



New Perspectives on Diagnosis and Therapy of Malignant Pleural Mesothelioma

Marika Rossini^{1†}, Paola Rizzo^{1†}, Ilaria Bononi¹, Anthony Clementz², Roberto Ferrari^{3,4}, Fernanda Martini^{1*} and Mauro G. Tognon^{1*}

¹Department of Morphology, Surgery and Experimental Medicine, Section of Pathology, Oncology and Experimental Biology, School of Medicine, University of Ferrara, Ferrara, Italy, ²Department of Natural Sciences and Geography, Concordia University Chicago, River Forest, IL, United States, ³Department of Medical Sciences, Section of Internal Medicine and Cardiorespiratory, School of Medicine, University of Ferrara, Ferrara, Italy, ⁴E.S. Health Science Foundation, GVM Care & Research, Maria Cecilia Hospital, Cotignola, Italy

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*Correspondence:

Fernanda Martini
mrf@unife.it;
Mauro G. Tognon
tgm@unife.it

[†]These authors have contributed
equally to this work.

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Malignant pleural mesothelioma (MPM) is a rare, but severe form of cancer, with an incidence that varies significantly within and among different countries around the world. It develops in about one to two persons per million of the general population, leading to thousands of deaths every year worldwide. To date, the MPM is mostly associated with occupational asbestos exposure. Asbestos represents the predominant etiological factor, with approximately 70% of cases of MPM with well-documented occupational exposure to asbestos, with the exposure time, on average greater than 40 years. Environmental exposure to asbestos is increasingly becoming recognized as a cause of mesothelioma, together with gene mutations. The possible roles of other cofactors, such as viral infection and radiation exposure, are still debated. MPM is a fatal tumor. This cancer arises during its early phase without clinical signs. Consequently, its diagnosis occurs at advanced stages. Standard clinical therapeutic approaches include surgery, chemo- and radiotherapies. Preclinical and clinical researches are making great strides in the field of this deadly disease, identifying new biomarkers and innovative therapeutic approaches. Among the newly identified markers and potential therapeutic targets, circulating microRNAs and the Notch pathway represent promising avenues that could result in the early detection of the tumor and novel therapeutic approaches.

Keywords: malignant pleural mesothelioma, asbestos, gene, biomarker, microRNA, simian virus 40, Notch, therapy

INTRODUCTION

Malignant pleural mesothelioma (MPM) represents about 80% of mesothelioma cases. MPM is a regional and highly aggressive tumor that arises from the mesothelium of the pleural surface. Rarely, other serosal membranes of the human body are also coated with mesothelium, such as peritoneum (peritoneal mesothelioma), pericardial (pericardial mesothelioma), and tunica vaginalis (tunica vaginalis mesothelioma), are affected. Although this malignancy is rare, the incidence of MPM has increased significantly with an estimated number of about 40,000 deaths each year worldwide for asbestos-related MPM (1, 2) due to the augmented and widespread use of these carcinogenic mineral fibers (3, 4). Asbestos refers to a group of naturally occurring mineral silicate fibers with physical

properties causing disease (5). The International Agency for Research on Cancer confirmed that all fibrous forms of asbestos (actinolite, amosite, anthophyllite, tremolite, crocidolite, and chrysotile) are carcinogenic to humans, causing mesothelioma. To date, asbestos includes about 400 forms of fibers that are known in nature, but among these, just the 6 forms mentioned earlier are regulated, due to their heavy commercial use. The World Health Organization estimates that 125 million people annually around the world are exposed to asbestos, both in the workplace and at home. Despite scientific evidences providing a clear and strong association between asbestos and MPM (6–9), many western countries, and newly industrializing economies, are still using asbestos (10–12). In addition, asbestos is defined differently, related to its context (commercial, mineralogical, analytical, and regulatory), and this definition has missed the cancer causing property of some minerals (5). Previous studies have reported cases of MPM in individuals exposed to erionite, regarded the most potent carcinogenic mineral fiber, but not regulated, because it is not defined as asbestos (13).

A widely accepted view assumes that the first step toward MPM is the interaction of asbestos fibers with human pleural mesothelial cells (HMC). Presumably, asbestos fibers enter the pleura and depending on the size, length of exposure, and type of deposit in different areas, cause inflammation (12), which leads to the activation of nuclear factor-kappa B (NF- κ B) signaling. This activation increases survival and proliferation of parietal HMC, giving rise to changes in the molecular signaling events, such as oncogenes activation, loss of tumor suppressor genes, and DNA damage, leading to an increased risk of developing MPM (14, 15). To date, the molecular mechanism(s) through which asbestos influences the selection of this HMC subpopulation(s) remains to be fully understood (16).

Several epidemiological studies demonstrated (17) an increased incidence of MPM cases among subjects, including women, with low levels or no history of occupational asbestos exposure (7). These studies indicate the existence of para-occupational exposure to asbestos, which includes exposure to asbestos workers clothes, asbestos-containing commercial products, asbestos-containing buildings, and natural asbestos in the soil, indicating that asbestos is becoming an environmental contaminant, which may act in combination with other cofactors in the MPM onset (18). Both para-occupational exposure and direct (occupational) exposure have shown to increase the risk of mesothelioma (19, 20).

In addition to asbestos exposure, other environmental interactions may increase the risk of developing MPM. Studies *in vitro* and *in vivo*, together with the detection of viral gene sequences in human specimens, have shown an association between MPM and the oncogenic simian virus 40 (SV40) (21–24), suggesting a transforming synergistic action between asbestos fibers and SV40 (25). In addition, recent immunological investigations detected a higher prevalence of SV40 antibodies in sera of MPM patients in comparison with healthy blood donors. These data strengthen the association between MPM and SV40 (26, 27). Genetic predisposition and radiation exposure seem to play a strong role as etiological factors that, alone or together with asbestos, may contribute to MPM development (17, 28, 29).

