

Current Concepts of Tumour Metastasis

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Abstract

Background: Tumour metastasis remains the principal cause of treatment failure and poor prognosis in patients with cancer. Recent advances in our understanding of the biology of metastasis are providing novel potential targets for anti-cancer therapies. **Aim:** This paper reviews the current concepts in tumour metastasis. **Methods:** A review of Medline publications relating to the molecular biology and therapy of human tumour metastasis was conducted. **Results and Discussion:** Early metastasis models were based upon the premise of uninterrupted tumour growth, with the inevitable formation of distant metastases and eventual death of the patient. However, current research suggests that metastasis is an inefficient process governed by several rate-limiting steps, and that failure to negotiate these steps can lead to tumour dormancy. Successful metastatic tumour growth depends upon appropriate tumour-host microenvironment interactions and, ultimately, the development of vascularised metastases post-extravasation in the target organ. An understanding of the molecular mechanisms involved in this dynamic process will aid in the identification of therapeutic targets that may allow earlier diagnosis and more specific therapies for patients with metastasis.

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Introduction

Tumour metastasis, or the spread of cancer cells from a primary tumour to distant sites, remains the principal cause of treatment failure and poor prognosis in patients with cancer. Early metastasis concepts were based upon the premise of uninterrupted tumour growth, stepwise spread of tumour cells with the inevitable formation of distant metastases and eventual death of the patient. Metastatic tumour cells were thought to disseminate on the basis of vascular or lymphatic drainage from the primary tumour, and this accounted for the common patterns of metastasis. However, tumour metastasis does not always conform to this model. In fact, as early as 1889, Paget¹ had suggested that the distribution of metastatic cells was organ-specific and not necessarily purely anatomic. The finding that patients with malignancy may have circulating tumour cells relatively early in their disease was additional evidence that the metastatic process was likely to be a more complex biological process than previously proposed. While much progress has been made in research on aspects of tumourigenesis, it was only in the last 10 years that research has made an impact on the understanding of metastasis.

It is now clear that metastasis is an active multi-step process that involves considerable biological complexity. Metastases may be present in more than 70% of patients at the time of their initial diagnosis of cancer,² suggesting that the process of invasion and dissemination is an early event in the disease. An understanding of the molecular mechanisms involved in this process will aid in the identification of therapeutic targets that may allow earlier diagnosis and more specific therapies for patients with metastasis. This article highlights key advances in knowledge of the metastatic process achieved during the past decade of metastasis research.

The Metastatic Process

Overview of Metastasis

Metastasis is a dynamic, multi-step process that tumour cells must successfully complete, aided by autocrine and paracrine stimuli. The metastatic cascade requires malignant cells to leave the primary tumour by invasion of the surrounding stroma and intravasate, survive in the circulation, arrest in a target organ, extravasate, proliferate and develop a new blood supply. These processes are not

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unique to malignancy, but constitute normal programmes for many physiologic events that are usurped by malignant cells. Therapeutic strategies that are directed at one or more of these steps have the potential to impact on cancer mortality. The challenge is to identify which of these steps will provide the most clinically relevant and practical target.

Invasion is a Vital First Step in Metastasis

The triad of adhesion, proteolysis and migration constitute invasion.³ Tumour cells begin the invasive process by losing cell-cell adhesive contacts and separating from their neighbours. Tumour and normal cells have a variety of adhesion receptors that may guide both organ-specific and invasion-associated behaviours. In addition, chemo-attractant cytokines and growth factors released from the extracellular matrix (ECM) provide homing signals for metastatic cells toward microcirculation in the primary environment, and may direct organ selectivity at distant sites. In support of this, *in vivo* imaging of primary tumours of highly metastatic and non-metastatic rat mammary adenocarcinoma cells shows that malignant cells in both types of tumour are motile and protrusive, but the metastatic cells display greater orientation toward blood vessels.⁴

Invasion also requires degradation and migration through ECM barriers, such as the basement membrane. This is a complex process that requires the production, release and activation of a number of ECM degrading enzymes, including members of the plasminogen activator system, matrix metalloproteases (MMPs) and cathepsins. Inappropriate expression of one or more of these enzymes has been demonstrated in almost all the cells of the tumour-host microenvironment, both tumour and stromal.⁵ Tumour cells have been shown to recruit stromal fibroblasts, macrophages and neutrophils to produce proteases important for metastasis (reviewed in Price et al³). It is now clear that cancer does not grow in a cell-autonomous fashion. Tumour progression may be best appreciated as a product of the evolving interactions between the different cell types within the tumour and the microenvironment (reviewed in Radisky et al⁶).

