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Therapeutic Landscape of Malignant Pleural Mesothelioma: Collateral Vulnerabilities and Evolutionary Dependencies in the Spotlight

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Malignant pleural mesothelioma (MPM) is the epitome of a recalcitrant cancer driven by pharmacologically intractable tumor suppressor proteins. A significant but largely unmet challenge in the field is the translation of genetic information on alterations in tumor suppressor genes (TSGs) into effective cancer-specific therapies. The notion that abnormal tumor genome subverts physiological cellular processes, which creates collateral vulnerabilities contextually related to specific genetic alterations, offers a promising strategy to target TSG-driven MPM. Moreover, emerging evidence has increasingly appreciated the therapeutic potential of genetic and pharmacological dependencies acquired en route to cancer development and drug resistance. Here, we review the most recent progress on vulnerabilities co-selected by functional loss of major TSGs and dependencies evolving out of cancer development and resistance to cisplatin based chemotherapy, the only first-line regimen approved by the US Food and Drug Administration (FDA). Finally, we highlight CRISPR-based functional genomics that has emerged as a powerful platform for cancer drug discovery in MPM. The repertoire of MPM-specific "Achilles heel" rises on the horizon, which holds the promise to elucidate therapeutic landscape and may promote precision oncology for MPM.

Keywords: malignant pleural mesothelioma, tumor suppressors, collateral and evolutionary vulnerabilities, targeted therapy, CRISPR/Cas9

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Malignant pleural mesothelioma (MPM) is a rare but highly aggressive cancer etiologically associated with asbestos exposure and inherently resistant to treatment options (1). Although asbestos is banned in most industrialized countries, MPM incidence and mortality still increase globally owing to long latency of the disease (up to 50 years) and continued use of asbestos in developing countries (2).

For patients with advanced, unresectable MPM, a chemotherapy regimen that combines cisplatin and pemetrexed has for long been the only FDA (U.S. Food and Drug Administration) – approved first-line treatment, which, disappointingly, elicits only modest efficacy due to prevalence of drug resistance and no validated treatment beyond front-line therapy has emerged. However, a recent phase 3 trial has showed that overall survival of MPM patients can be further improved by cisplatin/pemetrexed plus bevacizumab, an antibody against vascular endothelial growth factor (VEGF) (3).

Comprehensive genomic studies have revealed frequent deletions or loss-of-function mutations of tumor suppressor genes (TSGs) in MPM, most often cyclin-dependent kinase inhibitor 2A (*CDKN2A*), BRCA1 associated protein-1 (*BAP1*) and neurofibromatosis type 2 (*NF2*) (4, 5) (**Figure 1A**), for which direct targeting has proven difficult, contrasted to oncogene-driven malignancies that benefit from a vast majority of molecular targeted anti-cancer drugs. However, aberrant cancer genome rewires biochemical networks, leading to synthetic lethal or collateral vulnerabilities that are contextually linked with specific genetic alterations, providing alternative approaches for targeting TSG-driven MPM (**Figure 2**). Moreover, cancer-specific dependencies that evolve out of tumor deveoplment and drug resistance offers additional dimensions to expand therapeutic arsenal for MPM. Here, we review the current knowledge about collateral vulnerabilities and evolutionary dependencies in MPM, with an emphasis on the clinical implications for better treatment of the disease (**Figure 3** and **Table 1**).

COLLATERAL VULNERABILITIES CAUSED BY INACTIVATION OF TUMOR SUPPRESSORS

CDKN2A

The 9p21 locus harboring *CDKN2A* is frequently inactivated in mesothelioma (6). *Cdkn2a* inactivation is a key driver of MPM in a conditional mouse model (7), and *CDKN2A* loss is associated with shorter survival in patients with MPM (8). *CDKN2A* encodes two important tumor suppressor proteins via alternative open reading frames, $p16^{Ink4a}$ and $p14^{Arf}$ that govern the activity of the retinoblastoma (pRb) and p53 pathways, respectively (9). While the absence of $p16^{Ink4a}$, an inhibitor of cyclin-dependent kinases 4/6 (CDK4/6)-mediated phosphorylation of pRb, abrogates the G1/S cell-cycle arrest and promotes aberrant proliferation, functional loss of $p14^{Arf}$, a central negative regulator of mouse double minute 2 homolog (MDM2), suppresses apoptosis by escape from p53-mediated anti-tumor surveillance (**Figure 1B**).

Recent studies showed that *CDKN2A* deficiency render MPM cells particularly vulnerable to CDK4/6-targeted therapies, and that targeting PI3K further enhances the efficacy by precluding resistance to CDK4/6 inhibition (10). CDK4/6 inhibitors, e.g., palbociclib, ribociclib, and abemaciclib, are FDA-approved drugs that provide readily translatable therapeutics for MPM. Clinical trial for efficacy of Ribociclib in CDK4/6 pathway activated hematologic malignancies and solid tumors including MPM has been completed (NCT02187783). Abemaciclib as monotherapy is being investigated in MPM bearing $p16^{Ink4a}$ deficiency (Clinicaltrials.gov no. NCT03654833).

Strikingly, in around 30% MPM cases *CDKN2A* alterations co-occur with biallelic deletion in type I interferon (IFN-I; mainly IFN-α and IFN-β) locus. The IFN-I pathway plays a key antiviral role, suggesting that *CDKN2A*-deficient MPM might particularly benefit from oncolytic viral therapy (11), a novel anti-cancer strategy that exploits oncolytic viruses, which preferentially replicate in cancer but not in normal cells (12).

BAP1

BAP1, originally identified as an associated protein of the breast cancer susceptibility gene product BRCA1, is a nuclear deubiquitinase with ubiquitin carboxy-terminal hydrolase activity and contributes to the inhibition of E3 ligase function of BRCA1/BRAD during DNA damage response (13) (**Figure 1B**). Germline mutations in *BAP1* causes a predisposition syndrome with increased risk to renal cell carcinoma, MPM and uveal melanoma (14). *BAP1* is also frequently inactivated by somatic mutations and loss of the 3p21.1 locus in MPM (15) (**Figure 1A**). Other mechanisms leading to inactivation of *BAP1* includes chromosomal rearrangements, gene fusion and splice alterations (4).

