Malignant mesothelioma is a highly aggressive malignancy arising from the serosal lining. While most cases originate in the pleural lining of the thoracic cavity, a subset of cases primarily involves the peritoneum or, rarely, the pericardium or the tunica vaginalis (1). Studies have suggested that malignant mesothelioma comprises several clinicopathologic subgroups, with distinct site predilections and pathogenetic mechanisms. Here, we provide an overview on the recent discoveries on the genetics and pathogenesis of malignant mesothelioma, as well as the implications of these findings on the diagnostic workup.

Ever since the seminal study by Wagner et al. on the mesothelioma epidemic in South African crocidolite miners in 1960 (2), asbestos exposure has emerged as a significant risk factor for the development of mesothelioma. Various occupations associated with asbestos exposure, such as insulation workers and shipyard builders, demonstrate increased risks for developing malignant mesothelioma (3). Overall, malignant mesothelioma shows a predominance for male and older patients. Nonetheless, a subset of malignant mesothelioma, for instance peritoneal mesothelioma, is relatively more common in women, presents occasionally in young patients, and shows weaker to no association with asbestos exposure in epidemiologic studies. Given a latent period of several decades between asbestos exposure and mesothelioma development (4), the pathogenesis of mesothelioma in these patients has been hypothesized to be due to other mechanisms (5). For instance, a subset of patients who received prior therapeutic radiation for malignancies such as Hodgkin lymphoma developed malignant mesothelioma with a latency of 17–26 years (6). Compared to asbestos-related cases, radiation-associated malignant mesothelioma demonstrated unusual histology, including pleomorphic, myxoid, or signet-ring cell features, and showed better overall survival (6). In addition, aside from prior asbestos or radiation exposure, additional genetic mechanisms have been implicated in the development of malignant mesothelioma in a subset of cases, including: (I) germline \textit{BRCA1} associated protein-1 (\textit{BAP1}) inactivation syndrome, (II) structural gene rearrangements in \textit{Ewing sarcoma breakpoint region 1} (\textit{EWSR1}) or \textit{fused in sarcoma} (\textit{FUS}), and (III) \textit{anaplastic lymphoma kinase} (\textit{ALK}) rearrangements.

\textbf{Genetic characteristics of malignant mesothelioma}

Prior to the advent of large-scale genomic studies, cytogenetic studies and fluorescence \textit{in situ} hybridization have been used to demonstrate recurrent deletions in \textit{CDKN2A} and \textit{NF2} in malignant mesotheliomas. Homozygous deletion of chromosomal region 9p21 including \textit{CDKN2A} can be detected by fluorescence \textit{in situ} hybridization in ~70\% of pleural mesotheliomas and ~25\% of peritoneal mesotheliomas (7,8); whereas hemizygous 22q loss with inactivation of \textit{NF2} can be detected in ~20–40\% of pleural and peritoneal mesotheliomas (7,9).

The largest genome-wide study to-date on a series of 216 malignant pleural mesotheliomas has identified recurrent
somatic alterations in CDKN2A, BAP1, NF2, along with TP53 and SETD2 (9). Furthermore, recurrent gene fusions were detected leading to inactivation of BAP1, NF2, and SETD2. These findings implicated alterations in the cell cycle, DNA repair, chromatin-remodeling, and the hippo signaling pathways in the pathogenesis of malignant pleural mesothelioma (9). Similar findings have been observed in other genomic studies of malignant mesothelioma (10,11).

Overall, somatic mutations in NF2 and TP53 appeared to be more prevalent in pleural mesotheliomas with non-epithelioid histology as compared to epithelioid mesotheliomas; furthermore, TP53-mutant pleural mesotheliomas demonstrated poorer overall survival than those with wild-type TP53 status, highlighting an overall correlation of TP53 genetic alterations with histologic subtypes and clinical outcome (9).

Germline BAP1 inactivation syndrome and somatic BAP1 alterations

In two families with high incidence of mesothelioma in North America, Testa et al. identified germline mutations in BAP1, a tumor suppressor gene on the chromosomal region 3p21 (12). Patients with germline BAP1 inactivation syndrome are predisposed to developing multiple other tumors in addition to pleural mesothelioma, including renal cell carcinoma, uveal melanoma, cutaneous melanoma, and atypical epithelioid Spitz tumor (13). Germline BAP1 inactivation has also been reported in peritoneal mesotheliomas arising in the adolescents (14). BAP1 encodes a deubiquitylating enzyme involved in the regulation of multiple cellular pathways, including in DNA repair, cell cycle progression, and chromatin remodeling. Biallelic inactivation of BAP1 has been detected in the tumors in these patients, consistent with a two-hit model.

In addition to germline setting, somatic BAP1 alterations have also been detected in a large subset of sporadic mesotheliomas (9,10). In both the germline or somatic settings, the pathogenic BAP1 alterations are predominantly truncating mutations upstream of the nuclear localization sequence, leading to aberrant BAP1 protein expression with either complete absence or exclusively cytoplasmic localization in the BAP1-mutant tumors.

In fact, immunohistochemistry for BAP1 protein expression has emerged as a useful marker in the diagnosis of malignant mesothelioma (15,16), including in cytologic preparations. Loss of BAP1 nuclear immunoreactivity can be found in 40–70% of pleural and peritoneal mesotheliomas, whereas BAP1 nuclear expression is retained in all reactive mesothelial proliferations (7,15,16). Nonetheless, it is important to note that loss of BAP1 protein expression is a relatively specific but not a sensitive finding in the diagnosis of malignant mesothelioma, since a significant subset of malignant mesothelioma retained nuclear BAP1 expression, including those tumors with rare large structural alterations (see below) and most cases with sarcomatoid or desmoplastic histology (17).