The ECM is not simply an inert scaffold, but plays an active role in the control of tumour cells and tumour growth. Cryptic sites within the matrix, including proteases,⁷ growth factors⁸ and proteoglycans,⁹ are exposed by proteolysis which can further cause expression and activation of MMPs, thereby facilitating tumour cell invasion, proliferation and angiogenesis, all vital steps for the development of metastasis. The role of proteases in tumour progression and metastasis is beyond the scope of this review, but some specific examples of MMPs will be considered to illustrate the complex process of invasion.

There are four main classes of MMPs: collagenases, gelatinases, stromelysins and membrane-type MMPs (MT-MMPs) (reviewed in Johnson et al¹⁰). MMPs exhibit low activity in normal tissue, but are upregulated and/or activated during inflammation or tissue remodelling. MMPs are secreted in an inactive form (zymogen) comprising a propeptide, a catalytic domain and a substrate binding carboxyl (COOH)-terminal domain, while MT-MMPs have a transmembrane domain. The activation of MMPs occurs via a proteolytic cascade that requires signals from both malignant and stromal cells. For example, MMP-9 activation proceeds through an interacting cascade involving plasmin and stromelysin (MMP-3).¹¹ However, the majority of MMP-3 production in tumour tissue is by fibroblasts and macrophages, illustrating that in order to achieve vectorial tissue penetration, tumour cells often use host cells to stimulate their proteinase activity and to further bind host proteinases. Tumour proteolysis is a highly directed event. Active MMP-2 is localised to invadopodia on the cell surface of both invading tumour cells and angiogenic vessels by $\alpha v\beta 3$ integrins¹² or MT1-MMP,¹³ and is required for cell migration. Recently, CD44 has been found to serve as a docking molecule for active MMP-9 that retains MMP-9 proteolytic activity on the cell surface.^{14,15} Hyaluronan-induced CD44 clustering enhances MMP-9-CD44 co-localisation to membrane caps and invadopodia, and is required for MMP-9 cell surface docking.¹⁵ Cell surface-localised MMP-9 proteolytically activates latent transforming growth factor- β (TGF- β) and promotes tumour invasion and angiogenesis.¹⁶

Malignant tumours represent complex tissues that are destructive to the host organism and are the product not only of genetic alterations, but disordered signalling pathways and altered ECM. Accumulation of hyaluronan (HA) within the matrix of tumours is associated with poor prognosis (reviewed in Nehls and Hayen¹⁷) and high stromal levels of HA are more frequent in ovarian cancer metastases.¹⁸ HA fills intercellular spaces, provides cellular support and creates a low resistance, highly hydrated matrix. Consequently, HA is involved in a number of biological processes, such as inflammation (reviewed in Laurent and Fraser¹⁹), wound healing and tissue remodelling,^{20,21} morphogenesis,^{19,22} and angiogenesis,²³⁻²⁶ and may facilitate tumour cell migration and tissue penetration.²⁷

Besides facilitating tumour migration and proliferation, the matrix can profoundly alter tumour growth. Proteolytic activity can lead to the generation of endostatin, a non-collagenous component of type XVIII collagen that inhibits metastasis.²⁸ Similarly, non-collagenous fragments of collagen IV can inhibit basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)

activity and angiogenesis.²⁹ Therefore, the successful growth of metastatic cells is the result of altered homeostasis that leads to an increase in pro-metastatic factors over anti-metastatic influences.

