Malignant Mesothelioma
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Abstract
Review on mesothelioma, with data on clinics, and the genes involved.

Keywords
Mesothelioma; Tumor of the pleura; Asbestos; BAP1; CDKN2A; NF2; SETD2; TP53

Identity
Phylum
Lung, Heart, Skin, Other: Lung: Pleura: Malignant Mesothelioma

Note
Malignant mesothelioma is a rare, aggressive cancer usually associated with exposure to asbestos. Most (~80%) mesotheliomas originate from mesothelial cells lining the pleural cavity and are referred to as malignant pleural mesotheliomas (MPM); the remainder arise from mesothelial cells that line the peritoneum (15-20%), pericardium (1%), or tunica vaginalis (<1%) (Tischoff et al., 2011). MPM is characterized by a long latency, typically 20-40 years, from the time of asbestos exposure to diagnosis, suggesting that multiple somatic genetic/epigenetic events are required for tumorigenic conversion of a mesothelial cell (Murthy and Testa, 1999).

Clinics and pathology

Etiology
Asbestos is the major causative factor in the pathogenesis of MPM. Approximately 80% of MPM patients report histories of exposure (Prazakova et al., 2014), but it is unknown how asbestos exposure leads to cellular transformation of normal mesothelial cells. The remaining 20% of MPM cases without a recognized history of exposure to asbestos may be related to alternative factors, including radiation or thorotrast exposure (Carbone et al., 2002). Genetic predisposition can also play a prominent role in familial cases (Testa et al., 2011). Chronic inflammation related to exposure to asbestos fibers is thought to contribute to the etiology of MPM (Hillegass et al., 2010; Matsuzaki et al., 2012). Asbestos can be found in human lungs after many years, and asbestos fiber concentrations in lung tissues may not diminish significantly over time after exposure cessation (Feder et al., 2017). Recently, high mobility group box protein-1 (HMGB1), a non-histone chromatin-binding protein that regulates nucleosome assembly and chromatin structure, has been proposed as one of the factors responsible for the initiation and perpetuation of the inflammatory response in MPM (Carbone and Yang, 2012).

Clinics
Approximately 3,200 new cases of mesothelioma are diagnosed in United States annually, and the incidence worldwide is expected to rise over the next
two decades (Henley et al., 2013). MPM has a very poor prognosis, with the median survival being less than 12 months (Mineo and Ambrogi, 2012).

Pathology
The World Health Organization Classification of Tumors of the Pleura has recently updated the classification of MPM (Galateau-Salle et al., 2016). MPM is classified into 3 major histological subtypes accordingly to the morphology of the cells: epithelioid (≥90% epithelial-shaped cells), sarcomatoid (≥90% spindle-shaped cells), and biphasic (consisting of numbers of both epithelial-shaped and spindle-shaped cells). Although the histological classification remains the same, some distinctions have been made related to prognosis. For example, diffuse malignant mesothelioma (DMM) has been separated from other mesotheliomas, with a much better prognosis observed in localized malignant mesotheliomas (LMMs) and well-differentiated papillary mesotheliomas (WDPMs) (Galateau-Salle et al., 2016).

Cytogenetics
Karyotypic studies and chromosome microarray analyses of MPM have shown that all chromosomes contribute to numerical and structural changes, with chromosomal losses being more common than gains. Several sites of chromosomal losses occur more frequently, e.g., monosomy of chromosome 22, which occurs in 60-70% of MPMs (Cheng et al., 1999; De Rienzo et al., 2016). Chromosome microarray and loss of heterozygosity (LOH) analyses have revealed frequent losses of specific sites in 1p, 3p, 4, 6q, 9p, 11q, 13q, 14q, 15q, 17p, 18q, and 22q in MPM specimens and tumor-derived cell lines (De Rienzo et al., 2000, 2001; Lindholm et al., 2007; Ivanov et al., 2009; Cheung et al., 2010), suggesting that tumor suppressor genes may reside in the deleted regions. In fact, subsequent mutation screening studies uncovered frequent mutations and/or homozygous deletions of specific tumor suppressor genes at several of these recurrent sites of chromosomal loss (see below). Although less common, recurrent chromosomal gains of 5p, 7p, 8q, 12p, 17q and 18q have also been documented in some studies. Notably, losses of 1p, 3p, 6q, 9p, and 22q often occur in combination, suggesting a multistep cascade involving the inactivation of multiple tumor suppressor genes critical in MPM pathogenesis (Murthy and Testa, 1999). Data on malignant peritoneal mesotheliomas are fewer than for MPM, but two recent DNA copy number studies have revealed that the genomic pattern in peritoneal tumors is similar to that described for MPM, including recurrent losses of chromosomal regions 3p21, 9p21, and 22q12, although differences were also observed. For example, in one report of peritoneal mesotheliomas, novel genomic copy number alternations included loss of 8p11.2 and gain of 15q26.2 (Chirac et al., 2016). In another report, Borozuk et al. (2016) compared DNA array-based findings from 48 epithelioid peritoneal mesotheliomas and 41 epithelioid MPMs to identify similarities and differences in copy number alterations. Losses in 3p, 9p and 22q were seen in tumors from both sites, although 9p and 22q losses were seen at a higher rate in the pleural tumors (p<0.01). Moreover, regions of copy number gain were more common in peritoneal tumors, whereas losses were more common in MPM, with regions of loss containing known tumor suppressor genes and regions of gain encompassing genes encoding receptor tyrosine kinase pathway members. Deletions in 6q, 14q, 17p and 22q, and gain of 17q were seen in asbestos-associated peritoneal mesothelioma cases, but not in peritoneal tumors thought to be causally related to prior radiation exposure. The patterns of genomic imbalances suggest overlapping and distinct molecular pathways in mesothelioma of the pleura and peritoneum, and that differences in causation (i.e., asbestos vs. radiation) may account for some of these site-dependent genomic differences observed.