As a component of the polycomb repressive deubiquitinase (PR-DUB) complex, *BAP1* deletion causes defects in homologous recombination (HR), contributed by failure to deubiquitinate histone H2A on chromatin, which eventually leads to accumulation of DNA mutations and chromosomal aberrations (16). BAP1 has also been shown to regulate cell cycle through interactions with transcription regulators such as host cell factor-1 (HCF-1) and E2F transcription factor 1 (E2F1) (17). As *BAP1* loss causes deficient HR, *BAP1*-mutant tumors were reported to be particularly addicted to alternative DNA repair pathways, e.g., PARP1-mediated ones (16, 18). However, the sensitivity of mesothelioma cells to PARP inhibitors may be independent of the *BAP1* status (19, 20), warranting further studies to investigate the BAP1/PARP intersection. Interestingly, TNF-related apoptosis-inducing ligand (TRAIL) has been shown highly effective for *BAP1*-deficient MPM, likely via modulating the PR-DUB activity (21).

The heterozygous germline *BAP1* mutations were reported to increase aerobic glycolysis, also known as the "Warburg effect," due to impaired mitochondrial respiration (22), suggesting a role for BAP1 in metabolism. Indeed, recent evidence has indicated that loss of *BAP1* promotes cellular adaptability to metabolic stress by impairing ER stress gene regulatory network (e.g., *ATF3* and *CHOP*) and ferroptosis via modulating SLC7AL11 (23, 24). Informed by these findings, signaling pathways that regulate metabolic stress might be promising targetable vulnerabilities in *BAP1*-deficient MPM.

BAP1 has also been implicated in chromatin modulation by interacting with ASXL1 and polycomb repressive complex 1 (PRC1) (25), and further preclinical evidence revealed that *BAP1* loss renders MPM sensitivity to histone deacetylases (HDACs) inhibitors (26). However, a large phase 3 trial of MPM ($n > 600$) with Vorinostat, an FDA-approved HDAC inhibitor, showed disappointing results (27). Importantly, recent studies indicate that *BAP1* loss in MPM prioritizes the enhancer of zeste homolog 2 (EZH2)-targeted therapy (28), suggesting that aberrant expression of EZH2, known to lead to uncontrolled cell proliferation and tumorigenesis (29), might be an inherent feature enabled by the suppression of BAP1.

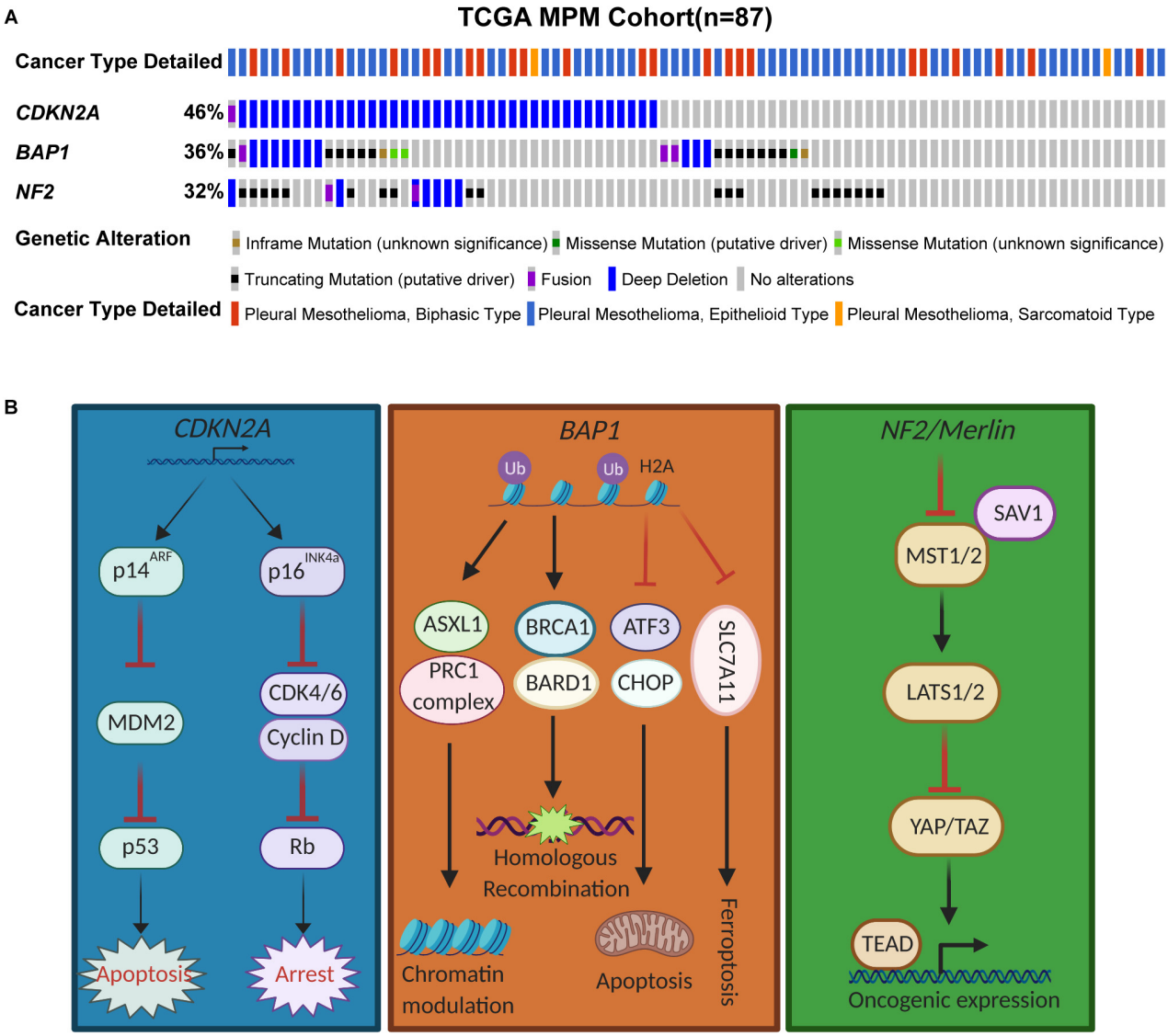

FIGURE 1 | Genomic landscape of *CDKN2A*, *BAP1*, and *NF2* in MPM. **(A)** Somatic mutations of *CDKN2A*, *BAP1*, and *NF2* in The Cancer Genome Atlas (TCGA) samples of MPM patients (*n* = 87). Data were downloaded from cBioPortal. **(B)** Schemtatic illustrating the pathways mediated by the tumor suppressor proteins.

