Mesothelioma: recent highlights

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Abstract: Recent discoveries have elucidated some of the mechanisms responsible for the development of mesothelioma. These discoveries are: (I) the critical role of chronic inflammation in promoting mesothelioma growth, driven by the release of high mobility group box protein-1 (HMGB1) following asbestos deposition in tissues and its potential role as a biomarker to identify asbestos exposed individuals and mesothelioma patients; (II) the discovery that inherited heterozygous germline mutations of the deubiquitylase BRCA-associated protein 1 (*BAP1*) cause a high incidence of mesothelioma in some families; and that (III) germline BAP1 mutations lower the threshold of asbestos required to cause mesothelioma in mice, evidence of gene X environment interaction. These findings together with the identification of novel serum biomarkers, including HMGB1, Fibulin-3, etc., promise to revolutionize screening and treatment of this malignancy in the coming years.

Keywords: Mesothelioma; BRCA-associated protein 1 (BAP1); asbestos; erionite; high mobility group box protein-1 (HMGB1); SV40

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Pathology

Mesothelioma is a tumor that occurs because of the malignant transformation of the mesothelial cells that form the pleura and peritoneum. Mesothelioma very rarely develops from the mesothelial cells that line the pericardium and tunica vaginalis. Mesothelial cells are the last remnant of mesoderm, so they are quite undifferentiated cells and maintain the ability to differentiate into different cell lines. Accordingly, some mesotheliomas have an epithelial morphology, others have a spindle cell morphology (often called sarcomatoid or fibrous mesothelioma) and others show a mixture of the two morphologies (called biphasic mesotheliomas) (1). More rare variants exist, but they are mostly a curiosity for the pathologist and have little clinical significance except that they are often misdiagnosed because they are rare and pathologists are not familiar with them. Histologically, the epithelial variants are less aggressive than the spindle cell variants (1). Biphasic malignancies tend to behave according to the prevalent histological composition: the more fibrous they are, the more malignant they are (1). Bueno *et al.* (2) identified molecular markers that match these histological characteristics and correlate with prognosis.

Although the diagnosis of mesothelioma is often straightforward, a large number of mesotheliomas are misdiagnosed. A panel of French thoracic pathologists reviewed 1/3 of all mesothelioma diagnoses in France in the previous year and confirmed the diagnoses in only 67% of them (3). In a recent study in collaboration with experts of thoracic pathology in China, we reviewed the diagnoses of mesothelioma in Eastern China and confirmed the diagnoses in 56.5% of them. The reasons for misdiagnosis include inexperience of the pathologist (due to the relatively infrequency of this malignancy), inadequate specimens (such as tiny needle biopsy or cytology without supporting open

biopsy), insufficient set of immunostains, and inadequate clinical information for the pathologist (e.g., a pleural fluid from a 10-year-old child with high fever can show very atypical mesothelial cells, if the pathologist is not aware of the age and of the fever he could easily diagnose a mesothelioma rather than a pneumonia). Moreover, spindle cell tumors of the pleura are very difficult to diagnose and differentiate from each other and in these cases immunohistochemistry may be of limited help. In general, a panel that includes calretinin, WT-1 and pankeratin as positive markers for mesothelioma, together with TTF1, P63, Moc31, CEA and PAX8 will help differentiate most carcinomas from mesotheliomas. The most specific marker for mesothelioma is WT1. However, for peritoneal mesotheliomas in women, WT1 is not helpful as it stains ovarian cancers; instead ER and PR staining should be used (4,5).

Asbestos and mesothelioma

Mesotheliomas are polyclonal malignancies (6) often caused by exposure to asbestos. The field effect of asbestos over the pleura causes numerous foci of atypical mesothelial hyperplasia and some of them over time may become malignant. Epidemiological and laboratory studies during the past decades concentrated almost exclusively on studies of "asbestos" fibers. These studies have demonstrated a clear connection between exposure to asbestos fibers and the subsequent development of mesothelioma (7,8). Asbestos refers to a family of six mineral fibers that were used commercially in the 1970s. They had very difficult names to identify them, so to facilitate their identification for regulatory purposes they were bundled together under the name of "asbestos" (9). Since then several other fibers have been used. However they are unregulated and their use is not restricted in spite of ample evidence that some of them (10), but not all of them (11), are as or more carcinogenic than the regulated mineral fibers (12). For example gravels containing erionite, to date the most potent fiber in causing mesothelioma, was used to pave over 300 miles of roads in North Dakota (10). Also, roads and urban developments were built over asbestos deposits present in the ground in Nevada (13).

