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Malignant pleural effusion: tumor-host interactions unleashed

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Abstract

Malignant pleural effusion (MPE) poses a significant clinical problem. Current non-etiologic management is suboptimal in terms of efficacy and safety. In light of recent research progress, we propose herein a new view of MPE development, which may rapidly translate into meaningful changes in therapeutics. In addition to tumor-induced impairment of pleural fluid drainage, pertinent findings point towards another pathway to MPE formation: a vicious loop of interactions between pleural-based tumor cells and the host vasculature and immune system that results in increased net fluid production via enhanced plasma extravasation into the pleural space. The ability of tumor cells to trigger this cascade likely rests on a specific and distinct transcriptional repertoire, which results in important vasoactive events in the pleural space. While the characterization of tumor-derived factors responsible for MPE development is in the making, an additional, indirect path to MPE was recently demonstrated: tumor cells recruit and co-opt host cells and mediators, which in turn, amplify tumor cell-primed fluid leakage and impact tumor cell functions. Importantly, recent evidence suggests that the biologic events that culminate in clinical MPE are likely amenable to therapeutic inhibition and even prevention. In this perspective, the scientific basis for an update of current concepts of MPE formation is highlighted. Key questions for future research are posed. Finally, a vision for novel, effective, safe and convenient treatment modalities that can be offered to outpatients with MPE is set forth.

Keywords

exudate; inflammation; angiogenesis; vascular permeability; adenocarcinoma

Introduction

Malignant pleural effusion (MPE) complicates the course of various malignancies, with most cases occurring secondary to pleural metastasis of lung and breast adenocarcinoma (1).

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The incidence of MPE equals that of lung cancer and its presence precludes curative surgery (1–3). As a result, patients with MPE face a limited survival of a few months, depending on the underlying malignancy. In addition, MPE causes debilitating breathlessness that requires palliation. First line treatment of MPE may include chemotherapy aimed at tumor shrinkage and pleural fluid absorption. However, most causative tumors are or become chemoresistant and many patients with MPE are not fit for chemotherapy. Therefore, treatment commonly relies on palliative measures aimed at alleviating breathlessness. Disappointingly, the standard palliative methods used currently are suboptimal. Pleurodesis (iatrogenic inflammation/fibrosis to obliterate the pleural space) is associated with hospitalization, pain, fever, impairment of gas exchange, and respiratory failure, and benefits only selected patients (4,5). The alternative, indwelling pleural catheters, cause discomfort and their consumables are costly (1). Therefore, novel, effective, safe and convenient treatment modalities for outpatients with MPE are needed. In light of recent research findings, a better understanding of the condition's pathobiology is available that will likely result in therapeutic innovations.

What mechanisms then, govern the emergence of a MPE? Pleural fluid accumulates when production outweighs removal, the latter mainly occurring via pleuropulmoanry lymphatics. Absorption is reduced when tumors invade the drainage system, anywhere from parietal pleural stomata to hilar and mediastinal lymph nodes (6). However, blockade of fluid removal alone is not adequate to explain MPE formation, as evidenced by the thoracoscopic demonstration of high-rate fluid extravasation (7), the dissociation between pleural fluid volume and tumor extent (8), and autopsy findings showing that only 55-60% of patients with pleural metastasis have effusions (9). Therefore, excessive plasma leakage through hyper-permeable pleural vasculature networks appears to be critical for MPE formation (10). But how do pleural vessels become leaky upon pleural tumor dissemination? Pioneering studies demonstrated that tumor-elaborated vasoactive mediators, such as vascular endothelial growth factor (VEGF), are key to this phenomenon (10–12). Newer evidence suggests that inflammatory, mesothelial and endothelial cells in the pleural microenvironment interact with tumor cells and contribute to the events that drive MPE formation. In the text to follow will be outlined new insights into tumor-host signaling events observed with MPE, which appears to be a preferential theater for the study of tumor-host interactions.