Strikingly, a phase II study showed that tazemetostat, an oral EZH2 inhibitor, demonstrated promising clinical benefit in patients with malignant mesothelioma (30). Notably, it has been reported that sensitivity of uveal melanoma to EZH2 inhibitors is independent of *BAP1* mutational status (31), suggesting a lineage-specific effect of BAP1 on the activity of EZH2i (EZH2 inhibitors).

Surprisingly, several studies have revealed that *BAP1* mutaions in MPM are associated with favorable prognosis in patients (32, 33). One possible explanation is that BAP1 loss is accompanined with impaired DNA repair capacity, which enhances sensitivity to chemotherapy and thus may improve patients' outcome. In addition, *BAP1* deletion is linked with fewer chromosome arm gain and loss, as well as less somatic copy number alterations (SCNAs) (4, 5). Finally, *BAP1*-inactivated tumors might have a stronger activity of cytotoxic T cells due to increased interferon regulator factor 8 (IRF8) (5, 34).

NF2

NF2 encodes Merlin (moesin-ezrin-radixin-like protein) that mediates tumor suppression and contact-dependent inhibition through the Hippo pathway (35) (**Figure 1B**).

The Hippo pathway is evolutionally conserved that regulates organ size, tissue homeostasis and apoptosis, best characterized as a downstream transducer of Merlin/NF2 signaling (36). Merlin exerts tumor-suppressor function by translocating to the nucleus, where it promotes the degradation of two paralogous transcriptional co-activators, Yes-associated protein (YAP) and WWTR1 (WW domain containing transcription regulator 1)/transcriptional coactivator with PDZ-binding motif

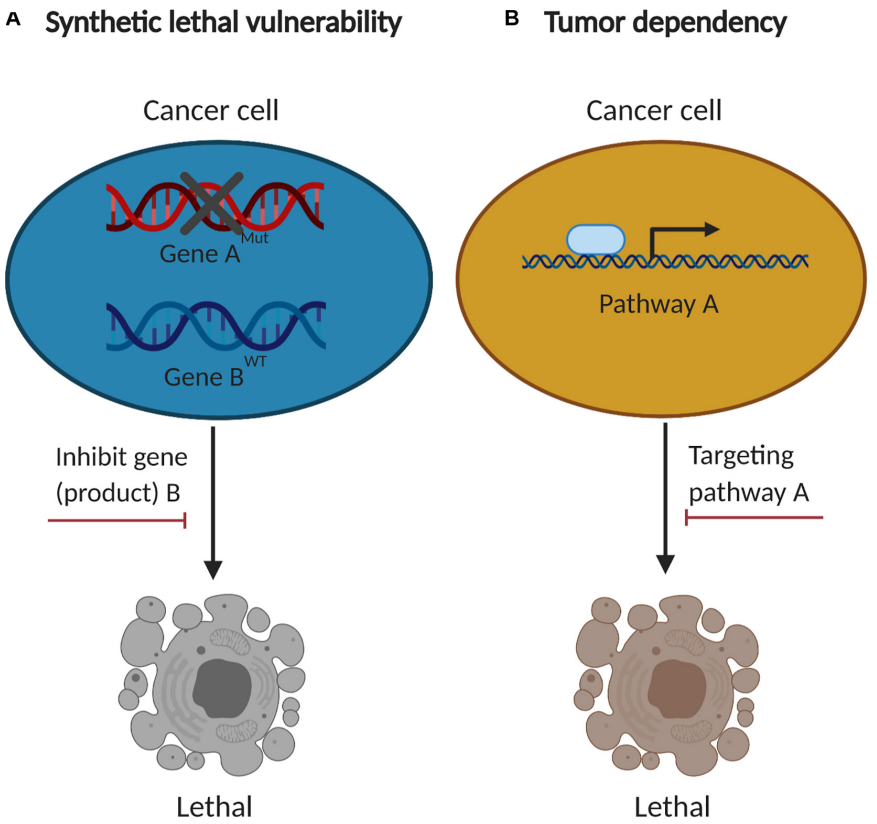

FIGURE 2 | The concept of synthetic lethal vulnerabilities and cancer-specific dependencies. **(A)** Cancer cells with functional loss of a tumor suppressor (gene "A") are contextually sensitive to inhibition of another gene product (gene "B"). **(B)** Cancer-specific dependencies co-opted by tumorigenesis are compelling therapeutic targets.

(TAZ) via the E3 ubiquitin ligase $CRL4^{DCAF1}$ (37). Merlin also activates serine/threonine kinase macrophage stimulating 1/2 (MST1/2), causing large tumor suppressor kinase 1/2 (LATS1/2)-dependent phosphorylation and degradation of YAP/TAZ (38). In addition to *NF2* mutations (**Figure 1A**), gene fusion and chromosomal rearrangements also result in nonfunctional NF2 and therefore inactivates Hippo pathway in MPM (4). In addition, other components of the Hippo pathway, such as *LATS2*, are also frequently inactivated in MPM (4), which inactivates the Hippo pathway as well. *LATS2* alterations (mutations, copy loss) occur in about 11% of MPM patients (5), and *LATS2*-deficient MPM might have similar vulnerabilities as those where the Hippo pathway is inactivated via other mechanisms. In particular, MPM with co-occuring mutations in *LATS2* and *NF2* has been reported to rely on an altered mTOR/PI3K/AKT signaling, and therefore highly sensitive to PF-04691502, a potent and selective oral inhibitor of PI3K and mTOR kinases (39). Finally, gene fusions involving *LIFR*, encoding a metastasis suppressor, was identified as an additional mechanism that inactivates Hippo pathway in MPM (4). The disrupted Hippo pathway constitutively activates oncogenic YAP/TAZ, which in turn transcriptionally activates cancer-promoting genes through interaction with TEA/ATTS domain (TEAD) transcription factors (40). Supporting this notion, verteporfin, an inhibitor against the YAP/TEAD interaction, exerts strong anti-MPM effects, suggesting that the YAP/TEAD axis might be a collateral vulnerability in *NF2*-deficient MPM (41). However, some other studies have shown that response to verteporfin can be independent on YAP activity (42, 43), indicating that the exact correlation between YAP activity and drug response remains to be determined. Further, inhibition of YAP/TAZ was reported to compensatorially activate the MAPK pathway and, as a consequence, co-targeting YAP/TAZ and MEK, a key constituent of the MAPK signaling cascade, synergizes in suppressing the growth of *NF2*-deficient tumors (44), providing a rational combination strategy for *NF2*-mutant MPM.

