6 Peritoneal Mesothelioma: Disease Biology and Patterns of Peritoneal Dissemination

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Mesothelioma is a rare neoplasm arising from the mesothelial cells lining the pleura, peritoneum, pericardium, and tunica vaginalis layer of testis [1]. Diffuse malignant peritoneal mesothelioma (DMPM) represents about one-fifth to one-third of all forms of mesothelioma.

Age-adjusted incidence rates of DMPM in the Surveillance, Epidemiology, and End Results (SEER) database were 1.2 per 1,000,000 person-year in men and 0.8 per 1,000,000 person-year in women during the years 1973–2003. In Europe, crude incidence rate during the years 1995–2002 was 1.3 per 1,000,000 person-year for both genders [2]. An increase of 5–10% in the annual mortality rate will be observed worldwide at least until 2020. The disease has likely already reached its incidence peak in the USA, but the peak is expected during the present decade in Europe and Australia [3].

The role of asbestos exposure in DMPM has not been clearly established as in the pleural forms. It is estimated that 58% of men and only 20% of women with DMPM had past asbestos exposure [4]. No asbestos exposure is documented in about 20–40% of DMPM, thus suggesting that other factors may be the culprit. Simian Virus 40 (SV40) is a possible co-factor in mesothelioma oncogenesis, and the hypothesis of a genetic susceptibility with an autosomal dominant pattern is based on observations gathered in Cappadocia [5, 6].

DMPM has been traditionally regarded to as an end-stage disease and treated with options that were merely palliative and minimally effective, such as surgical debulking and/or palliative systemic chemotherapy (sCT). The interest in this disease on part of biological and clinical researchers was poor. Only in recent years, an increasing number of patients with DMPM have been treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), resulting in remarkable survival improvements and increased interest in this disease. This chapter reviews several relevant issues regarding DMPM, with a special focus on basic science and translational researches carried out in our institution to investigate the molecular and cellular mechanisms underlying the proliferative potential and resistance to therapy of this disease.

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6.1 Pathology of Peritoneal Mesothelioma

Tumors arising from the mesothelial cells lining the abdominal cavity encompass a wide spectrum of biological aggressiveness [7]. Adenomatoid tumor and solitary fibrous tumor are truly benign lesions that very unlikely recur after simple excision. The former is a solitary asymptomatic lesion which most often involves genital region peritoneum in reproductive-aged women. Solitary fibrous tumor affects primarily men in their sixth decade [8]. The multicystic variant of PM (MCPM) and well-differentiated papillary variant of PM (WDPPM) are exceedingly uncommon entities with borderline malignant potential. At the other extreme, DMPM is a rapidly lethal malignancy, with a median survival of only 1 year when treated with standard therapies. Classification of PM according to clinical presentation, biological behavior, and pathological features is shown in Table 6.1.

DMPM is macroscopically characterized by multiple variably sized grey-white nodules throughout the abdominal cavity. As the disease progresses, the nodules become confluent to form plaques, masses, bowel encasement, or uniformly cover the peritoneal surfaces. Abundant effusion is often present.

Similar to its more frequent pleural counterpart, DMPM is classified as epithelial, sarcomatoid, or biphasic (mixed) [9]. However, the incidence of biphasic tumors is lower than in pleural disease, and pure sarcomatoid DMPM is rare. Epithelial DMPM is composed of polygonal, oval, or cuboidal cells exhibiting cytonuclear features and architectural formations ranging from well-differentiated to anaplastic/pleomorphic appearance. Sarcomatoid tumors and the sarcomatoid component of biphasic DMPM consist of spindle cells arranged in fascicle or storiform pattern [10].

