Review Article

Overexpressed genes in malignant pleural mesothelioma: implications in clinical management

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Abstract: Malignant pleural mesothelioma (MPM) is a very aggressive cancer poorly responsive to current therapies. MPM patients have a very poor prognosis with a median survival of less than one year from the onset of symptoms. The biomarkers proposed so far do not lead to a sufficiently early diagnosis for a radical treatment of the disease. Thus, the finding of novel diagnostic and prognostic biomarkers and therapeutic targets is needed. Gene overexpression has been frequently associated with a malignant phenotype in several cancer types; therefore the identification of overexpressed genes may lead to the detection of novel prognostic or diagnostic marker and to the development of novel therapeutic approaches, based on their inhibition. In the last years, several overexpressed genes have been identified in MPM through gene expression profiling techniques: among them it has been found a group of 51 genes that resulted overexpressed in more than one independent study, revealing their consistency among studies. This article reviews the clinical implications of confirmed overexpressed genes in MPM described so far in literature.

Keywords: Mesothelioma; overexpression; prognostic marker; diagnostic marker; therapeutic target; drug inhibitor

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Overexpressed genes identified in malignant pleural mesothelioma (MPM)

Global gene expression profiling studies have allowed quantifying gene expression in cancer cell lines as well as in human tissues, leading to the identification of several overexpressed genes in MPM. In recent years, a number of aberrantly expressed genes were suggested, but with a poor consistency among studies. In 2012, in order to find a consensus among nine independent transcriptome studies carried out between 2000 and 2010 (1-9), it has been performed a review and a data mining (10) and it has been identified a group of 96 overexpressed genes in MPM compared to non-malignant tissues and cell lines. This group of genes have been further evaluated in 2015 through a gene expression study performed on an independent cohort of mesothelioma tissues compared to non-malignant tissues: the overexpression of 51 genes (*Table 1*) have been confirmed (11).

Clinical implications of overexpressed genes in MPM

The identification of the overexpressed genes may lead to a deeper knowledge of the main pathways involved in mesothelioma carcinogenesis and could reveal also novel prognostic and diagnostic marker. Among the 51 overexpressed genes identified, only 14 have been further studied in MPM and they have been proposed as predictor of survival in mesothelioma patients or as marker

Table 1 Here are summarized the 51 overexpressed genes identified in MPM from transcriptome studies

Gene symbol	Gene name	Entrez gene
ALDOA	*Aldolase, fructose-bisphosphate A*	226
ASS1	*Argininosuccinate synthase 1*	445
BIRC5	*Baculoviral IAP repeat containing 5*	332
CALB2	*Calbindin 2*	794
CCNB1	*Cyclin B1*	891
CCNB2	*Cyclin B2*	9133
CCNO	*Cyclin O*	10,309
CDH11	*Cadherin 11*	1,009
CDC2	*Cyclin dependent kinase 1*	983
CENPF	*Centromere protein F*	1,063
CFB	*Complement factor B*	629
CHEK1	*Checkpoint kinase 1*	1,111
COL11A1	*Collagen type xi alpha 1 chain*	1,301
COL1A1	*Collagen type i alpha 1 chain*	1,277
CXADR	*Coxsackie virus and adenovirus receptor*	1,525
DSP	*Desmoplakin*	1,832
EFEMP1	*EGF containing fibulin like extracellular matrix protein 1*	2,202
EIF4G1	*Eukaryotic translation initiation factor 4 gamma 1*	1,981
FANCI	*Fanconi anemia complementation group i*	55,215
FEN1	*Flap structure-specific endonuclease 1*	2,237
GALNT7	*Polypeptide N-acetylgalactosaminyltransferase 7*	51,809
GAPDH	*Glyceraldehyde-3-phosphate dehydrogenase*	2,597
HCA112	*Transmembrane protein 176A*	55,365
HEG1	*Heart development protein with egf like domains 1*	57,493
HELLS	*Helicase, lymphoid-specific*	3,070
ITGA4	*Integrin subunit alpha 4*	3,676
KIF23	*Kinesin family member 23*	9,493
KRT18	*Keratin 18*	3,875
KRT5	*Keratin 5*	3,852
MCM4	*Minichromosome maintenance complex component 4*	4,173
MKI67	*Marker of proliferation Ki-67*	4,288
MSLN	*Mesothelin*	10,232
NME2	*NME/NM23 nucleoside diphosphate kinase 2*	4,831
NMU	*Neuromedin U*	10,874
NUSAP1	*Nucleolar and spindle associated protein 1*	51,203