Pleural tumors as MPE-driving forces

Early work recapitulated a clinical pearl in mice: not all tumors can cause a MPE once metastatic to the pleura (8,10–12). Tumor-elaborated VEGF was identified as an important tumor-expressed culprit, and the findings of these studies were the first to be translated to the clinic (13). Subsequently, immunocompetent mouse models of MPE were developed facilitating the discovery of additional MPE-promoting tumor-derived mediators (14,15). Strikingly, most of them were pro-inflammatory molecules, including tumor necrosis factor (TNF), chemokine ligand (CCL)2 and osteopontin (OPN), highlighting the importance of the newly described models (16–19). Vasculature-targeted mediators other than VEGF were next implicated in promoting or halting MPE formation, with examples being angiopoietins and endostatin, respectively (20–22).

The ongoing identification of a tumor “secretome” linked with MPE induction led to the search for tumor transcriptional programs that may trigger MPE. In 2006, an autocrine loop of interleukin (IL)-6-induced activation of signal transducer and activator of transcription (Stat) 3 in lung adenocarcinoma was identified, which led to VEGF-mediated MPE formation (23). Simultaneously, nuclear factor (NF)-κB activation in murine lung adenocarcinoma was found to be important for MPE induction (14). In turn, available evidence suggests that activation of MPE-associated tumor transcriptional programs might be driven by specific oncogenes. Epidermal growth factor receptor (EGFR) mutations are more common in pleural metastases as compared with primary lung adenocarcinoma sites and different EGFR and KRAS mutations were occasionally found at these two sites (24,25). These findings raise the questions whether specific mutation spectra predispose to pleural metastasis or MPE provocation and whether targeting of putative “MPE-driver” mutations could favorably impact MPE. In support of this, targeting of mutant RAS signals by zoledronic acid may explain some of its beneficial effects against experimental MPE (26).

The host as a co-player

In addition to mapping tumor hallmarks responsible for MPE, identification of host mediators that drive juxtapleural vasoactive events is in progress. As opposed to the multifaceted biologic behavior of the various pleural tumors, host factors may be more uniform and amenable to therapeutic intervention. In this regard, host-elaborated transforming growth factor (TGF)-β promotes VEGF elaboration by mesothelial cells and could be important in MPE formation (27). In our hands, host-derived IL-5 played a critical role in MPE promotion: exclusively host-originated IL-5 was present in several mouse and human effusions, while IL-5-devoid mice were specifically resistant to MPE but not solid tumor induction by lung and colon adenocarcinoma (15). Importantly, the MPE-resistant phenotype of genetic IL-5-deficiency was reproduced by exogenous antibody treatment (15). In addition to tumor-elaborated OPN, the host-derived cytokine was recently shown to be equally important. In a recently published article Psallidas et al. reported that host- and tumor-originated OPN exert distinct effects: host cell-OPN elicited macrophage recruitment and boosted angiogenesis, whereas tumor cell-OPN curtailed cancer cell apoptosis (19). Protective host-derived molecules have also been unveiled: mesothelial endostatin inhibited pleural tumor dissemination and angiogenesis (28).

But which host cells produce these MPE-promoting mediators? Evidence suggests that pleural macrophages are a significant source of immunomodulatory signaling molecules important in MPE, including IL-6, TGF-β, CCL2 and OPN (17,19,23,29). Macrophages do reside in the pleural cavity and are ideally positioned as first-line responders to tumor cells and key orchestrators of the tumor microenvironment (14,30). In support of this, zoledronic acid’s beneficial effects against experimental MPE appear to be partially mediated via modulation of macrophage function (26,31). A role for additional cells, such as mesothelial cells and lymphocytes, as primary responders to pleural carcinomatosis remains to be shown. In addition to resident, recruited cell populations have been identified in MPE. Mononuclear cells are probably the largest cellular population accrued to human and mouse MPE, and CCL2 is their major chemoattractant (17). Pleural eosinophils and young

myeloid-derived suppressor cells were recently described and were reduced in IL-5-devoid mice (15). Regulatory T cells recruited by CCL22 have been identified in human and murine MPE (32.33). Despite the advances accomplished, a functional role for most aforementioned inflammatory cell populations in MPE remains to be determined.