Epithelial DMPM can be further categorized according to the patterns of the epithelial component. The tubulopapillary pattern is one of the most common patterns. It consists of a mixture of small tubules and papillary structures with fibrovascular cores lined by bland flat, cuboidal, or polygonal cells. The solid pattern consists of nests, cords, or sheets of round, oval,

Table 6.1 Classification of peritoneal mesothelioma

Clinical presentation	Biological behavior	Histological subtype	Histological pattern	Prevalence %
Localized	Benign	Adenomatoid tumor		Uncommon
		Solitary fibrous tumor		Uncommon
	Malignant	Epithelial/ Sarcomatoid/ Biphasic (mixed)	Tubulopapillary, solid, signet-ring cells	Uncommon
Diffuse	Borderline	Multicystic		Uncommon
		Papillary well-differentiated		Uncommon
	Malignant	Epithelial	Tubulopapillary	75–80%
			Solid	
			Small cells	
			Adenomatoid	
			Acinar	
			Clear cells	
			Signet-ring cells	
			Deciduoid	
			Rhabdoid	
		Biphasic (mixed)		10–15%
		Sarcomatoid	Desmoplastic	4–6%
			Lympho-histiocytoid	
			Anaplastic	
			Giant cell	

or polygonal cells with abundant eosinophilic cytoplasm and round, vesicular nuclei with prominent nucleoli. The adenomatoid (microglandular), acinar, clear-cell, deciduoid, signet-ring cell, small-cell, and rhabdoid patterns are rare. Sarcomatoid DMPM may demonstrate anaplastic, giant-cell, and desmoplastic features, or osteosarcomatous/chondrosarcomatous areas [8–10]. A very rare form of localized malignant peritoneal mesotheliomas (LMPM) has been reported and characterized by uncommon sharply circumscribed tumors of the serosal membrane with the microscopic appearance of diffuse malignant mesothelioma but without any evidence of diffuse spread [11].

Lymph-node metastases within and outside the abdominal cavity can occur even at the initial manifestation of DMPM. Node involvement has been reported in 7–14% of patients undergoing extensive cytoreductive surgery. By contrast, metastatic disease outside the abdominal cavity is uncommon, except for direct invasion of pleural spaces through the diaphragm [12].

Multicystic and well-differentiated papillary peritoneal mesothelioma are rare variants that generally affect reproductive-aged women with no history of asbestos exposure and show indolent clinical behaviors. MCPM forms multiple variably sized thin-walled cysts involving primarily the pelvis, but often spreading throughout the abdominal cavity. Microscopically, these cysts are separated by fibrous/adipose septa and lined by single layers of flattened to cuboidal cells with no or little atypia. WDPPM is characterized by well-developed papillary structures with fibrovascular core. MCPM is often associated with previous abdominal surgery, inflammation, or endometriosis. However, early recurrences requiring multiple surgical interventions, transformation into truly malignant disease, lymph-node involvement, and even death have been described. This, along with the reported clear evidence of diffuse disease distribution throughout the peritoneum and invasion into peritoneal surfaces, suggests that MCPM and WDPPM should be considered as borderline or low-malignant potential conditions, rather than truly benign tumors [13, 14].

6.2 Diagnosis of Peritoneal Mesothelioma

According to initial symptoms, DMPMs were categorized into three groups: "wet type," presenting with symptoms of malignant ascites causing an increase in abdominal girth, a "dry-painful type" presenting with a focal mass seen at computed tomography (CT) scan usually causing pain, and a "combined type" characterized by both pain and ascites [4]. In a more recent series of 81 DMPM Italian patients, ascites, abdominal pain, and asthenia were the most frequent symptoms, followed by weight loss, anorexia, abdominal mass, fever, diarrhea, and vomiting; 13% of patients presented with abdominal hernia. Systemic symptoms such as thrombocytosis and anemia were present in 73% of cases. About 25% of female patients came to medical attention due to non-specific gynecological symptoms [15].

Contrast-enhanced CT scan is currently the preferred diagnostic radiological tools for DMPM. CT features of PM have been defined as "dry" and "wet," which correspond to wet or dry-painful type clinical types. The radiological "dry" appearance consists of peritoneal-based lesions and the "wet" appearance consists of ascites, irregular, or nodular peritoneum thickening and omental mass [16, 17]. CT scan is also useful in patient selection for a comprehensive surgical approach. The presence of a tumor mass >5 cm in the epigastric region and loss of normal architecture of the small bowel and its mesentery correlate with a low likelihood to perform an adequate surgical cytoreduction (residual lesions $\leq$2.5 cm), that is a predominant prognostic variable [18].