Finally, NF2/Merlin inactivation has been associated with upregulation of the focal adhesion kinase (FAK) activity in mesothelioma (45). FAK is a cytoplasmic tyrosine kinase that integrates signals from integrins and growth factor receptors to multiple cellular processes, ranging from cell proliferation and migration to renewal of cancer stem cells and resistance to chemotherapy (46). Merlin levels are predictive of sensitivity of MPM cells to the FAK inhibitor VS-4718 (47). Notably, the sensitivity to FAKi has also been shown independent of NF2/Merlin inactivation, and E-cadherin has been reported to be a predictive biomarker for FAK-targeted therapy (43, 48). Intriguingly, although a phase 1 study with FAK inhibitors

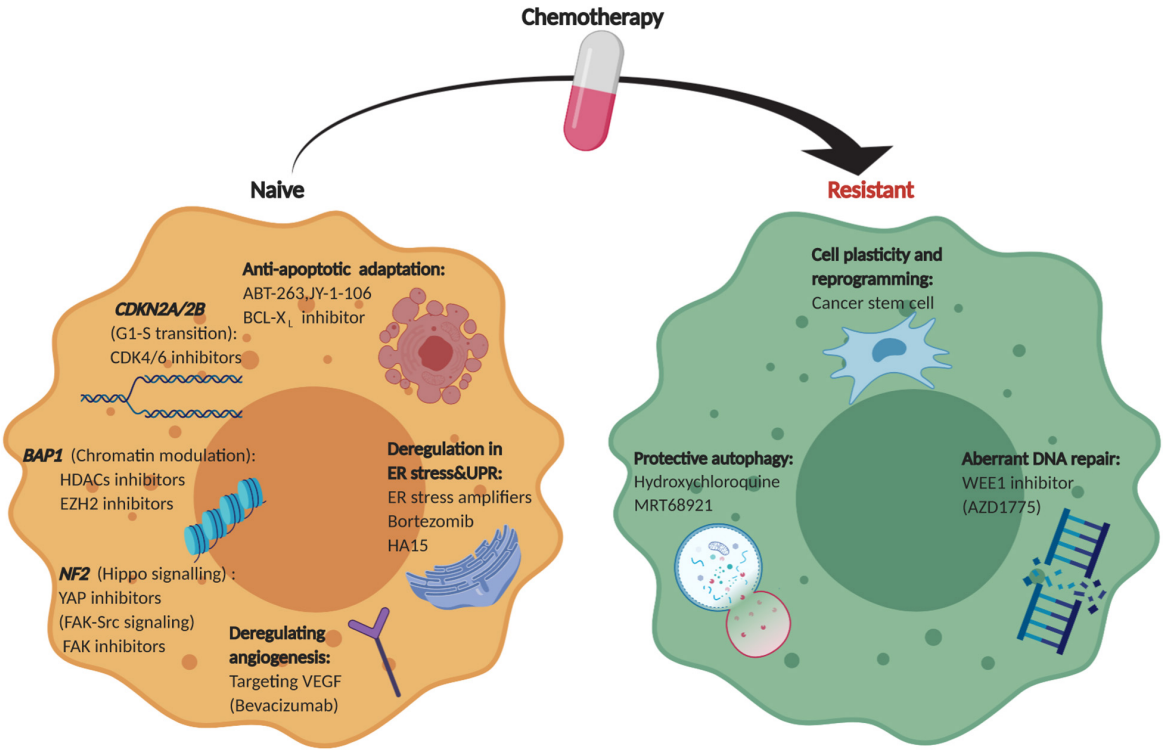

FIGURE 3 | Therapeutic landscape of MPM. An overview of collateral vulnerabilities and evolutionary dependencies identified in therapy-naïve and chemo-resistant MPM.

showed longer median progression-free survival (PFS) in patients with NF2-negative MPM than those with NF2-positive tumors (49), a large phase II COMMAND trial demonstrated that neither PFS nor OS (overall survival) was improved by FAK inhibitors in patients with NF2-low MPM and prior treatment with chemotherapy (50). Together, these results indicate that further investigations are required to establish the link between NF2 mutational status and response to FAK inhibition.

Other Genetic Alterations in MPM

In addition to the TSGs (*CDKN2A*, *BAP1*, and *NF2*) described above, several other genes, e.g., *TP53* (tumor protein p53), *LATS2*, *SETD2* (SET domain containing 2) and oncogenic changes in the *TERT* (telomerase reverse transcriptase) promoter are also altered by at non-negligible frequencies in MPM.

TP53 (encoding p53) is mutated in 6–16% MPM cases (51). Moreover, *CDKN2A* loss that depletes $p14^{Arf}$ and in turn releases MDM2 (mouse double minute 2 homolog), a negative regulator of p53, also inactivates p53, a key player in G1/S cell cycle regulation and apoptosis. We and others have shown that inactivation of *CDKN2A/2B* and *TP53* renders MPM cell particularly sensitive to G2 checkpoint inhibition, e.g., CBP501 (a peptide with G2 checkpoint-abrogating activity) and AZD1775 (selective inhibitor of the G2 checkpoint kinase WEE1) (52, 53).

