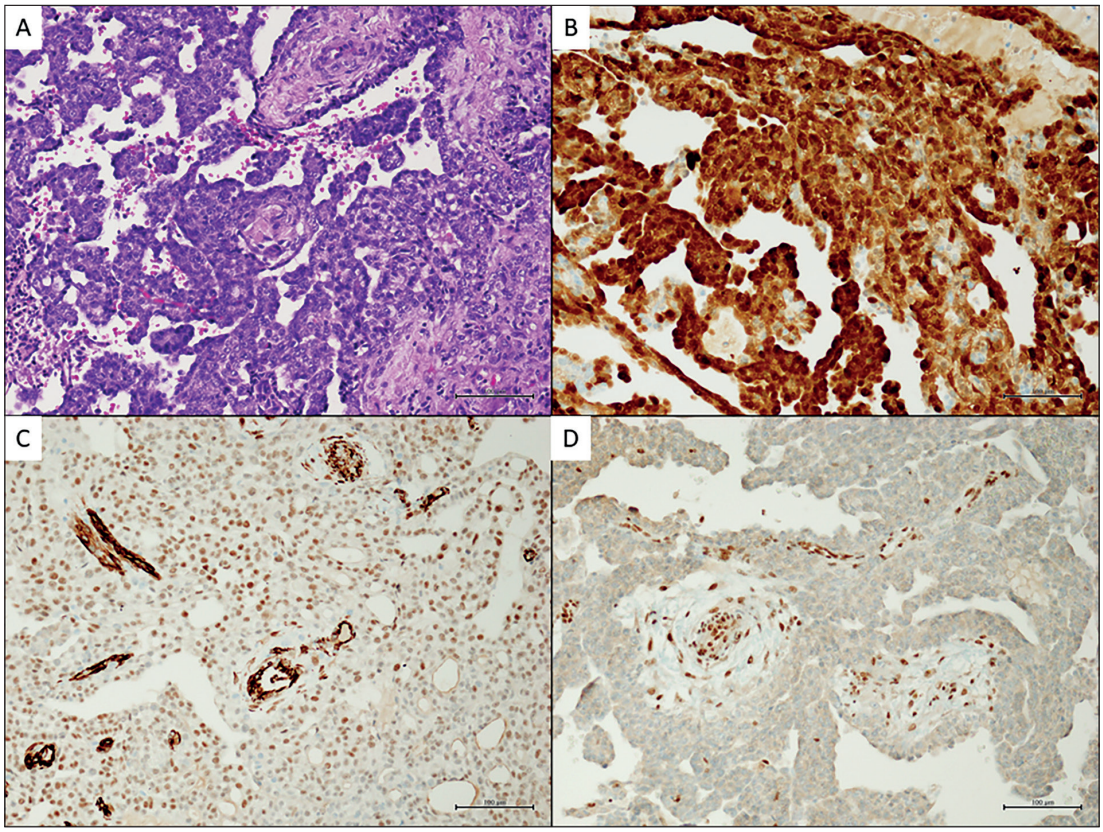

Figure 1. A case of MM with BAP1 loss. 66-year-old woman with right pleural mass. VATS biopsies show a proliferation of atypical epithelioid cells with a predominant papillary architecture (**A**). Immunohistochemical stains for calretinin (**B**) and WT-1 (**C**) were positive, supporting a diagnosis of epithelioid mesothelioma. The tumour was consistently BAP1-negative (**D**), with positive internal control of endothelial and stromal cells. (Original magnification: 200×).

Familial BAP1-Related MM: Clinical and Pathological Peculiarities

MM is recognised as one of the four main (or 'core') tumours associated with germline *BAP1* mutations, together with uveal melanomas, cutaneous melanomas/atypical Spitz tumours and clear cell renal cell carcinomas.