Circulating tumor markers could be used as an adjunct to clinical and radiological assessment. In 2006, our group reported CA125 above normal limits in 53.3% and CA15.3 in 48.5% of 60 patients undergoing CRS/HIPEC. On the contrary, CEA and CA19.9 were mostly normal. Also, serial CA125 measurements paralleled with tumor growth or regression after CRS/HIPEC [19]. More recently, we have assessed the diagnostic and prognostic role of mesothelin and osteopontin, which are markers currently used

in pleural mesothelioma [20]. Using the optimal diagnostic cut-offs selected by ROC methodology, mesothelin attained 100% specificity and 100% positive predictive value in the differential diagnosis between DMPM and peritoneal dissemination of unknown origin. Additionally, osteopontin correlated with survival at multivariate analysis (hazard rate 6.46; 95% CI 1.81–23.05; $p = 0.004$), and it might be a prognostic marker to select DMPM patients for aggressive treatment approaches.

According to the consensus of expert pathologists from the International Mesothelioma Interest Group (Chicago, IL, October 2006), the diagnosis of DMPM must always be based on an adequate biopsy in the context of appropriate clinical, radiological, and surgical findings [18]. Cytology still plays a limited role in the primary diagnosis. Laparoscopy is a tool to perform biopsies, especially when there is no tumor deposit amenable to imaging-guided percutaneous biopsy, due to the unfavorable anatomic sites or small volume disseminated disease. Laparoscopy can also provide an opportunity to evaluate the peritoneal disease burden and to assess the feasibility of optimal cytoreductive surgery [21].

The first step for the diagnosis is hematoxylin–eosin staining. Demonstration of stromal invasion into visceral or parietal peritoneum (or beyond) is the key feature in the differential diagnosis with reactive mesothelial proliferations [22, 23]. Any gastrointestinal carcinoma and, in women, ovarian, primary peritoneal, and, more rarely, lobular breast carcinoma should be considered for the differential diagnosis of epithelial DMPM. The differential diagnosis for sarcomatoid DMPM includes sarcoma and other spindle cells neoplasms, such as sarcomatoid renal carcinoma and, particularly for biphasic DMPM, synovial sarcoma [8]. Since no immunohistochemical marker is entirely specific and sensitive for mesothelioma, the standard is to use panels of positive and negative markers. Mesothelioma is characterized by positive staining for EMA, calretinin, Wilms tumor-1 antigen, cytokeratin 5/6, HBME-1, podoplanin, and mesothelin. Depending on the tumor being considered in the differential diagnosis, CEA, Leu-M1, Ber-Ep4, claudine, B72.3, Bg8, and MOC-31 can be used as negative marker [8, 9, 22–24].

6.3 Comprehensive Treatment of Peritoneal Mesothelioma

DMPM has been traditionally treated by palliative or debulking surgery. Systemic/intraperitoneal chemotherapy and abdominal irradiation have been used in malignant variants. The results of these treatments were quite disappointing, accounting for median survival of about 12 months [25–32]. However, DMPM tends to remain within the peritoneal surfaces of the abdominal cavity all over its clinical course. Lymph-node and extra-abdominal metastases develop rarely and mostly in the late disease progression. In the last two decades, these notions have evolved into the rationale base of a comprehensive local-regional approach to treat DMPM with a curative intent by extensive CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) to eradicate the microscopic residual disease [33].

In 1996, Sugarbaker described five peritonectomy procedures to surgically remove all of the peritoneal linings of the abdominopelvic cavity: (1) right upper quadrant peritonectomy; (2) left upper quadrant peritonectomy with greater omentectomy and splenectomy; (3) lesser omentectomy with stripping of the omental bursa; (4) right colectomy with stripping of the right paracolic gutter; (5) pelvic peritonectomy with sigmoidectomy and (in women) hysterectomy and bilateral adnexectomy [33].

In recent years, a few modifications have been undertaken to adapt the original technique to DMPM clinical and pathological features. The most relevant technical contributions from our center during a 20-year experience with this disease are the innovative concept that a systematic complete parietal peritonectomy (including both macroscopically involved and normal surfaces) regardless of disease distribution is associated with better survival because of DMPM biological characteristics and dissemination pattern with frequent microscopic (not visible) peritoneal disease

[34], the importance of nodal sampling and the impact of node metastases on prognosis [12], and the technique of mesenteric peritonectomy, with partial or complete stripping of the serosal layer from both sides of the mesentery [35].