One of the peculiarities of MPM is the long-term latency period between the asbestos exposure and the tumor onset (from about 25 to 70 years), with a poor prognosis and median survival of less than 1 year from the time of diagnosis (30, 31). The majority of affected patients are 60 years old at manifestation, with peaks of the age-specific incidence at 80–84 years for men and 75–79 for women (32). In the setting of occupational asbestos exposure, the prevalence is higher among males compared with females (at male–female ratio of approximately 4:1–8:1) (7, 33).

Malignant pleural mesothelioma is heterogeneous in its histological features (34). Indeed, it can be distinguished in three main histological subtypes (35), depending both on predominant cellular component and different biological behavior. Epithelioid mesothelioma, the most common form (50–70% of cases), is characterized by polygonal, oval, or cuboidal cells similar to carcinomas; the sarcomatoid type (10–20%), with a spindle cell morphology is similar to sarcomas; while the mixed or biphasic (30%) is composed of both epithelioid and sarcomatoid forms, in different proportion, within the same tumor (36). Cytological diagnosis of MPM supported by immunohistochemistry demonstrates that the median survival varied significantly among the histological subtypes. The epithelioid subtype is less aggressive than sarcomatoid subtype. It is high sensitive and responds better to chemotherapy resulting in a longer survival than the sarcomatoid or biphasic subtypes of MPM (37, 38).

The correct identification of the MPM histological subtype facilitates the differential diagnosis, influencing subsequent prognosis and therapeutic decisions in this disease. Nevertheless, MPM is still fatal, and big efforts are being put into basic and clinical research in the attempt to find a cure for this tumor.

The aim of this review is to describe currently available therapies and to discuss novel therapeutic targets and/or early detection markers that could be developed based on the dissection of the underlying molecular mechanism involved in the onset and progression of MPM.

MOLECULAR MECHANISMS UNDERLYING MPM

A large number of studies carried out in the last 20 years have led to the identification of dysregulated biological processes that may play a significant role in MPM development. These studies have shown that MPM is characterized by increased cell proliferation (downregulation of tumor suppressor genes, overexpression of oncogenes), inhibition of apoptosis (39, 40), and alteration of intracellular Ca²⁺ homeostasis (41, 42). There is evidence that some of these molecular alterations, such as overexpression of adenosine A3 receptor (43), purinergic receptor P2X7 (40) and dysregulation of cellular (44) and circulating microRNAs (miRNAs) (27, 45) could be used to diagnose and interfere with MPM growth. The literature related to the most commonly found alteration in MPM is discussed below, with special emphasis on those pathways that could be exploited in the future for early diagnosis and the treatment of MPM.

Tumor Suppressor Genes in MPM

Tumor suppressor genes play a crucial role in regulating the cell cycle. The inactivation and/or loss of their function is one of the fundamental events in the tumor development. Loss of heterozygosity, which commonly leads to unmasking a somatically mutated tumor suppressor gene through loss of the wild-type allele, seems to be a consistent feature in MPMs. Recent breakthrough studies have discovered a germline mutation/inactivation in *BAP1* (BRCA1-associated protein 1), a tumor suppressor gene located on chromosome 3p21.3 in families with a genetic predisposition to develop MPM (46, 47). *BAP1* is a deubiquitinating hydrolase that binds the RING finger domain of the BRCA1 protein, thought to be a regulator of many pathways germane to cancer (48). Previous studies reported *BAP1* involvement in various biological processes including regulation of cell cycle, response to DNA damage, and chromatin dynamics (49). *BAP1* is ubiquitously expressed and interacts with tissue and cell type-specific proteins, with a role in mediating metabolic stress response (50) and in promoting survival related to its deubiquitinating activity (51). A recently published study has shown that the heterozygous germline *BAP1* mutations (*BAP1*+/-) induce cell metabolic changes linked to the increase aerobic glycolysis, leading to reprogramming of the activities that create a favorable environment to carcinogenesis and tumor growth (52). The germline *BAP1* gene mutations lead to an abnormally short *BAP1* protein that is likely broken down prematurely. These mutations have been associated with various malignancies other than malignant mesothelioma such as, uveal melanoma (47, 53) and melanocytic *BAP1*-associated intradermal tumors (47). Somatic truncated *BAP1* mutations and aberrant *BAP1* expression are more common in sporadic MPM, with a frequency that varies widely among different histologic tumor types (46, 54). Specifically, the pathogenesis of epithelioid subtype MPM is associated with higher survival, rather than other subtypes of malignant mesothelioma, thus providing additional clinical significance by facilitating histological classification (55–57). Besides single-point mutations in the *BAP1* gene, copy number loss, rearrangements, and multiple alterations have also been found (58, 59). Interestingly, the analysis of chromosome 3p21, using a high-density microarray-based comparative genomic hybridization (aCGH) combined with targeted next-generation DNA sequencing (NGS), detected a much higher percentage of genetic alteration in *BAP1* than reported in previous studies conducted with the NGS sequencing approach or aCGH alone, respectively. Each of these strategies resulted insufficient and less precise to identify the minute or larger chromosomal deletions, underestimating the frequency of genetic alterations in MPM (60). To date, none of mesothelioma patients with germline *BAP1* mutation was an ex-exposed asbestos worker (61), demonstrating that the development of MPM is not always directly associated with the amounts of asbestos exposure, signifying a decisive role of genetic factors among risk factors of this neoplasia.

