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Biomarker-guided targeted and immunotherapies in malignant pleural mesothelioma

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***Abstract*:** Malignant pleural mesothelioma (MPM) is a lethal thoracic malignancy whose incidence is still increasing worldwide. MPM is characterized by frequent inactivation of tumor-suppressor genes (TSGs), e.g., the homozygous deletion of *CDKN2A/2B* and various genetic alterations that inactivate *BAP1, NF2, LATS1/2*, and *TP53*. The leading cause for the poor prognosis of patients with MPM is the lack of effective treatment options, with conventional chemotherapy being the standard of care in the clinic, which has remained unchanged for almost 20 years. Precision oncology, a burgeoning effort to provide precise cancer treatment tailored to unique molecular changes in individual patients, has made tremendous progress in the last decade in several cancers, but not in MPM. Recent studies indicate a high degree of tumor heterogeneity in MPM and the importance to optimize histological and molecular classifications for improved treatment. In this review, we provide an up-to-date overview of recent advances in MPM by focusing on new stratifications of tumor subgroups, specific vulnerabilities associated with functional loss of TSGs and other biomarkers, and potential clinical implications. The molecularly based subdivisions not only deepen our understanding of MPM pathobiology, but more importantly, they may raise unprecedented new hopes for personalized treatment of MPM patients with biomarker-guided targeted and immunotherapies.

Keywords: precision oncology, malignant pleural mesothelioma (MPM), tumor-suppressor gene, molecularly based stratifications, immunotherapy

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Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer arising from mesothelial cells of the pleural tissue that covers the lung. The cause of MPM is mainly attributable to occupational exposure to asbestos. The incidence and mortality of MPM are still increasing globally [Figure 1(a–d)], although enormous efforts have been made to reduce occupational exposure to asbestos.[1] Latest data from the public Global Burden of Disease database (http://www.healthdata.org/gbd) show that the survival time of patients with MPM has increased only slightly in the past decades [Figure 1(a, b)], underlining the need for improved therapeutic strategies. Currently, MPM-related deaths mainly occur in developed countries including Australia, Germany, Japan, and the United States, largely as a result of earlier industrialization [Figure 1(c)]. However, the incidence of MPM is expected to peak in the next two decades, especially in developing countries such as India, Ukraine and China [Figure 1(d)], as there is a long latency (typically 30–50 years) between asbestos exposure and disease onset.[2] This prediction is supported by recent evidence showing an increasing incidence trend and underestimated cases in developing countries,[3,4] and more attention to this deadly malignancy is needed.

The main reason for the poor prognosis of MPM is the lack of effective treatment options.[1,5] The majority of patients with MPM are diagnosed with advanced disease for which chemotherapy (cisplatin plus pemetrexed), introduced in 2003,

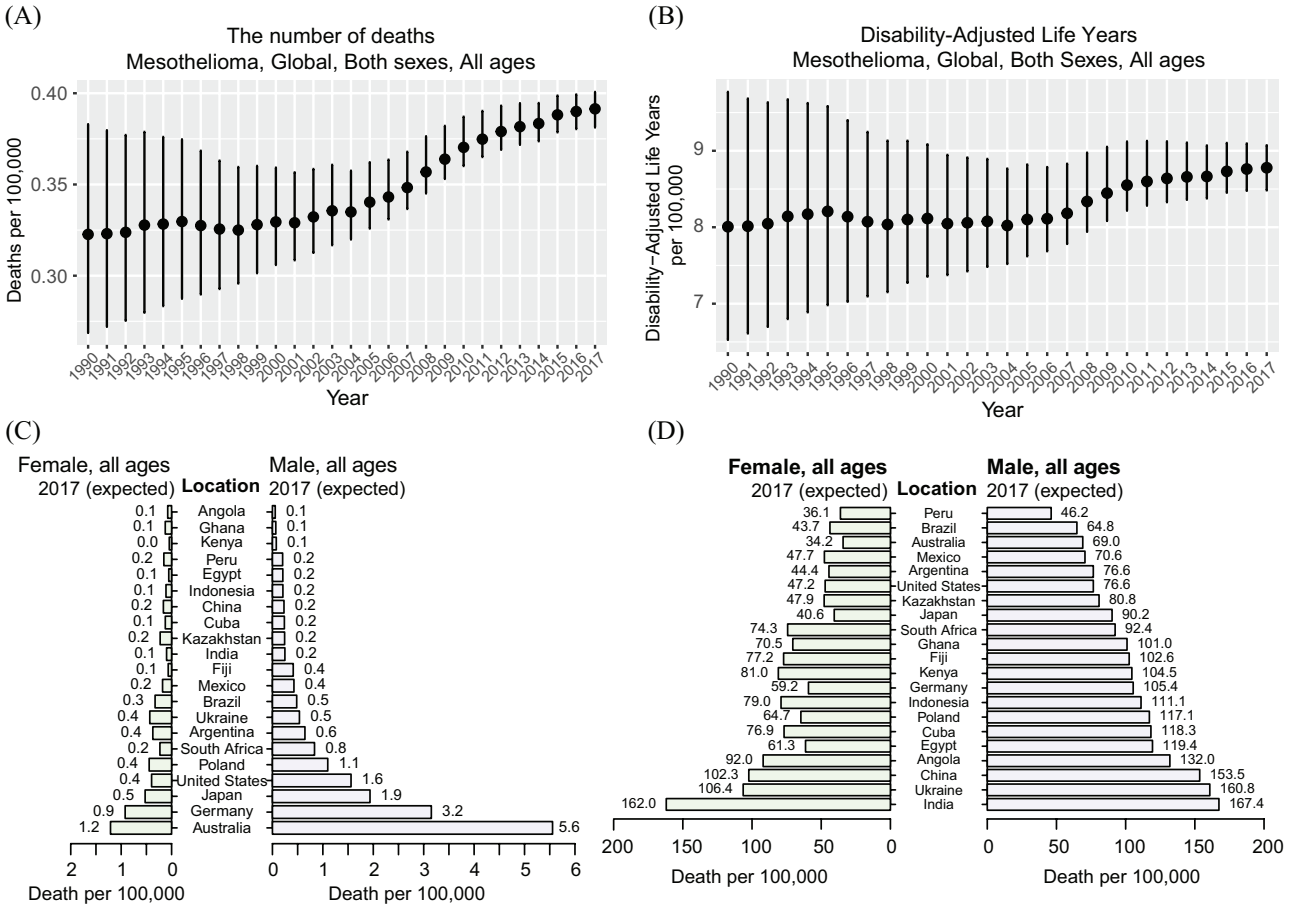

Figure 1. The global burden of MPM.
The number of death (a) and disability-adjusted life years (b) of patients with MPM over the last three decades (1990–2017). Data represented here were downloaded from the database of GBD 2017. The expected number of death (c) and the expected number at the risk of death (d) caused by MPM. GPD, Global Burden of Disease; MPM, malignant pleural mesothelioma.

remains the only clinically approved first-line regimen.[6] However, systemic chemotherapy only slightly improves the clinical outcome of MPM patients and increases the median survival time by 3 months only,[6] further underscoring the urgent need for new and more effective therapies.