Genetic alterations (mutation, gene fusion and splice alteration) in *SETD2*, an epigenetic tumor suppressor involved in histone methylation, are detected in more than 8% of MPM cases (4). *SETD2*-deficient MPM may respond favorably to inhibitors of histone methyltransferase EZH2 (54). In addition, synthetic lethality between *SETD2* deficiency and CDK7 inhibitor THZ1 has been recently reported in kidney cancer (55), although a similar efect on mesothelioma remains to be determined.

TERT promoter mutations, the first recurrent oncogenic muation identified in MPM, are frequent in MPM with sarcomatoid subtype and significantly associated with worse clinical outcome (56, 57). As expected, MPM cells carrying *TERT* promoter mutations show increased sensitivity to telomerase inhibition than those with wide-type *TERT*, indicating that targeting telomerase activity might be a promising treatment strategy for this MPM subset (57).

GENETIC AND PHARMACOLOGICAL DEPENDENCIES EVOLVE EN ROUTE TO CANCER DEVELOPMENT

In contrast with normal cells, tumor cells acquire unchecked cell growth en route to cancer development, a result of persistent activation of oncogenic pathways that concomitantly increases the level of cellular stresses (58). To deal with the stressful stimuli, cancer cells require the activity of a plethora of genes and cellular processes that become necessary to cancer cell survival.

TABLE 1 | Clinical trials investigating collateral vulnerabilities and evolutionary dependencies in MPM.

TSG/dependency	Target	Phase	No. patients	Results/trial status	Endpoint (experimental vs. control arms)	Biomarkers (Genetic or molecular)
CDKN2A/2B						
Ribociclib (NCT02187783)	CDK4/6	Phase 2	106	Completed (January, 2018)	ORR	CDK4/6, CCND1/3,CDKN2A
Abemaciclib (NCT03654833)	CDK4/6	Phase 2	120	Recruiting	DCR	p16INK4A
BAP1						
Vorinostat (27) (NCT00128102)	HDAC	Phase 3	661	Negative (November, 2011)	OS (30.7 vs. 27.1)	None
Tazemetostat (129) (NCT01897571)	EZH2	Phase 1	58	Positive (September, 2016)	Safety	None
Tazemetostat (NCT02860286)	EZH2	Phase 2	67	Completed (May, 2019)	Safety/DCR	BAP1
Niraparib (NCT03207347)	PARP1/2	Phase 2	57	Recruiting	ORR	BAP1/ DDR
NF2						
Defactinib (49) (NCT01870609)	FAK	Phase 2	372	Negative (January, 2016)	PFS (4.1 vs.4.0) OS (12.7 vs.13.6)	None
RTKs						
Erlotinib (NCT00039182)	EGFR	Phase 2	63	Negative (June, 2007)	OS	None
LY3023414 (NCT01655225)	PI3K/mTOR	Phase 1	156	Active Not Recruiting	Safety	None
Everolimus (NCT01655225)	mTOR	Phase 2	59	Negative (September, 2011)	4-month PFS	None
Tivantinib (NCT02049060)	Met	Phase1/2	31	Active Not Recruiting	Safety	None
Bemcentinib (NCT03654833)	AXL	Phase 2	120	Recruiting	DCR	None
Angiogenesis						
Thalidomide (76)	VEGF	Phase 3	222	Negative (December, 2009)	Progression (3.6 vs.3.5)	None
Bevacizumab (3) (NCT00651456)	VEGF	Phase 3	448	Positive (September, 2016)	OS (18.8 vs.16.1)	None
Deregulated UPR						
Bortezomib (130) (NCT00513877)	Proteasome	Phase 2	33	Negative (December, 2009)	CR/PR	None
Ganetespib (131) (NCT01590160)	HSP90	Phase1/2	27	Completed (November, 2019)	Safety PFS	None

Abbreviations: CR/PR, complete response/partial response; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

This phenomenon is referred to as non-oncogene addiction or cancer dependency (59), which represents the "Achilles' heel" of a specific type of cancers that can be therapeutically exploited without impairing normal cells. Recent studies have identified several genetic and pharmacological dependencies in MPM, covering various pathways involved in receptor kinase signaling, DNA damage repair and proteotoxic stress.

Receptor Tyrosine Kinases (RTKs)

Self-sufficiency in proliferative signaling, often through aberrant activation of receptor tyrosine kinases (RTKs), is a hallmark of cancer including MPM. Epidermal growth factor receptor (EGFR) is not mutated but overexpressed in MPM, leading to deregulation of EGFR signaling and aberrant activation of downstream pathways such as RAS/RAF/MAPK and PI3K/AKT/mTOR, which in turn promotes cell proliferation, tumor invasiveness and angiogenesis (60). Despite the high expression of EGFR, no clinical benefit was observed in MPM patients treated with erlotinib, an EGFR-specific inhibitor (61). Trametinib, a specific MEK inhibitor, exhibited anti-tumor effects in MPM, and displayed strong synergestic effects when combined with the FAK inhibitor GSK2256098 (62). Emerging evidence has also shown that multipoint targeting of PI3K/AKT/mTOR pathway is a promising strategy for therapeutic intervention of MPM (63). Although mTOR inhibition with specific inhibitors suppressed mesothelioma cell growth in pre-clinical models (64, 65), only limited clinical activity was observed in patients with advanced MPM (66). Additionally, preclinical studies identified MET and AXL as putative therapeutic targets in MPM (67, 68), and clinical trials testing Met-specific TKI (tivantinib; NCT02049060) and AXL-specific TKI (bemcentinib; NCT03654833) are ongoing.

Increasing evidence has indicated that other RTKs, including fibroblast growth factor receptor (FGFR) (69), insulin-like growth factor 1 receptor (IGF1R) (70), platelet-derived growth factor receptor (PDGFR) (71) and vascular endothelial growth factor receptor (VEGFR) are also aberrantly activated in MPM (72). In particular, preclinical studies have revealed that imatinib, a multi-target inhibitor of v-ABL, c-KIT and PDGFRβ, enhanced therapeutic effects of chemotherapeutic drugs (gemcitabine, pemetrexed) via AKT inactivation in malignant mesothelioma, which has encouraged the initiation of clinical trials (73, 74).