Metastasis is Fundamentally an Inefficient Process

Clinical and experimental data have shown that cancer metastasis is an inefficient process.³⁰ Wyckoff et al⁴ have provided some much needed insights into where the inefficiency of the metastatic cascade occurs. Non-metastatic cells appear to fragment when interacting with blood vessels, while metastatic cells successfully intravasate. However, a substantial number of patients with epithelial tumours, but without overt metastases, have been shown to have circulating tumour cells before treatment.³¹ This suggests that there is a second inefficient step in the metastatic cascade. Experimental metastasis models using *in vivo* videomicroscopy indicate that it is growth in the distant organ, not extravasation, that is the rate-limiting step in the formation of metastasis. These studies demonstrate that tumour cells injected into the circulation are initially arrested by size constraints in the microcirculation, and that over 80% extravasate as single cells by day 3. However, only a small fraction of extravasated cells (1 in 40) begin to grow (forming micrometastases by day 3) and only a small subset of micrometastases (1 in 100) progress to form macroscopic tumours by day 13.^{32,33} Many cancer cells persist as dormant single cells, neither dividing nor undergoing apoptosis. Furthermore, it has been shown in these models that highly metastatic cells extravasate at the same rate as non-tumourigenic non-transformed cells.³⁴ Post-extravasation, tumour cells preferentially migrate toward arterioles³⁴ and proliferate in the subcapsular region of the liver.³⁵ In the case of pulmonary metastases, preferential tumour growth is found along the lung surface and around the arterial and venous vessels.³⁰ Thus, organ selectivity may be a directional event and the common patterns of metastasis observed may result from biochemical signals and simple mechanical events, such as venous or lymphatic drainage. This concept of “seed” and “soil”, first introduced by Paget,¹ suggests that metastatic tumour growth (the seed) can only take place in a receptive host microenvironment (the soil). Metastatic inefficiency, therefore, is not only due to the failure of intravasation, but the failure of solitary cells to initiate growth and angiogenesis after extravasation. Hence, this stage of metastasis hence offers promising targets for new anti-metastatic drugs.

Tumour Dormancy

Patients with cancer experience one of three outcomes: unrestrained primary tumour growth, metastasis and eventual death; therapeutic intervention or immune response leading to the total eradication of malignant cells; or,

commonly, following extirpation of the primary tumour, metastatic cells become quiescent and reside in various tissues, but do not become evident clinically. It is the latter pathway that represents tumour dormancy. Besides breast cancer, there are numerous examples of tumour dormancy resulting in late relapse in melanoma, prostate and renal cell carcinomas. The potential for dormant tumour cell growth is further highlighted by reports of metastases occurring in recipients of solid organ transplants, including hearts.^{36,37} The development of metastatic prostate cancer following heart transplantation, an organ that is rarely associated with metastatic tumour implantation, provides evidence that dormant malignant cells exist in organs that do not support tumour growth, and that these cells can be activated when disseminated to a more receptive microenvironment.

Many patients with cancer have dormant cells. After treatment of the primary tumour, dormant tumour cells have been identified in patients using sensitive techniques such as polymerase chain reaction (PCR), flow cytometry and immunohistochemistry (reviewed in Uhr et al³⁸). The significance of these cells remains controversial. Sentinel lymph node studies of patients with melanoma^{39,40} and breast cancer⁴¹ have shown that PCR- or immunohistochemistry-detected micrometastases in lymph nodes portend a worse prognosis than node-negative patients for similar T stage, but better than the prognosis of patients with haematoxylin and eosin detectable disease. This suggests that some of these micrometastases will grow to become clinically significant recurrences, while other cells may remain dormant and not be a cause of morbidity. Similarly, bone marrow transplant can result in prolonged remissions or cure in some patients with chronic myeloid leukaemia (CML), but both states are accompanied by the long-term persistence of quiescent leukaemic cells. The level of *bcr-abl* positive clones can be monitored, and treatment initiated, if the cells exit their quiescent state.⁴² Thus, “functional cure” (the maintenance of malignant cells in a dormant state), rather than the total eradication of malignant cells, is an adequate (and achievable) therapeutic goal.

