Prodding the Beast: Assessing the Impact of Treatment-Induced Metastasis

John M.L. Ebos1,2

Abstract

The arsenal of treatments for most cancers fit broadly into the categories of surgery, chemotherapy, radiation, and targeted therapy. All represent proven and successful strategies, yet each can trigger local (tumor) and systemic (host) processes that elicit unwanted, often opposing, influences on cancer growth. Under certain conditions, nearly all cancer treatments can facilitate metastatic spread, often in parallel (and sometimes in clear contrast) with tumor reducing benefits. The paradox of treatment-induced metastasis (TIM) is not new. Supporting preclinical studies span decades, but are often overlooked. With recent evidence of prometastatic effects following treatment with targeted agents blocking the tumor microenvironment, a closer inspection of this literature is warranted. The TIM phenomena may diminish the impact of effective therapies and play a critical role in eventual resistance. Alternatively, it may simply exemplify the gap between animal and human studies, and therefore have little impact for patient disease and treatment. This review will focus on the preclinical model systems used to evaluate TIM and explore the mechanisms that influence overall treatment efficacy. Understanding the role of TIM in established and emerging drug treatment strategies may help provide rationales for future drug combination approaches with antimetastatic agents to improve outcomes and reduce resistance. Cancer Res; 75(17): 1–9. ©2015 AACR.

The Hydra Hercules defied,
Its nine diminished heads must hide
Before the baneful modern beast
Who has a thousand heads at least.
Oliver Herford—The Hydra

Background

The Lernaean Hydra that Hercules must slay in Greek mythology has multiple heads that, once cut off, have two more spring up to replace it. It would be unsettling to consider that any therapy might help cancer become like the hydra. Yet evidence in mouse cancer models suggest that most, if not all, treatments or actions (including surgery) against normal and malignant cell functions may create tumor cell phenotypes and permissive niche environments that can facilitate metastatic spread (1, 2). The phenomenon of treatment-induced metastasis (TIM) is not new in the preclinical literature—some dating back more than 60 years—but it is often overlooked as a mechanism that may contribute to eventual resistance and disease progression following therapy failure. The reason for this may stem, at least in part, from the fact that supporting data primarily come from studies in animals, and therefore must be put into context in terms of translational and clinical relevance. Approved anticancer treatments block or eliminate cancer growth and represent effective strategies proven in hundreds of thousands of patients worldwide over multiple decades. Evidence of TIM in animals, however, derives in large part from proof-of-principal studies that are condition dependent and contrast directly (and often simultaneously) with treatment benefits in primary (localized) tumors. Furthermore, therapy is likely only one of several stimulators of the metastatic process. For a localized primary tumor to acquire the aggressive and invasive properties necessary to colonize and spread systemically to grow into eventual metastasis, a multitude of tumor- and host-mediated conditions are required. This includes prometastatic stimuli intrinsic to the tumor, such as the multistep genetic and epigenetic alterations that can promote an increased ability to manipulate (and survive in) the surrounding microenvironment, and stimuli extrinsic to the tumor. For the latter, promotion of metastatic potential can involve stress reactions, degradation of the extracellular matrix, altered pH and oxygen levels, and adaptive immune responses. Regardless, recent studies have reinvigorated interest in whether therapy may play a major role in promoting changes in the tumor and stroma that, either independently or together, facilitate disease progression. Ultimately, no anticancer strategy has been consistently curative and resistance remains an enduring challenge for any treatment or tumor type, and therefore a careful study of the TIM literature is warranted.

This review will highlight the preclinical models used to show prometastatic properties of cancer management strategies and discuss the potential for common underlying mechanisms deriving from both the tumor and the host that may contribute to changes in a tumor’s metastatic potential.