Given the crucial role of VEGF signaling in tumorigenesis, several anti-angiogenic drugs, including bevacizumab, thalidomide and nintedanib, have been investigated in MPM either alone or in combination with cisplatin plus pemetrexed over the past decade (75). To date, three randomized phase 3 studies that assess anti-angiogenic inhibitors in patients with MPM have been performed. In the 2013 study, no clinical benefit was observed for the addition of thalidomide to first-line chemotherapy (76), while the large randomized Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) in 2016 showed that the triple combination of bevacizumab, cisplatin and pemetrexed significantly improved the median overall survival (OS) in MPM (3). More recently, another randomized phase 3 trial demonstrated no benefits of nintedanib addition compared to standard chemotherapy alone (77). The varied results highlight the need of further stratification for anti-angiogenic therapeutics in MPM.

Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR)

The endoplasmic reticulum (ER) is the principal organelle monitoring proteostasis. Physiological and pathologic stimuli e.g., nutrient deprivation, aberrant glycosylation, oxidative stress and DNA damage, can disturb the ER environment, eliciting ER stress and unfolded protein response (UPR) (78). The UPR is mediated by three effector arms: double-stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6) (79). At the steady state, the chaperone protein glucose-regulated protein 78 (GRP78, also known as BiP) binds and represses PERK, IRE1α and ATF6. When threatened by increased protein-folding demand (ER stress), BiP is released, which activates PERK, IRE1α, and ATF6, and in turn, their downstream effectors to alleviate proteotoxic stress placed on the ER and restore proteostasis in the ER (80).

Tumorigenesis entails aberrant proliferation, which is often confronted by limited oxygen supply and malfunctional vascularization, leading to increased demand for protein folding, assembly and transport (81). As such, the ER stress response or UPR is a cytoprotective mechanism that promotes survival and adaptation to adversary environment, which might render tumor cells particularly vulnerable to agents that further disturb ER stress. Indeed, therapeutic targeting of ER stress/UPR pathway has emerged as a promising strategy of cancer treatment (82). There is a positive correlation between expression of the ER stress-responsive phosphatase growth arrest and DNA damage 34 (GADD34) and differentiation status of mesothelial cells (83), suggesting that modulating ER stress might be effective for MPM. Consistently, we have recently showed that deregulated ER stress/UPR is a characteristic feature of MPM, and that therapeutic modulation of the signaling impairs the growth of MPM cells and overcomes resistance to standard chemotherapy (84, 85).

Anti-apoptotic Adaptation

Escape from apoptosis, a critical barrier of tumor development, is a prominent hallmark of cancer, including MPM. Apart from the loss of *TP53* tumor suppressor functions and increased expression of survival signals, overexpression of pro-survival B-cell lymphoma 2 (BCL-2) family proteins (BCL-2, BCL-X_L, MCL-1, BCL-W, BCL-B, BFL-1) that dampen apoptosis by sequestering pro-apoptotic activators (BAX, BIM, PUMA) is another pivotal strategy to circumvent apoptosis (86). In this scenario, cancer cells are thought to be "primed" for apoptosis, as they accumulate the pro-apoptotic activators (87). This trait can be exploited for cancer treatment by blocking specific or multiple pro-survival proteins with B-cell lymphoma

2 (Bcl-2) homology 3 (BH3)-mimetic therapy that overwhelms the anti-apoptotic defenses (88). In MPM, pro-survival or apoptosis suppression has been reported to be promoted by defects in core-apoptosis signaling (89), and the BH3 mimetic ABT-737 (targeting BCL-2/BCL-X_L/BCL-W) (90) and a pan-BCL-2 inhibitor (JY-1-106) are active against MPM cells (91, 92). More recently, BCL-X_L has been identified as a key anti-apoptotic mediator in MPM cells, further highlighting the promise of therapeutic strategies that modulate apoptotic threshold in MPM (93).

Tumor Microenvironment (TME)

A key feature of tumor microenvironment is hypoxia, which promotes acquisition of aggressive phenotypes. Emerging evidence has suggested that hypoxia-inducible factors (HIF-1α, -2α) play central roles in regulating hypoxic responses in MPM (94). HIF-1α/2α are transcription factors induced by hypoxic conditions, which in turn alter the expression of various target genes, such as those encoding the stem-like factor OCT4, anti-apoptotic BCL-2, glucose transporter 1 (GLUT1), VEGF, E-Cadherin and Vimentin, leading to the change of diverse biological functions, e.g., angiogenesis, anti-apoptosis, cell motility and metabolism (95, 96). Moreover, hypoxia is associated with increased genome instability by downregulating several DNA repair genes such as *MLH2*, *MSH2*, and *RAD51* (97). Thus, targeting tumor hypoxia might be a promising strategy for treating MPM.

A Roadmap to Cancer Dependencies

The Cancer Dependency Map Project (DepMap)[1] is dedicated to systematic identification of cancer-specific vulnerabilities for targeted therapy and further stratification based on genomic diversity and molecular characteristics for precision oncology (98). DepMap provides a range of information for the genetic landscape, expression profile, genetic essentiality and drug sensitivity across a broad spectrum of human cancers including MPM by incorporating The Cancer Cell Line Encyclopedia (CCLE), Project Achilles and PRISM, which may facilitate the prioritization of therapeutic targets for the development of precision cancer medicines.

EVOLUTIONARY VULNERABILITIES CO-OPTED BY CHEMOTHERAPY RESISTANCE

Despite decades of enormous efforts, cisplatin plus pemetrexed chemotherapy remains one of the few treatment options that achieve survival benefit in MPM. However, clinical evidence indicates that this combination therapy rarely achieves complete/durable clinical response in MPM patients due to drug resistance, intrinsic and/or acquired after initial treatment. Therefore, identification of therapeutic vulnerabilities to target chemoresistant MPM represents a significant yet unmet clinical challenge.

Cancer Cell Plasticity and Cancer Stem Cells

Cancer cells can shift at different cell states, most prominently the transition from epithelial to mesenchymal (EMT) or vice versa (MET). The epithelial state is a differentiated cell state while the mesenchymal more undifferentiated and reminiscent of cancer stem-like cells (CSCs), so coined as they recapitulate normal stem cells characterized by the capacity of self-renewal and differentiation. Cancer cell plasticity is an important process that generates CSCs and drives therapy resistance (99), partly due to relative dormancy of slowing cell-cycle kinetics, efficient DNA repair capacity and expression of multidrug-resistance transporters and resistance to apoptosis of the cells (100).