The high incidence (around 25–60%) of the somatic *BAP1* mutations reported in MPM (62) is also associated with frequent alterations in other major tumor suppressor genes, such as *p16/Cdkn2a*, *p19/Arf*, and *p19/Cdkn2b* (63). Independently of *BAP1* mutations, *p16/Cdkn2A*, *p19/Arf*, and *p19/Cdkn2b* have been

found frequently inactivated by point mutations, aberrant expression and epigenetic silencing, suggesting their role, together with asbestos exposure, in the induction of mesothelial transformation *in vitro* and *in vivo* (64). Moreover, *in vivo* studies have shown that the inactivation of both *p16* and *p19/Arf* expression accelerated the initiation of asbestos-induced MPM and decreased percent survival, as compared with the inactivation of either gene alone (65). Consistent with these data, whole-exome sequencing of asbestos-induced MPM showed the homozygous loss of *Cdkn2A* and alterations in other tumor suppressor gene (66).

Neurofibromin 2 (*NF2*) is another tumor suppressor gene frequently inactivated in MPM. A study has found that 38% of MPM samples displayed *NF2* gene mutations, and 29.4% displayed deletions, while no *NF2* mutations were found in non-small cell lung cancer patients (67). The *NF2* gene product shows a high similarity in its sequence with some members of the ERM (Ezrin, Radixin, Moesin) protein family. The *NF2* protein is a scaffolding protein located at the plasma membrane, where it propagates extracellular signals through several cell surface receptors. A fraction of *NF2* also interacts with other proteins that are involved in regulating ion transporters and in cytoskeletal dynamics (68).

Other studies in MPM have shown the lack of frequent mutations in two most notorious tumor suppressor genes: *p53* (64, 69) and *pRb* (70). Nevertheless, complexes between SV40 large tumor antigen protein (Tag) and both *p53* and *pRb* have been found in human mesothelioma specimens (71, 72), which results in inactivation of these important regulators of the cell proliferation and survival, thus leading to the transformation of human mesothelial cells (HM) (23, 73, 74).

Oncogenes in MPM

Oncogenes promote transformation by driving cell proliferation and preventing apoptosis. Some of these genes are involved in the regulation of intracellular levels of calcium (Ca^{2+}), an important regulator of many physiological processes, including the regulation of apoptosis of cancer cells (42, 75). The remodeling of intracellular Ca^{2+} homeostasis, as a consequence of the activity of different proteins with altered functions, is a general characteristic of cancer cells (75). It is widely accepted that both the Bcl-2 and Akt proteins are cofactors of the Ca^{2+} -dependent pathways leading to apoptosis (76, 77). An antiapoptotic member of the Bcl-2 family of proteins and the oncogene *Akt* were found to be dysregulated in mesothelioma cells (78, 79), and elevated levels of Akt activity were found in 65% of human mesothelioma specimens (80, 81).

Several studies have shown that increased mesothelioma cell proliferation derives from the activity of growth factors and their specific transmembrane receptors, aberrantly expressed in human MPM (82). Epidermal growth factor receptor (*EGFR*) is an important oncogene closely involved in many cancer types, and its gene product is a transmembrane glycoprotein belonging to the tyrosine kinase receptor family. The binding between *EGFR* and its ligand induces cellular proliferation and cell motility and inhibits apoptosis and expression of extracellular matrix proteins (83). Previous studies have shown overexpression of *EGFR* in MPM tissues and cell lines (84, 85). A correlation between the carcinogenicity of the asbestos fibers and the induction of

phosphorylation of *EGFR* was observed in rat pleural mesothelial cells (86, 87), suggesting its potential role in the pathogenesis of this cancer. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are overexpressed in MPM human samples (88) in which they may stimulate tumor growth and promote angiogenesis and lymphangiogenesis (89, 90).

Inflammation is known to contribute to tumors by promoting cell proliferation and activating antiapoptotic pathways. The hallmarks of asbestos fibers inhalation include early and sustained inflammation linked to generation of reactive oxygen species that cause oxidative DNA damage, thus contributing to asbestos-mediated carcinogenesis (91). In addition, when asbestos fibers penetrate the pleura, HM undergo programmed cell necrosis, releasing into the extracellular space the high-mobility group box-1 (HMGB1) protein, an abundant damage-associated protein with functions linked to its cellular localization. HMGB1 mediates chronic inflammation through recruitment of macrophages, which actively secrete tumor necrosis factor- α . The pro-inflammatory and pro-survival NF- κ B pathway is subsequently activated, leading to resistance to apoptosis, transformation of HM and the maintenance of the malignant phenotype (92, 93). A recent study has reported data on the high specificity of HMGB1 protein in a hyper-acetylated isoform in serum of ex-exposed mesothelioma patients, selectively discriminating against their respective healthy control. This could suggest a role for HMGB1 as a serological biomarker (94).

The major role of inflammation in MPM has been confirmed by another study showing increased concentrations of immune mediators in the sera of asbestos-exposed workers compared with controls (95). In addition, in asbestos-exposed rats, alveolar macrophages showed increased expression of transforming growth factor- β , indicating that in asbestosis these cells contribute to fibrosis as well as to an inflammatory response. Furthermore, natural killer (NK) cells demonstrated impaired cytotoxicity upon exposure to asbestos indicating that exposure to asbestos has an immune-suppressive effect, as well as a tumorigenic effect (96). Consistently, functional alteration of NK cells and cytotoxic T lymphocytes upon asbestos exposure and in MPM patients have been reported (97).