An additional important concept is that that CRS must be aimed at removing all visible tumors. Numerous studies have stratified survival on the basis of the completeness of cytoreduction and this surgical endpoint is the major prognostic factor not only in DMPM, but also in all peritoneal surface malignancies [36]. This is generally explained by the limited penetration of locally delivered drugs in tumor tissue: only 2–3 mm. On the contrary, the pharmacological advantages of intraperitoneal administration consist in higher local-regional drug concentration with minimal systemic toxicity. Also, the intra-operative time setting allows optimal distribution of chemotherapeutic agents before the development of postoperative adhesions and tumor cell entrapment in scar tissue, which can contribute to disease recurrence. Finally, mild hyperthermia (41–43 °C) has a direct cytotoxic effect, increases the efficacy of antiblastic agents, such as mitomycin-C and platinum compounds, as well as their penetration into tumor tissue [33, 35].

The most relevant literature series of CRS/HIPEC in DMPM are reported in Table 6.2. Median survival ranged from 30 to 92 months, and improved with growing experience, as it was 4–5 years in the most recent updates [37–51]. One French, one American, and one international multi-institutional series have collected 249, 211, and 405 patients, respectively [46–48]. The international study was sponsored by the Peritoneal Surface Oncology Group International (PSOGI) and included patients treated in eight centers from 1989 to 2009 with major operative morbidity of 46%, mortality of 2%, median survival of 53 months, and 5-year survival of 47% [46].

We reported operative long-term outcomes for 108 patients treated with complete CRS/HIPEC (post-cytoreduction residual disease ≤2.5 mm). Treatment-related morbidity and mortality were 38.9% and 1.9%, respectively. Median survival was 63.2 months. Interestingly, there were 19 (43.6%) actual survivors of the 39 patients with potential follow-up >7 years, suggesting that patients surviving >7 years may be cured. On multivariate analysis, epithelioid histology and negative lymph node correlated with both overall survival and progression-free survival [45].

Table 6.2 Selected literature series of CRS/HIPEC for peritoneal mesothelioma

Center [Ref.]	Pts n.	HIPEC	Follow-up (months)	Median OS (months)	5-year OS
Winston-Salem, NC [37]	34	CDDP or MMC	72	41	17%
Bethesda, MD [38]	49	CDDP	28	92	59%
Turin, It [39]	42	CDDP + DX	72	65	44%
New York, NY [40]	54	CDDP + MMC	48	55	50%
Washington, DC [41]	62	CDDP + DX	37	79	50%
Villejuif, Fr [42]	26	OX ± IRI	54	NS	68%
Sydney, Au [43]	20	CDDP + DX	18	30	NS
Basingstoke, UK [44]	76a	CDDP + DX	NS	98	NS
Milan, It [45]	108	CDDP + DX	49	63	52%
International [46]	401	Various	33	53	47%
Bethesda, Pittsburgh, Baltimore [47]	211	CDDP or MMC	NS	38	26%
Lyon, FR [48]	28	CDDP + MMC	34	37	NS
Pittsburgh, PA [49]	65	CDDP + MMC	37	46	39%
Washington, DC [50]	205	CDDP + DX	31	77	52%
RENAPE [51]	249	Various	24	NR	80%

CDDP cisplatin, *DX* doxorubicin, *MMC* mitomycin-C, *OX* oxaliplatin, *IRI* irinotecan, *NS* not stated, *NR* not reached, *5FU* 5 fluorouracil, *OS* overall survival, *HIPEC* hyperthermic intraperitoneal chemotherapy, *EPIC* early postoperative intraperitoneal chemotherapy

As patients not amenable to CRS/HIPEC, due to advanced or not resectable disease, are concerned, scarce data on the role of systemic chemotherapy are available. This may be, at least in part, explained by the rarity and inherent difficulties of radiologic assessment of DMPM. A variety of systemic agents have been extrapolated from pleural mesothelioma treatment. More recent studies have demonstrated improved outcomes with pemetrexed in combination with cisplatin/carboplatin. Pemetrexed is a multi-targeted antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. Activity of combinations of pemetrexed-based combinations was observed in two expanded access programs, with response rates of 15–30% and median survival 13–15 months in the palliative setting [52, 53]. Pemetrexed has been tested also in combination with gemcitabine [54].

