Review Article

BAP1, a tumor suppressor gene driving malignant mesothelioma

Mitchell Cheung, Joseph R. Testa

Cancer Biology Program Fox Chase Cancer Center, Philadelphia, PA, USA

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Correspondence to: Joseph R. Testa. Cancer Biology Program, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, USA.
Email: Joseph.Testa@fccc.edu.

Abstract: Like cancer generally, malignant mesothelioma (MM) is a genetic disease at the cellular level. DNA copy number analysis of mesothelioma specimens has revealed a number of recurrent sites of chromosomal loss, including 3p21.1, 9p21.3, and 22q12.2. The key inactivated driver genes located at 9p21.1 and 22q12.2 were discovered two decades ago as being the tumor suppressor loci *CDKN2A* and *NF2*, respectively. Only relatively recently was the *BAP1* gene determined to be the driver gene at 3p21.1 that is somatically inactivated. In 2011, we reported germline mutations in *BAP1* in two families with a high incidence of mesothelioma and other cancers such as uveal melanoma (UM). As a result of a flurry of research activity over the last 5–6 years, the *BAP1* gene is now firmly linked causally to a novel tumor predisposition syndrome (TPDS) characterized by increased susceptibility to mesothelioma, UM, cutaneous melanoma (CM) and benign melanocytic tumors, as well as several other cancer types. Moreover, results from recent *in vivo* studies with genetically engineered *Bap1*-mutant mouse models and new functional studies have provided intriguing biological insights regarding *BAP1*'s role in tumorigenesis. These and other recent findings offer new possibilities for novel preventative and therapeutic strategies for MM patients.

Keywords: BAP1; mesothelioma; tumor suppressor

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Introduction

Malignant mesothelioma (MM) is a relatively rare cancer frequently linked to prior exposure to asbestos. Approximately 3,000 new cases of MM are diagnosed annually in the United States. As a cancer of the mesothelial cell lining that surrounds various organs, the majority of MM (~80%) occurs in the pleural cavity surrounding the lungs, whereas most of the remaining (peritoneal) tumors arise in the abdominal cavity. Prognosis is generally very poor with a median survival of ~9–12 months for pleural cases (1,2). Similar to other cancers, MM is a disease that can result from the interactions between environmental carcinogenic factors (e.g., asbestos) and genetic predisposing factors, only one of which has been identified to date. At the somatic genetic level, losses of chromosome regions 3p21.1, 9p21.1, and 22q12.2 are frequently observed in MM. The critical driver genes located at 9p21.1 and 22q12.2 were first reported more than 2 decades ago as being the tumor suppressor loci *CDKN2A* and *NF2*, respectively (3,4). Only relatively recently was the *BAP1* gene determined to be the driver gene at 3p21.1 that is frequently somatically inactivated (5), and germline mutations of *BAP1* predisposing to MM were reported independently at about the same time (6). Numerous studies have confirmed that *BAP1* is a major MM susceptibility gene (see below), and that most MMs (>80%) harbor somatic alterations of the *CDKN2A* locus, which encodes the tumor suppressor proteins p16INK4A and p14ARF (regulators of the critical Rb and p53 pathways, respectively), 60% harbor somatic mutations and exonic deletions of the *BAP1* gene and 30–50% show inactivation of *NF2*.

Somatic and germline mutations of *BAP1*

A seminal paper by Jensen *et al.* described the localization of the *BAP1* gene to chromosomal region 3p21.2–p21.31, a region that is frequently deleted in lung carcinomas and many other cancers (7). The group identified somatic *BAP1* deletions/mutations in two non-small cell lung cancer and one small cell lung cancer cell lines. Although several noteworthy functional studies would ensue between 2008 and 2010 (8-12), more than a decade would pass before the seminal genomic report of frequent (~85%) involvement of somatic *BAP1* mutations in metastatic uveal melanomas (UM) (13). These ocular tumors are categorized as either class 1 (low metastatic potential) or class 2 (high metastatic potential tumors), the latter strongly correlated with monosomy 3. Utilizing exome and Sanger sequencing technology, somatic *BAP1* mutations were identified in 26 of 31 (84%) class 2 primary UMs but in only 1 of 26 class 1 primary tumors, thus implicating *BAP1* mutations in UM metastatic capacity. Of particular interest to us was the discovery of a germline *BAP1* mutation in one of the patients with a class 2 UM, though no extended family history studies were performed (13). Somatic *BAP1* mutations in MMs were first reported in 2011 by Bott *et al.* (5). They used a candidate gene sequencing approach to scrutinize tumors for mutations in genes located in chromosomal region 3p21 and discovered that *BAP1* was mutated in 12 of 53 (23%) MMs.