The Oncogene Notch

The Notch signaling pathway has been found to be dysregulated in MPM human biopsies (98). In a large number of solid tumors (99–101) and leukemias (102, 103), Notch acts as an oncogene, but its role as tumor suppressor gene has been reported in other cancers, such as squamous cells carcinoma (104, 105). The Notch pathway is as a mediator of short-range cell-to-cell communication system, which involves the regulation of genes controlling developmental processes, such as proliferation, cell death, acquisition of specific cell fates, and activation of differentiation. Notch is active throughout development and during maintenance of self-renewing adult tissues, in a context-dependent manner (106). The maturation process of the Notch receptor involves a cleavage during intracellular trafficking in the Golgi complex, resulting in a single-pass transmembrane protein to shuttle to the cell membrane. The transmembrane protein is composed of a large extracellular domain linked through non covalent interactions to the transmembrane portion (107). Activation of the Notch signaling

is mediated by a direct contact between the extracellular domain of Notch receptor (four members Notch1–4) and one of five canonical ligands (Delta-like 1, 3, 4 or Jagged 1, 2) on neighboring cells (108). This interaction triggers two proteolytic cleavages, initially by metalloproteases of the ADAM family, followed by a cleavage by the γ -secretase complex at the cell membrane, releasing the intracellular domain of the Notch receptor (NICD), that represents the active form of the receptor (109, 110). NICD translocates into the nucleus and interacts with the transcription factor CSL (suppressor of hairless in *Drosophila*, Lag-2 in *C. elegans*, and CBF1/RBPJ- κ in mammals), and, after replacing a co-repressor complex, converts it into a potent transcriptional activator of downstream target genes (111). This constitutes the “canonical” Notch pathway (106, 112). Recently, a “non-canonical” Notch pathway, which acts independently of CBF1/CSL and plays important roles in normal and transformed cells, has been identified (113, 114).

There is a functional diversity among the Notch receptors, in particular among their intracellular active forms that are capable of inducing specific genes (115–117). There is evidence that, in breast carcinoma, Notch2 has opposite effects on cell survival, compared with Notch1 and Notch4 (118). Furthermore, it has been observed that the transcriptional activity of Notch1 and Notch3 is reduced by co-expression with the intracellular domain of Notch2 (119). A detailed description of the biochemical processes regulated by Notch and the implications of dysregulation of this pathway in the development of cancer have been widely discussed and reviewed elsewhere (106, 120–123).

In cell lines established from human MPM biopsies, elevated Notch1 and reduced Notch2 expression have been observed (98) with their normal counterparts. Genetic and chemical modulation of the Notch pathway indicated that MPM cells are dependent on Notch signaling. Specifically, in MPM cells, Notch 1 inhibits PTEN (phosphatase and tensin homolog) and activates the PI3K/Akt/mTOR signaling pathway indicating that this receptor is an MPM oncogene and its activation is strictly necessary for growth and survival of MPM cells (98). On the contrary, in MPM cells, Notch2 is a positive transcriptional regulation of PTEN and therefore an inhibitor of the PI3K/Akt/mTOR signaling pathway and re-expression of Notch-2 was toxic to MPM cells (98). Previous studies conducted by the same group have shown that SV40 activates Notch1 leading to immortalization and transformation of primary HMC (124–126). These data indicate that Notch1 can mediate the process of transformation of mesothelial cells, downstream of mutagenic events caused by the exposure of carcinogenic factors, such as asbestos and viral infection (125, 127–129). The effect of SV40 on Notch1 in mesothelial cells is similar to what reported in uterine cervical cancer, in which the infection of human papilloma virus has been linked to the activation of Notch1 (101, 130, 131).

CURRENT THERAPEUTIC APPROACHES TO MPM

Surgical Treatment

Surgery, also used in combination with chemo- and/or radiotherapy, attempts to eradicate the malignant tissue and is an essential option to help the patient relieve symptoms by reducing pain

and by controlling pleural effusions (132). Nevertheless, surgical resection of the tumor is controversial and limited to MPM patients with early stage disease and good cardiopulmonary functions (133, 134). The intent and the role of surgical procedure influence the survival rate of MPM patients. In the analysis of the International Association for the study of Lung Cancer Mesothelioma Database (3, 101), MPM patients undergoing curative-intent surgery had a median survival of 18 months (stage I, 21 months; stage II, 19 months; stage III, 16 months; and stage IV, 12 months) vs 12 months with the palliative intent (135). A large study (14,288 patients) has shown that surgery alone, compared with no treatment, is associated with a significant improvement in survival [adjusted hazard ratio (adj HR) 0.64 (0.61–0.67)], but not radiation [adj HR 1.15 (1.08–1.23)]. The similar survival obtained with surgery alone has been observed after surgery and radiation combined [adj HR 0.69 (0.64–0.76)] (136). There are two surgical procedures commonly used in MPM: (1) pleurectomy/decortication (P/D) that involves the radical removal of all visible disease of the pleura, both the inner and outer lung lining. If the mesothelioma only affects one lung, a pneumonectomy may be performed to remove the entire organ; (2) extra-pleural pneumonectomy (EPP), a type of more radical surgical option which aims to eradicate all macroscopic tumors *via* the removal of the areas surrounding it, including other mesothelial tissue (137). The optimal procedure for resection (EPP or P/D) of MPM is controversial and depends on clinical factors and on individual surgical preference and expertise. Flores et al. have shown that operative mortality following EPP is higher compared with P/D (7 vs 4%, respectively); however, P/D has better survival, compared with EPP (16 vs 12 months, respectively). All things considered, the authors of the study highlight similarities between the two approaches and conclude that there is no evidence to support the use of EPP vs P/D (138). A multicenter randomized clinical trial [Mesothelioma and Radical Surgery (MARS)] compared the clinical outcomes between MPM patients assigned to EPP within trimodal therapy (chemotherapy, EPP, and postoperative hemithorax irradiation) and patients with chemotherapy, but no EPP. The median survival for the EPP group was 14.4 months, while for the no EPP group was 19.5 months (139). The higher mortality related to EPP (3–15%) compared with extended P/D (1–5%) and, the observation that both techniques can achieve prolonged median survival has been reported by other groups (140). When balancing these considerations has been emphasized that surgery should be aimed to obtain macroscopic complete resection while limiting surgery-associated mortality and given the high rates of local failure/recurrence after surgery, incorporation of intracavitary therapeutics into the multimodality treatments (MMT) protocol would be desirable (140).