Table 1 *(continued)*

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Gene symbol	Gene name	Entrez gene
PCNA	*Proliferating cell nuclear antigen*	5,111
PDGFRB	*Platelet derived growth factor receptor beta*	5,159
PKM2	*Pyruvate kinase, muscle*	5,315
PTGIS	*Prostaglandin I2 synthase*	5,740
RAN	*RAN, member RAS oncogene family*	5,901
SMARCA4	*SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4*	6,597
SMC4	*Structural maintenance of chromosomes 4*	10,051
SOD1	*Superoxide dismutase 1*	6,647
SPINT2	*Serine peptidase inhibitor, Kunitz type 2*	10,653
SULF1	*Sulfatase 1*	23,213
THBS2	*Thrombospondin 2*	7,058
TIMP3	*TIMP metallopeptidase inhibitor 3*	7,078
TNPO2	*Transportin 2*	30,000
TOP2A	*Topoisomerase (DNA) II alpha*	7,153
UPK1B	*Uroplakin 1B*	7,348
XPOT	*Exportin for tRNA*	11,260

able to differentiate MPM from other types of cancers. Moreover, they have been proposed as potential therapeutic targets: several *in vitro* and *in vivo* studies reported their role in MPM progression and carcinogenesis, showing a decrement of the malignant phenotype after target-inhibition. Here are summarized the last findings describing the clinical implications of these 14 overexpressed genes in MPM (*Table 2*).

The gene *MSLN* codifies a preproprotein that is proteolytically processed to generate two protein products, megakaryocyte potentiating factor and mesothelin. Normal mesothelial cells show low levels of *MSLN* and it is undetectable in most normal tissues. On the contrary, mesothelin is overexpressed in several human cancers, including MPM (10,11). In the last years mesothelin has become an active topic of investigation in MPM. It has been proposed as a promising candidate for tumour-specific therapy, given its limited expression in normal tissues and high expression in mesothelioma tissues (31). Three main anti-mesothelin therapeutic strategies have been developed including the monoclonal antibody amatuximab (MORAb-009), an antibody-drug conjugates with the fully human anti-mesothelin antibody (for example the anetumab ravtansine), and recombinant immunotoxins. Although there were no objective tumour response to amatuximab, it was well tolerated and disease stabilization was observed in some patients (33,37). In a phase II study the addiction of amatuximab to cisplatin and pemetrexed did not prolong progression free survival longer than historical controls, but an extension of the median overall survival (OS) was observed (34). A phase II double-blind study, which involved 49 sites, is still ongoing (clinicaltrials.gov NCT02357147). The antibody-drug conjugate anetumab ravtansine selectively binds to mesothelin allowing the internalization of the conjugated tubulin inhibitor DM4 into MPM cells. Recently a phase I study showed that 31% of patients treated with anetumab ravtansine had a partial response and 44% of patients have stable disease for an overall disease control rate of 75% (38). A phase II trial in 2nd-line metastatic pleural mesothelioma (clinicaltrials.gov NCT02610140) is still ongoing. Two recombinant immunotoxins have been engineered for the targeted elimination of cancer cells that express mesothelin: SS1P and RG7787 (39). The efficacy of these agents have been demonstrated *in vitro* (32,36) and this preclinical potential