Precision oncology, a strive for personalized medicine that targets unique molecular aberrations in patients, has made tremendous progress in the last decade in various cancers,[7] but is lagging far behind in MPM.[8] Comprehensive genomic studies have shown a rarity of oncogenic driver mutations in MPM,[9,10] while inactivating mutations [e.g. homozygous deletion (HD) and point mutation] in tumor-suppressor genes (TSGs) predominate, such as the cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/2B*), BRCA1-associated protein-1 (*BAP1*), neurofibromin 2 (*NF2*), large tumor-suppressor kinase 2 (*LAST2*), and tumor protein p53 (*TP53*) [Figure 2(a)]. While numerous drugs that exploit oncogene dependence have been successful in oncogene-driven cancers, targeted therapies that exploit mutated TSGs have proved to be far more difficult. Consequently, little progress has been made in MPM treatment, as clinical trials without molecularly directed biomarkers for patient selection have generally failed.[8,11–13]

Given the poor clinical outcomes and the enormous need for effective treatment, it is of utmost importance to expand the therapeutic arsenal to combat MPM. Like many other types of cancer, MPM is highly heterogeneous and varies in prognosis and response to anticancer drugs.[14,15] Therefore, a better understanding of the mechanisms underlying the heterogeneity of MPM is crucial for patient stratification tailored to selective therapeutics or precision medicine. In this review, we update recent

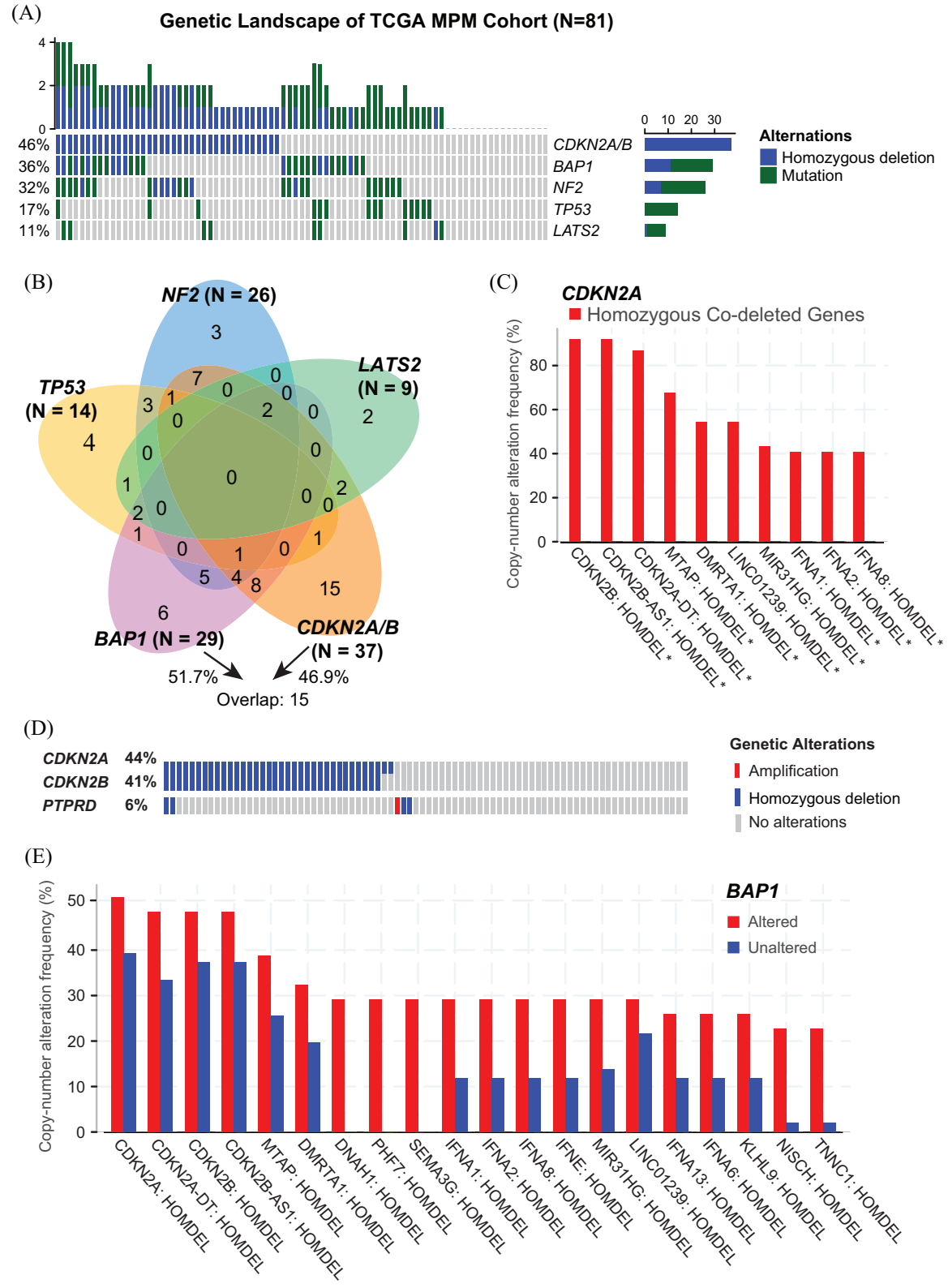

Figure 2. The landscape of major genetic alterations in MPM.
(a) Frequency of the major genetic alterations in TCGA MPM cohort (n=81). Data were downloaded from cBioPortal (https://www.cbioportal.org/). (b) Venn diagram visualizing the intersections of the major genetic alterations in a. (c) The top 10 genes co-deleted with *CDKN2A* in MPM. Data were downloaded from cBioPortal for subsequent re-analysis. (d) The frequency of genetic alterations of *CDKN2A/2B* and *PRPRB* in MPM. Data were downloaded from a TCGA cohort of patients with MPM (n=81). (e) The top 20 genes co-deleted with *BAP1* in MPM. Data were downloaded from cBioPortal and reanalyzed.
MPM, malignant pleural mesothelioma; TCGA, The Cancer Genome Atlas.