Radiotherapy

Radiation therapy is relatively common for MPM. Several studies have shown that radiotherapy is unable to cure MPM (141), but administered either pre- or postoperatively, in combination with other treatments or alone, is useful to control pain, limit tumor spreading and, only in combination with other approaches, improved the 2-year rate of overall survival from 20 to 34% (142). It has proven to be extremely difficult to identify the effective

radiation dose and the site of the radiation, due to the unique way that MPM spreads along the pleura, surrounding the lungs, adjacent to the heart, the spinal, and other vital organs. Once the cancerous cells spread, they can form small tumor called nodules. This process, known as seeding, may occur in 20–50% of MPM patients. Prophylactic radiation has been used to prevent spreading and procedure-tract metastases, but this approach remains controversial and without a standardized clinical practice, due to mixed results obtained (143). Differences in surgical procedures, closely related to the ability to administer radiation, could explain the mixed results (144). In the neoadjuvant setting, the development of new intensity-modulated radiation therapy (IMRT), followed by early EPP, allowed the optimization of the administration of high-dose radiotherapy to the hemithorax, providing in selected MPM patients an improved median overall survival up to 39.4 months (145, 146). In contrast with these results, multicenter clinical trials observed the not promising outcomes of IMRT after adjuvant chemotherapy and EPP, not supporting the routine use of hemithoracic therapy for MPM in trimodality approach, due to the high toxic effects (147). The concerns related to the radiation treatment in the trimodality approach were the high rate of patients excluded, due to disease progression, surgical mortality, hemithoracic radiation morbidity, and not satisfactory risk/benefit ratio (148). With the lack of randomized trials, Wald and Sugarbaker recommends the application of radiation following EPP surgical procedure to selected patients with good postoperative recovery, excluding those patients who had local chest wall invasion (140).

Chemotherapy

Despite the toxic effects of chemical drugs, systemic chemotherapy for MPM remains the only and primary treatment modality and reasonable option that has been shown to increase median survival from 9 to 12 months in most advanced stage MPM patients, who are not candidates for aggressive surgery (149). Almost every chemotherapy regimen has been tested in mesothelioma (150, 151). Although these treatments are not curative, they can alleviate symptoms, improve quality of life and prolong survival, depending upon the tumor stage, histological differentiation, and the patient's overall health when treatment begins (132). Platinum containing regimens have a greater activity than non-platinum containing combinations (152). Vogelzang et al. were the first to demonstrate that pemetrexed/cisplatin combination chemotherapy is more effective in MPM than cisplatin monotherapy (153, 154). A few other combinations were evaluated in randomized trials, but they did not demonstrate an important improvement of overall survival (155). Of note early clinical trials of MPM patients included heterogeneous groups of patients with divergent risk factors and were therefore often not powerful enough to assess therapeutic efficacy of a particular treatment (156). New generation of antifolates (pemetrexed and raltitrexed) and novel platinum derivatives (157) have shown low efficacy and limited outcomes, with a 3 months survival benefit in their combination over cisplatin alone: the median survival ranged from 9 to 12 months, as shown by the EMPHACIS trial in patients with advanced disease (153).

There are still many unanswered questions regarding chemotherapy and MPM. However, chemotherapy remains a central pillar of systemic therapy for MPM and the goal today is still to develop novel targeted chemotherapy agents, to be used either alone or in combination to increase efficacy and to minimize and/or avoid side effects (157). A number of novel therapeutic agents are under investigation with the aim to provide further treatment options for MPM in the future (158).

Multimodality Therapy

According to the 2007 UK Department of Health's Mesothelioma Service Framework and the British Thoracic Society's Statement on Mesothelioma (159), progress has been made in the management of MPM patients by involving experienced multidisciplinary team recommended by other guidelines for mesothelioma patients (160, 161). For more effective results, treatment options include the combination of two or more different methods of treatment, such as surgery, radiation therapy, and chemotherapy. However, timing, type of agent, and modality still debated. Selected patients with operable disease and a good performance status should be considered candidates for the multimodality therapy. For instance, surgery is recommended for patients with clinical stage I disease where the tumor is localized and non-metastatic to lymph nodes or other organs or tissues and has potential for surgical tolerance. Patients who are not operable because impaired cardio-pulmonary function can be treated with chemotherapy. Patients with stage II where the tumor is larger and has invaded nearby organs, such as the lung or diaphragm, lymph nodes, may also be involved and stage III where mesothelioma has invaded a region or area, such as the chest wall, esophagus, or lymph nodes should be offered trimodal therapy with surgery, chemotherapy, and radiotherapy. Chemotherapy alone is recommended for patients who are not medically fit for surgery have stage IV disease and/or show sarcomatoid histology (162). A recent study has confirmed that the combination of surgical treatment, such as EPP and chemotherapy with radiotherapy led to a median survival that ranged from 18 to 24 months (163). In the MARS study, radical EPP within trimodal therapy showed no benefits on the quality life overall survival, compared with chemotherapy (139). Wald and Sugarbaker discussed that without clinical studies comparing both chemotherapy or chemoradiotherapy to surgery-based MMT protocols and different surgery-based MMT approaches, there remains considerable uncertainty about the right therapeutic protocol and the right type of surgery for the individual patient (140). In agreement with their observation, data from the Cochrane Lung Cancer group's Specialized Register, Cochrane Central Register of Controlled Trials, Medline, Embase, and the strength of the evidence collected by Abdel-Rahman et al. revealed that there is still a lack of available evidence to support the use of radical multimodality therapy in routine clinical practice (164).

Immunotherapy and Targeted Therapy

As for other cancer types, immunotherapy is opening new options for the treatment of MPM. Clinical trials with dendritic cells and live-attenuated *Listeria* vaccination have produced encouraging results and are being considered for multicenter phase II trials (165). Intrapleural injection of oncolytic viruses (herpesvirus,

poxvirus, adenovirus, and several attenuated RNA viruses) has also been considered as a possible treatment for unresectable MPM, due to the sensibility of MPM cells to their action, by direct killing or by immune-mediated mechanisms (166). In the light of the high levels of treatment-related adverse events or limited benefits of immunotherapeutic approaches in many clinical trials, the application of oncolytic virotherapy in MPM treatment is still being investigated (167).