At about the same time, the first description of germline *BAP1* mutations being associated with familial MM was reported (6). We described two U.S. families with a high incidence of MM and other types of cancers, such as renal carcinoma; additionally, two UMs were seen in one family. A germline splice site mutation in *BAP1* intron 6 in DNA from one family (W family) was shown to lead to aberrant skipping of exon 7 during mRNA processing and a predicted protein truncation. A nonsense mutation in exon 16 was present in the second (L) family, also leading to a predicted protein truncation. Published simultaneously in the same issue of *Nature Genetics*, another report described germline mutations of *BAP1* in two families with atypical melanocytic tumors, UMs, and cutaneous melanomas (CMs) (14). In a subsequent report published later in 2011, a third independent study reported results of a mutation screen of 53 unrelated UM patients with known high risk for hereditary cancer, and notably, a single patient was identified with a germline *BAP1* truncating mutation that was associated with UM and multiple other cancers in this patient's family (15). Biallelic inactivation of *BAP1* and decreased BAP1 expression were identified in the UM, lung adenocarcinoma and meningioma from three family members who were mutation carriers. Notably, other cancers observed in this family include MM, CM, and meningioma. Since then, numerous reports have expanded on the discovery of germline mutations in families or individuals with these and other cancers [*BAP1* tumor predisposition syndrome (TPDS)] (16-29). In the OMIM (Online Mendelian Inheritance in Man) database, the disorder is now referred to as TPDS #614327 (http://www.omim.org/entry/614327?search=bap1&highlight=bap1), which is inherited in an autosomal dominant manner with individuals carrying a heterozygous *BAP1* mutation being at high-risk for various tumors, including benign melanocytic tumors (atypical Spitz tumors) and multiple malignant tumors, such as UM, CM, "MM on exposure to asbestos", and other cancer types (i.e., lung adenocarcinoma, meningioma, and renal cell carcinoma). A list of the tumors that are associated with the BAP1 TPDS was recently summarized by Pilarski *et al.*, 2016; (https://www.ncbi.nlm.nih.gov/books/NBK390611/) (30). Confirmed *BAP1*-TPDS tumors include the following: atypical Spitz tumors, UM, MM, CM, clear cell renal cell carcinoma, and basal cell carcinoma. Unconfirmed neoplasms (with conflicting evidence regarding inclusion in the syndrome) include the following (in alphabetic order): breast cancer, cholangiocarcinoma, meningioma, neuroendocrine tumors, non-small cell lung adenocarcinoma, and thyroid cancer.

Unique MM clinical characteristics associated with *BAP1* mutations

A comprehensive analysis of MM high-risk families has led to the discovery of some interesting differences in the clinical features of MM patients with or without germline *BAP1* mutations (16). We examined the germline *BAP1* mutation status of 150 MM patients with a family history of cancer, 50 asbestos-exposed control individuals with a family history of cancers other than MM, and 153 asbestos-exposed control individuals without familial cancer. No *BAP1* mutations were identified in the control cohorts, but were identified in 9 of 150 (6%) individuals with a family history of cancer. Firstly, the median age of MM diagnosis was significantly younger among the 9 *BAP1* mutation carriers as compared to non-carriers (58 *vs.* 68 years). This earlier age of tumor onset is similar to that observed in other cancer predisposition syndromes (31), such as Hereditary

Breast and Ovarian Cancer Syndrome (32) and Li-Fraumeni Syndrome (33). Secondly, there was an overrepresentation of peritoneal MMs (5 of 9) and a tendency for epithelioid MM among the mutation carriers compared to non-carriers (16). Finally, but very remarkably, these 9 MM individuals have a better overall survival after MM diagnosis (60 *vs.* 17 months among the non-carriers) (16), which is similar to survival data findings from another group of investigators (34). This notable clinical characteristic is likely due to the mutation carriers being younger and predominantly having peritoneal, epithelioid disease, which has an overall better prognosis than pleural and sarcomatoid MM, respectively (1,2). Collectively, these findings suggest that MM patients presenting with a family history of cancer should be considered for *BAP1* mutation screening to identify carriers who might benefit from routine monitoring for the purpose of early detection and intervention.