Table 2 Overview table of the most promising diagnostic, prognostic and therapeutic target for MPM

Gene	Prognostic and predictive value	Diagnostic marker	Therapeutic target
MSLN	Cristaudo 2007 (12); Grigoriu 2007 (13); Schneider 2008 (14); Linch 2014 (15); Tian 2017 (16)	Robinson 2003 (17); Hassan 2006 (18); Scherpereel 2006 (19); Creaney 2011 (20); Creaney 2013 (21); Ferro 2013 (22); Bayram 2014 (23); Felten 2014 (24); Creaney 2014 (25); Creaney 2015 (26); Santarelli 2015 (27); Demir 2016 (28); Battolla 2017 (29); De Santi 2017 (30)	Hassan 2004 (31); Zhang 2006 (32); Hassan 2010 (33); Hassan 2014 (34); Hassan 2014 (35); Hollevoet 2014 (36); Fujisaka 2015 (37); Blumenschein 2016 (38); Zhao 2016 (39)
PDGFRB	Buikhuisen 2016 (40)	–	Bertino 2007 (41); Buckstein 2007 (42); Bertino 2008 (43); Laurie 2011 (44); Tsa 2013 (45); Melaiu 2017 (46)
BIRC5	Hmeljak 2013 (47); Goričar 2015 (48)	–	Xia 2002 (49); Rodel 2003 (50); Zhu 2006 (51); Zhang 2006 (52); Zaffaroni 2007 (53); Jin 2010 (51); Cheung 2010 (54); Bertino 2013 (55); Soleimanpour 2015 (56); Hoffmann 2015 (57)
CALB2	Yukio 2010 (58); Kao 2010 (59); Kao 2011 (60); Linton 2014 (61); Thapa 2016 (62)	Doglioni 1996 (63); King 2006 (64); Ordóñez 2007 (65); Shield 2008 (66); Dinu 2012 (67); Mohammad 2012 (68); Hyun 2012 (69)	–
MKI67	Beer 2001 (70); Leonardo 2001 (71); Ghanim 2015 (72)	Taheri 2008 (73)	–
KIF23	Kato 2016 (74)	–	Kato 2016 (74)
PKM2	Gordon 2009 (75)	–	–
THBS2	N/A	Shigematsu 2009 (76)	–
RAN	–	–	Xia 2008 (77); Ly 2010 (78); Røe 2010 (9)
CHEK1	Walter 2016 (79)	–	Røe 2010 (9)
HEG1	–	Tsuji 2017 (80)	Tsuji 2017 (80)
ASS1	–	–	Gordon 2005 (81); Barbone 2016 (82)
EFEMP1-FIBULIN3	Pass 2012 (83); Creaney 2014 (25); Kirschner 2015 (83)	Pass 2012 (83); Kaya 2015 (84)	–
CDC2	–	–	Romagnoli 2009 (85); Linton 2013 (86)

MPM, malignant pleural mesothelioma.

has been confirmed in 24 MPM patients chemotherapy-naïve, treated with SS1P in combination with standard recommend doses of cisplatin/pemetrexed (35).

Worth to note that, so far, mesothelin is the only Food and Drug Administration (FDA) approved (HDE id: H060004) biomarker for MPM (25). In 2007, serum mesothelin has been reported, for the first time, as a prognostic marker in MPM: high soluble mesothelin level significantly correlates with shorter survival, leading to a poor prognosis (12). Its prognostic value has been strongly debated: many following studies confirmed this association (13-15) but others did not endorse serum mesothelin prognostic significance (26,87). While a recent meta-analysis performed on 579 MPM patients further corroborates the inverse association of serum SMRP concentration with the OS (16). The mixed results observed are due to the small samples size and to the heterogeneity of the treatment among the studies and lead to the necessity of further investigations.