Clinical trials are also being conducted to test effectiveness of immune checkpoint inhibitors in MPM patients. In a large clinical study, treatment with tremelimumab, a monoclonal antibody against cytotoxic-T-lymphocyte-associated antigen 4, expressed on the surface of activated T lymphocytes and interfering with their ability to kill cancer cells did not significantly prolong overall survival, compared with placebo (median survival of 7.3 months) in patients with previously treated MPM (median survival of 7.7 months) (168). Safety of pembrolizumab, an antibody against PD-L1 (programmed cell death ligand 1), and an inhibitor of immune response expressed on cancer cells have also been tested in MPM patients. It appears to be well tolerated, and it might confer antitumor activity in patients with PD-L1-positive MPM. Response, durability, and efficacy in this patient population warrant further investigation (169). Nevertheless, one of the biggest trials for immune checkpoint blockade has reported death of 81% of MPM patients died, without significant difference in overall survival between therapeutic treatments against placebo (168).

A promising type of immunotherapy based on adoptive cell transfer employs chimeric antigen receptor (CAR) T cells, in which T cells are generated to recognize specific antigen receptors (TSA or TAAs) on cancer cells. Numerous trials are currently being explored for MPM. Specifically, phase I clinical trials for genetically modified T cells to recognize specific antigens on MPM cells, such as mesothelin and fibroblast activation protein (FPA), are being conducted in MPM patients (170).

In preclinical setting, the dysregulation in MPM of ErbB, a protein structurally similar and a ligand to EGFR, is being exploited for immunotherapy (171). To this aim, patient T-cells were engineered by retroviral transduction to express a panErbB-targeted CAR and co-expressed with a chimeric cytokine receptor, to induce interleukin-4 mediated CAR T-cell proliferation. These cells were activated upon contact with a panel of four mesothelioma cell lines, leading to cytotoxicity and cytokine release in all cases (171). Preclinical studies are also providing proof of concept that combination treatment of chemotherapy/radiotherapy and immunotherapy with immune checkpoint inhibitors could lead to better outcomes for MPM. Specifically, it has been demonstrated *in vivo* that short course of high-dose non-ablative radiation could promote an antitumor immune response (165).

In the context of targeted therapy, phase I and phase II trials, which tested inhibitors of receptors with tyrosine kinase activity (RTK) in MPM patients with dysregulated of EGFR and VEGFR pathways have given poor results (172). The best results to date are with combination of bevacizumab and chemotherapy leading to 2.6 months increase of survival when compared with patients who did not receive bevacizumab (173). Inactivation of plasminogen activators inhibitor PAI-1, implicated in tumor progression by

increasing angiogenesis, could constitute a strategy for inhibiting angiogenesis and growth of MPM. In a preclinical setting, tumor mass and the degree of angiogenesis in intrapleural tumors were reduced when PAI-1 inhibitor was administered to mice in which MPM cells expressing high levels of VEGF (VEGF-A) which were intrapleurally transplanted (174).

A detailed list of the ongoing clinical trials based on immunotherapy has been recently published (167). Based on the recent results of the studies conducted so far Bakker and colleagues conclude that this therapeutic approach for MPM has been disappointing probably due to the chronic inflammatory state and hypoxia that define this tumor. To further complicate the immune-therapeutic approach to MPM, it has been recently shown that MPM is a pool of independent clones that would need to be simultaneously targeted for an effective immunotherapy (175).

NEW THERAPEUTIC APPROACHES AND NOVEL MOLECULAR TARGETS

Despite progresses, survival time and response rate to cytotoxic agents used for MPM treatment are still not satisfactory (176), plus a high degree of variability in treatment outcome in cancer patients undergoing chemotherapy has been observed (177). Furthermore, the cancer is still diagnosed at an advanced stage. Therefore, there is a strong need for early and accurate diagnosis markers and new therapeutic approaches in MPM.

Circulating Biomarkers of MPM

Analysis of liquid samples, such as serum and pleural effusion, due to their ease of collection represents a promising approach for the characterization of markers related to cancer progression (178). Recently, proteins (179–183), metabolites (184), and miRNAs (45) have been identified which are differentially expressed in the serum of MPM patients and could be used as biomarkers of the onset and progression of MPM. However, these studies still require a definitive validation in larger populations.

Soluble mesothelin is a cell surface glycoprotein highly expressed in several human cancers, including mesothelioma (185). Several studies have shown a sensitivity of 84% for advanced status of MPM, a specificity of 95%, and a correlation with histological subtype of the tumor (186–188). The MPM patients with epithelioid subtype had higher levels of mesothelin than those with sarcomatoid subtype (189). Another highly promising biomarker is the circulating glycoprotein fibulin-3 (190). A study population conducted by Pass et al. showed elevated fibulin-3 levels both in plasma (specificity of 94% and sensitivity of 100%) and pleural effusion (specificity of 93% and sensitivity of 84%) of MPM patients, distinguishing healthy persons with exposure to asbestos from patients with MPM (180). The prognostic potential of fibulin-3 is superior compared with mesothelin, which instead results more useful as diagnostic biomarker of MPM (181). Pass and colleagues have also shown that the osteopontin levels, an extracellular cell adhesion protein, were significantly higher in serum of MPM patients than healthy asbestos-exposed individuals (179). However, it has been observed that osteopontin is unable to distinguish between MPM, pleural metastatic carcinoma or

benign pleural lesion, associated with asbestos exposure, due to very high number of false-positive (191).