The Challenge of Studying Metastasis

The paradox of cancer therapies having simultaneous tumor-inhibiting and metastasis-promoting effects may derive in part...
from the varied mouse tumor models used to tease out treatment effects in different disease stages. In patients with solid tumors, metastasis is the most common cause of mortality, and (where possible) it follows surgical removal of a primary tumor at an earlier stage. However, preclinical experimental therapeutics historically (and most typically) evaluate only localized tumor growth (5). The initiation of a primary tumor in mice can include chemical induction, genetic engineering (i.e., conditional or unconditional expression of tumorigenic genes), or implantation—the latter of which can include ectopic or orthotopic insertion of tumor cells or tissue fragments (6). Preclinical metastasis models mostly involve spontaneous disease deriving from a primary tumor and that can be assessed while (i) the primary tumor is in place (typically this is done at an endpoint dictated by primary size) or (ii) following surgical removal (which more faithfully recapitulate the clinical scenario, though are less commonly performed; ref. 7). Alternatively, an experimental metastasis model can be used that involves directly injecting tumor cells into the bloodstream thereby circumventing the initial growth and intravasation stages (see detailed reviews in refs. 5, 7).

Therapeutic Impact and Metastasis

A significant challenge in treating metastasis in animal models tends to be variability, which may stem in part from nonstandardized protocols for endpoints and techniques for disease quantification. Although therapeutic effects in primary/localized tumor models can be empirically quantified with relative ease at later stages (i.e., by caliper measurement or manual palpation), assessing the multistage process of metastasis is more arduous. Metastasis formation from a primary tumor includes several steps, such as cellular adhesion loss; increased motility and invasions; intravasation into the bloodstream; extravasation and micrometastases formation; and colonization in a new distant site (8). For this reason, replicating this process in mice has several obstacles. These include: (i) poor metastatic potential (tumor cells and models often do not consistently metastasize); (ii) high variability (progression and distribution rates can dramatically influence endpoint assessments such as survival); and (iii) difficult quantification (empirical assessment of metastatic spread and burden is often inconsistent). Importantly, techniques are rapidly improving metastasis models. This includes the selection of tumor cells with high metastatic potential (achieved by repeated in vivo selection), the use of molecular markers (i.e., luciferase) to track in vivo spread, and the increasing use of clinically relevant surgical models (9).

However, the real challenge in assessing the impact of treatment on metastasis is that tumor growth can respond differently, depending on location and stage. For instance, cells implanted ectopically or orthotopically can respond differently to treatment, something shown by Fidler and colleagues in murine colon cancer tumors treated with chemotherapy (10). As well, primary tumors and metastatic disease can respond differently to treatment (11). Such variability can lead to a number of different outcomes in preclinical study. Besides having no effect, a treatment may cause: (i) reductions in primary tumor and metastasis; (ii) only primary tumor reduction (no effect on metastasis); or (iii) only metastasis reduction (no effect on primary; see ref. 11 for review). In the last instance, discovery of “metastatic-only” treatments tend to be rare, owing in large part to the lack of studies where metastasis is quantified alone or separately from localized tumor effects following treatment. Nevertheless, such antimetastatic treatments have been noted in preclinical models with inhibitors of c-Met and low doses of chemotherapy, to name only a few (see detailed review ref. 12).

Treatment-Induced Metastasis

Radiation and chemotherapy

Variability in metastatic preclinical studies can also include the promotion of disease, though the many examples in the literature are often overlooked. For instance, radiotherapy has been used for more than a century and represents an established and effective tool in the treatment of multiple cancers, including in the prostate, breast, lung, and head and neck, among others (13). However, evidence that irradiation in animal models can promote metastasis also has a long history. In the 1940s, Kaplan and Murphy were among the first to show spontaneous mouse tumors serially passaged subcutaneously in vivo were reduced in size following thoracic radiation yet paradoxically produced increased metastatic nodules in the lungs (14). By the 1980s, numerous studies had demonstrated that irradiated normal tissue, either adjacent to the tumor or at distant sites, created a more permissive venue for metastatic cell dissemination while simultaneously slowing localized tumor growth. For example, Brown and Marisa showed that preirradiation of mice 48 hours before i.v. inoculation with mouse KHT sarcoma cells could increase the number of pulmonary metastatic foci 100-fold (ref. 15; see ref. 2 for extensive reviews). This phenomenon is known as the "tumor bed effect" and has since been shown to be time, dose, cell, and mouse strain dependent (16). Although the prometastatic outcome of preirradiation suggests a dominant role of the host in facilitating this effect, similar metastasis-inducing changes have been shown to originate from the tumor as well. For example, in what is now referred to as the "Reverez effect" following its discovery in the 1950s (17), tumor cells that have been lethally irradiated can also assist nonirradiated tumor cells in promoting tumor growth when they are mixed together and injected into animals.