Tumour models provide a means of understanding tumour biology and are powerful tools guiding clinical research and practice. Most models make the assumption that all tumours demonstrate uninterrupted growth and continuous Gompertzian,⁴³ growth kinetics has been the cornerstone of current cancer understanding. It is also the basis of many current treatments, but this is inadequate for understanding the long-term recurrence risk in breast cancer, which may occur 20 to 25 years after treatment of the primary tumour.⁴⁴ Mathematical modelling shows that the uninterrupted growth hypothesis cannot explain either local or distant

breast cancer recurrence rates (reviewed in Demicheli⁴⁵). However, tumour dormancy prior to a continuous growth phase is supported mathematically by clinical breast cancer series.^{46,47} These studies have shown that both axillary and distant recurrences occur at two time peaks, which are also at odds with continuous growth. These observations imply that there are tumour cells at different biological steady states. Thus, relapse-free survival (RFS) is the sum of dormancy and tumour growth time.

These findings, combined with *in vivo* videomicroscopy models, imply that cancer is usually a systemic disease. Dormancy is the result of dynamic interactions between metastatic tumour cells and the host microenvironment involving the immune system and angiogenesis, but the exact mechanisms responsible are not known. The stroma is important in dynamic processes, such as wound healing and organogenesis. In cancer, the abnormal stroma manifests as desmoplasia. This is largely due to carcinoma-associated fibroblasts (CAFs) that represent a change in phenotype from “benign” tissue fibroblasts, including the expression of α -smooth muscle actin, increased collagen,^{48,49} MMP,^{50,51} tissue inhibitor of metalloprotease (TIMP),⁵² growth factors,⁵³ HA^{54,55} secretion and altered laminin production.⁵⁶ This change in phenotype results in the liberation of oncogenic signals from CAFs that support primary and metastatic tumour growth. Indeed, experimental evidence has shown that signals derived from CAFs can initiate tumourigenesis in non-tumourigenic cell lines.⁵⁷ MMPs (particularly stromelysin) derived from CAFs are needed to support engrafted breast cancer growth in mice, possibly through growth factor release from the ECM. Malignant cells also produce signals that induce changes in stromal cells which, in turn, support tumour growth via a paracrine exchange.⁵⁸ Finally, the stroma provides much of the surrounding matrix that, in itself, alters proliferation⁵⁹ and motility,⁶⁰ and may induce genetic changes in the tumour.⁶¹

The mechanisms that control the activation of dormant cells remain equally unclear and these cells may prove to be a significant clinical problem, as they will not be affected by conventional therapies that are directed against actively growing cells. Therapeutic strategies that maintain tumour dormancy may be the key to effective cancer treatments. T-cell mediated immunity has been shown in both animal models and breast cancer patients to play a role in tumour dormancy (reviewed in Schirrmacher⁶²). Alternatively, strategies directed against the host tissue stroma may effectively retard metastatic growth. Examples under investigation include angiogenesis inhibitors⁶³ and protease inhibitors.⁶⁴ However, such agents used in isolation may allow tumour growth to eventually escape dormancy due to signalling pathway redundancy in malignant cells. Part of the therapeutic future will include more specific therapies directed against cellular targets that prevent

critical pathways for continuous tumour growth, and encouraging results have been obtained with Herceptin (anti-*her2/neu* antibody, trastuzumab⁶⁵) and imatinib (STI-571, Glivec⁶⁶).

Role of the Microenvironment

The observed clinical patterns of organ-specific metastasis have two major implications. First, tumours are a heterogeneous group of malignant cells and the metastatic process, by its very nature, selects only those clones that survive in distant organ sites. Second, the microenvironment of the host organs plays a vital role in growth, dormancy or apoptosis of metastatic cells. Gutman et al⁶⁷ have shown that subcutaneously implanted human colorectal carcinoma cells demonstrate accelerated growth in partially hepatectomised mice, but not in nephrectomised mice. In contrast, human renal cell carcinoma cells established as lung micrometastases undergo growth acceleration in mice following nephrectomy, but not hepatectomy. These findings indicate that metastatic cells can respond to physiological signals when tissue homeostasis is disturbed, and tumour cells which have an affinity for growth in a particular organ can respond to these signals. Microenvironment has also been shown to play a role in the multi-drug resistance phenotype. Animal models have demonstrated organ-specific responses of malignant cells to chemotherapeutic drugs related to alterations in *mdr-1* and P-gp expression induced by interactions with the specific organ microenvironment.⁶⁸