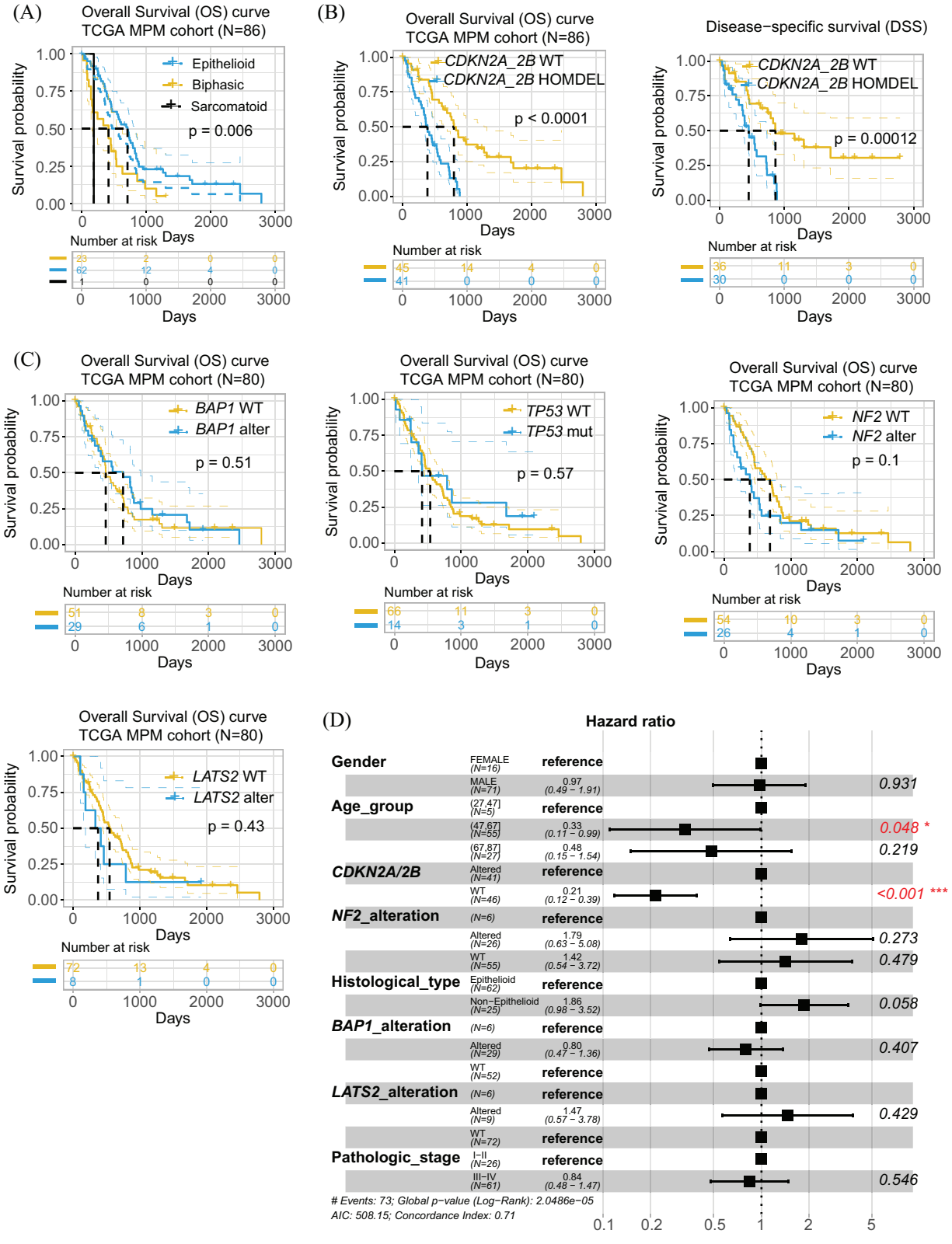

Figure 3. Prognostic values of histology and major genetic alterations in patients with MPM.
Association of histology (a), *CDKN2A/2B* homozygous deletions (b) and other major genetic alterations (c) with prognosis in patients with MPM. The *p*-value was calculated using the log-rank test. (d) Multivariate Cox regression analyses-based forest plot shows the factors significantly influencing overall survival of TCGA patients with MPM.
MPM, malignant pleural mesothelioma; TCGA, The Cancer Genome Atlas.

advances in MPM, focusing on new approaches in histology and molecular-based stratification, the underlying vulnerabilities and the potential clinical implications.

Histology-related molecular characteristics and vulnerabilities

Histological subtyping remains the primary indicator for prognostic assessment and therapeutic decisions in MPM that is divided into three subtypes based on tumor cell morphologies: epithelioid, biphasic (or mixed) and sarcomatoid, where the epithelioid is associated with the best prognosis and the best therapy response [Figure 3(a)], while the sarcomatoid is the worst.[16] However, in some MPM cases, histological classification can be challenging. A recent study reported the use of a deep-learning approach to characterize a transitional histo-subtype of MPM,[17] where integrative molecular analysis showed that this particular MPM type is more similar to nonepithelioid MPM and is a subset of sarcomatoids.

Molecular signatures and associated vulnerabilities of different histological subtypes were investigated.[9,18] Using an unbiased hierarchical clustering approach, it was shown that the ubiquitin–proteasome signaling pathway in biphasic peritoneal mesothelioma is upregulated compared with the epithelioid.[18] In support of this observation, our recent studies suggested that biphasic MPM cells are more sensitive to the clinically approved proteasome inhibitor bortezomib and that bortezomib synergistically increases the efficacy of platinum-based chemotherapy.[19,20] In a comprehensive integrated genomic study,[21] the immune-checkpoint gene *VISTA* was identified, but not PD-1 or PD-L1. *VISTA* is highly expressed in the epithelioid MPM, suggesting a rationale for anti-VISTA therapy in the epithelioid MPM.[9] A recent study confirmed the association between *VISTA* and epithelioid MPM.[22]

Large-scale genomic studies have refined the histological classification in MPM. Based on transcriptomic data, Bueno *et al.* proposed four major histological subtypes: (1) epithelioid (E) and (2) sarcomatoid (S) subtypes, enriched for epithelioid and sarcomatoid tumors, respectively; (3) biphasic-E subtype, enriched for biphasic and epithelioid tumors; and (4) biphasic-S subtype for biphasic and sarcomatoid tumors.[10] Remarkably, the sarcomatoid MPM has a significantly higher PD-L1 level than other groups. A more recent study further decomposed the histological heterogeneity of MPM and demonstrated that each tumor could be broken down into epithelioid and sarcomatoid components,[22] and that the proportion of the epithelioid and sarcomatoid components not only predicts the prognosis and drug sensitivity, but also underpins the underlying oncogenic, epigenetic, immunological and stromal molecular signatures. Of particular note, the ratio of epithelioid and sarcomatoid components is associated with the immune response, with the sarcomatoid component being enriched for infiltration of T cells and monocytes as well as fibroblasts and endothelial cells, associating the sarcomatoid components with an enriched environment of immune and angiogenesis. In contrast, the epithelioid component is preferentially associated with natural killer cells. This subtle histo-molecular characterization of MPM heterogeneity facilitates the development of personalized therapies, especially immunotherapies and targeted therapies.

Overall, MPM tumors are highly heterogeneous and the conventional histological classification (epithelioid, biphasic and sarcomatoid) is rather limited in predicting the most effective therapeutic strategies. Refinement of MPM characterization in higher dimensions, for example, through integrative molecular profiling, could improve patient stratification towards personalized treatment.

Molecularly driven targeted therapies

In contrast to histological classification, molecular-based biomarkers provide more informative information for personalized treatment. Recent studies have highlighted potential vulnerabilities associated with the major genetic alterations in MPM.

CDKN2A/2B *deletion*

The tumor-suppressor gene, *CDKN2A*, encodes the proteins $p16^{INK4a}$ and $p14^{ARF}$, which play a crucial role in the cell cycle by regulating cyclin-dependent kinase (CDK)4/6 and cyclin D. In particular, $p16^{INK4a}$ acts as a CDK inhibitor that negatively regulates CDK4/6, thus blocks the progression of the cell cycle from G1 to S phase.[23] The crucial role of *CDKN2A* in MPM pathogenesis is demonstrated by the re-expression of $p16^{INK4a}$ in mesothelioma cells, which leads to cell-cycle arrest, cell death and tumor suppression,[24] and by the importance of the *CDKN2A* deletion as a biomarker for the diagnosis of MPM

from benign pleural lesions.[25,26] In addition, among the most common genetic alterations in TSGs, only those in *CDKNA2A/2B* are associated with poor survival of patients with MPM [Figure 3(b, c)], and loss of *CDKNA2A/2B* is an independent survival predictor after adjusting for other clinical and genetic factors [Figure 3(d)]. Therefore, the identification of therapeutically exploitable vulnerabilities co-opted by the HD of *CDKN2A* in MPM is essential.