In 2003 serum mesothelin was declared, for the first

time, as a diagnostic marker for MPM (17) and it resulted strongly associated with tumour volume (18,20). Serum soluble mesothelin related peptides (SMRPs) levels have been proposed for the differentiation of MPM patients from patients with pleural metastases of different types of carcinomas (18,19). The diagnostic accuracy of mesothelin has been evaluated in several studies (21,23-25) and the systematic review and meta-analysis recently performed showed a high specificity (around 89% and 96%) but a low sensitivity (between 32% and 47%) of mesothelin as a diagnostic marker; thus although SMRPs may help to discriminate the MPM from the non-MPM subjects, the sensitivity of the assay is still inadequate (88). In order to better characterize the sensitivity and specificity of SMRP as a biomarker for MPM it should take in consideration that SMRP performance as diagnostic biomarker could be influenced by genetics variants, as show in the recent work by De Santi *et al.* (30) and SNP located in the promoter or in the 3'UTR of *MSLN* gene could affect protein expression levels (89). SMRPs diagnostic value has been evaluated also in pleural effusion (25,26,29) and it has been observed a higher diagnostic performance in pleural effusion than in serum assessment (22). The need to detect the MPM at the early stages led several authors to investigate whether mesothelin can contribute towards the evaluation of the carcinogenic risk in populations exposed to asbestos: high level of SMRPs have been proposed as a marker for early diagnosis in combination with two epigenetic marker (27) or alone (28). Interestingly higher levels of SMRP have been found in the asbestos exposure group than in the control group and the increment observed was gradual among the controls, the asbestos exposed and mesothelioma patients (28).

PDGFRB encodes for a cell surface tyrosine kinase receptor for the platelet-derived growth factor beta; this receptor specifically binds the B isoform of PDGF (PDGF-BB). Preferentially MPM cell lines express PDGF beta-chain and PDGF beta-receptor transcripts, whereas normal mesothelial cell lines do not express PDGF B-chain mRNA and little or no PDGF beta-receptor mRNA; in contrast normal mesothelial cell lines were found to express PDGF alpha-receptor mRNA, not detected in mesothelioma cell lines and in non-neoplastic mesothelium (90,91). PDGFRB has been recognized as an attractive therapeutic target for several cancers (92) due to its involvement in increased proliferation, dissemination and metastasis of cancer cells (93-95) and to its overexpression in cancer cells and tissues, as compared to the non-malignant counterpart (94-96). For this reason, a plethora of PDGF/PDGFR pathway inhibitors have been developed in the last years and assayed in clinical trials for leukemia, gastrointestinal stromal tumors, and glioma (https://clinicaltrials.gov/). Among them, Imatinib mesylate is a potent inhibitor of the PDGF-R kinase (97). In 2007, for the first time, MPM cells were treated with the tyrosine kinase inhibitor Imatinib mesylate (41); the treatment induced cytotoxicity and apoptosis selectively on PDGFR-beta positive mesothelioma cells via blockade of receptor phosphorylation, suggesting a novel therapeutic approach for MPM. Combined treatments of imatinib with imatinib/gemcitabine and imatinib/pemetrexed showed a significant synergism in reducing cancer cell viability *in vitro* and *in vivo*, indicating that very low doses of chemotherapeutic agents should be sufficient to exert a therapeutic effect (41,43). A phase I trial of cisplatin, pemetrexed, and imatinib mesylate in chemonaive patients with unresectable malignant pleural mesothelioma revealed a clinical benefit for MPM patients, but, to improve the tolerability of this treatment further studies are needed (45). Imatinib efficacy for MPM treatment has been recently compared to another PDGFRB inhibitor, crenolanib: according to *in vitro* evaluations crenolanib resulted more effective in the inhibition of the malignant phenotype of MPM cells (46), suggesting a new therapeutic option for MPM. In past also PDGFRB inhibitor Sunitinib (SU11248) was proposed for MPM patients (42) but it showed limited activity in MPM (44). In 2016 a new promising tirosin kinase inhibitor has been proposed for MPM treatment: it is called nintedanib and it is still under evaluation in three active trials on MPM patients (clinicaltrial.gov ID: NCT01907100, NCT02863055, NCT02568449). In a recent clinical study performed on 25 MPM patients has been observed that the mRNA expression level of PDGFRB; measured before and after systemic therapy, was strongly correlated with worse outcome: partial regression was observed only in patients with the lowest expression levels of PDGFRB, suggesting its possible use as a prognostic marker (40). This is the only publication reporting a prognostic value for PDGFRB expression in MPM.