Angiogenesis

Primary and Metastatic Tumour Growths

Angiogenesis is the formation of new capillaries from existing vessels and is an important part of normal physiological processes, such as wound healing,⁶⁹ placentation⁷⁰ and embryogenesis.⁷¹ Angiogenesis is an absolute requirement for the development of macroscopic metastases. Experimental evidence has shown that, in the absence of angiogenesis, tumour mass is limited to 0.2 mm in mice.⁷² Folkman has proposed the “angiogenic switch”, suggesting that neovascularisation is controlled by the balance of pro- and anti-angiogenic signals.⁷³ Under normal circumstances, angiogenesis is limited in time and restricted in place. However, the process is exploited by tumour cells to promote primary tumour growth and metastasis. Mouse models have revealed that the angiogenic switch is activated in the early stages of tumour development⁷⁴ and high vessel density in invasive cancers is associated with poor prognosis.⁷⁵ The process of tumour angiogenesis is the result of tumour-host interactions. A study by Fukumura et al⁵³ elegantly shows that tumour cells can induce VEGF expression by stromal cells and with time stromal cells, both endothelial cells and fibroblasts, invade the tumour.

This suggests that there is a two-way paracrine exchange of growth factors between tumour cells and vascular endothelial cells.

A number of angiogenesis promoters and inhibitors have been identified. Molecules implicated in promoting angiogenesis include VEGF,⁷⁶ bFGF,⁷⁷ interleukin-8,⁷⁸ hepatocyte growth factor (HGF)⁷⁹ and platelet derived growth factor (PDGF),⁸⁰ as well as ECM components such as HA fragments.⁸¹ The precise molecular mechanisms controlling their activity *in vivo* are not yet clear.

While anti-angiogenesis targets are very attractive anti-metastasis strategies, angiogenesis is biologically heterogeneous and there is redundancy of angiogenic growth factor expression in specific organ environments. This must be taken into account when considering these agents for metastasis therapy. It is likely that the factors governing microvasculature in different organs may not be the same and may potentially complicate anti-angiogenesis therapies (reviewed in Jung et al⁸²). Animal models have demonstrated that anti-angiogenic treatments, such as an anti-VEGF antibody, have differential effects on tumour angiogenesis related to the site of tumour implantation and growth.⁸³

Potential Clinical Targets

The current models of metastatic inefficiency and dormancy, prior to continued metastatic tumour growth, have several implications for further research and potential clinical targets. First, the earliest steps in metastasis, that is, invasion of the stroma, have typically occurred in most patients with cancer at the time of presentation. Similarly, animal models suggest that intravasation is an early event after degradation of the basement membrane. Clinical studies of patients with breast cancer,⁸⁴ non-small cell lung cancer,⁸⁵ melanoma⁸⁶ and oesophageal cancer⁸⁷ have shown that many patients without overt metastatic disease will have circulating tumour cells, thus confirming that intravasation will have already occurred in most patients prior to presentation. Hence, while these steps may contribute to metastatic inefficiency, the process of metastasis has already selected a population of cells capable of completing these early steps; targeting invasion and intravasation are unlikely to provide an effective anti-metastasis therapy (Fig. 1).