CDK4/6-targeted therapy. It has been reported that deregulation of CDK4/6 in *CDKN2A*-deficient MPM renders patients potentially susceptible to CDK4/6-targeted therapies.[27–29] Importantly, inhibitors of CDK4/6, such as palbociclib, ribociclib, and abemaciclib, are clinically approved drugs for hormone receptor-positive breast cancer, which facilitates the translational effect of the finding for patients with MPM. Therefore, patient selection based on *CDKN2A/2B* loss of function is critical to clinical trials investigating the efficacy of CDK4/6 inhibitors in the treatment of MPM, as exampled by two ongoing studies [ClinicalTrials.gov identifiers: NCT02187783; NCT03654833].

Notably, numerous mechanisms of resistance to CDK4/6 inhibitors have been identified, which favor the use of combination therapies to improve the efficacy of CDK4/6 inhibitors.[30] For example, inhibition of the PI3K/AKT/mTOR pathway in MPM has shown synergistic inhibitory effects with CDK4/6-targeted therapy.[27]

Oncolytic viral therapy. Oncolytic viral therapy is a novel anticancer strategy based on the observation that some viruses, known as oncolytic viruses, replicate preferentially in cancer but not in normal cells. Due to the thoracic location, which facilitates the intratumoral injection of the viruses, MPM may particularly benefit from oncolytic viral therapy.[31]

Delaunay *et al.* showed that the type I interferon (IFN-I; mainly IFN-α and IFN-β) pathway plays an antiviral role[32] and that HDs of the IFN-I signaling pathway genes are common in MPM, making MPM cells sensitive to oncolytic measles virus (MV) therapy. Importantly, HDs of the IFN-I genes coincide with those of *CDKN2A* in MPM, underscoring the promise of oncolytic viral therapy for a subset of MPM with *CDKN2A* loss. It is noteworthy that not all (8 of 15) MV-sensitive MPM cell lines contain an HD in the *IFNB1* gene (encoding IFN-β), and *CDKN2A* loss was also observed in three of the four MV-resistant MPM cell lines, implying additional mechanisms independent of *IFNB1* and *CDKN2A* loss that are involved in MPM responses to oncolytic MV therapy.

BAP1 inactivation is also common in MPM [Figure 2(a)], which may be critical for tumorigenesis.[33] Remarkably, a significant overlap between HDs of *CDKN2A/B* and genetic alterations in *BAP1, NF2, TP53*, and *LATS2* was observed: 46.9% of MPM patients (15 out of 38) had *CDKN2A* loss and co-occurring *BAP1* mutations [Figure 2(b)]. Interestingly, we showed that *BAP1* expression is significantly correlated with IFN-I gene signature through integrated analysis of transcriptomic and whole-exome data from an MPM cohort in the Cancer Genome Atlas (TCGA).[34] Specifically, genes that are negatively correlated [Spearman's $r < -0.4$ and adjusted p (q-value) < 0.01] with *BAP1* mRNA levels, but not positively correlated ones, are significantly enriched in the IFN-I pathway, suggesting that MPM with BAP1 loss may be resistant, whereas *BAP1* wild-type MPM is sensitive to oncolytic viral therapy. The connection to the IFN-I pathway is consistent with the notion that BAP1 performs pleiotropic functions.[35] Therefore, patient stratifications based on genetic status of *CDKN2A* and *BAP1* in MPM may be critical for the response to oncolytic viral therapy, although further investigation is needed on how the loss of BAP1 function is related to insensitivity to oncolytic viral therapy.

Co-deletions with CDKN2A. In MPM, the *CDKN2A* loss of function is caused by HDs [Figure 2(a)] .*CDKN2A* is chromosomally located at 9p21.3., so genes co-deleted with *CDKN2A* [Figure 2(c)] might also play a role in MPM tumorigenesis.

Methylthioadenosine phosphorylase (*MTAP*), a gene that is about 100-kb telomeric to *CDKN2A*, encodes an enzyme essential for the salvage synthesis of cellular adenine and methionine. The co-deletion of *MTAP* with *CDKN2A* was investigated in MPM.[36] Utilizing a fluorescence *in situ* hybridization assay, Illei *et al.* determined the prevalence of homozygous *MTAP* co-deletion with *CDKN2A* based on a cohort of patients with MPM ($n = 95$). In a total of 70 (74%) cases the HD of *CDKN2A* is present, of which 64 (91%) have a homozygous co-deletion with *MTAP*. In particular, all samples with *MTAP* deletions simultaneously have HDs of *CDKN2A*. Remarkably, the loss of MTAP renders the cells

highly dependent on the *de novo* synthesis of purine derivatives, which represents a rational and targetable vulnerability (e.g. by l-alanosine, an inhibitor of *de novo* AMP synthesis) for a subgroup of MPM with *CDKN2A* deletion.

It has been reported that other genes co-deleted with *Cdkn2a*, for example, *Ptprd*, cooperate with *Cdkn2a* HD to promote tumorigenesis in mouse models.[37] In clinical patient samples co-deleted *PTPRD* accounts for 5.4% of the MPM harboring HDs of *CDKN2A* [Figure 2(d)]. However, addiction pathways driven by co-deleted *PTPRD* have yet to be defined.

Genetic alterations in the Hippo pathway

The Hippo signaling pathway, an extensive network of proteins (at least 35 in mammals) that control normal tissue development and regeneration and play a critical role in tumorigenesis,[38] is often dysregulated in MPM.[10,39] At the heart of the Hippo pathway is a core kinase cassette: mammalian STE20-like protein kinase 1 (MST1; also known as STK4) and MST2 (STK3), large tumor suppressor 1/2 (LATS1/2), and the adaptor proteins Salvador homolog 1 (SAV1), MOB kinase activator 1A/B (MOB1A/B). Hippo signaling transduction converges in the LATS1- and LATS2-dependent phosphorylation of the Yes-associated protein (YAP; encoded by *YAP1*), a transcriptional regulator, and WW domain-containing transcription regulator 1 (WWTR1; also known as TAZ), a transcriptional co-activator. Phosphorylation of YAP and TAZ inhibits their activities by creating binding sites for 14-3-3 proteins, which promotes the sequestration of YAP and TAZ in the cytoplasm and subsequently ubiquitin-mediated proteolysis. YAP and TAZ regulate the activity of a variety of transcription factors including Sma and Mad protein (SMAD) and transcriptional enhanced associate domain (TEAD) transcription factors, which may underpin the tumorigenic potential of YAP and TAZ. Interestingly, about 11% of MPM patients carry genetic alterations in *LATS1/2* [Figure 2(a)].