A new view of MPE pathogenesis

The above research findings dictate a contemporary pathophysiologic concept of MPE development based on current paradigms of a complex tumor biology (Figure 1) (34). Accordingly, tumor cells in the pleural cavity coexist with a multitude of host cells, including mesothelial, endothelial, myeloid and lymphoid cells. In addition to cell-autonomous tumor hallmarks that drive intrapleural tumor growth, paracrine signaling to host cells impacts the vasoactive events that culminate in MPE. In pleural tumor cells, specific oncogenes (e.g., mutant EGFR?) drive or coexist with distinct transcriptional programs (e.g., Stat3, NF-κB) resulting in intracavitary elaboration of a range of signaling molecules. The pleural levels of permeability-inducing (e.g., VEGF, TNF, CCL2, OPN, etc) or -inhibiting (e.g., endostatin) mediators govern the occurrence of vasoactive events and, ultimately, the development of a MPE. In addition, this set of signals determines host cell accrual and/or activation. In turn, incoming/activated host cells indirectly influence tumor cells or interact with other host cells to further regulate inflammation, angiogenesis, vascular leakage, and tumor dissemination. Interestingly, cells and mediators “hosted” in the pleural fluid may, apart from providing floating cells with nutrients, function as a reservoir of growth factors and other mitogenic or anti-apoptotic stimuli. Relatively to this, malignant ascites stimulates the proliferation of cancer cells and protects cancer cells from apoptosis (35–37). Hence a possible role of pleural exudate *per se* in the progression of pleural malignancies is worth to be explored.

Translational therapeutics: bringing findings from experimental MPE to clinical investigation

The above research findings are collectively summarized in Table 1. Based on these mechanistic results, preclinical therapeutic interventions against experimental MPE have been undertaken, including monoclonal neutralizing antibodies, soluble receptors, and small molecule inhibitors. To cite a few, blockade of VEGF, TNF, IL-5, and angiopoietin signaling, all exerted beneficial effects against experimental MPE (11,15,16,20). However, which of all pathways should we target in this complex condition; is broad-based inhibition of multiple targets an alternative? To this end, a sulindac analogue targeting multiple angiogenic receptors, including VEGFR and Tie2 attenuated MPE formation; zoledronic acid achieved experimental MPE control via multiple direct anti-tumor and indirect immunomodulatory effects (26,38). Broad-based modulation of transcriptional activity of tumor cells is another attractive approach: bortezomib was effective against mouse MPE at low doses tailored to inhibit tumor cell NF-κB transcription rather than viability (39). Finally, delivery of host-originated protective molecules, such as endostatin prevented angiogenesis and vascular leakage (41). These preclinical success stories suggest that novel insights into MPE pathobiology may be useful in the clinic.

Based on the above revised concept of MPE, therapeutic targeting of biologic pathways of tumor or host cells that participate in MPE formation may present a viable palliation strategy for patients with MPE. In fact, this revised view of MPE is reflected by some contemporary clinical trials (42). Intracavitary endostatin is currently tested in patients with MPE and malignant ascites (NCT01327235). Another phase II study exclusively dedicated to patients with MPE is looking at the effects of ZD6474, a VEGFR/EGFR tyrosine kinase inhibitor (NCT00402896). Cediranib (AZD2171), another VEGF inhibitor, is currently tested in patients with malignant ascites or pleural effusion (NCT01262612). A concluded phase I trial showed feasibility of repeated intrapleural adenoviral-mediated interferon-β gene transfer for mesothelioma and MPE (43). Median survival of the mesothelioma group was 22 months, comparing favorably with 12-14 months of historic controls (44). A randomized phase II trial of zoledronic acid for MPE trial is ongoing (UKCRN8877), and a multi-center observational study comparing patients receiving the drug or not is hopefully going to examine MPE as a surrogate end-point (NCT00099541). Several agents (Raf, HER2, EGFR, ABL, and VEGFR inhibitors; folate antagonists; immunostimulatory cytokines; farnesyltransferase inhibitors) are currently tested in patients with advanced non small-cell lung cancer; however, patients with MPE are recruited along with patients with other metastatic sites, rendering conclusions on a possible palliative role of these agents against MPE unlikely (NCT00231465, NCT00351039, NCT00351039, NCT00533585, NCT00408460, NCT00879866, NCT01069328, NCT00005842, NCT00652574).