EWSR1 or FUS rearrangements in mesothelioma

EWSR1-ATF1 and FUS-ATF1 gene fusions have been reported in rare cases of pleural and peritoneal mesotheliomas (18). Focusing on a cohort of children and young adults with malignant mesothelioma, Desmeules et al. identified four tumors, including three peritoneal mesotheliomas and one pleural mesothelioma, all harboring EWSR1-ATF1 or FUS-ATF1 gene fusion. These patients were all under 40 years of age, with no known history of asbestos or radiation exposure. Histologically, the tumors demonstrated conventional epithelioid morphology with retained BAP1 protein expression, suggesting that EWSR1-ATF1 or FUS-ATF1 as the driver event in the pathogenesis of malignant mesothelioma in these patients.

Of note, EWSR1-ATF1 and FUS-ATF1 gene fusions are present in other rare soft tissue neoplasms, such as clear cell sarcoma and angiomatoid fibrous histicocytoma. Molecular detection of these gene fusions is therefore not specific for the diagnosis of mesothelioma, which still relies on histologic and immunophenotypic confirmation of mesothelial differentiation. Other large structural alterations including EWSR1-YY1 gene fusion and translocation X1;12 have also been reported in rare cases of malignant mesothelioma, although clinicopathologic characteristics of these tumors remained not well-studied (18-20). In the setting of malignant mesothelioma with unusual clinical presentation, for instance in young patients with no history of asbestos exposure, identification of these gene rearrangements may be diagnostically helpful in the appropriate histomorphologic context. Nevertheless, at this point, the therapeutic implications of EWSR1 or FUS rearrangements in these cases of malignant mesothelioma remain unknown.

ALK rearrangements in peritoneal mesothelioma

Novel gene rearrangements in ALK have been identified
in a subset of peritoneal mesotheliomas (21,22). ALK rearrangement was first reported in a 10-year-old girl with biphasic peritoneal mesothelioma, although the ALK fusion partner was not investigated (22). Subsequently, a comprehensive study by Hung et al. on a large cohort of 88 patients with peritoneal mesothelioma identified ALK rearrangements in three women, including two patients under 40 years of age (21). All three patients with ALK-rearranged peritoneal mesothelioma lacked asbestos or radiation exposure. All ALK-rearranged peritoneal mesotheliomas showed diffuse strong cytoplasmic ALK protein expression by immunohistochemistry, with ALK gene rearrangement confirmed by fluorescence in situ hybridization. Targeted next generation sequencing of both tumor DNA and RNA demonstrated ATG16L1-ALK, STRN-ALK, and ALK-TPM1 fusion in one case each. Notably, ALK rearrangements represent a novel pathogenetic mechanism and a somatic driver event for developing malignant peritoneal mesothelioma in these patients, as these tumors lacked alterations typical of other mesotheliomas (loss of chromosomal region 9p or 22q or genetic alterations in BAP1, SETD2, or NF2). Histologically, ALK-rearranged peritoneal mesotheliomas were epithelioid or biphasic and were confirmed to show a mesothelial phenotype by both electron microscopy and immunohistochemistry. ALK rearrangements were apparently confined to a subset of peritoneal mesotheliomas and not detected in pleural mesotheliomas in this and other studies (9,21,23). ALK, located on chromosome 2p23, is a pivotal therapeutic target with the use of the small-molecule tyrosine-kinase inhibitor in patients with non-small-cell lung cancers, lymphomas, and other rare soft tissue tumors with ALK rearrangements (24,25). Identification of ALK rearrangement suggests that a subset of patients with peritoneal mesothelioma may be identified by immunohistochemistry for ALK and considered for tyrosine-kinase inhibitor therapy. Nonetheless, given the rare cases of ALK-rearranged peritoneal mesothelioma identified so far, more investigations on their clinicopathologic features and outcomes are needed.

Implications of the genetic findings on the pathologic diagnosis of malignant mesothelioma

In the prototypical clinical scenario of an old patient presenting with multiple serosal masses or diffuse thickening, the diagnosis of malignant mesothelioma is often straightforward by examining tumor histology and applying select immunohistochemical or cytogenetic testing. However, the diagnosis of malignant mesothelioma in adolescents, young adults, or patients lacking asbestos or radiation exposure can be challenging. Recent identification of somatic BAP1 alterations, EWSR1-ATF1 or FUS-ATF1 fusion, and ALK rearrangements in a subset of mesotheliomas suggests novel pathogenetic mechanisms. These alterations can be routinely identified by laboratory studies (fluorescence in situ hybridization testing for EWSR1/FUS and immunohistochemistry for BAP1 and ALK in patients with malignant mesothelioma, particularly those with atypical clinical presentation. Future efforts to dissect the pathogenetic heterogeneity of malignant mesothelioma would hopefully uncover novel mechanisms and identify therapeutic targets of this enigmatic and highly aggressive disease.

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None

Footnote

Conflicts of Interest: Dr. Lucian R. Chirieac served on the Advisory Board for Merck Sharp & Dohme and undertakes medicolegal work related to mesothelioma and lung cancer. Dr. Yin P. Hung has no conflicts of interest to declare.

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