Genetic alterations in *NF2*, which encodes neurofibromin 2 or Merlin (moesin-ezrin-radixin-like protein), are frequent in MPM [Figure 2(a)], which deregulates several signal pathways including the Hippo pathway. Merlin is plasma membrane localized and binds α-catenin and angiomotin at adherens and tight junctions, respectively, to suppress cell growth. Although it is not yet fully understood how angiomotin and Merlin interact with the Hippo pathway, angiomotin may serve as a scaffold for MST1/2 and LATS1/2 to physically bind and inhibit YAP1. Angiomotin may also bind and activate Merlin, thereby promoting the binding of Merlin to LATS1/2.

Furthermore, YAP activation in MPM can also be achieved by increasing the copy number of *YAP1*.[40] Thus, the aberrant activation of YAP/TAZ due to genetic alterations in *NF2, LATS1/2* and *YAP1* (amplification) represents a promising therapeutic target in MPM.

Targeting YAP1/TAZ. However, restoring the expression of altered TSGs (e.g. *NF2* and *LATS1/2*) in patients with MPM is technically challenging. An alternative approach is to disrupt the interactions of YAP/TAZ with their targeted transcription factors.[41]

Several compounds have been developed in an attempt to disrupt the interactions. The first small molecule that was shown to work as a YAP–TEAD-binding inhibitor was verteporfin (Visudyne), which is clinically used as a photosensitizer in the photodynamic therapy for neovascular macular degeneration. The effect of verteporfin on the inhibition of YAP activity has been validated in MPM cells, which is associated with reduced viability, invasion, and sphere formation.[42,43] Several other YAP–TEAD inhibitors have also been developed, such as the bioengineered cyclic YAP1-like peptides (17-mer),[41] the synthetic peptide (48-mer),[44,45] which may compete with YAP to bind to TEADs.

Recently, it has been reported that an oxadiazole molecule (compound 2) uniquely degrades YAP through LATS1 activation, although the underlying mechanisms are unclear.[46] This compound could be very promising for MPM, as genetic alterations of *LATS1* are rare in MPM as opposed to *LATS2*, suggesting that an intact LATS1 may still be present in most patients with MPM.

Targeting HMG-CoA reductase. Beyond its canonical role in controlling tissue growth and regeneration, YAP/TAZ also interacts with the mevalonate metabolic pathway.[47,48] HMG-CoA reductase is the rate-limiting enzyme of the mevalonate–cholesterol biosynthesis pathway. Statins, inhibitors of HMG-CoA reductase, are clinical drugs for patients with hypercholesterolemia and cardiovascular disease. Interestingly, statins have also been shown to have anticancer effects on human

MPM cells.[49] However, this study did not investigate the association between the observed anticancer effects of statins and the genetic background of the MPM cells used. In another study by Tanaka *et al.*, it was shown that the anticancer effects of statins are specific to MPM with dysregulated Hippo signaling.[50] In particular, statins suppress the growth-stimulating axis of YAP/CD44. Notably, the same study demonstrated that the presence of *BAP1* mutations in MPM appears to associate with resistance to statins, providing a rationale for further stratification of MPM patients based on co-occurring genetic alterations in *BAP1* and *NF2* [Figure 2(b)]. The exclusive effects of statins on MPM with dysregulated Hippo pathway may explain the earlier observation that statins do not affect the incidence of mesotheliomas in asbestos-exposed mice or humans.[51] Statins have also been shown to be highly effective against therapy-resistant solid tumor cells,[52] and in MPM, statins enhance the efficacy of doxorubicin, likely by reducing the ability of MPM cells to develop resistance to doxorubicin treatment.[53]

Targeting SRC and FAK tyrosine kinase. Despite its potential as attractive therapeutic targets, YAP/TAZ also has essential functions in healthy tissues, which limits the feasibility of direct targeting of YAP/TAZ. Therefore, the identification of pathways that are preferentially activated in cancer cells and are required for YAP/TAZ activity could be an alternative to the inhibition of YAP/TAZ, while minimizing the adverse effects.

Lamar *et al.* have recently showed that the SRC proto-oncogene, a nonreceptor tyrosine kinase (SRC), is a major driver of YAP/TAZ activity in human breast cancer and melanoma cells.[54] Specifically, activation of endogenous SRC through integrin–ECM adhesion promotes YAP/TAZ activity by repressing LATS-mediated phosphorylation of YAP and TAZ. In addition, the GTPase-activating protein GIT ArfGAP 1 (GIT1) has been identified as an SRC effector that regulates LATS-mediated phosphorylation of YAP and TAZ. SRC inhibitors such as dasatinib have been clinically approved for patients with leukemia, but dasatinib as monotherapy has failed to achieve an objective response in unselected patients with MPM.[13,55] Nonetheless, dasatinib decreased the p-Src (Tyr419) level, which was correlated with an improved median progression-free survival.[55] Further studies are needed to investigate the association between the efficacy of dasatinib and NF2/LATS1/2 loss of function in patients with MPM.

A previous study showed that the activity of focal adhesion kinase (FAK), a cytoplasmic tyrosine kinase that regulates cell migration and proliferation, is dramatically increased and contributes to the pathogenesis of NF2-null MPM.[56] In a pharmacological screening with a FAK inhibitor, VS-4718, across a diverse panel of cancer cell lines, Merlin *et al.* showed that sensitivity to VS-4718 correlates with NF2 expression, with low NF2 level associated with high sensitivity both *in vitro* and in xenograft models.[56] Based on the strong preclinical evidence, a phase II study investigated the FAK inhibitor defactinib in patients with MPM after being treated with first-line chemotherapy and further stratified based on the *NF2* status. However, defactinib improves neither progression-free survival nor overall survival in patients with low NF2 status.[57] In particular, a subset of primary MPM cells harboring both *NF2* and *LATS2* mutations have been shown to be more sensitive to defactinib, suggesting that NF2 status alone may not be sufficient to predict response to FAK-targeted therapy.[42] These results suggest that NF2 may also have Hippo-independent functions.[58]

Ferroptosis-based therapy. Recent evidence has suggested a link between the Hippo signaling pathway and susceptibility to ferroptosis,[59,60] a newly characterized form of programmed cell death induced by iron-dependent lipid peroxidation.[61]

Wu *et al.* showed that E-cadherin-mediated cell–cell interactions inhibit ferroptosis in epithelial cells by activating the intracellular NF2-Hippo signaling pathway,[60] which provides mechanistic insights into the hypersensitivity of therapy-resistant mesenchymal cancer cells to ferroptosis-inducing compounds.[52] In line with these observations, genetic inactivation of *NF2* rendered cancer cells more susceptible to ferroptosis in an orthotopic mouse model of MPM, which confirms the role NF2-YAP signaling in dictating ferroptotic death. These results have direct clinical implications for MPM, as dysregulated NF2–YAP signals may predict the response to ferroptosis-inducing therapies and sorafenib, a clinically approved multikinase inhibitor, has been shown to effectively induce ferroptosis.[62] Notably, sorafenib has been tested in clinical trials as anti-MPM therapy, resulting in heterogeneous therapeutic responses in unselected

MPM,[63,64] again highlighting the need for patient stratification based on the genetic status of the NF2–Hippo pathway.[60]

A previous study convincingly demonstrated that BAP1 plays a critical role in the metabolic regulation of ferroptosis by suppressing the expression of SLC7A11, a key regulator of ferroptosis, so it is not surprising that BAP1-deficient tumors are more resistant to ferroptosis.[65] This finding suggests that the presence of BAP1 mutations might interfere with the therapeutic effects of drugs (e.g. sorafenib) that induce ferroptosis.[66] As a significant proportion of MPMs have co-occurring *BAP1* and *NF2* mutations [Figure 2(b)], future clinical trials based on molecularly driven biomarkers are warranted.

