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Review Article

Drug development against the hippo pathway in mesothelioma

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Abstract: Advances in the treatments for malignant pleural mesothelioma (MPM) have been disappointing until recently. Conventional cytotoxic drugs fail in MPM in part because they do not address the cancer stem cell population or stem cell pathways that drive tumor resistance and resurgence following treatment. The Hippo stem cell pathway regulates cell contact inhibition with tumor suppressor genes such as *NF2 (Neurofibromatosis 2)* upstream controlling *YAP (Yes-associated protein 1)* oncogenes. NF2 is mutated in 40–50% of all MPM and downstream YAP is constitutively active in greater than 70% of MPM, making the downstream YAP/TEAD (transcriptional enhancer associate domain) complex the ultimate target. Novel small molecule YAP inhibitors are showing promising results in preclinical studies and may prove to be effective chemotherapy drugs in MPM.

Keywords: Cancer stem cell; small molecule inhibitors; Neurofibromatosis type 2 (NF2); Yes-associated protein (YAP)

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Introduction

Malignant pleural mesothelioma (MPM) is a deadly disease with a poor prognosis that remains a treatment challenge. The diffuse nature of malignant cells throughout the entire pleural cavity preclude a complete surgical resection and therefore developing successful treatments to eradicate all microscopic sites of disease is the only way by which we can hope to achieve long-term survival. However, MPM is notoriously resistant to conventional cytotoxic chemotherapy regimens. Surveillance, epidemiology, and end results (SEER) medicare data show that medicare patients treated with only first-line chemotherapy of carboplatin or cisplatin plus pemetrexed have a median survival of only 7 months (1).

Drug development challenges

In the last 20 years there has been little progress to develop effective new therapies or dramatically improve survival. Countless failed clinical trials for novel chemotherapy agents against mesothelioma have floundered with bleak overall survival times and few patients responding to therapy. A review of British phase I MPM clinical trials between 2003 and 2015 had an 8-month median survival time with only 6% of patients having RECIST partial responses to therapy and 40% having RECIST stable disease for more than 3 months (2). The Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial represented the first true clinical benefit in many years when it demonstrated a survival benefit of adding bevacizumab to cisplatin and pemetrexed with median survival times of 18.8 months among patients treated with the triple drug regimen versus 16.1 in patients treated with cisplatin and pemetrexed alone (3). Most recently, the explosion of immunotherapy has dramatically reshaped the oncology landscape for all cancers including MPM. Preliminary abstract data in MPM has been promising for some patients

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and immunotherapy has become an area of intense interest.

Importance of cancer stem cell pathways

Cancer stem cells are defined by their properties of self-renewal, pluripotency, a high proliferative capacity and the ability to resist standard chemotherapy and radiation. Cancer stem cell subpopulations having been identified in MPM using multiple cancer stem cell markers including aldehyde dehydrogenase (ALDH) and CD44 and by an OCT4/SOX2 reporter approach. These cancer stem cell subpopulations of cells have been shown to be resistant to cisplatin in multiple MPM cell lines and these cancer stem cells have been shown to be more tumor-initiating in xenograft mouse models (4,5). The presence of cancer stem cells and the stem cell like behavior of MPM account for some of the difficulty in treating MPM and blocking these stem cell pathways is a critical component of future successful MPM treatments.

Preclinical work is underway in several of these pathways including the Sonic Hedgehog (SHH) pathway where is has been shown rate models that vismodegib, a smoothened inhibitor approved in basal cell cancer, impairs MPM growth. In a rat xenograft model, vismodegib has been shown to downregulate SHH target genes of Gli1 and Ptch1 as well as reducing tumor volume and tumor growth (6). Combining stem cell pathway inhibitors with standard chemotherapy can improve the efficacy of chemotherapy, for example in the Wnt stem cell pathway combining cisplatin with Wnt pathway inhibitors *in vitro* induces synergistic cell cycle arrest and colony formation (7).