MMs related to germline *BAP1* mutations account for approximately 1-5% of unselected MM cases[38]. They seem to show distinctive

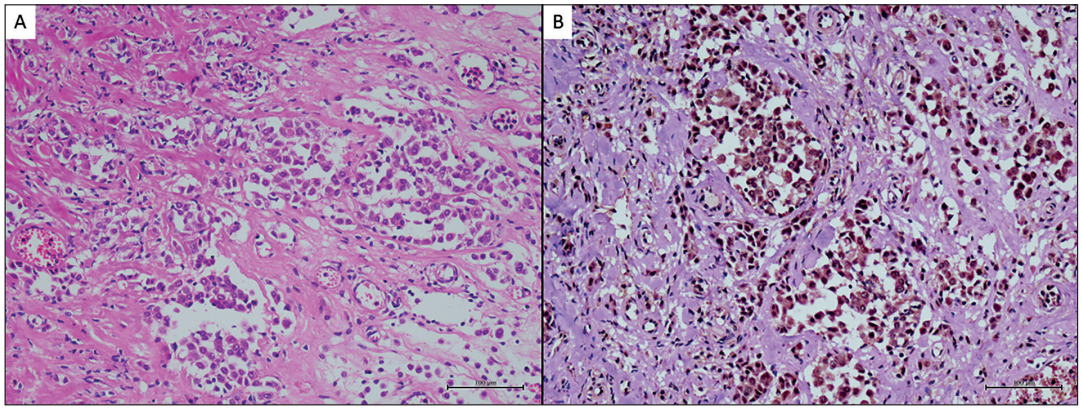

Figure 2. A case of MM with retained BAP1 expression. This tumour showed epithelioid morphology (**A**) and positive BAP1 nuclear staining (**B**). Interestingly, the patient was from a family with clustered MM cases (Original magnification: 200×).

clinical-pathological features and some striking differences in terms of prognosis and outcome when compared to sporadic MMs. The very first study to assess MM survival and clinical features among patients with germline *BAP1* mutations was published in 2015[39]. Compared to a general cohort composed of all MM cases recorded at the Surveillance, Epidemiology and End Results (SEER) program between 1973 and 2010, germline *BAP1* mutated MMs had seven times longer survival, with a 5-year survival rate of 47% *vs.* 6.7% in the control cohort. *BAP1* mutation carriers had a statistically significant earlier mean age at diagnosis (56.3 *vs.* 72 years), a lower M:F sex ratio with slight predominance of female patients (0.73:1 *vs.* 4:1) and a higher proportion of peritoneal MMs (50% *vs.* 14.2%). Each case in this group showed epithelioid morphology. Additionally, more than half of *BAP1* mutation carriers (56.5%) had at least one other cancer diagnosed apart from MM. 13% had multiple MMs, with both pleural and peritoneal location. Another interesting finding from this study was that survival was not related to age in the *BAP1* cohort. In fact, 5-year survival rate was 45% in patients younger than 55 years (*vs.* 17.4% in the SEER cohort) and 51% in patients older than 55 years (*vs.* 5.1% in the SEER cohort). According to such observations, the improved survival in the *BAP1* cohort should not be related to the younger mean age of patients in this group, although the limited number of patients did not allow studies of significance. Moreover, patients with peritoneal MM in the *BAP1* cohort exhibited significantly longer median survival than patients with pleural MM (10 years and 2 years, respectively). In contrast, no differences in survival between peritoneal and pleural MMs were noted in the SEER cohort (8,69 and 8,55 months respectively). Similar findings were reported by Ohar et al[40] in 2017. Their work was designed to assess the frequency of *BAP1* germline mutations in a cohort of 150 MM patients with familiar history of cancer in comparison with a cohort of asbestos-exposed patients with no neoplasms other than MM and a cohort of asbestos-exposed individuals with no history of cancer. Nine out of 150 patients (6%) in the study cohort harboured germline *BAP1* mutations while none was detected in the control cohorts. *BAP1* mutation carriers developed MM at an earlier mean age (58.5 *vs.* 68.2 in the control cohorts), exhibited an excess of peritoneal MMs (55.6% *vs.* 17.7% in the control cohorts) and an increased prevalence of epithelioid subtype (88.9% *vs.* 74.6%). Furthermore, they had a 3.5-fold prolonged median survival (60 months *vs.* 17 months)[40]. In summary, from an epidemiological point of view, familial *BAP1*-related MM cases present earlier and more frequently affect female patients. They can be multiple and often occur in association with other synchronous or metachronous neoplasms. Finally, they are more commonly located in the peritoneum than sporadic MMs. Despite lacking absolutely specific histopathological features, the vast majority of familial *BAP1*-related MMs shows an epithelioid morphology. The most noticeable peculiarities, however, concern their prognosis. In fact, familial *BAP1*-related MMs demonstrate a dramatically longer median survival than sporadic MMs, independently of patient age at presentation and, supposedly, of received therapies. Studies on larger cohorts of patients are needed to confirm these data. The main epidemiological and pathological differences between sporadic MMs and familial *BAP1*-related MMs are summarized in Table I.