The current experimental and clinical data suggest that post-extravasation growth represents the rate-limiting step in the metastatic cascade, and that strategies targeting the pathways involved may provide the most promising anti-metastasis therapies. Current metastasis models suggest that the failure of metastatic tumour cells to negotiate two checkpoints leads to tumour dormancy. First, malignant cells must initiate growth in the distant organ. In this phase,

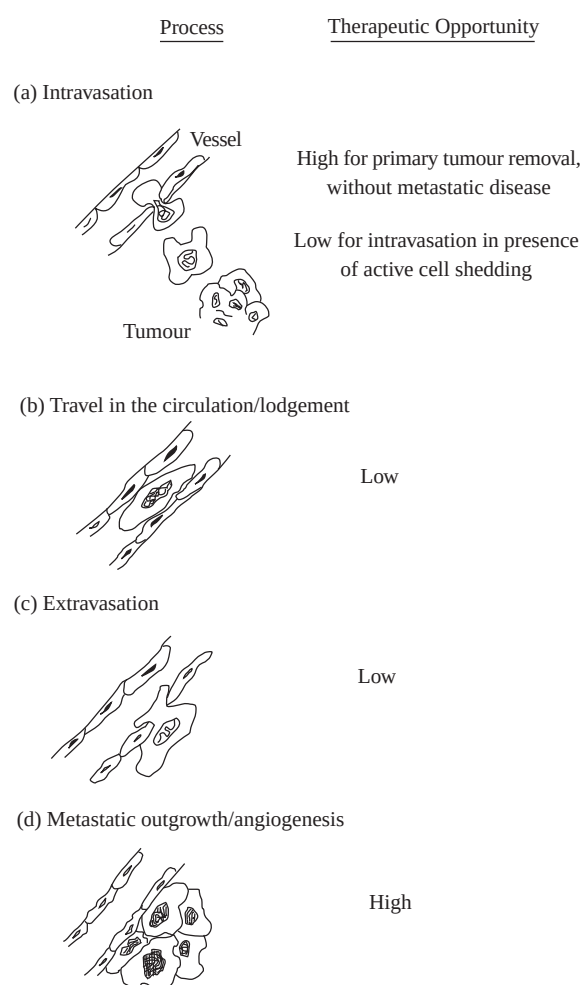


Fig. 1. Steps in the metastatic cascade and the potential for therapeutic intervention for each step. Intravasation (a) requires vessel invasion and cell shedding into vascular or lymphatic channels. Therapeutic intervention to inhibit intravasation will only be effective in the absence of distant metastatic disease. Travel in the circulation and lodgement at a distant site (b) and extravasation (c) present little therapeutic opportunity, especially in cases where the primary tumour is resectable. With current knowledge, metastatic outgrowth and angiogenesis (d) present the most promising opportunities for therapeutic intervention in metastatic disease.

tumour cells that do not begin to proliferate will remain quiescent until the malignant cells, or seeded tissues, change to promote proliferation. Proliferating micro-metastases will then grow continuously to the second dormancy phase, which relies on angiogenesis. However, only a small proportion of metastatic cells (4% to 10%) have the ability to negotiate this checkpoint, and growth occurs either by removal of angiogenesis inhibitors or by tumour cells releasing pro-angiogenic signals (reviewed in Demicheli⁴⁵). The metastatic cells then move to the final phase with uninterrupted growth of vascularised metastases. The maintenance of tumour dormancy, by preventing metastatic tumour cells from initiating post-extravasation growth or angiogenesis, is likely to provide the most

realistic anti-metastasis therapies for the future.

How might these processes be targeted? Proteolysis has been shown to be a key component not only of invasion, but homotypic and heterotypic cell signalling as well. Therefore, strategies aimed at inhibiting proteolysis would have the potential to prevent both the initiation of post-extravasation growth of disseminated cells and block activation of the angiogenic switch. Experimental metastasis studies using the MMP inhibitors marimastat (available orally) or batimastat (parenteral administration only)⁸⁸ have shown that these proteinase inhibitors can block the growth of metastases *in vivo*. These promising animal studies have led to clinical trials of these compounds in patients with advanced cancer. Phase II clinical trials have shown that marimastat, either alone⁶⁴ or in combination with standard chemotherapeutic agents,⁸⁹ can lead to stabilisation of disease and improved survival. However, other studies have not shown a benefit from MMP inhibitors.⁹⁰ Despite contradictory findings, the results are encouraging and support further therapeutic evaluation of MMP inhibitors in the management of advanced malignancy and the potential maintenance of tumour dormancy.