Sanger sequencing has revealed somatic *BAP1* point mutations in 20–25% of sporadic MM samples (5,6,35-37). Subsequent studies using next-generation and multiplex ligation-dependent probe amplification (MLPA) platforms have revealed a significantly higher incidence (~60%) of *BAP1* alterations in MMs from both *BAP1*-TPDS individuals, sporadic cases and cell lines, with most of the additional alterations consisting of deletions of one or more *BAP1* exons, which was not detectable by Sanger sequencing (5,6,35-37). MMs with either point mutations or deletions were each found to exhibit loss of nuclear BAP1 staining due to protein truncation and loss of the BAP1 carboxyl-terminal nuclear localization signal (NLS) (38). Tumors harboring somatic *BAP1* alterations were also found to possess unique pathological and clinical characteristics. Thus, BAP1 immunohistochemical analysis of 123 MM samples indicated that high BAP1 expression (indicative of no mutations) correlated with a shorter survival time (39), which is similar to findings from studies of MM patients with germline *BAP1* mutations (16,34). Also comparable, was the association of somatically inactivated *BAP1* with the epithelioid MM subtype (36). Since *BAP1* can influence the regulation of gene expression epigenetically or through deubiquitination of transcription factors (see below), it is plausible that these different patterns of gene expression can lead to variations in MM tumor subtypes (35,40,41).

Similar to Li-Fraumeni syndrome (33), there are a number of reported *BAP1* mutation families where individuals are afflicted with more than one type of primary tumor (23,42-44), strongly suggesting multiple tissue lineages being targeted by BAP1 deficiency. Cancer incidence data from published papers reporting germline *BAP1* mutations indicated that the two most common primary tumors observed together are MM and UM (7 cases), melanocytic tumors and CM (7 patients), CM and basal cell carcinoma (7 patients), and MM and CM (6 cases) (*Table 1*).

Table 1 Recurrent tumor types reported in *BAP1* mutation carriers to date

Tumor type	Number of cases
Malignant mesothelioma	56 (+44) = 100
Uveal melanoma	57 (+36) = 93
Cutaneous melanoma	37 (+32) = 69
Renal cell carcinoma	18 (+27) = 45
Melanocytic tumor	34 (+4) = 38
Basal cell carcinoma	17 (+12) = 29
Breast carcinoma	12 (+16) = 28
Lung carcinoma	7 (+15) = 22

Many *BAP1* mutation carriers develop multiple tumors types. The numbers in parentheses indicate the number of cancer cases found in *BAP1* families for which DNA sequence analysis was not performed due to unavailability of germline DNA. The most common reported to date being MM and UM (7 patients), melanocytic tumors and CM (7 patients), CM and basal cell carcinoma (7 patients), and MM and CM (6 patients). MM, malignant mesothelioma; UM, uveal melanomas; CM, cutaneous melanoma.

BAP1 gene, protein structure, and function

Rauscher, Prendergast and colleagues were the first to clone and characterize the *BAP1* gene (7). *BAP1* was discovered through a yeast two-hybrid screening for BRCA1 ring finger domain interacting proteins. Cloning of the full-length *BAP1* cDNA and analysis of the predicted protein product indicated that gene encodes a 729-amino acid protein with a molecular weight of 81 kDa, although subsequent immunoblot studies revealed a protein 90 kDa in size, likely due to post-translational modifications. The amino terminus of the BAP1 protein has amino acid homology with a class of thiol proteases, designated Ubiquitin C-Terminus Hydrolases (UCH). A BARD1 binding site and HCF-1 (host cell factor 1) binding domain are located at the amino terminus and middle of the BAP1 protein, respectively. The C-terminal region encompasses protein interacting domains for YY1 (Ying Yang 1), BRCA1

and ASXL1/2. A NLS is positioned near the very end of the protein at residues 717 to 722. Similar to the better-known post-translational modifications through phosphorylation, ubiquitination can play a role in modifying proteins to cause changes in cellular signaling. As a nuclear localized, deubiquitinating enzyme, the BAP1 protein complexes with ASXL1/2 to form the Polycomb repressive group deubiquitinase Complex (PR-DUB) that functions in epigenetic regulation of gene expression through chromatin structure modifications (11,45). The PR-DUB complex functions in the deubiquitination of monoubiquitinated histone H2A K119 to promote gene expression via chromatin relaxation. The PR-DUB works in opposition to the Polycomb Repressive Complex 1 (PRC1) that catalyzes the monoubiquitination of H2A, which plays a physiological role in stem cell pluripotency, differentiation, and embryonic development (11,45).