Table I. Real time PCR primers.

	Sporadic mm	Germline *BAP1*-mutated mm
Sex distribution	M:F = 4:1	M:F = 1:1
Mean Age at Diagnosis (years)	72	56.3
Association with asbestos exposure	Very strong	Nd
Location	Pleura>>>peritoneum	Pleura = peritoneum
Multiple locations	Nd	13%
Association with other tumors	Nd	Uveal melanoma bap1 inactivated melanocytic tumors of skin
Histological subtype	Epithelioid Biphasic Sarcomatous	Epithelioid (100%)
5-year survival rate	6.7%	47%

BAP1 Germline Mutations and Well-Differentiated Papillary Mesothelioma

Well-differentiated papillary mesothelioma (WDPM) is a rare variant of epithelioid mesothelioma. It is characterised by a papillary growth, with a myxoid fibrovascular core lined by bland mesothelial cells, and only initial and limited tendency, if any, to stromal invasion[41]. It mostly develops in the peritoneum of young women, often as multifocal disease and in absence of any correlation to asbestos exposure. It portends a good prognosis with excellent long-term survival. Few cases of WDPM have been reported in literature to date. As a consequence, the biology and related risk factors are still poorly understood[42]; similarly, their optimal management has to be still defined. Ribeiro et al[43] reported the first (and unique) description of WDPMs clustering in a family with a germline *BAP*1 mutation. In a retrospective analysis on a series of 8 WDPMs, Lee et al[44] found complete immunohistochemical *BAP1* loss in three of their cases. Interestingly, all these 3 patients had also developed a synchronous or metachronous MM, which also showed absent *BAP1* expression. However, published data about the relationship between WDPM and *BAP1* are controversial and need further investigation.

Germline BAP1 Mutations and Exposure to Asbestos: a Supposed Paradigm of Gene-Environment Interaction

Whether exposure to asbestos or other carcinogenic mineral fibres is strictly required or not for MM development in germline *BAP1* variant carriers still represents an open issue. Based on published data, members affected by MM within some *BAP1*-mutated families had no known occupational or environmental history of exposure to asbestos[45]. However, in vivo experiments on $BAP1^{+/-}$ knockout mouse models have shown that knockout animals presented a markedly higher incidence and accelerated onset of MM in comparison to their wild-type littermates when exposed to asbestos; on the other hand, no spontaneous MMs were detected in $BAP1^{+/-}$ mice during a 20 month-follow up. Such findings suggest that low or even minimal levels of exposure to carcinogenic fibres could be sufficient to trigger tumorigenesis in germline mutation carriers[46].