A clinical study has shown that total or hyper-acetylated isoform of HMGB1 is a sensitive and specific biomarker that allows to differentiate early the serum samples of MPM patient asbestos-exposed from healthy unexposed ones and other pleural diseases patients (94). In subjects from a hyperendemic area for MPM, the C–C chemokine Regulated on Activation, Normal T-cell-Expressed and Secreted (RANTES) was found associated with the exposure to asbestos fibers. RANTES showed an increased gradient of concentration from healthy subjects to asbestos-exposed workers and MPM patients. Independently of SV40 infection, increased concentrations of other immune mediators were observed in the sera of the asbestos-exposed workers compared with controls (95). Analyses carried out on serum samples from MPM patients have detected the presence of antibodies against SV40 viral capsid protein (27, 192–194). Since SV40 could synergize with asbestos in causing MPM (21, 125), these antibodies in the serum could help to predict the risk of developing MPM in a population of asbestos-exposed worker.

The discovery of miRNAs, which are small sequences of RNA involved in regulation of gene expression, has changed the approach to diagnosis and therapy of many diseases, including cancer (44). miRNAs regulate a plethora of cellular activities, such as proliferation, apoptosis, metabolism, and angiogenesis. They are characterized by high stability, under different conditions and typology of sample treatment, processing, and isolation (195–197). Furthermore, these circulating miRNAs, moving through the circulatory system naked or inside microparticles, such as exosomes, microvesicles, and apoptotic bodies, represent an innovative form of distant intracellular communication (45, 198, 199). The miRNAs expression profile has been found to be abnormal in several human cancers, thus pointing at their role in cancer progression, as oncomiRNAs and tumor suppressor miRNAs (200–202). Based on their characteristics of measurable indicators of physiological and pathological conditions, miRNAs could be used for prognosis, diagnosis, and treatment outcome assessments of cancers, including the MPM (8, 45).

A specific circulating miRNAs signature discriminating MPM patients from ex-exposed asbestos and healthy subjects have been identified (27, 45, 203). It has been proposed that the detection of circulating miRNAs, i.e., miR-197-3p, miR-1281, and miR-32-3p, in sera of MPM affected patients and workers ex-exposed to asbestos fibers could be used as a novel, non-invasive, predictive biomarkers for this cancer (45). This signature could also help to design targeted therapies for MPM (8, 204), exploiting the use of antagomir (oligonucleotide sequences) or anti-miRNAs (mimetic miRNA) (44), to silence the overexpressed oncomiRs or substitute the lost miRNA in cancer, respectively (205, 206).

Targeting the Notch Pathway in MPM

A large body of evidence shows that inhibition of Notch signaling causes a reduction of tumor cell proliferation *in vitro* and arrests tumor growth *in vivo* (99, 207), thus the targeting of Notch offers an attractive potential therapeutic strategy in oncology. Notch inhibition is able to shrink the tumor not only by increasing the apoptotic rate in the bulk of tumor but also by inhibiting the

growth of cancer stem cells, one main culprit for tumor recurrence (208), and by interfering with angiogenesis (209). Small molecules inhibiting γ -secretase, the enzyme required for Notch activation are being investigated in clinical trials (for a list of trials the reader is referred to <http://clinicaltrials.gov>). The molecules seem to work best in combination treatment (210). Other agents able to reduce angiogenesis by inhibiting Notch in are also being developed, i.e., antibodies against Dll4 (211, 212).

As previously discussed, Notch1 is overexpressed in MPM and it is therefore possible to envision the targeting of this receptor, in combination with other agents already used to prevent MPM progression by interfering with angiogenesis (172) and cancer stem cells survival (213). The efficacy of Notch inhibitors could be evaluated also in experimental model of MPM in which less known pathways crucial for mesothelioma stem cells, such as Wnt (91, 214) and Hypos, downstream of *NF2* (215), are being investigated. The rationale for this co-treatment is based on evidence of the cross talks between the Notch, Hypos, and Wnt pathways (210).

Targeting Notch in tumors has been challenging due to the fact that γ -secretase have many side effects (101). In this context,

MPM may be a good model to test the efficacy of novel therapies that target Notch1 because of its location in a closed space (the pleural cavity) that could limit the toxicity due to γ -secretase inhibition. It should be noted that targeting Notch in tumor has been challenging also due to the complexity of Notch signaling. First, not all Notch receptors are sensitive to inhibition of γ -secretase (115) and second, whereas canonical Notch signaling is very well documented in cancer, the non-canonical activation of Notch signaling, which plays a role in cancer, is still not well understood (216, 217). Consequently, it is not always possible to assess Notch inhibition by a certain agent. The clear dissection of the canonical and non-canonical Notch signaling is necessary to fully understand this complex pathway to develop a targeted therapy that includes Notch.

Precision Oncology and Future Directions in the Treatments of MPM Patients

Studies conducted in the last decades have identified several pathways that could be targeted to give new hopes to MPM patients (Figure 1). Due to the rapidly evolving field of precision medicine,