Limited data are also available on systemic chemotherapy (sCT) in combination with CRS/HIPEC in the adjuvant or neoadjuvant setting. We have retrospectively analyzed 116 DMPM patients treated with CRS/HIPEC from 1995 to 2011. Sixty of them had preoperative sCT, 30 had postoperative sCT, and 26 no sCT. Platinum and pemetrexed were given to 55 cases. Preoperative sCT was not associated with complete cytoreduction or severe morbidity, but also with no survival differences among preoperative, postoperative, and no sCT groups [55]. In a recent multi-institutional French study, preoperative sCT was associated with worse survival at multivariate analysis (HR = 2.30; 95% CI = 1.07–4.94; $p = 0.033$) [56].

6.4 Clinical and Pathological Prognostic Factors

Several predictive factors for overall survival in patients with DMPM have been identified. Beside the completeness of cytoreduction, disease stage, which is generally quantified by peritoneal cancer index (PCI), was identified as a prognostic factor by Yan [57]. Schaub created a nomogram to predict survival that was partly based on PCI [58]. Male sex and older age have been also associated with poorer prognosis [47, 49, 59]. The histological type is one of the most consistent prognostic factors, as worse outcomes have been repeatedly reported for sarcomatoid and biphasic DMPM [45, 46, 58]. Magge showed that there may be no benefit from CRS-HIPEC in sarcomatoid and biphasic groups, with a median survival of 10.5 as compared with 51.5 months in epithelioid DMPM [49]. On the contrary, a recent PSOGI registry study reported better results in patients with biphasic histology undergoing CCR-0 cytoreduction, with a median survival of 7.8 years, thus suggesting that biphasic DMPM should no longer be considered as an absolute contraindication [60].

The prognostic impact of lymph-node metastases has been reported in both single center and multi-institutional series [45, 46]. Individual studies have also identified mitotic rate [40, 45, 61], GLUT-1 expression [48], preoperative CA-125 [19, 58], telomere maintenance mechanisms [62], estrogen receptors [63], BCL2 [64], MUC-1 [65], BAP1, NF2, CDKN2A [66], mitotic index and pattern of growth [67], PD-L1 [61], and preoperative thrombocytosis [68] as predictors of poorer survival.

We recently developed an algorithm by means of conditional inference tree model [69]. This model relies on pre-cytoreduction PCI and tumor proliferative index measured by Ki-67 using immunohistochemistry. Three prognostic subsets were defined: (I) Ki-67 ≤9%; (II) Ki-67 >9% and PCI 17; and (III) Ki-67 >9% and PCI >17. The median OS for subsets I, II, and III were 86.6, 63.2, and 10.3 months, respectively. The model had an acceptable discriminant capacity with a bootstrap-corrected Harrell c-index of 0.74.

6.5 Prognostic Biomarkers and Therapeutic Targets (Fig. 6.1)

The discovery of new targeted therapies could be the key for improving the prognosis of patients affected by diffuse malignant peritoneal mesothelioma (DMPM) which is known to be relatively resistant to traditional chemotherapy. Thus