Asbestos, inflammation and mesothelioma

The important role of chronic inflammation in promoting asbestos carcinogenesis has been known for many years, although the exact mechanisms were unclear (14). A key mechanism by which asbestos-induced inflammation causes the transformation of mesothelial cells has recently been elucidated. Working with primary diploid human mesothelial (HM) cells obtained from pleural fluids of patients with non-malignant conditions we (15,16) discovered that asbestos induces necrotic cell death with resultant release of HMGB-1 into extra-cellular space. High mobility group box protein-1 (HMGB1), a prototypical damage-associated molecular pattern molecule (DAMP) that is normally present in the nucleus of the cells, is a critical mediator of asbestos-induced mesothelioma initiation. Within the nucleus, HMGB1 is a non-histone chromatin-binding protein that regulates nucleosome assembly and chromatin structure. As a DAMP, HMGB1 is passively released by necrotic cells or actively secreted by immune and cancer cells, and is responsible for the initiation and perpetuation of the inflammatory response. Asbestos causes primary HM necrosis that result in the passive release of HMGB1 into the extracellular space. This, together with the prolonged bio-persistence of asbestos fibers, initiates a vicious cycle of chronic cell death and inflammation that over a period of many years can lead to mesothelioma (17). Thus, HMGB1 functions as a 'master switch' by which the chronic inflammation that drives mesothelioma growth is initiated and maintained. Accordingly, HMGB1 serum levels are elevated in asbestos-exposed individuals and in MM patients. HMGB1 hyper-acetylation has been functionally associated to its active release by inflammatory cells. We compared the serum levels of total and hyper-acetylated HMGB1 in individuals occupationally exposed to asbestos, mesothelioma patients and healthy unexposed controls. HMGB1 serum levels reliably distinguished asbestos-exposed individuals and mesothelioma patients from unexposed controls. Moreover, the levels of total and hyper-acetylated HMGB1 were significantly higher in the sera of mesothelioma patients compared to asbestos-exposed individuals, and did not vary with tumor stage, suggesting that early lesions are also associated with increased HMGB1 levels. At a cutoff value of 2.00 ng/mL, the sensitivity and specificity of hyper-acetylated serum HMGB1 in differentiating mesothelioma patients from asbestos-exposed individuals was 100%, outperforming in parallel experiments other previously proposed biomarkers: osteopontin, fibulin-3, and mesothelin. When comparing mesothelioma patients to patients, other pleural effusions

cytologically benign or non-mesothelioma malignant pleural effusions, the combination of these two biomarkers, HMGB1 and fibulin-3, provided the highest sensitivity and specificity in differentiating mesothelioma patients from the other two groups. Therefore, total and hyper-acetylated HMGB1 may be valuable biomarkers to differentiate mesothelioma patients from individuals occupationally exposed to asbestos and from unexposed people (18). A clinical trial will start in 2017 to validate these findings and to validate other biomarkers discovered by our collaborator Dr. Harvey I. Pass (19,20). The availability of biomarkers to identify asbestos-exposed individuals and mesothelioma patients would represent a major step forward to prevent and treat this deadly cancer.

Since inflammation is important in the etiology of MM, agents that possess anti-inflammatory properties may decrease serum HMGB1 levels and suppress or delay mesothelioma growth. We found that therapeutic levels of aspirin and its metabolite salicylic acid suppress the growth, migration, invasion, wound healing, and anchorage-independent colony formation of HMGB1-secreting human mesothelioma cells. Moreover, *in vivo*, aspirin significantly inhibited mesothelioma growth in a xenograft model (21). These findings illustrated a novel mechanism by which aspirin may exert its anti-tumorigenic properties (e.g., HMGB1 inhibition) while remaining consistent with its well-described anti-inflammatory properties. The potential benefit of therapies aimed at interfering with HMGB1 is supported by studies with ethyl pyruvate (EP), the ethyl ester of pyruvic acid. EP has been shown to be an effective HMGB1 inhibitor, by decreasing its secretion and the consequent signaling in inflammation-related diseases and several cancers. We found that EP, similarly to aspirin, inhibits the malignant growth of human mesothelioma cells both *in vitro* and *in vivo* (22).