Focal adhesion kinase (Fak) is critical for cancer stem cell survival and maintenance and the molecule Fak inhibitor defactinib or VS-6063 showed promising results in preclinical studies. Fak is overexpressed in epithelial and mesenchymal tumors and regulates cell adhesion, proliferation, migration and survival. There was much anticipation of Fak as a drug target in MPM because cells with Merlin deficiency, commonly lost in mesothelioma, are very sensitive to Fak inhibition (8). Also encouraging was that cancer stem cell enriched MPM cell subpopulations have been shown to be more sensitive to defactinib *in vitro* (4). Fak signaling is associated with resistance to cytotoxic chemotherapy and Fak inhibition also enhances cancer cell sensitivity to taxanes *in vitro* (9). However a phase II clinical trial of defactinib in mesothelioma was ended in late 2015 after interim analysis failed to show any benefit. There may be a future for clinical testing of Fak inhibitors with the addition of predictive biomarkers, such as Merlin deficiency, to better identify MPM patients who will respond to Fak inhibition (10). Targeting cancer stem cell pathways remains an important area of active research.

The hippo pathway and mesothelioma

The Hippo pathway is a highly conserved regulator of organ size and of stem cell proliferation and maintenance (11). Only a small handful of genes are frequently mutated in MPM and many of these gene are in Hippo pathway suggesting that Hippo plays a critically important role in the development and growth of MPM (12). One of the most frequently mutated genes in MPM is *Neurofibromatosis type 2 (NF2)* tumor suppressor, located at chromosome 22q12, and is detected in 40% to 50% of MPM tumors (12,13). *Large tumor suppressor homolog 2 (LAST2)* gene, which is located at chromosome 13q12, is another frequently inactivated gene that is detected in 13% of MPM tumors (12,14). Inactivation of *NF2* and *LATS2* by deletion and/or mutation often contributes to dysregulation of Hippo pathway (15). In addition to *LATS2*, its closest gene family member *LATS1* another Hippo pathway gene, has also recently been identified to be dysregulated in MPM, though less commonly than *LATS2*. *LATS1* is located on chromosome 6 and changes in copy number variation and fusions to *Presenilin 1 (PSEN1)* on chromosome 14 have been observed in MPM (12,16). Mammalian sterile-20 like kinase 1 (MST1) is an important upstream kinase in the Hippo pathway that has also been found to be dysregulated in MPM (16). The largest and most comprehensive genomic analysis to date of transcriptomes, whole exomes and targeted exomes from 216 MPM samples found Hippo pathway signaling to be the number one most significantly mutated pathway in mesothelioma with a Q-value of 1.70E-17, driven by mutations, copy number variations and fusions in *NF2*, *LATS1*, *LATS2* and *MST1 (Figure 1)*.

The Hippo pathway controls organ size primarily by regulating cell contact inhibition (17). In normal cells, Merlin, a protein encoded by NF2, and LATS2 contribute to the phosphorylation of the transcription factor Yes-associated protein (YAP) at S127 (18), resulting in YAP ubiquitination and activation of Hippo pathway to control cell proliferation. In MPM tumor cells, inactivation of *NF2* and *LATS2* prevent the phosphorylation of YAP at S127, which results in YAP relocation from the cytosol to nucleus where it interacts with TEA domain transcription factors

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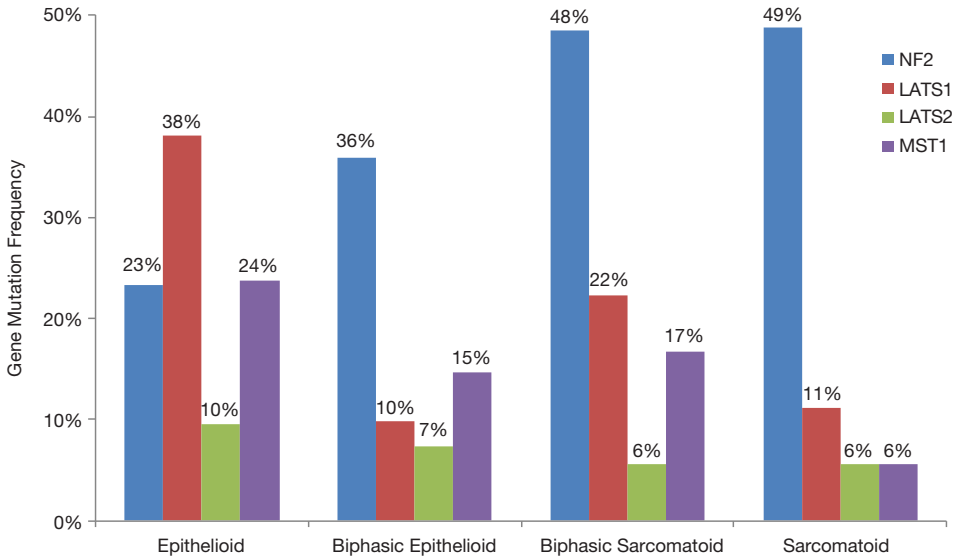