However, clearly not all effects of irradiation are metastasis promoting. In striking contrast, tumor cells that are directly irradiated can elicit genotoxic effects on adjacent cells, thereby promoting cell death (called the "by-stander effect"; ref. 18), or even reduce tumor growth at distant site (called the "abscopal effect"; ref. 19). Though such opposing effects may be challenging to reconcile, they highlight the complexity and consequences that a single treatment can have on tumor growth and how the outcome of progression can depend on context and experimental condition.

In the case of systemic therapies such as chemotherapy, the modification of tumor cell behavior to increase metastasis has also been shown to have tumor-reducing effects that juxtapose with metastasis-promoting capability. For example, cyclophosphamide (among many other agents), when given in low or high doses to animals before inoculation with tumor cells, can produce accelerated experimental metastasis and reduced overall survival (see Table 1 for examples). These "opposite effects" have been demonstrated recently (20, 21) and several decades ago (22, 23), and contrast strikingly with the tumor-reducing benefits of the same drug and same tumor cells given in a different context (i.e., following ectopic or orthotopic implantation; ref. 21).

Other drugs and conditions

It is important to note that such effects are not isolated to radiation and chemotherapy. Surgical removal of a tumor was first
Table 1. Preclinical experimental evidence of treatment-induced metastasis

<table>
<thead>
<tr>
<th>Metastasis model</th>
<th>Example</th>
<th>Treatment</th>
<th>Cancer</th>
<th>Noncancer</th>
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<tbody>
<tr>
<td>Tumor-mediated</td>
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<tr>
<td>In vitro treatment of tumor cells prior to in vivo implantation (Experimental or spontaneous metastasis models used)</td>
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<td>Chemotherapy</td>
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<td>Targeted Therapy</td>
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<td>CTX (low and high dose)</td>
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<td>Dacarbazine</td>
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<td>Sun sensitizers</td>
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<td>Host-mediated</td>
<td></td>
<td>actinomycin D</td>
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<td>SU10944</td>
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<tr>
<td>In vivo treatment of animals prior to in vivo implantation. (Typically experimental metastasis models used)</td>
<td></td>
<td>Mithramycin</td>
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<td>DC101</td>
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<tr>
<td></td>
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<td>Doxorubicin</td>
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<td>Methotrexate</td>
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<tr>
<td>Tumor- and Host-mediated</td>
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<td>Cytarabine</td>
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<td>done26503</td>
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<tr>
<td>In vivo treatment after in vivo tumor implantation (Experimental or spontaneous metastasis models used)</td>
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<td>5-azacytidine and aphidicolin</td>
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<td>MTOR</td>
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<td></td>
<td></td>
<td>Bleomycin</td>
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<td>Rapamycin</td>
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<td>BATIMASTAT</td>
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</table>

NOTE: Preclinical studies of metastasis promoted by therapy. Metastasis models include: (i) experimental (tumor cell injection into bloodstream) or (ii) spontaneous metastasis (occurring from localized tumors, ectopic or orthotopic, left in situ or surgically removed). Study examples include several variations of how prometastatic growth was shown. These include: (i) reduction (or no change) of primary tumor growth and spontaneous metastasis but increased experimental metastasis when animals ‘preconditioned’ prior to cell inoculation; (ii) decreased metastasis (experimental or spontaneous) in one organ (i.e., lung) but increased in another (i.e., liver), etc. Studies were largely conducted in mice (used for illustration), but some were carried out in rabbits, rats, dogs, and zebrafish. *, example includes treatment-induced in vitro selection of tumor cells with metastatic phenotype with no corresponding in vivo experiments.

Abbreviations: LPS, lipopolysaccharide; NAC, N-acetylcysteine; TX, treatment; i.v., intravenous; CTX, cyclophosphamide; Refs, references.
shown to accelerate growth of tumors at distant sites more than a century ago, with evidence suggesting that disruption of the tumor site can exacerbate residual disease growth (see detailed review in ref. 24). Furthermore, a diverse set of treatments (many not cancer related) have demonstrated metastasis-promoting effects in mouse models. Examples include steroids, antidepressants, analgesics (such as morphine), antioxidants, and vitamin supplements, as well as general perturbations of normal homeostatic processes such as stress, thermal regulation (i.e., hyperthermia), and oxygen regulation (including both hypo- and hyperoxia; Table 1).