Baculoviral IAP repeat-containing 5 (*BIRC5*) encodes the well-known protein survivin. Survivin overexpression in MPM has been confirmed in different independent cohort of mesothelioma patients (7-9,11,47,53). Survivin is a multifunctional protein that plays critical roles in several crucial cell processes: several studies described its anti-apoptotic function (49,98,99), a role in microtubule

dynamics, in cell proliferation, in cell migration and control bipolar spindle formation (100). It has been demonstrated that *BIRC5* inhibition in mesothelioma cells decreases cell growth and enhances the rate of spontaneous and drug-induced apoptosis (53), induces mitotic cell arrest and strong cytoxicity (51). For these reasons, in the last years, several research groups attempt the development of survivin-based cancer therapeutics (51,56). Interestingly the vaccine strategy proposed in 2013 (55) effectively suppresses MPM tumor growth *in vivo* without induction of autoimmune response and the cytotoxic activity induced by this vaccine proved to be specific for MPM cells (57). Furthermore survivin expression proved to be linked to resistance to chemotherapeutic agents, including vincristine, cisplatin, bortezomib, tamoxifen, paclitaxel, TNF-a and TRAIL in tumour cells (52,54) and it is also responsible of the suppression of radiation-induced apoptosis (50). Thus survivin-targeting in combination with anti-cancer drug could be useful to enhance the effect of chemotherapeutic agents and may be promising for mesothelioma treatment. Survivin expression alone did not seem to show any prognostic value but it has been proposed as a predictive marker of treatment response (47). A more recent study confirmed these results reporting that serum survivin levels before and during chemotherapy could be useful in the prediction of MPM treatment response (48).

CALB2 gene encodes an intracellular calcium-binding protein called calretinin. Several studies on the value of this marker were published since 1996 (63). Among the current immunomarkers, calretinin appear to be the most valuable in differentiating MPM from lung and breast adenocarcinoma (64). Calretinin expression resulted highly specific for MPM in fact 97% of mesothelioma samples compared to only 3% of adenocarcinomas were positive for calretinin (66). This specificity has been confirmed in independent sets of mesothelioma samples (67,68) and calretinin proved to be 96% sensitive and 100% specific (P<0.01) for identifying mesothelial differentiation (mesothelioma and benign reactive effusions) from adenocarcinoma (69). Calretinin is considered the most sensitive and specific positive mesothelioma marker, above all for epithelioid mesothelioma subtype (65). Also the prognostic role of calretinin has been explored: in several studies higher calretinin expression was observed in tumours with more favourable prognosis (58-61). Lately the correlation of increased calretinin expression with a better survival has been confirmed and its higher expression has been also associated with epithelioid histology subtype (62).