In addition, BAP1 loss of function is predominantly associated with the epithelioid histotype,[67] whereas NF2 deficiencies are mainly associated with the sarcomatoid histotype, which is more similar to a mesenchymal phenotype.[22] This observation is consistent with a previous study in which tumor cells with therapy-resistant mesenchymal status were reported to be highly dependent on a lipid peroxidase signaling pathway and susceptible to ferroptotic cell death.[52]

BAP1 alterations

BAP1 is frequently altered in MPM, which is a critical oncogenic event in the tumorigenesis of MPM [Figure 2(a)].[33]

BAP1 alterations and PARP-targeted therapy. As a tumor suppressor, the canonical role of BAP1 includes maintenance of genomic stability and repair of DNA double-strand breaks (DSBs).[68] Thus, the loss of BAP1 function is associated with defects in the repair of DSBs.[68]

Poly (adenosine diphosphate-ribose) polymerase (PARP) is a synthetic lethal target in tumors where homologous recombination (HR) repair of DSBs is defective, and susceptibility to PARP inhibitors has been reported in cancer with *BAP1* loss, including MPM.[68,69] However, a recent study[70] showed that sensitivity to PARP inhibitors is independent of *BAP1* mutational status in MPM cells, which is surprising and in contrast with previous observations.[68,69]

We have interrogated high-throughput drug sensitivity data from the Genomics of Drug Sensitivity in Cancer (https://www.cancerrxgene.org/), which assays the effects of drug compounds on cancer cells, including several selective PARP inhibitors and 20 MPM cell lines, and the genetic landscape of the MPM cells in the Cancer Cell Line Encyclopedia project.[71] Our integrative analysis revealed that a fraction of MPM cells, including *BAP1*-altered (H2804, IST-MES1, H2795) and wild-type cells (H2803, MSTO-211H), are particularly sensitive to PARP inhibitors (talazoparib, olaparib, veliparib, and rucaparib) determined by a low IC_{50} Z-score ($\leqslant -1$) compared to other targeted agents. Importantly, some *BAP1*-mutant MPM cells (H2452, H2731, H2722) are highly resistant to PARP inhibitors.[71] Thus, *BAP1* mutations in MPM cells are neither predisposed nor uncoupled for sensitivity to PARP inhibitors.

Several possibilities can be envisioned to explain the apparent discrepancies associated with *BAP1* alterations and sensitivity to PARP inhibition. First, other co-occurring mutations might contribute to the heterogeneous response in MPM [Figure 2(b,e)]. Second, different BAP1 splice isoforms may affect the sensitivity of MPM cells to PARP inhibition,[69] which underscores the need for further stratification to guide PARP-targeted therapy for patients with *BAP1*-mutant MPM. Third, BAP1 has multifaceted functions beyond the involvement in genomic stability and DSB repair,[65] which means that subtype-specific alterations in BAP1 may assume different biological functions. Finally, cell lineage (MPM *versus* non-MPM) might also play a role in the response to PARP inhibition.

In summary, *BAP1* mutational status appears to be irrelevant for sensitivity to PARP-targeted therapy in MPM. Further studies are needed to investigate the association of *BAP1* mutations with HR deficiency and sensitivity to PARP inhibition.

BAP1 in metabolic regulation of ferroptosis. BAP1 has other functions beyond DSB repair, including metabolic control of ferroptosis,[65] a cell death program independent of apoptosis and necroptosis.[61] Specifically, BAP1 regulates ferroptosis by suppressing the expression of SLC7A11, a cystine/glutamate transporter, which leads to a reduction of glutathione and a decreased antioxidant capacity in the cell. Thus, the tumor-suppressing function of BAP1 is at least partially mediated by its ability to promote ferroptosis, and loss of BAP1 is associated with resistance to

ferroptosis. Therefore, a clinically relevant task is to identify drug targets and ways to overcome ferroptosis resistance.

BAP1 in tumor immunity. IFN-I modulates tumor immunity,[72,73] and, as described above, the genes of the IFN-I pathway and *CDKN2A* are often co-deleted in MPM, making this MPM subset highly susceptible to oncolytic viral immunotherapy.[32] However, our recent study showed that BAP1 also plays a role in the regulation of the IFN-I pathway and consequently in the sensitivity to oncolytic viral immunotherapy.[34] Specifically, the loss of BAP1 is negatively associated with a defective IFN-I pathway, so that *BAP1*-mutant MPM cells may be resistant to oncolytic viral immunotherapy. On the other hand, a defective IFN-I pathway may increase sensitivity to immune-checkpoint inhibitors, as sustained IFN-I signaling is a key mechanism of resistance to PD-1/PD-L1 blockade.[72,73] Consistent with this notion, BAP1 loss of function has recently been identified as a predictive biomarker for immunotherapy in peritoneal mesothelioma, a cancer that is etiologically and biologically similar to MPM.[74] Specifically, BAP1 deletion is positively correlated with tumor inflammation characterized by activation of immune-checkpoint receptors, suggesting that peritoneal mesothelioma subsets deficient in *BAP1* may benefit from immune-checkpoint inhibitors. These results emphasize the need for further stratification based on *BAP1* mutation status to improve immunotherapy response rates in patients with mesothelioma.

BAP1 in chromatin modulation

Targeting EZH2. BAP1 and ASXL1 interact to form a polycomb deubiquitinase complex that removes mono-ubiquitin from lysine 119 of histone H2A. Bap1 loss in mice has been shown to be associated with increased expression of trimethylated histone H3 lysine 27 (H3K27me3) and the enhancer of zeste 2 polycomb repressive complex 2 subunit (Ezh2), and the repression of polycomb repressive complex 2 (PRC2) targets.[75] High EZH2 level was also observed in samples from patients with MPM compared with matched normal samples, and evidence from the same study showed that BAP1-altered MPM cells were selectively sensitive to EZH2 inhibitors, both *in vitro* and *in vivo* xenograft models. These data suggested that EZH2 is a promising target for *BAP1*-mutant malignancies. Importantly, Tazemetostat (Tazverik™), a first-in-class EZH2 inhibitor, received accelerated US Food and Drug Administration approval in January 2020 specifically for the treatment of patients with unresectable locally advanced or metastatic epithelioid sarcoma,[76] a rare tumor biologically similar to epithelioid mesothelioma, where BAP1 loss of function is a major form of genetic alterations.[67]

Of note, the association of BAP1 mutation status with EZH2 expression observed in MPM does not exist in uveal melanoma,[77] where *BAP1* mutations also predominate. These results imply tissue-specific targets of the polycomb machinery and highlight that BAP1 loss in different cancers may respond differently to EZH2-targeted therapy.