BAP1 heterozygosity likely influences inflammatory response to external injuries, thus contributing to the creation of an immunosuppressive and pro-tumorigenic microenvironment. In their original study, Napolitano et al[47] found that peritoneal inflammatory response after exposure to low doses of asbestos in $BAP1^{+/-}$ mice was radically altered, with preferential, alternative M2-polarization of macrophages and lower levels of pro-inflammatory chemokines and cytokines. Moreover, incidence of MM was significantly higher in $BAP1^{+/-}$ mice exposed to standard (i.e. very low) doses of asbestos than in wild-type mice. In particular, $BAP1^{+/-}$ mice exposed to low doses of asbestos developed MMs at a similar rate as $BAP1^{+/+}$ mice exposed to 10 times higher doses. Taken together, the discussed results indicate that germline *BAP1* mutations confer exaggerated sensibility to the carcinogenic effect of mineral fibres, promoting the development of MM in their carriers even for minimal-dose background exposition.

Detection of Germline BAP1 Mutation: Proposed Strategies and Practical Implications

Currently, the importance of recognizing *BAP1*-mutated families and starting a surveillance program for the early identification of *BAP1*-related malignancies is widely accepted. In fact, some of these tumours, uveal melanomas and renal cell carcinomas in particular, seem to have a more aggressive course, portending a less favourable prognosis than sporadic cases. Active surveillance in *BAP1*-mutated patients could allow early diagnosis of *BAP1*-related malignancies, with precocious treatment and improved survival. Nevertheless, well-established screening guidelines for patients harbouring a germline *BAP1* mutation are still lacking as well as thorough assessment of lifetime risks of developing *BAP1*-associated cancers in mutation carriers. In 2014 Pilarski et al[48] proposed a screening program with annual medical check-ups. As a general rule, ophtalmological and dermatological examinations should be started at the age of 11 and of 22 years respectively. However, it is advisable to start surveillance programs even earlier in those families where the proband is diagnosed with a *BAP1*-related neoplasm at a younger age, as suggested by the same research group in another paper[49]. In addition, yearly physical examinations for MM and a renal screening protocol consisting of abdominal ultrasound once a year and magnetic resonance imaging every two years has been proposed. The authors also recommend to undertake genetic testing for *BAP1* mutations in all patients

with two or more 'core' *BAP1*-related tumours (namely: uveal melanoma, cutaneous melanoma, MM and renal cell carcinoma) in themselves and/or first- or second-degree relatives. Families with multiple cutaneous melanomas only should not be taken into account, due to the higher frequency of melanoma in the general population. However, the rarity of pathogenic BAP1 variants in unselected patients with *BAP1*-associated malignancies rises the need to further discriminate patients with an increased risk for *BAP1* germline mutations to be sent for genetic counselling. As a consequence, Chau et al[50] propose to age-adjust the previously mentioned criteria as follows: uveal melanoma with onset before 40 years of age; cutaneous melanoma with onset before 18 years; MM with onset before 50 years; renal cell carcinoma with onset before 46 years. In populations with high incidence of melanoma a minimum of three cutaneous melanomas per patient should be diagnosed to initiate genetic counselling in cases in which multiple cutaneous melanomas are the only *BAP1*-associated malignancy[51]. In patients receiving genetic counselling and suspected to be *BAP1* mutation carriers, the presence of the mutation must be confirmed with direct sequencing techniques. However, when formalin-fixed paraffin-embedded tumour tissue is already available, *BAP1* immunohistochemistry could be considered an easy, cheap and rapid screening test. Patients showing complete loss of nuclear *BAP1* expression could then undergo genetic sequencing[52].

Regarding active surveillance in *BAP1* mutation carriers, no evidence that screening for MM of high-risk patients improves survival has been provided yet. In addition, it must be highlighted that an early diagnosis of pleural and peritoneal MM is difficult to achieve and still strictly relies on advanced imaging techniques (computed tomography, magnetic resonance) and tissue biopsies[53].