The protein encoded by *MKI67* gene is widely used as a marker of proliferation in routine pathological investigations and the nuclear protein Ki67 is an established prognostic marker in cancer (101-105). The prognostic value of Ki67 in mesothelioma is known since 1998 when it has been reported a statistically significant difference between the survival of patients having a low and high Ki67 index (P<0.001) (106); subsequently other studies confirmed its prognostic significance (70,71). Recently it has been reported that patients with high Ki67 expression had significantly (P<0.001) shorter median OS (7.5 months) than those with low Ki67 (19.1 months) (72). In particular Ki67 proved to be an independent prognostic factor in epithelioid but not in non-epithelioid MPM (72). Interestingly ki67 index was lower in patients who received the induction chemotherapy (n=33, mean Ki67 index: 10.5±8.5) as compared to patients who had not received chemotherapy before sample collection (n=124, mean Ki67 index: 18.3±13.9, P<0.001), giving evidence of decrease of the MPM proliferative capacity after induction chemotherapy (72). Ki67 may be also a promising molecular candidate for the diagnosis of MPM: used in combination with repp86 (also called TPX2, Microtubule Nucleation Factor) showed a significant ability in differentiating MPM from benign reactive mesothelial hyperplasia (73).

KIF23 overexpression has been recently confirmed in a tissue microarray of 53 mesothelioma samples and a shorter overall survival has been observed in patients who received curative resection with tumors displaying high KIF23 expression (P=0.0194 by a log-rank test) (74). This suggests a potential value as a prognostic marker that needs to be validated in a different set of mesothelioma patients, due to the small sample size in this study. *KIF23* gene encodes for a member of kinesin protein involved in the regulation of cytokinesis (107) and its inhibition suppresses midbody formation, hence the completion of cytokinesis (108) hampering cancer cells proliferation *in vitro* and *in vivo* (109). The critical role of this gene in proliferation and survival of mesothelioma cells suggests the possibility to consider this gene in the development of future therapeutic approaches in mesothelioma.

PKM2 gene encodes for a pyruvate kinase involved in glycolysis and many studies report its role in the achievement of the nutrient demands of proliferating cancer cells (110,111). RNA inhibition on mesothelioma cell lines did not produce significant change in apoptosis and mitosis (112) thus its overexpression in mesothelioma does not seem to influence the progression of this cancer. In 2009 *PKM2* has

been proposed as a predictor of MPM outcome in a four-gene expression ratio test: this test resulted able to predict survival in multivariable analysis [hazard ratio for death =2.09; 95% confidence interval (CI), 1.27–3.45; P=0.004] (75).

THBS2 has been found overexpressed in 3 independent transcriptome studies on mesothelioma tissues (10) and, previously, the titers of the antibody against *THBS2* has been proposed as a tumor marker for the diagnosis and follow up of patients with MPM. *THBS2* antibody has been detected in the 88.9% of the mesothelioma patients sera analysed and interestingly, the serum antibody titers decreased after surgical treatment of MPM and increased after recurrence of the disease (76).

RAN gene encodes for a small GTP binding protein that is abundantly expressed in many human cancers; its overexpression in mesothelioma has been observed in three independent transcriptome studies. *RAN* overexpression could be involved in the development of chemoresistance, as suggested by Roe (9): in particular *RAN* has been suggested as an antitubulin (the taxanes and vinca alkaloids) resistance related gene. Until now little is known about its role in malignant pleural mesothelioma but emerging evidences show that RAN signalling is a dominant pathway for tumour cell maintenance (77,78) and it has been proposed as a novel drug co-target against mesothelioma (9).

The gene *CHEK1* encodes for a kinase required for checkpoint mediated cell cycle arrest in response to DNA damage or in the presence of unreplicated DNA. *CHEK1* expression in MPM samples has been found correlated with tumour progression (P=0.0362) and appear to be a predictive marker for platin-response in the adjuvant-treated patients, showing a significant correlation to the overall survival (P=0.0162) (79). Moreover *CHEK1* expression seems to be involved in chemoresistance (113): loss of *CHEK1* enhances camptotecins toxicity and sensitized mesothelioma cell-lines for pemetrexed (114) suggesting that *CHEK1* could be a putative co-drug target for mesothelioma (9). Worth to note is that *CHEK1* appears to be selectively expressed in mesothelioma cells (9) and not expressed in most of the normal tissues (115), making it a suitable target for mesothelioma treatment.