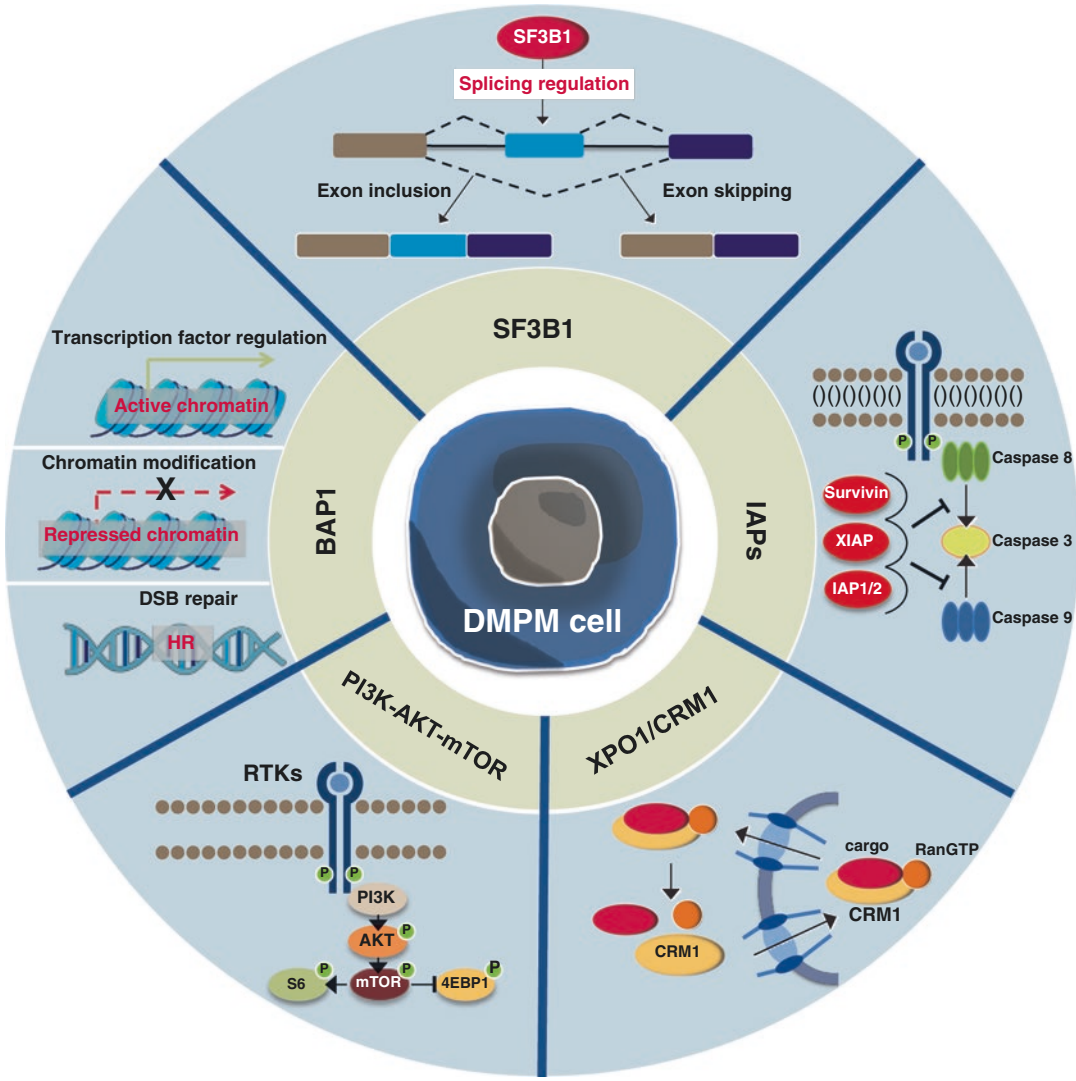

Fig. 6.1 Genes/pathways altered in DMPM with potential as biomarkers and/or therapeutic targets

far, a limited number of studies have focused on the identification of deregulated pathways in DMPM that can be specifically targeted to obtain a direct therapeutic effect or to increase the tumor sensitivity to conventional anticancer agents.

It was initially demonstrated that the dysregulation of apoptotic pathways may play a role in the relative chemoresistance of DMPM and that survivin and other members of the inhibitors of apoptosis protein family (i.e., IAP-1, IAP-2, and X-IAP), which are overexpressed in most DMPMs, could represent new therapeutic targets. Indeed, it was found that RNAi-mediated survivin knockdown in DMPM cells enhanced both spontaneous and drug-induced apoptosis [70], thus supporting the notion that survivin inhibitors may provide new approaches to the treatment of the disease. In this context, it was reported that nortopsentin analogues (1H-pyrrolo[2,3-*b*]pyridine derivatives) reduced proliferation and induced a caspase-dependent apoptotic response in DMPM cell lines, which were paralleled by a significant decline of the expression of the active Thr(34)-phosphorylated form of the anti-apoptotic protein survivin, as a consequence of CDK1 inhibition [71]. Survivin