A role for *BAP1* in cell proliferation has been suggested from studies showing BAP1's ability to deubiquitinate the HCF-1 transcriptional cofactor (8,9,12). HCF-1 normally associates with E2F1, E2F3, and E2F4 transcription factors to help recruit repressors and activators to promote cell cycle progression at different stages. BAP1 was shown to deubiquitinate HCF-1 leading to a modest increase in HCF-1 protein levels (8,9). BAP1 and HCF-1 were also shown to be recruited to promoters to control gene regulation through the ability of the two proteins to bind to the YY1 transcription factor (12). Gene pathway analysis indicated that this interaction appears to control a number of different processes including cell cycle progression, cell survival, and metabolism (12).

A functional RNAi screen identified BAP1 as being a central player for efficient BRCA1 and RAD51 recruitment to ionizing radiation (IR)-induced foci in DT40 cells, a chicken B cell lymphoma cell line (46). Further studies using *Bap1* knockout DT40 cells demonstrated that the cells had decreased survival after DNA damaging IR treatment. Accordingly, increased chromosomal instability was also observed in *BAP1* KO cells, as indicated by chromosomal breakage. Furthermore, ChIP (chromatin immunoprecipitation) analysis demonstrated that BAP1 proteins are located at regions of double strand DNA breakage (DSB) (46). An independent study by Ismail *et al.* similarly revealed that BAP1 protein was co-recruited with phosphorylated histone H2AX (γ-H2AX; a marker for DSB) after human U2OS cells were laser microirradiated (47). ChIP assays also showed that BAP1 and γ-H2AX were recruited to sites of endonuclease-induced DSB (47).

The BAP1 protein was recently demonstrated to play an important role in inhibiting apoptosis caused by metabolic stress such as glucose deprivation (48). The unfolded protein response (UPR) protects cells from stress caused by misfolded proteins in the endoplasmic reticulum (i.e., glucose deprivation), and if the stress is unresolved, this leads to induction of apoptosis by depleting ATP and generating reactive oxygen species (ROS). The investigators demonstrated that under metabolic stress, BAP1 complexes with PRC1 to promote the expression of genes essential for UPR by directly binding to the genes' promoters (48). Studies performed with several *BAP1*-null lung and renal cancer cell lines showed increased apoptotic induction following glucose deprivation, suggesting that the increased survival reported in patients with *BAP1*-negative MM may be due to the inability of these cancer cells to actively proliferate due to the stress caused by the high demand for glucose (48). Accordingly, it would be important in future work to test if *BAP1*-null MM tumor cells are more sensitive to ROS-promoting therapeutics.

Lessons from mouse models

The use of *Bap1* genetically engineered mouse models provided undeniable evidence for *BAP1* being an important tumor suppressor gene. Utilizing zinc-finger mediated genomic DNA modifications, we created three *Bap1* mouse models (49,50). In the first study (50), a heterozygous *Bap1*-null model in the FVB mouse strain was created by introducing a deletion of exons 6 and 7. Similar to a previous study (51), homozygous mice were found to be embryonic lethal, indicating an essential embryonic function for the gene. More importantly, was the discovery that heterozygous *Bap1* knock out (KO) mice were more susceptible to MM development after peritoneal injection of crocidolite asbestos (50). Compared to wild type (WT) littermates, there was a greater than 2-fold increased incidence of MM tumors in *Bap1* KO mice (32% versus 72%, $P<0.01$) as well as an overall decrease in survival after asbestos exposure (55 versus 43 weeks median, $P<0.0001$). Moreover, MM tumors from KO mice were more aggressive than the tumors from WT mice. Greater staining for Ki-67, larger tumor sizes, and increased metastasis to the pancreas, liver, and intestine were observed in the tumors from KO mice. Moreover, RT-PCR analysis of MM cell lines derived from ascites demonstrated loss of expression of *p16Ink4a*, *p19Arf*, and *p15Ink4b* genes in MM cells derived from three WT mice but not in MM cells from two KO mice.

Notably, however, normal mesothelial cells and MM cells from *Bap1* KO mice showed downregulation of Rb through a p16Ink4a-independent mechanism, suggesting that predisposition of *Bap1* KO mice to MM may be facilitated, in part, by cooperation between Bap1 and Rb. Finally, PCR analysis of genomic DNA indicated loss of the WT copy of the *Bap1* gene from the MM cells of two KO mice but not in the MM cells of WT mice, consistent with *Bap1* being a cancer predisposition gene (50). These unbiased genetic findings in an experimental model suggest that humans carrying a germline *BAP1* mutation may likewise be predisposed to the carcinogenic effects of asbestos fibers.