Nevertheless, in the latest years, several biomarkers have been proposed for the monitoring and early detection of MM in high-risk patients. Circulating tumour proteins such as mesothelin, osteopontin and fibulin-3 are the best characterized so far. New promising markers include circulating tumour DNA, circulating tumour cells and circulating microRNAs[54-56]. They all hold the advantage of being analysed through sampling of easily obtained biological fluids, with no risks for the patients and reduced health costs. Currently, none of them has been validated for clinical practice but encouraging results about the feasibility of liquid biopsy-based strategies for the early diagnosis of MM come from the research field.

Beyond BAP1: Are There Other Genes Responsible for Inherited Predisposition to MM?

As previously underlined, *BAP1* is not the only gene accounting for inherited predisposition to mesothelioma. In 2014, Betti et al[57] assessed the prevalence of germline *BAP1* mutations in five families with multiple MMs and in 103 sporadic cases. While *BAP1* pathogenic variants were seen in none of the sporadic cases, only one family showed a truncating mutation, suggesting that germline *BAP1* alterations are not so easily encountered among familial MM cases. Other studies from the same research group aimed to assess the prevalence of germline pathogenic variants in 39 patients with familial pleural MM, which was found to be only 7.7%[58] They also investigated with a next-generation sequencing approach the prevalence of germline pathogenic variants in 94 cancer predisposing genes in 93 patients with pleural MM with quantified levels of asbestos exposure[59].

Truncating pathogenic variants were identified in ten different tumour suppressor genes (*PALB2, BRCA1, FANCI, ATM, SLX4, BRCA2, FANCC, FANCF, PMS1 AND XPC*), all involved, like *BAP1*, in DNA repair mechanisms. Such variants were demonstrated to be exceedingly infrequent in a general population database. Importantly, patients harbouring pathogenic variants in one of the mentioned genes showed statistically significant lower levels of asbestos exposure than other patients. Globally, these findings indicate that an inherited deficiency in cellular machineries dedicated to DNA repair enormously amplifies the carcinogenic effects of mineral fibers[60].

BAP1 Mutations in MM: Translational Significance

Undoubtedly, one of the most relevant aspects of unveiling the genetic background of a certain tumour is the opportunity to translate the novel biomolecular discoveries in the development of alternative therapeutic strategies. This would be particularly important for a tumour like MM, whose response to standard treatments is so poor. Regarding *BAP1*-mutated MMs, interesting results are emerging from recent literature. A recent work has demonstrated *in vitro* that *BAP1* status regulates the sensitivity of MM cells to

gemcitabine, the elective second-line chemotherapeutic agent for advanced MM. In particular, a functional *BAP1* protein seems to be required for gemcitabine-induced tumour cell apoptosis. Consequently, *BAP1*-mutated MMs show resistance to gemcitabine effect[61]. On the other hand, given the role of *BAP1* in DNA repair and chromatin remodelling, it has been postulated that BAP1 mutations could confer sensitivity to DNA repair targeted therapy, such as Poly(ADP-ribose) polymerase (PARP) inhibitors and dual phosphoinositide 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) inhibitors, or to drugs known as 'epigenetic' modulators, such as Vorinostat[62,63]. *In vitro* studies are ongoing to test this intriguing hypothesis, but the results obtained so far are not univocal and still insufficient for *in vivo* translation, which is much awaited[64].

Conclusions

The study of inherited genetic factors predisposing to the development of MM constitutes an emerging and promising field of research. Germline *BAP1*-mutated MMs, as part of a recently characterized tumour syndrome, have specific epidemiological and pathological features and are likely to respond to unconventional therapies, as *in vitro* studies suggest. Meanwhile, identifying and including in appropriate surveillance programs patients carrying germline *BAP1* mutations is of primary importance, as early diagnosis still is, and always be, the best and more effective treatment. This paper provides a concise overview on current knowledge about BAP1-related tumour predisposition syndrome and emerging insights on genetic susceptibility to MM.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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