Clinical perspective

Among this new knowledge, where should future translational studies be directed? Most of the molecules discussed were identified in lung adenocarcinoma-induced MPE. Whether these mediators are equally important in MPE secondary to other tumor types has not been explored. In other words, available data come from one mouse model using mainly a small number of cancer cell lines. It is quite possible that different cancers may employ different pathways to attain the same results. Therefore, animal models that emulate the whole spectrum of human MPE are required. Immunocompetent models that fully recapitulate host-tumor interactions should be preferred. In addition, a recently described genetic model of mesothelioma may provide more clinically relevant experimental settings (45).

Could key mediators of MPE induction be used as tools for diagnosis or prognosis? Disappointingly, malignant and inflammatory pleural effusions share a common inflammatory milieu, and the available evidence suggests that such mediators, although important in pathobiology, present poor diagnostic markers (46). However, such markers may be useful to predict disease progression or response to therapy: pleural VEGF levels predicted survival and MPE control in one study (47). In this regard, serial marker determination may be superior to isolated measurements and therefore indwelling pleural catheters may present important research tools (48).

Could modern knowledge be translated into clinical trials aiming to improve patient outcome? How should such trials be designed? Clinical research should strive towards testing drugs that target MPE-promoting mechanisms. Such agents could effectively curtail pleural fluid production independent from the tumor’s response to chemotherapy. We do

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believe, however, that MPE trial design necessitates careful consideration of drug candidates, patients, and end-points. When examining candidate drugs, important considerations are novelty (full clinical development of new agents versus off-label use of existing ones), the range of molecular targets (e.g., monoclonal antibody versus small molecule inhibitor), and the mode of action (antiangiogenic; anti-permeability; immunomodulatory). The impact of single-mediator antagonists may be blunted by backup redundancy, i.e., compensation of loss-of-function by other mediators with MPE-promoting capacity. Biologic diversity of the various tumors, as well as heterogeneity of tumor cells within a tumor, present additional issues of importance: different molecules may play cardinal roles in MPE induction by different neoplasms or by different cellular subgroups within a tumor. Therefore, strategies to account for the above pitfalls are best included in study design early on. Markers that can predict response (i.e., genetic alterations, tumor or fluid content of a protein, etc.) may direct individualized treatment, as in a recent trial of molecular-directed chemotherapy for non small-cell lung cancer (49). Broad-based agents that block multiple targets may have a greater chance of success. The same may be true for host-targeted therapies that circumvent both tumor diversity and heterogeneity, which are marked in MPE (50). The study population also needs careful selection. Patients with MPE are often grouped with patients without MPE or with other metastases. The development of a MPE is often not recorded as a surrogate end-point. Even pleural-focused trials commonly aggregate patients with metastatic MPE and mesothelioma (43). Due to tumor heterogeneity, focused selection of patients with MPE due to the same tumor type may yield superior results. Another important issue is setting clinically relevant end-points: symptom control and quality of life, rather than survival or radiologic progression may be more relevant primary end-points when studying palliative interventions.

Conclusion

Substantial progress has been achieved towards unveiling the mechanisms of pleural fluid accumulation in patients with pleural malignancies, largely facilitated by the use of relevant animal models. Future research should be expanded to include models of MPE induced by different tumor types with different oncogenes. Translation of preclinical knowledge into clinical investigation may focus more specifically on MPE and may prioritize strategies targeting multiple steps of MPE pathogenesis. In addition to treatment innovations, translational MPE research may aid in developing diagnostic or prognostic tools. Finally, some lessons learnt from MPE investigations may be broadly applicable to cancer biology.