HEG1 gene codifies for a mucin-like membrane protein, the sialylated protein *HEG homolog 1* that recently proved to be a highly specific marker for MPM (80). The monoclonal antibody used for the identification of *HEG1* protein (SKM9-2), is able to recognize both *HEG1* peptide and its sialylated O-glycosylation and reached 99% of specificity and 92% of sensitivity in 130 MPM cases compared to 310 cases of non-mesothelioma tumours. These characteristics make SKM9-2 antibody a suitable marker for pathological diagnosis (80). *HEG1* silencing on mesothelioma cell-lines revealed a survival role of this gene in MPM suggesting *HEG1* as a novel putative therapeutic target (80).

ASS1 encodes for the argininosuccinate synthase 1 that catalyzes the penultimate step of the arginine biosynthetic pathway. *ASS1* loss, observed in different cancers, results in an intrinsic dependence on extracellular arginine due to an inability to synthesise arginine for growth. For this reason arginine deprivation has been proposed as a promising therapeutic strategy in *ASS1*-negative tumours. In the multicenter phase 2 randomized clinical trial, conducted between March 2011 and May 2013, has been observed that arginine deprivation with ADI-PEG20 in *ASS1*-negative mesothelioma patients improved the progression free survival (116). About 50% of mesothelioma appeared to be *ASS1*-negative (117) but *ASS1* has been found overexpressed in a significant number of mesothelioma patients (10,11,82). *ASS1* overexpression is linked with chloroquine and cisplatin resistance in mesothelioma: high *ASS1* expression in mesothelioma cells decreased their sensitivity to chloroquine toxicity (118) and *ASS1* silencing in MPM spheroids increased the apoptotic response to cisplatin plus pemetrexed (82), rather suggesting an important contribution to the onset of chemo-resistance in MPM.

EFEMP1 codifies for epidermal growth factor containing fibulin like extracellular matrix protein 1, best known as Fibulin-3. It has been found overexpressed in MPM (81) and it is expressed at low levels in normal tissues (83). In 2012 Fibulin-3 has been declared, for the first time, a highly promising diagnostic and prognostic marker for MPM, able to distinguish MPM patients from asbestos-exposed persons without MPM with 94% specificity and 100% sensitivity (83). Surprisingly in the external validation cohort, the diagnostic accuracy decreased (AUC, 0.87) (119) but later, in the study performed by Creaney *et al.* (25) pleural effusion fibulin-3 was proven a more potent prognostic marker than mesothelin. Afterwards the potential prognostic value of pleural effusion FBLN3 has been confirmed in two independent mesothelioma cohorts (120). The first evidence of the diagnostic value of fibulin-3 appeared in 2012 (83), but in 2014 these data were not confirmed and soluble mesothelin related peptide was declared a more potent diagnostic marker in serum than fibulin-3 (25). In 2015 its diagnostic value has been claimed again with

Table 3 Therapeutic approaches investigated, so far, for MSLN and PDGFRB

Gene	Clinical trial identifier	Target-specific therapeutic approaches
MSLN	NCT03126630	Phase 1: anetumab ravtansine: human anti-mesothelin antibody conjugated to the maytansinoid tubulin inhibitor DM4
	NCT01675765	Phase 1: immunotherapy: cancer vaccine CRS-207 against the tumor-associated antigen mesothelin
	NCT01355965	Phase 1: autologous mesothelin re-directed T cells administered intravenously
	NCT02610140	Phase 2: anetumab ravtansine
	NCT03054298	Phase 1: autologous T cells lentivirally transduced with chimeric anti-mesothelin immunoreceptor SS1 fused to the 4-1BB and CD3ζ signaling domains
	NCT02159716	Phase 1: autologous T cells lentivirally transduced with chimeric anti-mesothelin immunoreceptor SS1 fused to the 4-1BB and CD3ζ signaling domains.
	NCT02357147	Phase 2; amatuximab: anti-mesothelin monoclonal antibody MORAb-009
	NCT01445392	Phase 1: SS1P (dsFv) PE38: a recombinant immunotoxin targeting the tumor antigen mesothelin
PDGFRB	NCT02303899	Phase 2: imatinib mesylate (Glivec): a multi-target inhibitor of tyrosine kinase with inhibition for v-Abl, c-Kit and PDGFR
	NCT00402766	Phase 1: imatinib mesylate (Glivec)
	NCT02568449	Phase 2: nintedanib: triple kinase inhibitor targeting the angiogenesis factors VEGF, PDGF, and FGF
	NCT02863055	Phase 2: nintedanib
	NCT01907100	Phase 3: nintedanib
	NCT00392444	Phase 2: sunitinib malate (SU11248): tyrosine kinase inhibitor with inhibition for PDGFRb, VEGFR2 and FLT3