Similar phenotypic differences were observed between WT mice and two other *Bap1* mutant mouse models in FVB background that harbor knock-in mutations analogous to the germline L and W mutations reported in humans (49). The median survival of asbestos injected W and L mice was significantly shorter than in WT mice (48 and 46 *vs.* 60 weeks, respectively). Moreover, the incidence of MM development was at least 2-fold higher among the *Bap1* knock-in mice compared to WT mice (74% and 71% *vs.* 35%, respectively). Interestingly, combining the data from all three mouse models (KO, L, and W) revealed that about two-thirds of the *Bap1* mutant mice developed spontaneous tumors, with the majority of the tumors comprising ovarian sex cord stromal tumors (SCSTs) (49). Virtually all female mice developed SCST (some bilaterally) within 12–30 months of age. Array CGH and immunoblot analysis showed loss of the wild type copy of *Bap1* in three SCST tested, indicating the importance of the *Bap1* gene in SCST tumorigenesis. MMs were found in one KO (pleural and biphasic) and one W mouse (peritoneal and biphasic) that were not exposed to asbestos, i.e., spontaneous MMs. While no MMs were seen in a cohort of WT littermates, the difference in the incidence of MM between WT and *Bap1*-mutant mice was not statistically significant. Based on the very high incidence of MM formation in asbestos injected *Bap1*-mutant mice, there thus appears to be a very strong role for gene-environment interaction (i.e., exposure to asbestos) in MM development. A study published the following year provided further support for the increased susceptibility of *Bap1* KO mice to asbestos-induced MM, including upon exposure to relatively low doses of these carcinogenic fibers (52).

Additionally, a study by a separate group of investigators demonstrated increased H3K27me3 levels in bone marrow cells from Cre-induced homozygous *Bap1* KO mice (53). The tri-methyl modification of histone H3 has been previously shown to be accomplished by the EZH2 subunit of the PRC-2 complex. Other experiments showed that *BAP1* mutant human MM cell lines were more susceptible to shRNA and small molecule targeting of *EZH2*, suggesting a novel therapeutic approach for *BAP1*-mutant malignancies (53). Interestingly, the use of BAP1 and EZH2 staining was proposed as a diagnostic tool to differentiate epithelioid/biphasic MM from benign mesothelial lesions in humans (54). The researchers reported combined loss of BAP1 staining and high EZH2 staining in the majority of MM specimens examined, but not in any benign lesions (54).

Quantitative proteomic analysis of tissues from inducible *Bap1* KO mice revealed a role in metabolic homeostasis in the pancreas and liver (55). Elevated cholesterol biosynthesis but reduced expression of gluconeogenic and lipid homeostasis proteins were observed in the liver. In the pancreas, expression of pancreatitis protein markers was increased whereas expression of mitochondria proteins was decreased. These mice also exhibited hypercholesterolemia, hypoglycemia, lipid reduction in the liver, and pancreatic acinar cell degeneration (55). How such metabolic dysregulation is related to cancer predisposition or tumorigenesis is yet to be determined. However, it is known that increased cholesterol and lipid synthesis is required in cancer progression due to the high demand for both membrane lipids as well as for cell signaling [reviewed in (56,57)]. As a consequence, it may be possible to identify possible molecular targets for therapeutic and/or preventative regimens in MM patients and *BAP1* mutation carriers, respectively. For example, Hedgehog inhibitors, such as GDC-0449 already available for basal cell carcinoma treatment, can be evaluated for efficacy in *BAP1* deficient MM cells (57).

Preventative and therapeutic strategies for MM

Since MM, CM, and UM are universally lethal diseases, the best approach would be to prevent the development of these cancers in *BAP1* mutation carriers through appropriate proactive measures. It has been suggested that these individuals avoid asbestos and smoking to decrease the possibility of developing MM (30). Furthermore, arc welding and excessive sun exposure should be avoided to decrease the likelihood of developing UM and CM, respectively. *BAP1* mutation carriers are at risk of developing additional primary tumors during their lifetime. Thus, cancer survivors should have regularly scheduled dermatologic, ophthalmologic, pulmonary and renal

evaluations to enhance the possibility of early detection and timely intervention.