Treatment
Patients receiving first line combination chemotherapy with cisplatin and pemetrexed have a median survival of about 12 months (Vogelzang et al., 2003). Some patients with early MPM who undergo multimodality therapy that includes surgical resection and chemotherapy may benefit significantly, with longer-term survival at 5 years seen in up to 20% of cases (Richards, 2009).

Genes involved and proteins
Work performed in the 1990s implicated tumor suppressor loci at two of the recurrent sites of chromosomal loss first identified cytogenetically and/or by deletion mapping. One of these loci, CDKN2A (Cheng et al., 1994), is located at 9p21.3, and the second, NF2 (Bianchi et al., 1995; Sekido et al., 1995), resides at 22q12. The identity of the critical 3p21 gene in mesothelioma remained a mystery until 2011, however, when somatic point mutations of BAP1, located at 3p21.3, were identified in 20-25% of sporadic MPMs (Bott et al., 2011; Testa et al., 2011). In 2012, a Japanese group reported frequent biallelic alterations of BAP1, including homozygous deletions of part or all of this tumor suppressor gene as well as sequence-level mutations, in 61% of sporadic mesotheliomas (Yoshikawa et al., 2012). Subsequent studies with newer next generation and multiplex ligation-dependent probe amplification platforms confirmed a similarly high incidence of BAP1 alterations in this disease (Lo Iacono et al., 2015; Nasu et al., 2015). Importantly, germline mutations of BAP1 have also
been found in families with a high incidence of mesothelioma and other cancers, and the existence of a germline BAP1 mutation may predispose to the carcinogenic effects of asbestos (Testa et al., 2011).

**BAP1**

**Location**
3p21.1

**Note**
Point mutations observed in 22-25% of MPM; additional ~40% may show deletions of one or more exons.

**CDKN2A**

**Location**
9p21.3

**Note**
Locus consists of overlapping genes encoding tumor suppressors p16(INK4) and p14(ARF), both of which are usually inactivated in MPM due to loss of shared exon 2 sequences. Homozygous deletions are observed in ~90% of MPM cell lines, and heterozygous and homzygous deletions are detected by FISH in 75-80% of primary MPMs.

**NF2**

**Location**
22q12.2

**Note**
LOH due mostly to monosomy 22 in 60-70% of MPMs; point mutations observed in 25-55% of MPMs.

**TP53**

**Location**
17p13.1

**Note**
Mutated in 15-20% of MPM, often reciprocally with p19(ARF) loss.

**SETD2**

**Location**
3p21.31

**Note**
Point mutations observed in 8% of MPMs; biallelic gene inactivation in up to 27% of MPMs.

**Result of the chromosomal anomaly**

**Hybrid Gene**

While most MPMs have complex genomic profiles consisting of numerous genomic imbalances, two peritoneal mesothelioma cases were reported to have a t(14;22)(q32;q12) as the sole chromosomal aberration (see, by Ioannis Panagopoulos entry Mesothelioma: t(14;22)(q32;q12) EWSR1/YY1; http://atlasgeneticsoncology.org/Tumors/t1422q32q12MesotheliomID.html). More recently, among 25 mesothelioma patients aged 40 years or less, a subset of 4 cases (16%) were found to have EWSR1/FUS-ATF1 fusions, including 2 patients with MPM and two with peritoneal mesothelioma (Desmeules et al., 2017). The fusion-positive cases displayed classic epithelioid morphology, immunoreactivity for cytokeratins and WT1, and negativity for S100. BAP1 expression was retained in the 3 fusion-positive cases with available material. Overall, features of this unique mesothelioma subset include young age at presentation, lack of asbestos exposure, and retained BAP1 expression.

**References**


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