Putative CSCs identified in MPM express high levels of CD24, ABCG2, ABCB5 and OCT4 and confer drug resistance (101). We have showed that MPM cells populated as spheroids are highly resistant to standard chemotherapy (84). Mesothelioma stem cells (MSCs) might be responsible for tumor repopulation after chemoradiation in murine mesothelioma (102), and cisplatin-resistant, CSC-like subpopulations could be enriched by aldehyde dehydrogenase $(ALDH)^{high}$ and $CD44^{+}$ in mesothelioma cell lines (103). Despite the progress, the molecular mechanisms underlying cancer cell plasticity and the malignancy of CSCs remain incompletely understood.

Aberrant DNA Repair

The DNA damage response (DDR) synchronizes DNA repair and checkpoint signaling activation to arrest cell cycle progression (104). Compelling evidence suggests that DDR protects against genomic instability and affects responses to genotoxic agents (105), although loss of some elements involved in DNA repair pathways is predisposed to malignancy. Conversely, upregulated DDR signaling confers resistance to DNA-damaging chemotherapy and inhibitors targeting the altered pathways have the potential to revert resistance and augment the efficacy of conventional chemotherapy (106). MPM patients with germline mutations in *BAP1* or other DNA repair genes (*CHEK2*, *PALB2*, *BRCA2*, and *MLH1*) show increased sensitivity to cytotoxic chemotherapy due to impaired DDR (107). Moreover, the Fanconi anemia (FA)/BRCA2 pathway involved in the homologous recombination DNA repair has been shown to play a key role in MPM chemoresistance (108), and a potential link of deregulated G2/M checkpoint pathway with tumor progression and sensitivity to chemotherapeutic agent cisplatin has been proposed (109). Notably, p53 signaling is frequently inactivated in MPM (4, 51), a consequence of *TP53* mutaions (6–16% in MPM) and, more often, of inactivating alterations in *CDKN2A*, which depletes $p14^{Arf}$ and promotes proteasome-mediated degradation of p53. Consequently, p53 deficient MPM cells might have greater dependence on G2/M checkpoint to protect the toxicity of chemotherapy, and abrogation of the G2/M checkpoint activity,

[1] https://depmap.org/portal/depmap/

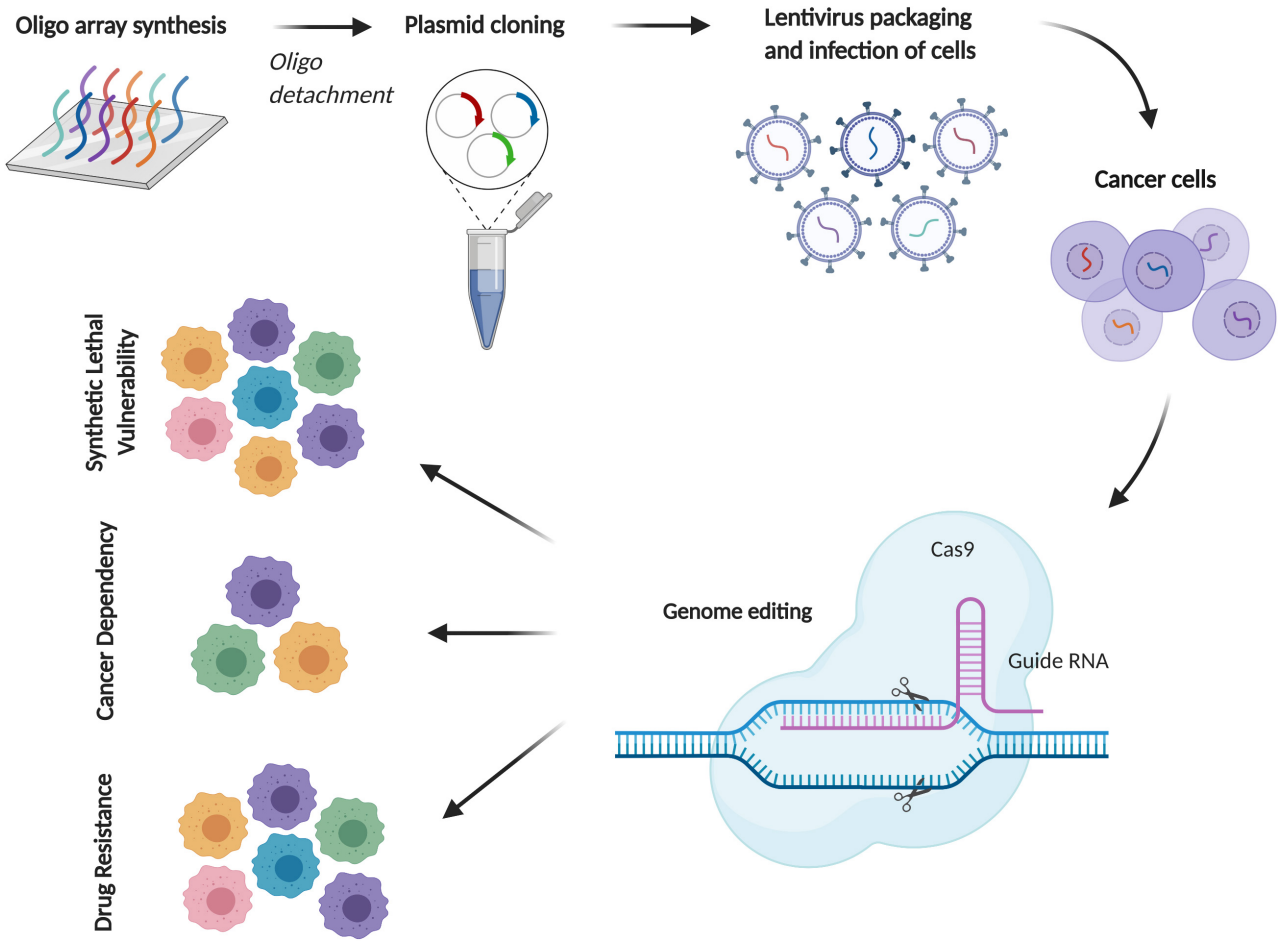

FIGURE 4 | CRISPR/Cas9 screening for cancer drug discovery in MPM. A schematic diagram of CRISPR/Cas9 screening using pooled sgRNA libraries. Depending on the experimental setting, comparison of sgRNA abundance with reference samples can identify essential genes for drug resistance, cell proliferation or context-dependent events (e.g., synthetic lethal vulnerability with specific mutations).

e.g., WEE1 inhibition, sensitizes MPM cells to chemotherapy (53, 110).