Exposure to asbestos and other carcinogenic mineral fibers, however, is not the only cause of mesothelioma. In spite of stringent regulations introduced in the 1970s and 1980s in the US (and other countries) to limit asbestos exposure, the incidence of mesothelioma reached 3,200 cases/year in the US in 2003 and it has remained stable since (23). The incidence of mesothelioma has also increased worldwide over the past 50 years (23). A growing number of mesotheliomas, estimated at 20–50%, develop in individuals with no history of asbestos exposure suggesting that other factors cause mesothelioma or that some individuals may be very susceptible to even minimal amounts of asbestos (1,12). Fortunately, only a fraction of people exposed to asbestos developed mesothelioma. For example, among South African miners who worked continuously in crocidolite asbestos mines for over 10 years, ~4.6% developed mesotheliomas (24), suggesting that additional factors may render some individuals more susceptible than others to asbestos (12).

BRCA-associated protein 1 (BAP1) and mesothelioma

Through a 14-year study of an epidemic of mesotheliomas in Cappadocia, Turkey, where over 50% of the population exposed to erionite fibers died of mesotheliomas (25), we discovered that susceptibility to mesothelioma was transmitted in a Mendelian fashion and formulated the hypothesis that the cause of the epidemic was gene X environment interaction (25-27). Subsequently, we discovered that germline *BAP1* truncating mutations caused a very high incidence of mesothelioma in some US families in the absence of occupational asbestos exposure (28). Moreover, using a *BAP1*$^{+/-}$ mouse model, we demonstrated that mice carrying germline *BAP1* mutations develop mesothelioma following exposure to very low doses of asbestos that rarely cause mesotheliomas in wild-type mice (29). Our data, confirmed and expanded by others, showed that germline *BAP1* mutations are also associated with uveal melanoma (28) and other malignancies (30-37). We named this the "*BAP1* cancer syndrome" (38). At a young age, carriers of *BAP1* germline mutations start developing characteristic benign melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITs) (38). MBAITs provide physicians with a visual clue to identify *BAP1* mutation carriers that we are monitoring for early detection of eye and skin melanoma, mesothelioma and other malignancies. So far, all carriers of germline *BAP1* mutations have developed one or more cancers during their life-span (39). We identified four families that share the same *BAP1* point mutation and discovered that these four families are related and descend from a common ancestor born in Switzerland in 1588. The founder couple migrated to Germany and subsequently in the early 1700s to Pennsylvania, United States (40). From this extended family, we built a pedigree of ~80,000 people, and are identifying additional branches of this family that carry the mutation. We are enrolling *BAP1*$^{+/-}$ carriers in a screening program for early detection of eye and skin melanoma, cancers that are curable when

detected early, and for biomarker studies (18). *BAP1* is somatically mutated in several cancers (41-43) including over 60% of sporadic MM, making *BAP1* the most commonly mutated gene in mesothelioma (2,28,41). Recently (44), we screened for genetic alterations in the chromosome 3p21 in 33 mesotheliomas using a high-density array comparative genomic hybridization (aCGH), followed by targeted next generation sequencing (tNGS) to validate the alterations detected and to investigate for nucleotide sequence mutations. We found multiple biallelic genome rearrangements involving 46 genes on 3p21. Many of these deletions were not contiguous but rather they alternated along normal DNA segments, as in chromothripsis although sequential independent deletion events could not be entirely ruled out. We found that *BAP1* was the most frequently mutated gene in MM. In addition, we found that mutations of *SETD2*, *PBRM1* and *SMARCC1* are frequent in mesothelioma. These results suggest that high-density aCGH combined with tNGS provides a more precise estimate of the frequency and types of genes inactivated in mesothelioma and probably in all types of human cancer, than approaches based exclusively on NGS (next-generation sequencing) strategy. Overall these studies underscore the pivotal role of *BAP1* in causing mesothelioma in both a hereditary and sporadic setting.