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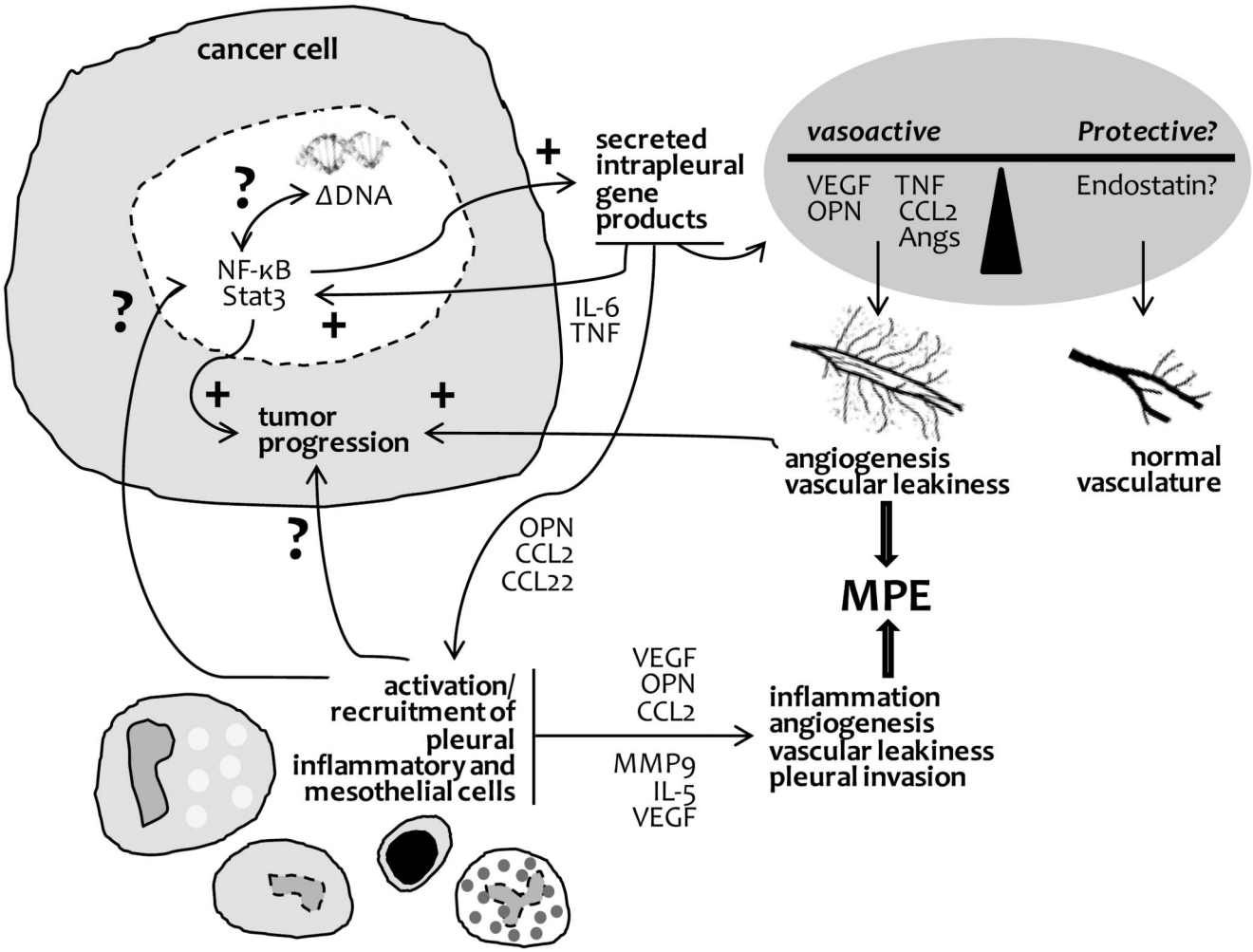

Figure 1. A revised concept of malignant pleural effusion (MPE) pathogenesis.

Primary or metastatic pleural tumor cells coexist with mesothelial, endothelial, myeloid lymphoid and other cells. Oncogene signals and/or transcription factor activation in tumor cells determine paracrine gene expression. The balance between vasoactive mediators (e.g., VEGF, TNF, CCL2, OPN, etc) and possible protective molecules (e.g., endostatin) in the pleural space dictates the occurrence of vasoactive signaling with subsequent MPE development. Moreover, this signal cocktail determines further host cell activation and recruitment. In turn, resident and incoming host cells exert a multitude of functions, including direct effects on tumor cells (transcription factor stimulation; rejection, tumor promotion, immunoediting and/or tumor escape) and indirect effects on the pleural vasculature, immune cell populations, and mesothelium to further impact inflammation, angiogenesis, vascular leakage, and/or intrapleural metastasis with establishment of additional pleural-based tumor foci.