Targeting histone deacetylase. Recent studies have also suggested a role for BAP1 in modulating sensitivity to histone deacetylase (HDAC)-targeted therapies. Using an unbiased siRNA screen, Sacco *et al.* found that loss of BAP1 function decreases HDAC2 but increases HDAC1 in MPM cells.[78] Mechanistically, BAP1 regulates HDAC2 by increasing its transcript abundance rather than opposing its ubiquitination. In addition, Bap1 was shown to regulate the transition from pluripotency to commitment during *Xenopus* development through H3K27ac-mediated transcriptional activation by modulating Hdac4,[79] confirming the earlier finding in human uveal melanoma.[80] Importantly, Bap1-deficient phenotypes can be rescued by human BAP1, pharmacological inhibition of HDAC or Hdac4 knockdown, and BAP1-deficient uveal melanoma cells show selective susceptibility to HDAC4 depletion. These findings provide insight into BAP1 loss in cancer development and progression, although it is unclear whether they also apply to MPM. Clinical trials with pan-HDAC inhibitors are currently being investigated in MPM [ClinicalTrials.gov identifiers: NCT00365053, NCT00128102, and NCT00535951].

TP53 *mutations. TP53* mutations account for about 20% of all MPM cases [Figure 2(a)]. However, p53 loss of function without a genetic mutation is more common in MPM, suggesting that p53 is subjected to posttranslational regulation by other mechanisms. MDM2, a well-defined nuclear E3 ubiquitin ligase that binds and targets p53 for proteasomal degradation, is detected in 21.3% of clinical MPM samples and its expression is significantly associated with poor survival.[81] To restore p53 function, several small molecules, such as Nutlin-like drugs that interfere with MDM2/p53 interaction, were tested in

MPM.[82,83] In addition, NF2 has been shown to antagonize the inhibitory effect of MDM2 on p53,[84] and *NF2*-mutant MPM cells have been shown to be preferentially sensitive to anti-FAK-targeted therapy.[56] Consequently, co-targeting of FAK could improve MDM2-targeted therapy in MPM, probably through a coordinated mechanism that reactivates p53.[85]

mTOR is dysregulated in MPM,[10] and activation of the PI3K/AKT/mTOR pathway was observed in MPM subsets.[86] Interestingly, inhibiting PI3K/AKT/mTOR has been reported to be associated with MDM2-p53-dependent cell-cycle regulation, as conditional inactivation of *Tsc1* (a repressor of mTOR) and *Trp53* is able to induce mesothelioma in mice,[87] and combined inhibition of AKT/mTOR and p53 synergizes in cancer cells including MPM.[88,89] Thus, targeting MDM2 may be promising for *TP53* wild-type MPM.[90] Finally, we and others have shown that inactivation of *CDKN2A/2B* and *TP53* is associated with an increased dependence on the G2/M checkpoint, which is a targetable vulnerability in MPM.[91,92]

MicroRNAs and epigenetic biomarkers. MicroRNAs (miRNAs) are short noncoding RNAs that post-transcriptionally regulate gene expression. A growing list of miRNAs have been shown to be aberrantly expressed in MPM,[22,93,94] most of which are downregulated, suggesting a therapeutic strategy by restoring the tumor-suppressor function of miRNAs, for example, by reconstituted expression of their mimics.[95] Among others, miR-16 and miR-145 mimics were ectopically expressed in MPM cells, which downregulate the expression of PD-L1 and OCT4, respectively,[96,97] and a miR-137-3p mimic has been shown to significantly inhibit the proliferation and migration of MPM cells.[98] The miR-137-3p-induced phenotype may be due to its suppression of YBX1 (Y-Box binding protein 1), an oncoprotein involved in various cellular functions such as protein translation, mRNA localization and stability, transcriptional control, and cell-cycle modulation.[99] In particular, mimics of several miRNAs (e.g. miR-16, miR-34, miR-145, miR-193a, miR-215) have been shown *in vivo* to have anti-MPM efficacy,[96,100–103] and miR-16-based therapy has been investigated in a phase I clinical trial in patients with MPM.[104]

Epigenetic alterations have been shown to be associated with asbestos-induced carcinogenesis,[105,106] which provides the rationale for the development of epigenetic regimens to target MPM.[107] Among others, DNA methyltransferase and HDAC are often deregulated, which may contribute to the suppressed TSG gene expression in MPM[108,109] and may therefore be potential targets for MPM therapy.[107] However, previous clinical studies inhibiting DNA methyltransferase activity in MPM have produced disappointing results.[110,111] Similarly, despite encouraging preclinical data,[112] efforts to target HDAC in MPM have also been discouraging.[113] These results underline the need for patient stratification in future clinical trials. It might also be appropriate to consider combination strategies, as demonstrated by the use of flavopiridol to enhance HDAC inhibitor-mediated growth arrest and apoptosis in MPM.[114]

It is noteworthy that genetic alterations in SETD2 (Set domain-containing 2), an epigenetic tumor suppressor involved in histone methylation, are detected in about 8% of MPM cases.[10] SETD2-deficient MPM can respond positively to inhibitors of the histone methyltransferase EZH2.[115] In addition, a synthetic lethality between SETD2 deficiency and CDK7 inhibitors has recently been reported in renal cancer,[116] although a similar effect on mesothelioma remains to be determined.

Molecularly driven immunotherapy

Immunotherapies, such as immune-checkpoint inhibitors, T-cell and natural killer cell therapies and oncolytic viral therapies, have achieved tremendous success in human cancers. Recent clinical studies also suggest immunotherapy as a potential alternative to chemotherapy in MPM.[117,118] However, heterogeneous and unfavorable results have often been observed,[119,120] suggesting that biomarker-driven stratification is needed to identify subsets of patients who respond to immunotherapy. In MPM, several key factors should be considered for the design of future clinical trials.

First, as discussed above, oncolytic viral immunotherapy has showed promising results in MPM with *CDKN2A* loss;[32] however, co-occurring *BAP1* mutations may impair the efficacy of oncolytic viral immunotherapy.[34] Since *CDKN2A* inactivation and *BAP1* mutations significantly overlap (around 50%) in MPM, the genetic status of both *CDKN2A* and *BAP1* should be considered in patients treated with oncolytic viral immunotherapy.