Mechanisms of TIM
Exactly how therapy can alter the natural history of cancer progression and allow for circumstances that permit and promote metastasis remains unclear. Prometastatic responses to treatment may play a significant role in treatment resistance, potentially undercutting overall benefits and hastening failure. Of significance is whether such negative effects originate primarily from the tumor or the host. As Stephen Paget theorized in 1889 with the "seed and soil hypothesis" (25), the host organ environment (soil) and the tumor (seed) must act in concert to promote metastasis. Therapy may therefore be priming both tumor and microenvironment to create metastasis-permissive conditions (26). In this regard, coordinated DNA damage responses (DDR) following treatment may be responsible, at least in part, for increased metastatic phenotypes. Nelson and colleagues have demonstrated that sustained or even transient treatment insults would tax the DNA repair machinery in both the tumor and the surrounding cells (27). For instance, genotoxic chemotherapeutics (such as alkylating agents) can cause DNA double-strand breaks promoted by DNA interstrand cross-links, initiating cellular senescence and apoptosis (for detailed reviews see refs. 27, 28). Simultaneously, a myriad of host and tumor cell secretory programs may be initiated, all of which may contribute to a prometastatic phenotype. These can include overlapping components of the senescence-associated secretory phenotype (29, 30), senescent-inflammatory responses (31), and a DDR-associated secretory program (27), among others. Together such responses can regulate the secretion of a multitude of proinflammatory cytokines, chemokines, and extracellular-matrix remodeling factors such as IL6 and IL8, to name only a few (see 29). Indeed, recent evidence using experimental models where mice were conditioned by chemotherapeutic pretreatment have suggested host-responses act as strong drivers of the prometastatic response. Daenen and colleagues showed that paclitaxel and cisplatin given to mice 4 days before intravenous tumor cell inoculation could lead to an upregulation of VEGFR-1 on endothelial cells, which, in turn, coincided with increased metastasis. Specific VEGFR-1 inhibitors were then shown to mitigate the treatment-mediated metastasis and extend survival (32).

However, where do systemic changes induced by therapy originate? There is ample evidence that treatment damage induces multiple cell types to be mobilized to the tumor and secrete paracrine and systemic factors that aid in tumor protection and growth. Gingis-Velislki and colleagues showed that paclitaxel pretreatment in mice stimulated circulating bone marrow-derived cells (BMDC) to secrete matrix-metalloproteinases (MMP) such as MMP-9. They further demonstrated that abrogation of MMP-9 expression in BMDCs using chimeric mice reduced paclitaxel-mediated experimental metastasis and improved survival. In addition, recent studies by Sun and colleagues showed that DDR programs activated by chemotherapy could stimulate fibroblast secretion of WNT16B, which in turn could activate tumoral increases in proliferation, migration, invasion, and epithelial-to-mesenchymal (EMT) phenotypes (33). Together, such chemotherapy-induced "reactions" can create a niche permissive for metastatic growth, something that has now been shown to include a multitude of drugs and depend on both cell and organ environment (for extensive reviews, see refs. 34, 35).

In the case of radiation, Ruegg and colleagues have examined the tumor bed effect and identified numerous prometastatic changes in preirradiated tissue that could assist in facilitating local invasion and dissemination to the lymph nodes and other organs [reviewed extensively elsewhere (16)]. As an example, irradiation-induced damage to endothelial cells has been shown to induce apoptosis and senescence via p53 and p21, which in turn could weaken barriers and assist in extravasive tumor potential (1). In addition, elevations in hypoxia and hypoxia-regulated metastasis genes such as plasminogen activator receptor (uPAR), have been shown to contribute to metastatic niches in preirradiated tissue (36).