Table 1

Tumor- and host-derived factors likely involved in malignant pleural effusion (MPE) development.

Factor	Source/mode of involvement	References
Secreted mediators		
Osteopontin (OPN; secreted phosphoprotein 1)	Elaborated by tumor (adenocarcinoma, mesothelioma) and host (macrophages) cells. Short intracellular isoform promotes tumor cell survival. Long secreted isoform signals to tumor, myeloid, and endothelial cells. Different roles for tumor and host cell-secreted cytokine. Recruitment of macrophages, provocation of vascular permeability, induction of new vessel formation, inhibition of apoptosis.	18, 19
C-C motif chemokine ligand 2 (CCL2; monocyte chemoattractant protein-1)	Elaborated by tumor and host cells. Signals to tumor, myeloid, and endothelial cells. Role of host-originated chemokine not known. Recruitment of macrophages and mast cells, provocation of vascular permeability, induction of new vessel formation.	17
Vascular endothelial growth factor (VEGF)	Secreted by tumor and host cells. Signals to endothelium and VEGFR-expressing macropahges. Provokes vascular permeability, induces new vessel formation, and facilitates leukocyte transendothelial migration.	10–12
Tumor necrosis factor (TNF)	Low level production by tumor cells; high levels secreted by activated macrophages. Provocation of vascular permeability, induction of new vessel formation, inhibition of tumor cell apoptosis via activation of nuclear factor-κB.	16
Angiopoietins 1 and 2	Secreted by tumor and (mainly) host endothelial cells. Induction of new vessel formation, regulation of vascular assembly. Recruitment of neutrophils and macrophages.	20, 38
Interleukin-5	Produced exclusively by host myeloid and lymphoid cells. Recruitment/activation of eosinophils and tumor-promoting myeloid suppressor cells.	15
Interleukin-6	Expressed by both tumor and host cells. Activates signal transducer and activator of transcription 3 in tumor cells.	23
Tumor cell transcription factors		
Signal transducer and activator of transcription 3	Activated by interleukin-6, leads to enhanced vascular endothelial growth factor expression by tumor cells.	23
Nuclear factor-κB	Activated by tumor necrosis factor, promotes tumor cell survival, vascular endothelial growth factor and C-C motif chemokine ligand 2 expression.	14, 39
Tumor cell genetic alterations		
Epidermal growth factor receptor	Mutations found more frequently in pleural metastasis compared with primary lung cancer site. Cases of mutation discordance between pleural metastasis and matched primary lung cancer site identified. Common mutation in lung adenocarcinoma, the most common cause of MPE. EGFR signaling promotes tumor angiogenesis and vascular leakage.	24,25,40
KRAS	Cases of mutation discordance between pleural metastasis and matched primary lung cancer site. Common mutation in lung adenocarcinoma, the most common cause of MPE.	25
Host cell populations		
Neutrophils	Recruited to mesothelioma and polarized to N2 pro-tumorigenic phenotype by transforming growth factor-β. N2 promote mesothelioma growth, but impact on MPE formation uncertain.	29
Mononuclear cells/macrophages	Recruited to pleural space by CCL2. Role in MPE formation uncertain.	17
Myeloid-derived suppressor cells	Immature myeloid cells expressing both monocyte and granulocyte markers. Known pro-tumor function via suppression of effector T cells. Role in MPE uncertain.	15
Eosinophils	Low numbers present in most human and mouse MPEs examined. Reduced numbers were found in interleukin-5-deficient mice. Role in MPE formation uncertain.	15
Regulatory T cells	Recruited to pleural space by CCL22. Role in MPE uncertain.	32–33
Mesothelial cells	Produce VEGF and express its receptor. Role in MPE formation uncertain.	27