exclusively relies on exportin 1 (XPO1/CRM1) to be shuttled into the cytoplasm and performs its anti-apoptotic function. It was demonstrated that selinexor, a clinical stage XPO1/CRM1 inhibitor, induced dose-dependent inhibition of DMPM cell growth, cell cycle arrest at G1-phase, and caspase-dependent apoptosis, which were paralleled by a time-dependent reduction of cytoplasmic survivin levels. Most importantly, orally administered selinexor caused a significant antitumor effect in subcutaneous and orthotopic DMPM xenografts without appreciable toxicity [72]. Collectively, these findings highlight the interference with survivin expression and function as a novel therapeutic option for DMPM.

Additional interesting targets that may have clinical utility in DMPM are represented by PI3K-AKT-mTOR pathways. Indeed, expression and activation of PI3K, AKT, mTOR, S6, and 4EBP1 have been documented by biochemical analyses in a series of DMPM clinical samples and activity of mTOR inhibitors has been demonstrated in vitro in a human DMPM cell line [73]. Consistently, a gene expression profile study revealed the upregulation of genes related to PI3K and mTOR signaling pathways, which was significantly correlated with shortened survival of DMPM patients [74]. Activation of these pathway is likely sustained by NF2 deletion and a ligand-dependent activation and co-activation of multiple receptors tyrosine kinase, such as EGFR, PDGFRB, and MET, described in DMPM [73, 75]. Such finding may explain the low efficacy of single-agent anti-EGFR therapy reported in DMPM patients, despite a predominant EGFR overexpression/activation, thus supporting the use of combined treatments [76, 77]. Coherently, a combined inhibition of PI3K and mTOR signaling was effective in two young women with papillary indolent DMPM enabling long-term survival despite disease recurrence [78].

In the last years, results from studies aimed at dissecting the genomic landscape of DMPM improved the knowledge of the molecular biology of this rare tumor and identified additional potential therapeutic targets. Specifically, it was revealed that over 70% of DMPMs harbor *BRCA1* associated protein 1 (*BAP1*) inactivating mutation or copy number loss and/or loss of protein expression, making *BAP1* the most commonly altered gene in this malignancy [79–82]. BAP1 is a tumor suppressor and deubiquitinase, localized to the nucleus where it regulates chromatin remodeling and maintains genome integrity. Thus, a reduced BAP1 activity results in the accumulation of DNA-damaged cells and in an increased susceptibility to the development of malignancy. Results from several studies support the specificity of BAP1 protein loss assessed by immunohistochemistry as a helpful diagnostic marker for the pathologic identification of mesothelioma [83, 84]. By contrast, the prognostic role of loss of BAP1 in DMPM is still controversial. Indeed, a study showed that loss of BAP1 immunostaining did not correlate with DMPM patients' outcome [61], whereas better overall survival for patients with BAP1 mutations, protein expression loss, or at least one of these alterations, independently of tumor histological subtype, age, and sex, was reported in another study [82].

Inactivating mutations and focal deletion of neurofibromin 2 (*NF2*), which encodes the cytoskeletal scaffolding protein Merlin, and mutations of the two epigenetic regulatory genes DDX3X and SETD2 are also relatively common in DMPM, indicating that transcriptional deregulation is a key oncogenic mechanism in mesothelial tumorigenesis [80, 81]. This notion is also supported by the finding that a significant fraction of DMPMs show loss of 3p21 locus, in which are located other chromatin modifiers and epigenetic regulatory genes, such as SMARCC1 and PBRM1 [85]. Interestingly, DMPMs harboring 3p21 locus or presenting BAP1 loss (BAP1 haploinsufficiency) also show a differential expression of a set of genes involved in both chromatin remodeling and DNA damage repair mechanisms [85]. DMPMs carrying inactivating alterations affecting BAP1 and other transcriptional regulators may represent a molecular subgroup with altered transcriptional programs that may benefit from inhibitors of epigenetic modifiers, including histone deacetylases and the histone methyltransferase EZH2, that seem to be promising in preclinical setting [86, 87].