Due to the important role BAP1 has with BRCA1 in homologous recombination repair (46), poly (ADP ribose) polymerase (PARP) inhibitors were tested for their efficacy in *BAP1*-null tumor cells. In one report, no differential sensitivity was observed between *BAP1* WT and *BAP1*-mutant MM cells with the MK4827 (Merck) inhibitor (5). In another study using chicken DT40 cells (46), increased sensitivity to the PARP inhibitor, Olaparib, was observed in homozygous *BAP1*-null cells as compared to WT and heterozygous *BAP1*-null cells. A recent study implicated the importance of the levels of an alternative splice variant of *BAP1* in conferring sensitivity to PARP inhibition (58). This alternative splice isoform leads to the loss of 12 amino acids within the catalytic and BARD1 binding domains. Transfection of *BAP1*-deficient ZL55 MM cells with this *BAP1* isoform resulted in a 2- to 3-fold increased sensitivity to Olaparib compared to cells transfected with the full length *BAP1* construct (58). Additional tests were carried out to determine if phosphoinositide 3-kinase (PI3K) inhibition, which can deplete BRCA1 protein levels, could have an additive effect with PARP inhibition. MM cells wild type for *BAP1* were separated into two groups based on the ratio of the expression of the *BAP1* splice isoform to that of the full-length isoform. Cells with higher splice isoform expression showed greater cell viability inhibition after combination treatment with Olaparib and GDC0980, a dual PI3K-mTOR inhibitor (58).

A histone deacetylase (HDAC) inhibitor, vorinostat, was previously evaluated in a phase 3 clinical trial involving MM patients who previously progressed after chemotherapy (59). Unfortunately, no improvements in overall survival resulted from vorinostat treatment (59). A recent study of MM cells and HDAC expression may have provided a reason for this disappointing clinical study result (60). The authors demonstrated that BAP1 can transcriptionally promote the expression of *HDAC2*. *BAP1* knockdown led to a decrease in HDAC2 but an increase in HDAC1 expression (60). Interestingly, this altered HDAC imbalance led to an increase in MM cell sensitivity to vorinostat and other HDAC inhibitors. Thus, clinical trials of MM with HDAC inhibitors might prove more successful if recruitment of patients were to take into account the *BAP1* mutation status of individual tumors.

As mentioned previously, EZH2 was proposed as a possible therapeutic target in MM tumors with *BAP1* mutations (53). A clinical trial using an EZH2 inhibitor is already underway to test efficacy in human MM patients (ClinicalTrials.gov Identifier: NCT02860286). This Phase 2 trial is recruiting patients with relapsed or refractory MM using the drug, Tazemetostat (EPZ-6438), which was developed by Epizyme. The study has been split into two parts. Part 1 involves a pharmacokinetics study of MM patients, without regard to *BAP1* status, following a single drug dose. The second part of the study will recruit MM patients with *BAP1*-deficient MM tumors for continuous Tazemetostat treatment.

Conclusions

The steadily increasing number of reports of germline *BAP1* mutations in high-risk cancer families has led to the discovery of a novel autosomal dominant, highly penetrant hereditary cancer syndrome that frequently predisposes to MM, UM, CM, atypical melanocytic tumors, and RCC, as well as other cancers such as basal cell carcinoma and meningioma. The tumor suppressor function of the *BAP1* gene in MM has been definitively demonstrated genetically through *in vivo* experimental studies with *Bap1*-mutant mouse models. Although spontaneous MMs are rare in these mice, exposure to asbestos induced a highly significant increase in the incidence of aggressive MM in several different mouse models tested. Collectively, these findings provide genetic evidence that *Bap1* is a bona fide tumor suppressor gene and offer key insights into the contribution of carcinogen exposure to enhanced cancer susceptibility. The continuing interest in elucidating mechanisms by which *BAP1* inactivation contributes to cancer susceptibility and tumorigenesis has led to the discovery of a number of different BAP1 substrates and functions. Collectively, recent investigations suggest that BAP1 is a multifunctional protein that plays a role in cell cycle progression, DNA damage response/repair, and genomic instability in MM tumorigenesis. In turn, these novel findings have led to several proposed treatment options for this dreaded disease, such as the use of an EZH2 inhibitor in an ongoing clinical trial. Finally, the findings suggest that *BAP1* mutation carriers who develop UM or atypical melanocytic tumors are at high risk of developing MM, CM or other cancers and, thus, should be closely monitored, with the goal of early intervention.

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Footnote

Conflicts of Interest: JRT has served as a genetics consultant, and on one occasion, as an expert witness in a case involving the role of inherited mutations of *BAP1* in mesothelioma. Both authors have a pending patent application on *BAP1* genetic screening.

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