Figure 1 Hippo pathway gene mutation frequency in mesothelioma. Mutations in Hippo pathway genes are shown here by histologic subtype of mesothelioma. More aggressive and poor prognosis sarcomatoid tumors have a higher frequency of NF2 mutations than epithelioid tumors. All subtypes display a high frequency of mutations in genes at some point in the Hippo pathway. Often, though not always, these mutations are mutually exclusive and the combined presence of *NF2*, *LATS1*, *LATS2*, and *MST1* mutations accounts for a driving Hippo mutations in a large portion of MPM tumors. Gene mutation here includes mutations, copy number variations and fusions. *NF2*, *Neurofibromatosis 2; MST1*, *mammalian sterile-20 like kinase 1*.

(TEAD). In addition, constitutively activation of YAP has been identified in over 70% of primary MPM tumors (12,15,19), and YAP activation leads to Hippo signaling attenuation and transcription of downstream target genes, such as *connective tissue growth factor (CTGF)* and *Cyr61* (17). Low Merlin expression (*NF2*), results in YAP1 activation, and has been shown to be associated with worse clinical outcomes with shorter times to recurrence and shorter overall survival times in patients with MPM (20). Blocking YAP activation therefore may be an important novel drug target.

Upstream signals that regulate YAP activation

There are multiple upstream signals and pathways which regulate the Hippo pathway activity that might be exploited as novel therapeutic targets to inhibit YAP in MPM (*Figure 2*). These include specific G-protein coupled receptors (GPCR), Rho kinase (ROCK), the epidermal growth factor receptor (EGFR) pathway, direct interruption of YAP-TEAD mediated transcriptional activity, cyclin-dependant kinase 1 (CKD1) and cyclin-dependant kinase 9 (CKD9).

$G\alpha_{12/13}$, $G\alpha_{q11}$, $G\alpha_s$ and GPCR signaling

GPCRs function as transducers, by using heterotrimeric G proteins, to activate internal signal transduction pathways in response to specific extracellular signals. There are thousands of tissue specific GPCR heterodimers, that couple to fifteen different Gα proteins. Recent studies have highlighted the capability of GPCR signaling to regulate the inhibition or activation of the Hippo pathway depending on the grouped Gα proteins. For instance, activating $G\alpha_{12/13}$ or $G\alpha_{q11}$ coupled receptors by serum-borne lysophosphatidic acid (LPA), sphingosine 1-phosphophate (S1P), thrombin and protease-activated receptor (PAR) agonist peptides resulted in inhibition of LATS1/2 kinases and activation of YAP (21-23). Conversely, activating $G\alpha_s$ coupled receptors by adrenaline, glucagon and dihydrexidine turns on the cAMP-dependent protein kinase A (PKA) signaling pathway and promotes LAST1/2 activity, resulted in YAP suppression (24,25). Therapeutic approaches targeting GPCR to attenuate YAP/Hippo pathway in cancers have been evaluated in clinic trials, including S1P-blocking antibody Sphingomab and Phosphatase-resistant LPA analog (26,27). In pre-clinical studies, G protein-coupled