For none of the others genes listed in *Table 2* has been proposed a target-specific therapeutic approach for MPM.

the observation that MPM patients had significantly higher serum levels of fibulin-3 than controls (84). Two subsequent studies in 2015 and 2017, did not confirmed this result and declared FBLN3 detection in pleural effusion not useful as a biomarker for the diagnosis of MPM (29). The discordant results obtained until now do not lead to a final judgement on the relation between fibulin-3 and MPM, thus more studies are needed to clarify its clinical significance.

CDC2 codifies for a *cyclin dependent kinase 1* (*CDK1*) and it has been found overexpressed in mesothelioma in three independent transcriptome studies (10). *CDK1* knockdown could provide a novel therapeutic approach to arrest cell-cycle progression in MPM cells: in 2009 it has been observed that *CDC2* silencing increased the apoptotic fraction of MPM cells (85) and in 2014, the RNA-interference screening performed on MPM cell-lines confirmed its role in cell-cycle and in the apoptosis (86). *CDC2* inhibition with roscovitine reduced MPM cells growth and sensitised cells to cisplatin by 2.5 to 4 fold (86). These results revealed an interesting therapeutic potential of this target, alone or in combination with cisplatin-based therapy.

Conclusions

MPM is a highly aggressive disease with a poor prognosis. In the last years many efforts have been done to find new therapeutic strategies and to improve the clinical management of MPM through the detection of new potential markers. The identification of overexpressed genes is an important starting point for the comprehension of the main pathways involved in MPM carcinogenesis and progression, that may help to achieve a customized therapy in MPM (*Table 3*). The development of antibody-conjugated drugs or of monoclonal antibody and inhibitors, that directly suppress the activity of the overexpressed genes, is an attractive therapeutic approach (*Table 3*). Several biomarkers of diagnostic and prognostic significance have been analyzed but, to date, there are no solidly established markers for MPM. At the present time, among the selected genes described in this review, MSLN seems to be the most

promising and unique FDA approved, marker for MPM.

The prognostic and diagnostic value of some of these genes (i.e., fibulin3) is still inconclusive due to the conflicting results observed; to overcome this problem it could be useful to analyze, with the same method and using the same patient stratification, the expression of these candidate markers in a larger sample size cohort. Due to the heterogeneity of the disease, it could be more effective the evaluation of a panel of markers instead of one independent marker, as recently suggested for the differential diagnosis of MPM (121). Moreover, the identification of reliable markers for early diagnosis of asymptomatic MPM is a very interesting research field because advances in therapy for patients with MPM may result in an improved outcome if they are applied to stage I disease.

It is plausible that a combination of the most relevant markers validated by the ongoing studies will allow a more specific MPM diagnosis and earlier detection in the next future.

The knowledge of driver genes of mesothelioma tumorigenesis and of the molecular interaction between the overexpressed genes hopefully will result in a personalized and more effective therapeutic approach in which several target-specific agents will be combined with chemotherapeutic regimes.

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Footnote

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