Disordered intra- and intercellular signalling is one of the fundamental changes in malignancy. Therefore, targeting homotypic and heterotypic cell signalling pathways may also provide effective anti-metastasis therapies. *In vivo* metastasis models have shown that perturbing the function of cell adhesion molecules with soluble peptides⁹¹ or anti-sense messenger ribonucleic acid (mRNA)⁹² can effectively inhibit metastasis. Specifically, targeting tyrosine kinases involved in disordered signalling pathways have been shown to retard tumour growth and metastasis. The most dramatic example that is now used in the clinical setting is STI-571 (imatinib), a small molecule tyrosine kinase inhibitor that targets the *kit* signal transduction pathway. Imatinib induces a sustained objective response in more than half of patients with an advanced unresectable or metastatic gastrointestinal stromal tumour, which resists conventional chemotherapy.⁶⁶ It has also been shown to induce high rates of cytogenetic and haematologic responses in patients with chronic phase CML, in whom previous interferon therapy had failed.⁹³ Antibodies can also be used to target specific pathways. The anti-*her2/neu* antibody, trastuzumab, has been shown to be active in *her2*-overexpressing metastatic breast cancer⁶⁵ and it increases the clinical benefit of first-line chemotherapy.⁹⁴

The immune system plays a role in tumour surveillance and immunotherapies have been shown to have activity in patients with metastatic disease.⁹⁵ However, the induction of anti-tumour immune responses has not consistently translated into a clinical benefit for this group of patients. It remains to be seen whether patients with micrometastatic

or dormant malignant disease may benefit from the induction of anti-tumour immune responses. Immunotherapies do not specifically target proliferating tumour cells and, therefore, may be an effective strategy for eliminating micrometastatic disease or maintaining the dormant phenotype.

Solid tumours depend on angiogenesis for their growth. In a transgenic mouse model of pancreatic islet cell carcinogenesis, pro-angiogenic activity occurs in premalignant lesions, and angiogenesis persists during progression to expansive solid tumours and invasive carcinomas. AGM-1470, angiostatin, BB-94 and endostatin each produced distinct efficacy profiles in trials aimed at preventing the angiogenic switch in premalignant lesions, intervening in the rapid expansion of small tumours or inducing the regression of large end-stage cancers. Thus, anti-angiogenic drugs may prove most efficacious when they are targeted to specific stages of cancer.⁹⁶ Anti-angiogenic therapies are potentially powerful tools for maintaining micrometastases in a dormant state, thus achieving a “functional cure”. Experimental evidence has shown that both slowly growing, poorly vascularised tumours respond as well as rapidly growing, highly vascularised tumours to therapy with angiogenesis inhibitors,⁹⁷ thereby supporting their potential efficacy against early micrometastasis. Several strategies are currently being developed, including angiostatin,⁹⁸ endostatin,⁹⁹ antibodies directed against VEGF receptors,¹⁰⁰ combretastatin A-4 phosphate,¹⁰¹ and Vitaxin (an anti- α v β 3 antibody). These compounds have been shown to possess some anti-tumour activity in patients with advanced disease, but further work is required.

Conclusion

Recent developments have highlighted the complex nature of the metastatic process, and only the most highly specialised malignant cells that can interact efficiently with the stroma accomplish successful metastatic outgrowth. It seems likely that strategies targeting post-extravasation tumour growth will provide the most clinically relevant anti-metastasis therapies of the future. These strategies are beginning to emerge that target specific pathways and tumour cell requirements for successful outgrowth. Early clinical trials with these therapies have focussed on patients with advanced disease and one class of new agent alone, or in combination with standard chemotherapeutic agents. However, these approaches do not take into account the heterogeneous nature of disseminated malignant cells or the diverse nature of the seeded organs. To overcome these problems, therapeutic regimens will need to combine more than one class of specific therapy (such as anti-angiogenesis and protease inhibitor) in order to impede redundant pro-

metastasis pathways. The past decade has seen enormous advances in metastasis research; the next will likely realise these advances in the clinic.

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