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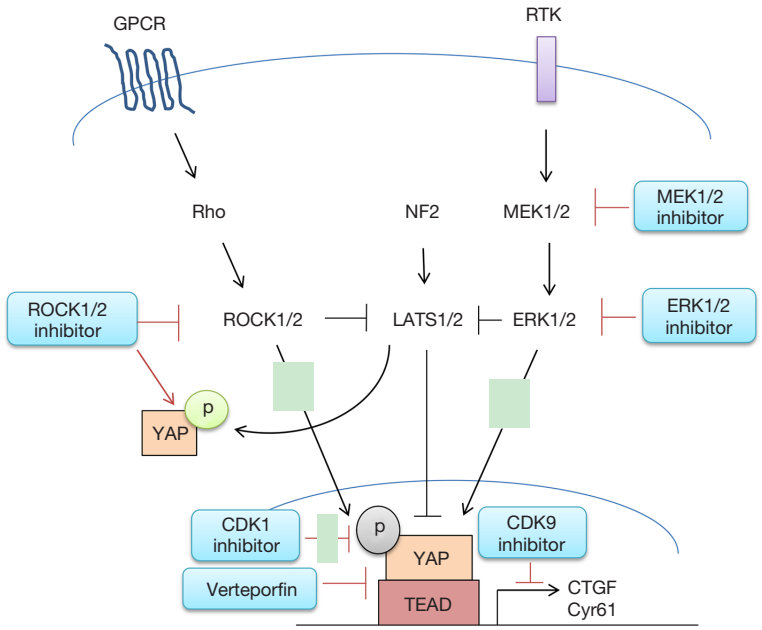

Figure 2 Potential therapeutic targets that regulate YAP/Hippo activity in mesothelioma. (I) Activation of EGFR, a receptor tyrosine kinase (RTK), leads to phosphorylation and activation of MEK1/2 and ERK1/2 signaling in cancer cells. Inhibitors of MEK1/2 and ERK1/2 have been shown to reduce YAP-TEAD mediated transcriptional activity in cancer cells; (II) activation of certain GPCR, specifically $G\alpha_{12/13}$, $G\alpha_{q11}$, $G\alpha_{s}$, turns on Rho/ROCK1/2 signaling in cancer cells. ROCK1/2 inhibition has been shown to promote YAP phosphorylation at S127, reduce YAP-TEAD mediated transcriptional activity, and suppress cell proliferation of mesothelioma; (III) CDK1 can directly phosphorylate YAP and promote YAP nuclear accumulation, suggesting that CDK1 is a potential target in cancer treatment; (IV) interrupting the YAP/TEAD interaction by Verteporfin has been shown to reduce YAP-TEAD mediated transcriptional activity and inhibit cell proliferation of mesothelioma; (V) CDK9 drives transcription-elongation process, and has been shown to suppress YAP-TEAD mediated transcriptional activity in cancer cells, suggesting CDK9 can be a potential therapeutic target for mesothelioma. GPCR, G-protein coupled receptors; YAP, Yes-associated protein 1; EGFR, epidermal growth factor receptor; MEK1/2, MAPK/ERK Kinase; ERK1/2, extracellular signal-regulated kinase; TEAD, transcriptional enhancer associate domain; ROCK1, Rho-associated kinase 1; CDK1, cyclin dependent kinase 1.

β-adrenergic receptor agonist dobutamine has been proposed as anti-cancer treatments (28). In MPM cells, LPA has been shown to stimulate YAP activation and promote cell proliferation (29), and PAR1 expression has been shown to contribute to MPM tumor growth *in vivo* (30). These studies suggest that targeting GPCR, specifically by activating $G\alpha_{s}$ or inhibiting $G\alpha_{12/13}$ or $G\alpha_{q11}$ coupled receptors to suppress YAP could be an effective therapeutic approach in human mesothelioma.

ROCK

The YAP/Hippo pathway is involved in contact inhibition and mechanotransduction in MPM cells. Cellular components of adherens and tight junctions have been reported to inhibit YAP nuclear accumulation (18,31). It has also been demonstrated that F-actin promotes YAP nuclear translocation and inhibits the Hippo pathway, and that destabilization of F-actin results in the nuclear exportation of YAP (32,33). The clinical use of anti-cytoskeletal therapies has been limited due to toxicity (34). Current therapeutic approaches to target mechanotransduction signals in cancer work through inhibiting Rho-associated kinase (ROCK) signaling (34,35). ROCK inhibition was recently reported to suppress YAP activity in MPM cells harboring LAST2 mutation, suggesting that ROCK could regulate the Hippo pathway through a LATS2-independent mechanism (36). These findings also suggest that targeting ROCK could be an effective therapeutic strategy in MPM.