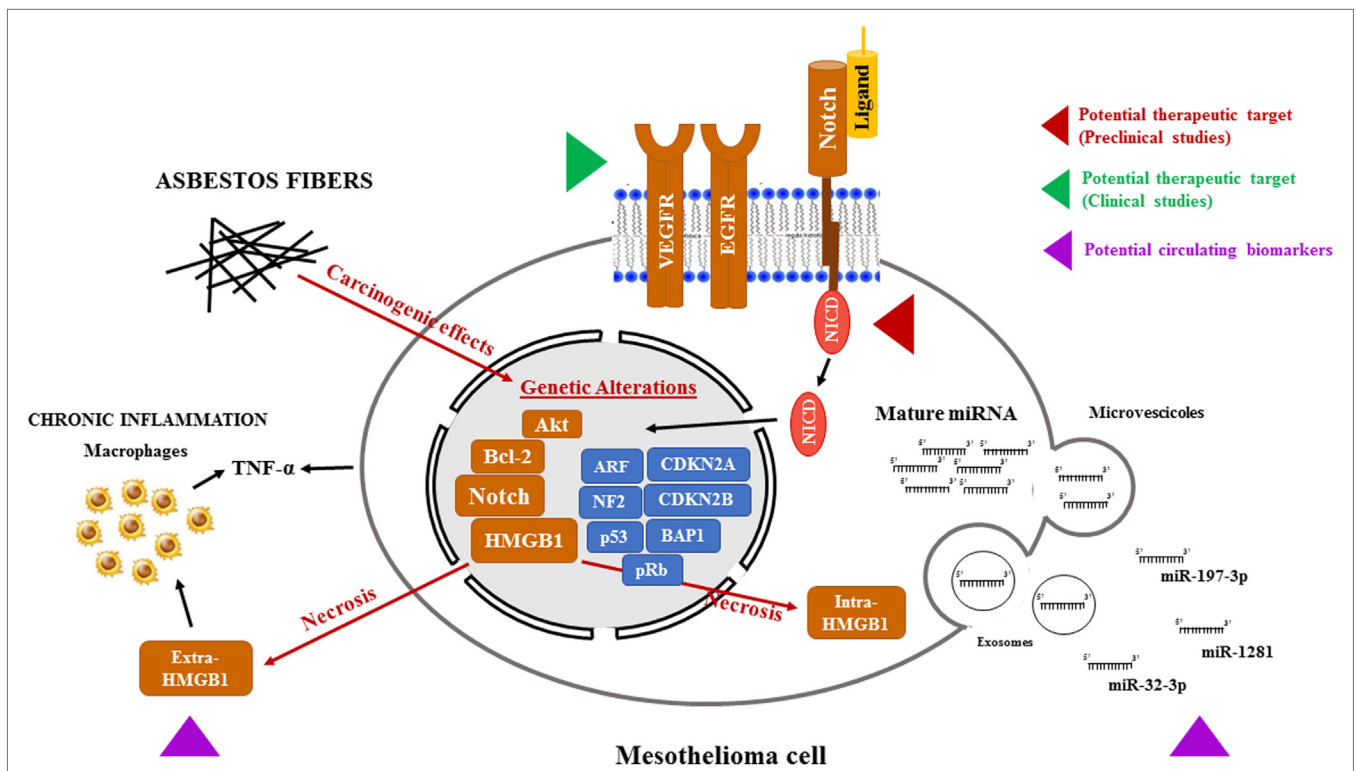


FIGURE 1 | Potential therapeutic targets and biomarkers in the mesothelioma. Asbestos fibers, alone or with other cofactors, such as viral infection or genetic predisposition, may cause mutagenic changes resulting in the alterations of oncogenes and tumor suppressor genes leading to the transformation of normal mesothelial cells. In addition, following necrosis caused by asbestos exposure, HMGB1 primarily located in the nucleus, translocates to the cytosol and extracellular space, triggering the inflammatory response and TNF- α secretion, both by mesothelial cells and macrophages, further contributing to mesothelial cells transformation. All these events may contribute to the activation of the Notch signaling. Targeting Notch, as it is already been pursued with VEGFR and EGFR, could help to stop the progression of mesothelioma. Mesothelioma is also accompanied by changes in microRNA (miRNA) expression in cancer cells and, consequently, in biological fluids. In particular, miRNAs (miR-197-3p, miR-1281, and miR-32-3p) could become a tool for early diagnosis of mesothelioma. In this figure, the red and green arrows represent clinical and preclinical studies, respectively, aimed to sensitize mesothelioma cells to cytotoxic treatments by targeting newly discovered pathways altered in mesothelioma. The purple arrow indicates the novel potential circulating biomarkers under study for a no invasive MPM screening. Abbreviations: VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; HMGB1, high-mobility group box-1; TNF- α , tumor necrosis factor- α ; MPM, malignant pleural mesothelioma.

identification of novel biomarkers is promising as it may provide the best therapeutic options for each patient, considered the genetic background and the specific characteristics of the tumor. This hope is supported by a recent study on polymorphisms in gemcitabine, pemetrexed, and cisplatin metabolism, transport and other drug target genes and DNA repair pathways, which has led to a clinical-pharmacogenetic model that could predict the best chemotherapeutic treatment for a specific MPM patient (177). Furthermore, oncogene-targeted depth sequencing on a tumor sample and paired peripheral blood DNA from a patient with malignant mesothelioma of the peritoneum revealed a mutation leading to 13-amino acids neo-peptide of the truncated BAP1 protein, which is predicted to be present on this examined patient's HLA-B protein. This tumor-specific neoantigen is an example of potential molecular biomarker for personalized diagnosis of mesothelioma (177, 218). Comprehensive genomic analysis, followed by integrated analyses of 216 MPM biopsies, has identified recurrent mutations, gene fusions and splicing alterations leading to inactivation of *NF2*, *BAP1*, and *SETD2* and alterations in Hippo, mTOR, histone methylation, RNA helicase, and p53 signaling pathways (219). Furthermore, in a proof-of-concept study including five MPM patients, it was shown that the composition of pleural effusion is dynamic, influenced by treatment and that the immune cell composition of the pleural effusion does not automatically reflect the properties of tumor tissue. These findings could have major consequences when applying precision immunotherapy based on pleural effusion findings in patients (199). In conclusion, with the aim to achieve

early detection of MPM and increased survival of these patients, with minimal side effects: (1) the comprehensive genomic profiling of MPM; (2) the targeting of pathways already known to be dysregulated in MPMs, such as the Notch pathway; (3) the characterization of dysregulated circulating miRNAs, and (4) the assessment of risks, such as exposure to asbestos and the presence of germline BAP1 mutations, should all be taken under consideration.

AUTHOR CONTRIBUTIONS

PR and MR participated in the designing of the manuscript and draft it. IB, AC, and RF participated in drafting the manuscript and critically revised it. FM and MT designed and coordinated the manuscript. All the authors read and approved the final manuscript.

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