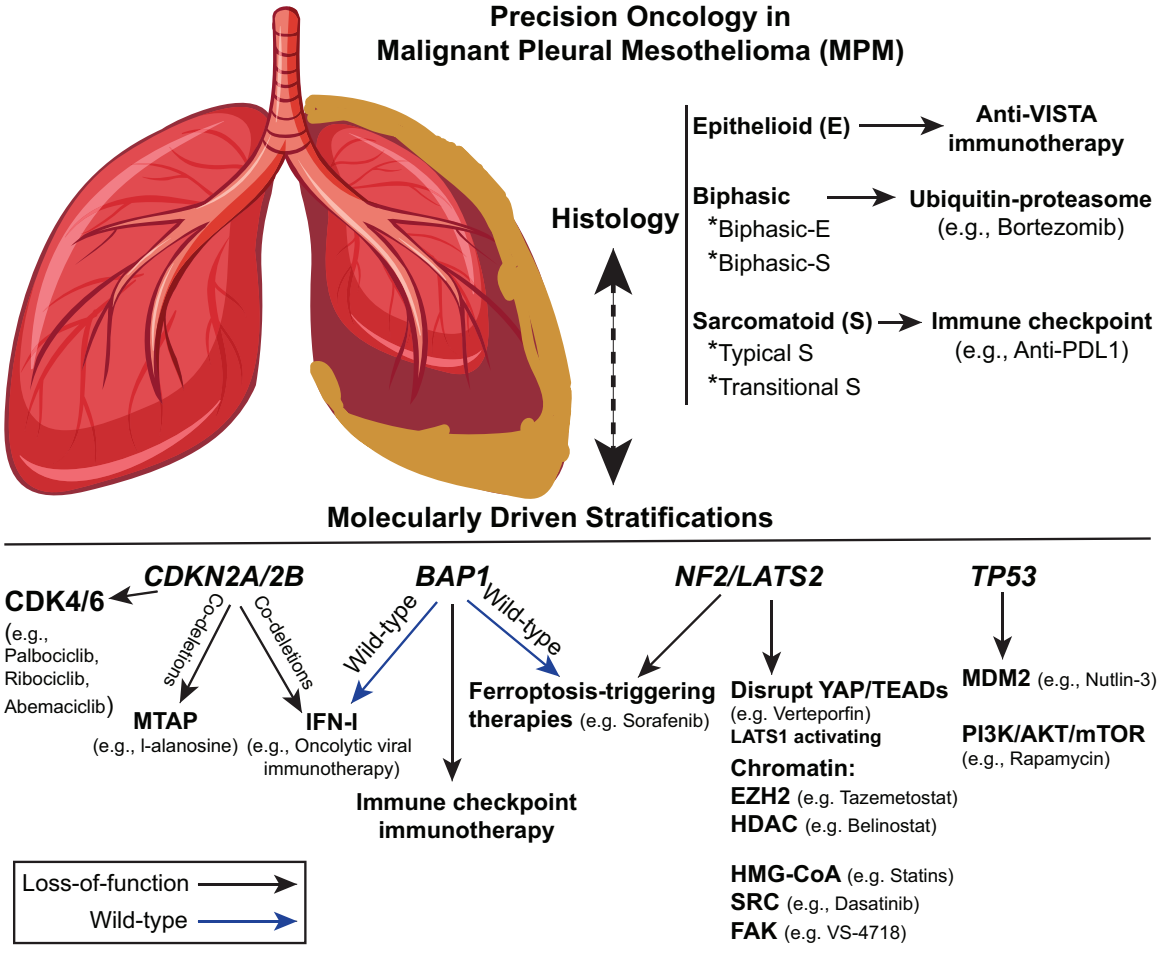

Figure 4. Precision oncology tailored to histology subtypes and major genetic alterations in MPM.

Secondly, it has been shown that the proportion of epithelioid and sarcomatoid components is associated with different immune patterns, with the sarcomatoid component being enriched by infiltration of T cells and monocytes as well as fibroblasts and endothelial cells, whereas the epithelioid component is preferentially associated with natural killer cells.[22] In another study, the sarcomatoid group was reported to show significantly higher PD-L1 expression than the other group,[121] which means that different MPM histotypes should be treated with different immunotherapies. Similarly, the immune-checkpoint gene *VISTA*, but not PD-1 or PD-L1, is particularly associated with the epithelioid MPM, suggesting a rationale for anti-VISTA therapy against this MPM subtype.[21,22] In a more recent study, the authors investigated the immune-angiogenesis interaction and refined the MPM classification:[122] (1) a "hot" profile mainly in non-epithelioid subtypes, characterized by poor prognosis, high lymphocyte infiltration, increased expression of immune checkpoints and proangiogenic genes; (2) a "cold" profile with poor prognosis, low lymphocyte infiltration and high expression of proangiogenic genes; (3) a "VEGFR2^{+}/VISTA^{+}" group with high *VISTA* and proangiogenic *VEGFR2* and favorable prognosis. This molecular-based refinement of the MPM classification may facilitate the selection of patients who could benefits from a combined targeted therapy and immunotherapy.

Future development of treatment options

Over the past decade, remarkable progress has been made in MPM, which has laid the foundation for the future development of new treatment options for the disease.[123] In particular, combination treatment with chemotherapy and immunotherapy, such as PD-1 (or PD-L1)/CTLA-4 dual inhibition[124] and the combination of PD-1 (or PD-L1) blocking with standard

chemotherapy, has shown promise in MPM, encouraged by the first results of combining durvalumab (PD-L1 blocking) with cisplatin/pemetrexed in patients with MPM.[125] It is expected that combination treatment, like the other therapies described above, could bring hopes for a selected subset of patients with MPM, but biomarkers that predict the patients most likely to respond to combined chemo/immunotherapy still need to be identified. Given the complex interplay of tumor cells and the microenvironment, multiple parameters, including a patient's clinical characteristics (e.g. histological subtype), molecular characteristics of tumor and immune cells (e.g. PD-1/PD-L1 expression, T-cell infiltration), genomic mutations, and transcriptomic signatures, as we have recently reported,[126] will need to be prospectively investigated to facilitate this decision.

In addition, new technologies such as nanotechnology are playing an increasingly important role in the development of novel cancer treatments.[127] Nanoparticles in particular have proved to be a promising platform for the development of combinatorial therapies that generally induce synergistic drug effects, delay or prevent the occurrence of drug resistance and minimize dose-associated toxicity.[128] However, some major problems, including the different pharmacokinetics of different drugs and nonspecific drug delivery, have so far limited the application of combinational therapies and, on the contrary, nanoparticles may have the potential to improve the performance of anticancer drugs.[129–131] First, cancer drugs encapsulated in a nanoparticle system allow for improved drug stability, which can increase the therapeutic index and reduce side effects. Second, nanoparticles can be designed to administer several therapeutic agents together. Third, nanotechnology-assisted combination therapies can be engineered not only to control drug release but also to selectively target the diseased tissue and respond to an external or internal stimulus. Several nanoparticle-based combinatorial therapies, including the chemotherapy drug cisplatin, are being investigated in clinical trials in patients with MPM [ClinicalTrials.gov identifiers: NCT00609791; NCT00748163; NCT02194829].

Although nanoparticle-mediated combinatorial therapies are still in development and have some limitations for clinical implementation (e.g. batch-to-batch variability and high production cost), they have the potential to become the next generation of cancer treatments. An interdisciplinary effort between academics, clinicians, the pharmaceutical industry and regulatory authorities is critical to bring this promising approach to clinical application.

Concluding remarks

MPM is a highly fatal cancer. Unlike many other solid tumors, MPM is predominantly driven by the inactivation of TSGs, most often *CDKN2A/2B, BAP1, NF2, LATS1/2* and *TP53*. There is an enormous need for effective treatments. Precision oncology has achieved great success in a variety of cancers, but is still in its infancy in MPM. Recent studies have highlighted the importance of molecular-based classifications tailored to the high histological and biological heterogeneity of MPM. This has not only shed light on MPM pathobiology but also introduced new targeted and immunotherapeutic strategies for personalized treatment of patients with MPM. An emerging set of biomarkers would make an important contribution to provide MPM patients with optimal targeted therapies and immunotherapies in the future (Figure 4).

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The authors declare that there is no conflict of interest.

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