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EGFR

A direct link between EGFR signaling and YAP has been reported. Studies have shown that YAP regulates EGF-mediated cell migration and promotes transcription of EGF-like growth factor AREG (37-39). In addition, inhibition of MAPK/ERK Kinase (MEK1/2) or extracellular signal-regulated kinases (ERK1/2) accelerates YAP degradation, reduces transcriptional activities of downstream genes, and decreases the abilities of migration and invasion in non-small cell lung cancer (NSCLC) cells (40). These studies suggest that targeting EGFR signaling could effectively inhibit YAP activation in cancer cells; however, YAP activation can also regulate drug resistance to EGFR inhibitor erlotinib in NSCLC (41), implying the complexity of YAP regulatory mechanisms in human cancer.

Direct interruption of YAP-TEAD mediated transcriptional activity VP

One way to disrupt YAP transcriptional mechanisms is to block the interaction of YAP to TEAD transcription factors. Two small molecule inhibitors that block the YAP-TEAD interaction were identified from John Hopkins Drug Library by drug screening (42). Both Verteporfin (VP, trade name Visudyne by Novartis) and protoporphyrin IX (PPIX) inhibit the YAP-TEAD complex formation at 10 μM in Co-immunoprecipitation assays (43). VP is a FDA-approved photosensitizer in the photodynamic therapy of neovascular macular degeneration; however, when used as an inhibitor of the YAP-TEAD interaction, light activation is not required (43,44). VP alters YAP conformation when binding to it, and abolished its interaction to TEAD (45). In addition, VP was shown to inhibit the oncogenic activity of YAP *in vivo* and reduced cell growth and viability in various human malignancies (42,46-48). Moreover, VP treatment has been shown to inhibit cell proliferation, viability, and invasion of MPM cells (36,49).

Cyclin-dependent kinase 1

Posttranslational modification of YAP during mitosis and the mechanism that controls YAP phosphorylation at different locations have been an area of interest (50-52). In eukaryotic cells, the cell cycle is controlled by cyclin dependent kinases (CDKs), and CDK1 was shown to phosphorylate YAP at multiple sites during the G2/M phase of the cell cycle (50-52). YAP phosphorylation at T119 and S289 by CDK1 during G2/M phase was shown to enhance cell migration and invasion of immortal cell lines (52); however, YAP phosphorylation at S128 by CDK1 during anti-tubulin treatment was shown to induce cancer cell death (53). The physiological outcome of CDK1 induced YAP phosphorylation highlighted the complexity mechanisms of CDK1 induced YAP phosphorylation in cancer cells.

Cyclin-dependent kinase 9 (CDK9)

The interaction of YAP and TEAD recruits a transcriptional mediator complex and promotes elongation of downstream mRNA molecules (54). YAP has been shown to promote acetylation of histones located in enhancers and depletion of YAP reduces recruitment of the mediator complex and promoter-proximal polymerase II levels in cells (54). In addition, phosphorylation of CDK9, a key component of transcription mediators and the elongation complex, promotes transcriptional activation driven by YAP (54). CDK9 inhibitors including flavopiridol, dinaciclib, seliciclib, SNS-032 and RGB-286638 have been evaluated in clinical studies (55,56). It has recently been reported in MPM studies *in vitro*, that CDK9 inhibition reduces cell proliferation and viability (36).

Conclusions

The Hippo pathway has proven to be of critical importance in MPM. Mutations along this pathway, specifically in *NF2* and *LATS* lead to YAP activation in the majority of MPM tumors. Blocking YAP activity, either via upstream inhibition of one of the several pathways that regulate YAP and Hippo or via direct YAP/TEAD inhibition is an area of active interest. Several novel small molecule YAP inhibitors are in preclinical development with promising results and may enter clinical trials in the near future.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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