Autophagy

Macroautophagy (hereafter autophagy) is an evolutionally conserved catabolic process, whereby long-lived proteins and damaged organelles are sequestered in a double-membraned vesicle (autophagosome) and delivered to the lysosomes for degradation and recycled to fuel cellular growth (111). Autophagy is regulated by a variety of autophagy-associated genes (ATGs), with its contribution to cancer being controversial, as autophagy can be either pro-survival (oncogenic) or tumor suppressive at different stages of cancer progression (112). It has been reported that MPM cells display a generally high basal level of autophagy, which is critical for tumor growth (113). Albeit autophagic cell death (also known as type II programmed cell death) is potentially exploitable as an anticancer therapy, the vast majority of studies have demonstrated that autophagy is a protective mechanism linked with increased resistance to chemo and targeted therapy (114, 115). Supporting this notion, autophagy inhibition was shown to effectively improve chemosensitivity in mesothelioma (116).

SYSTEMATIC APPROACHES FOR CANCER DRUG DISCOVERY IN MPM

RNA Interference (RNAi) Screening

RNAi confers transient or stable gene silencing by small interfering RNAs (siRNA) or short hairpin RNAs (shRNA). Genome-wide screens with pooled shRNA libraries are widely pursued to identify cancer drivers and context-dependent events such as synthetic lethal interactions and collateral vulnerabilities (117). Experimentally, cancer cells infected with shRNA vectors that are specifically identified by molecular barcodes are monitored for growth and subsequently subjected to genomic DNA isolation, polymerase chain reaction (PCR) amplification and quantification of the molecular barcodes. Comparison of barcode abundance between experimental and reference samples, genes required for cancer cell proliferation can be identified.

Several groups have performed shRNA screes in MPM (118, 119), which however, surveyed relatively few cell lines and none represented the diversity of MPM. Although RNAi is ideal to evaluate the temporary gene disruption (e.g., to mimic the effect of cancer drugs), the utility of RNAi is limited by incomplete silencing, high off-target effects and stimulated immune response.

CRISPR/Cas9 Mediated Genome Editing

CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR- associated 9) is a gene-editing technology allowing for rapid and accurate assessment of gene functions with fewer off-target effects compared to RNAi, which, due to its scalability, has emerged as an important tool for large-scale screens. Functional genomics using CRISPR have to date focused on identifying genes required by cancer cells for growth or response to a therapy, which provides a novel genetic tool to ascertain gene functions by customizing the single guide RNA (sgRNA) sequence. After transduced by pooled sgRNA library, the recipient cells become genetically heterogeneous, each one with a knockout of a different gene. Following culture and selection, e.g., drug treatment, cells expressing sgRNAs that target the genes essential for proliferation or drug resistance will die, thereby depleting them from residual tumor cells after culture or treatment (**Figure 4**).

CRISPR screens of genome and customized sgRNA libraries in numerous disease models have identified novel oncogenic drivers and cancer dependencies (120, 121), synthetic lethal interactions with mutant *RAS* and *BRAF* (122, 123) and mechanisms of resistance to anti-cancer drugs (124). Amenability to *in vivo* systems greatly enhances CRISPR applicability in clinically relevant settings (125). CRISPR-based functional genomics in MPM is still at its infancy, we recently screened MPM kinome and delineated that deregulated G2-M checkpoint activity dictates MPM response to chemotherapy (53).

Further Considerations in Systematic Approaches

MPM displays high heterogeneity, characterized by inter- and intratumor variability at cellular and molecular levels (4, 5, 126, 127). Heterogeneity represents a key mechanism underlying the poor response of MPM patients to current therapeutic interventions and is a challenge in systematic studies aimed at identifying effective treatment and curtailing drug resistance. Notably, cancer cell lines utilized predominantly in current RNAi- and CRISPR-based functional genomic studies poorly recapitulate the condition under which heterogeneous tumors arise and evolve. More instrumental *in vitro* models that more closely capture the heterogeneity of patient samples include cancer stem cells and patient-derived organoids (128). Moreover, *in vivo* models that recapitulate the cellular and genetic complexity of human cancer during tumor evolution and progression amid drug treatment, such as genetically engineered mouse models (GEMMs), syngeneic mouse models, and patient-derived xenografts (PDX), should be considered in systematic approaches (125). Despite in its infancy, future studies taken into account of tumor heterogeneity is likely the only way toward the development of precision medicine for MPM patients.

CONCLUDING REMARKS

Unlike many other solid tumors, MPM is characterized by overwhelming prevalence of loss of function alterations in tumor suppressor genes, for which direct pharmacological targeting proves difficult. However, collateral genotoxic, proteotoxic, and metabolic stresses caused by abnormal tumor genome or anti-cancer drugs can generate context-dependent vulnerabilities and dependencies, which has profound implications for alternate treatment of TSG-driven MPM. Recent studies have identified previously unappreciated vulnerabilities contextually linked with aberrant TSGs and dependencies acquired during cancer development and drug resistance, which provides unprecedented insights into MPM pathobiology and may bring about unprecedented hopes for the development of biomarker-guided precision medicine for the disease (**Figure 3**). Integrative molecular characterization enabled by large-scale RNA and proteomic profiling studies, partnered by functional genomics, holds importance to completely unfold the therapeutic landscape for MPM.

AUTHOR CONTRIBUTIONS

DX conducted literature search, drafted and revised the manuscript, and prepared the figures and table. HY and RS reviewed the manuscript. R-WP designed the study and revised and proofread the manuscript. All authors contributed to the article and approved the submitted version.

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