BAP1 haploinsufficiency also seems to predict a distinct immunogenic class of DMPMs. Indeed, this subgroup is characterized by both the presence of an inflammatory tumor microenvironment and PD-1/PD-L1 expression [85]. If confirmed, these interesting findings could open an additional therapeutic opportunity for this subset of DMPM patients since BAP1 haploinsufficiency may confer sensitivity to immune checkpoint inhibitors. In this context, the combination of anti-CTLA4 and anti-PD-L1 monoclonal antibodies was active and safe in mesothelioma patients recently enrolled into the phase 2 trial NIBIT-MESO-1 [88]. PD-L1 expression had already been reported in half of DMPMs, with a frequency similar or even higher compared to pleural mesothelioma [89, 90]. Although, in the trial NIBIT-MESO, PD-L1 expression did not seem to correlate with clinical response or overall survival, the correlation between BAP1 loss and PD-L1 expression deserves further investigations.

ALK rearrangements have been described in a small subset (3%) of younger women (>40 years) affected by DMPM without genetic alterations in BAP1, SETD2 or NF2. This was an exciting finding suggesting that a restricted subset of selected patients may benefit from treatments with ALK inhibitors [91].

Results from an extensive exome sequencing of a large collection of pleural mesothelioma specimens showed the presence of mutations affecting the splicing factor 3b subunit 1 (SF3B1), which encodes an essential component of the spliceosome, as well as the histone methyltransferase SETD2 and the DEAD-box RNA helicases DDX51 and DDX3X, which are also involved in RNA processing and splicing [92]. In addition, this study unraveled several mesothelioma-specific splice alterations, most of which were independent of splice site mutations. Recently, we found that spliceosomal genes are differentially upregulated in DMPM cells compared to normal tissues. In addition, the expression of SF3B1, as assessed by immunohistochemistry in tissue microarrays of 64 DMPM specimens, was found to correlate with poor patients' clinical outcome in univariate and multivariate analysis [93]. SF3b modulators (Pladienolide-B, E7107, Meayamycin-B) showed potent in vitro cytotoxic activity in the low nanomolar range. Differential splicing analysis of Pladienolide-B-treated cells revealed abundant alterations of transcripts involved in cell cycle, apoptosis, and other oncogenic pathways. E7107 demonstrated remarkable in vivo antitumor efficacy, with significant improvement of survival rates compared to vehicle-treated controls [93]. Collectively, such data indicate SF3B1 as a novel potential prognostic factor and designate splicing as a promising therapeutic target in DMPM.

MicroRNAs (miRNAs) are endogenous small non-coding RNA molecules that negatively regulate gene expression in a variety of biological processes by translation inhibition, cleavage, or degradation of target mRNAs. The value of miRNAs as novel biomarkers and targets for cancer therapy is now widely recognized. In this context, several preclinical studies utilized miRNA targeting approaches for improving the therapy of pleural mesothelioma [94]. However, no information is currently available on the expression/functional role of miRNAs in DMPM with the only exception of miR-34a [95]. The expression and biological effects of miR-34a, which is one of the most widely deregulated miRNAs in cancer, have been evaluated in a cohort of 45 DMPM and 7 normal peritoneum specimens as well as in 5 DMPM cell lines. The miRNA was found to be significantly downregulated in DMPM clinical specimens and cell lines. In addition, miR-34a reconstitution in DMPM cells significantly inhibited proliferation and tumorigenicity, induced an apoptotic response, and declined invasion ability, mainly through the downregulation of c-MET and AXL and the interference with the activation of downstream signaling. Interestingly, a persistent activation of ERK1/2 and AKT in miR-34a-reconstituted cells was found to counteract the anti-proliferative and pro-apoptotic effects of miRNA, yet not affecting its anti-invasive activity. Overall, these preclinical data strongly suggest the potential clinical utility of a miR-34a-replacement therapy for the treatment of DMPM and, on the other hand, provide the first evidence of a potential cytoprotective/resistance

mechanism that may arise towards miRNA-based therapies through the persistent activation of RTK downstream signaling [95].

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