Targeted Therapy and the Tumor Microenvironment
Although the primary mechanism of action for genotoxic chemotherapy and radiation is direct tumor cytotoxicity and includes nonspecific targeting of proliferating cells, there is an increasing focus on targeted therapies, some of which are primarily cytostatic, and their impact on treatment on metastasis. Approved anticancer treatment strategies now include numerous molecular-targeted drugs that block either specific malignant aberrations on cancer cells (i.e., HER2/neu expression on breast neutralized by the antibody Herceptin) or block the tumor microenvironment (TME). For the latter, TME inhibitors can aim to target the extracellular components of tumor cells as well as the nonmalignant stromal, bone marrow-derived, and immune regulatory cells, which directly support tumor growth (see detailed review in ref. 37).

TIM and the TME: lessons from angiogenesis inhibitors
While there are several examples of strategies to block elements of the TME in development, perhaps the most successful clinically has been the use of angiogenesis inhibitors, which aim to block the blood vessels tumors require for survival. Since 2004, ten VEGF pathway inhibitors have been approved in 13 late-stage cancer types as first- or second-line therapy (38). One of the underlying theoretical advantages of antiangiogenic therapy was that blockade of the tumor-supporting "normal" cells may be less prone to drug resistance; however, enduring responses in patients have been elusive. Indeed, the majority of treated patients eventually succumb to disease and multiple mechanisms of antiangiogenic drug resistance, stemming from both the tumor and the host, have been described (39).

Perhaps more provocatively, there are increasing clues that targeting nontumor stromal components may have unintended consequences. This includes activation of an array of microenvironmental compensatory mechanisms that may limit overall efficacy as well as augment metastatic disease in certain instances (39). For example, VEGF inhibition has been shown in preclinical studies to inhibit tumor progression while simultaneously eliciting...
more aggressive phenotype (40, 41). Several mechanisms have been proposed to explain this, many of which offer potential clues about therapeutic strategies to reverse this effect (42). These include induced periery and PDGF activation (43–46), c-met pathway promotion (47–50), control of vascular mimicry (51, 52), hypoxia and HIF1α activation (53), altered metabolic function (54), collagen signaling (55), increases in IL12b (56), IL8 (57), HTATIP2 (58, 59), heparinas (60), and Semaphorins 3A and 3E (refs. 61, 62; for review, see ref. 42). In addition, VEGF pathway inhibition has also shown to promote metastatic potential via cellular activation (and increased expression) of natural killer cells (63), neutrophils (64), and circulating cancer stem cells (CSC; ref. 65). Yet such findings remain controversial and likely depend significantly on critical variables such as the specific inhibitors (i.e., TKIs do not always behave as antibodies) and the dose (44, 66). Most critically, and similar to other instances of TIM, these preclinical results stand in stark contrast with the benefits of antiangiogenic treatment, often observed in the same models, simply with modified experimental conditions (such as treatment before tumor cell inoculation; see ref. 39; Table 1).

One intriguing possibility is that the impact of TIM following TME disruption may not occur during therapy, but instead only once therapy has been stopped. Indeed, persistent suppression or stimulation of tumor-mediating host responses could facilitate putative vascular “rebounds” when treatment is halted or lead to increased invasive and metastatic potential once primary or metastatic tumors are surgically removed (67). This may be of significance for certain antiangiogenic therapies with frequent breaks in dosing periods, or intermittent cessations because of toxicity (39). For example, some preclinical and clinical evidence suggests that rapid vascular regrowth may occur when VEGF pathway inhibition is halted (68, 69) and studies in mice have demonstrated that CCL2-CCR2 signaling blockade can reduce metastasis-associated macrophage accumulation (70), but can result in rapid metastatic growth once antibodies to CCL2 are removed (71, 72).

Clinical Implications and Future Directions

The most significant question related to the preclinical TIM phenomenon is whether it can translate into human disease and, if so, to what extent. To date, this question has been difficult to assess as clinical evidence is limited. In radiotherapy, the prometastatic tumor bed effect remains controversial, with the risk of distant metastasis developing following localized recurrences after treatment seen in some, but not all instances (16). Likewise for angiogenesis inhibition, no increases in metastatic disease progression have been observed in retrospective examinations of clinical data following treatment cessation. This includes VEGF pathway inhibitors such as bevacizumab and sunitinib (73, 74), as well as with α,β inhibitors such as clindigide (75), which had previously been shown to promote tumor growth in mice (76).