SV40 and mesothelioma

We proposed a link between SV40 infection and mesothelioma in 1993, when we published that when hamsters were injected with SV40 into the pleural space, all of the animals developed mesotheliomas within 3–6 months (45). The finding that SV40 caused mesothelioma in hamsters prompted investigations into the possibility that some mesotheliomas in humans could be attributed to SV40 infection directly or with SV40 acting as a co-carcinogen with asbestos (46-48). Mesothelioma samples studied in 1994 showed that 60% of the samples contained SV40 DNA and expressed the SV40 large T (tumor) antigen. The results were confirmed by numerous laboratories using a variety of techniques such as PCR, *in situ* hybridization, Western blot, immunohistochemistry, Laser dissection/PCR, etc., but the percentage of positive samples varied from 6–83%, and a few studies were completely negative. Technical and geographical differences may account for some of these variances. Significant geographical differences in human exposure to SV40 were confirmed by a study showing that the polio vaccines used in the former USSR and in the countries under its influence contained live, infectious SV40 until at least 1978 (49). These findings supported a previous conclusion of the Institute of Medicine of the National Academy of Sciences that the epidemiological data were flawed and therefore it was not possible to accept or reject a causal association between SV40-containing polio vaccines and cancer because it was not possible to clearly distinguish exposed from non-exposed cohorts. Although the epidemiological data are not available, mechanistic experiments in HM cells and animal experiments support a pathogenic role of SV40 in the pathogenesis of some mesotheliomas, including as a co-factor with asbestos. As for the unusual susceptibility of mesothelial cells to SV40 mediated transformation, we discovered a novel biological mechanism responsible for the suppression of late viral gene products, which takes place in primary HM cells and in primary brain cells. We found that in these cells, late gene suppression is achieved through the production of antisense RNA molecules. Because the late genes are not expressed, the cells are not lysed. The virus remains episomal because there is no selective pressure for integration, the viral oncogenes (the large and the small T antigens) are expressed and they cause a high rate of malignant transformation. Lack of late gene expression may also help SV40-transformed mesothelial cells to escape immune recognition *in vivo* (50). In these cells the high levels of SV40 T antigen bind and activate the IGF1 receptor promoting tumor cell growth (51).

Unexplained findings and opportunities for research

As we were reviewing the accuracy of the diagnoses of mesothelioma in Eastern China (5,52) in collaboration with Chinese experts, we noted that the mesothelioma cases in the province of Zhejiang have very different demographics compared to mesothelioma cases in the US, Europe and Hong Kong (53,54). Among 52 mesothelioma cases, we found the M:F ratio was 1:4 compared to 4:1 in the US; the pleura:peritoneum ratio was 1:3 compared to 5:1 in the US; and the average age of diagnosis was 50 compared to 72 in the US (53). Nine out of 52 (17%) of these Chinese MMs occurred in individuals 40 years old or younger, compared to less than 1% in the same age group in the US (53). These demographics are rarely associated with mesotheliomas caused by asbestos, but are often found

in mesotheliomas linked to inherited germline *BAP1* mutations, to environmental exposure occurring since birth, radiation or to other yet unknown carcinogens (13,39). In the absence of occupational asbestos exposure, the expected M:F ratio is close to 1:1 (12). The association with asbestos was 38.4% among the two hospitals that contributed cases for our study: 7.1% in Zhejiang Cancer Hospital (2/28) and 75% in the Yuyao People's Hospital (18/24) where patients had been exposed to asbestos. Yuyao Hospitals are located close to the center of the asbestos industry in Eastern China. There were no other differences in demographics among patients from these two hospitals.

Therefore, in the province of Zhejiang in Eastern China, there is a unique high prevalence of young women with peritoneal mesothelioma and no evidence of asbestos exposure. Studying the causes of peritoneal mesothelioma in these young Chinese women may also help elucidate the possible causes for the increasing number of young women in the US and Europe who develop peritoneal mesothelioma in the absence of asbestos exposure.

Conclusions

During recent years, science has made significant progress in elucidating the mechanisms of asbestos carcinogenesis and of mesothelioma pathogenesis. These findings have led to the identification of novel targets for screening and therapy. We are optimistic that as the precise mechanisms of BAP1 mediated carcinogenesis are elucidated in the near future, we will be able to effectively interfere with gene-environment interaction and prevent at least some mesotheliomas. Similarly we have high hopes that the ongoing trials will validate HMGB1 and/or other biomarkers to identify patients exposed to asbestos and to identify mesothelioma patients early in the course of the disease. This would provide new tools to prevent and treat this malignancy. It is also hoped that resources will become available to test the possible efficacy of HMGB1 inhibitors in clinical trials. It is anticipated that such inhibitors would most benefit those who have been exposed to asbestos, by reducing HMGB1-driven inflammation and thus delaying or suppressing the emergence of malignant transformation.

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Footnote

Conflicts of Interest: M Carbone has pending patent applications on BAP1 and HMGB1 (1 pending, 1 awarded). H Yang has pending patent applications on HMGB1 (1 pending, 1 awarded). M Carbone provides consultation for mesothelioma diagnosis at no cost to patients and colleagues and for a fee to lawyers.

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