More bad or less good? Challenges interpreting TIM in human cancer

However, the gap between clinical and preclinical cancer study must be considered in the context of TIM. Clinical analyses often derive from retrospective investigation of completed clinical trials and often involve patients with highly metastatic treatment-refractory disease, something rarely modeled in animal tumor studies. In addition, animal studies used to show the TIM phenomena often utilize conditions not tested in human cancers. This can include the nonclinically relevant models involving experimental (intravascular) metastasis systems, ex vivo manipulated cancer cell lines, or even conditions not applicable to human cancer treatment. For the latter, this can include the study of metastatic growth concurrent with a primary tumor that is not surgically resected (surgery is often the first option in patients), the lack of multiple or sequential (heroic) treatments upon failure, or the disparity that exists between endpoint definitions in terms of human and mouse progression and survival (77).

It is also possible that TIM effects may coincide with treatment efficacy and play a role in eventual onset of resistance, as others have recently described (34). Similar TIM mechanisms may influence disease progression at earlier stages of micrometastatic progression, such as in the perioperative neoadjuvant and adjuvant setting, where induced metastatic niches can be created. Indeed, this raises an important question relating to the clinical translation of TIM to human cancer, namely, whether the net effects presented in patients would actually represent a worsening of disease. It may be the case that preclinical TIM studies may uncover mechanisms that explain why treatment efficacies are more limited than predicted or why benefits are not as durable in the long term. One possible example of this may come from the case of antiangiogenic therapy in the adjuvant setting. Despite approvals in established metastatic disease, there are now six failed phase III trials with VEGF pathway inhibitors in the postsurgical setting. This includes four with the VEGF neutralizing antibody bevacizumab in combination with chemotherapy in colorectal carcinoma (CRC) and triple-negative and HER2+ breast carcinoma (BR; AVANT, C-08, BEATRICE, and BETH, respectively; refs. 78, 79), and two with VEGF receptor tyrosine kinase inhibitors (RTKIs) in renal cell carcinoma and hepatocellular carcinoma (ASSURE and STORM, respectively; refs. 80, 81). In the case of the CRC, BR, and RCC trials, disease-free survival following treatment suggested initial benefits (nonsignificant) but these were later muted following treatment discontinuation and subsequent follow-up. At least in the case of the AVANT trial, bevacizumab and chemotherapy-treated patients actually had numerically worse outcomes than chemotherapy alone.

Together, this has raised speculation about the potential for longer treatment periods (82) and suggests that macro- and micrometastatic disease may respond differently to antiangiogenic treatment (39). Whether treatment-induced changes in tumor biology are occurring as a result of mechanisms related to the preclinical TIM remain to be investigated in more detail.

Conclusions

The results from preclinical studies demonstrate that both systemic and localized treatments that manage cancer can impact tumor growth by facilitating metastatic disease, at least under specific experimental conditions. While clinical benefits of cancer treatments are well established, animal models have provided evidence that conflicting impacts of treatment may be reducing overall benefit. A more detailed investigation into the clinical translation of studies in animals is beyond this current review but is critical to consider in a more expanded discussion. It is possible that TIM-related mechanisms may mask overall benefits of cancer therapy. If so, then strategies to examine how the
TLM phenomena may be mitigated, potentially including treatments that specifically block metastasis promotion, may require greater consideration to delay resistance and enhance therapy outcomes.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Disclaimer**

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**References**


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101. Hirata H, Tanaka K. Arti...
100. Peters LJ, Mason K, McBride WH, Patt YZ. Enhancement of lung colony...
96. Withers HR, Milas L. In...
87. Vollmer TL, Conley FK. Effect of cyclophosphamide on survival of mice...
85. McMillan TJ, Rao J, Hart IR. Enhancement of experimental metastasis...
86. Steel GG, Adams K. Enhancement by cytotoxic agents of arti...
83. McMillan TJ, Hart IR. Enhanced experimental metastatic capacity of a...
891
72. Yin T, He S, Ye T, Shen G, Wan Y, Wang Y. Antiangiogenic therapy using...
41. Organisation...


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