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The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis

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Abstract

Recent pre-clinical and clinical research has provided evidence that cancer progression is driven not only by a tumour's underlying genetic alterations and paracrine interactions within the tumour microenvironment, but also by complex systemic processes. We review these emerging paradigms of cancer pathophysiology and discuss how a clearer understanding of systemic regulation of cancer progression could guide development of new therapeutic modalities and efforts to prevent disease relapse following initial diagnosis and treatment.

Solid tumours are composed of heterogeneous populations of neoplastic cells and an elaborate array of recruited mesenchymal and inflammatory cells of host origin that form the tumour-associated stroma, and are collectively known as the tumour microenvironment (TME)[1]. Traditionally, the biology of solid tumours has been portrayed as being governed by the genetic and epigenetic alterations that neoplastic cells undergo during the course of multi-step tumour pathogenesis. However, over the past two decades, the TME has also emerged as an equally important determinant of tumour behaviour. Paracrine interactions between cancer cells and the TME have been shown to regulate overall tumour growth, homeostasis and progression[2]. Moreover, molecular profiling of stromal cells from a variety of different human tumour specimens has yielded information of prognostic value, further highlighting the critical role that the TME plays in directing tumour development[3–7].

Investigations into the role of the TME and the mechanisms of stromal cell recruitment have also provided insights into a distinct and intriguing aspect of tumour biology: cancer progression may also be directed by the body's systemic responses to malignancy and by the involvement of organ systems located at sites distant from the site of primary tumour growth. Some of the most compelling evidence that cancers exert unique and specific systemic effects comes from studies showing that tissues can be altered at the structural,

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histopathological and molecular levels in the presence of a distant malignancy, as we discuss in this Review. Thus, the view of cancer as a systemic disease, which was once a matter of speculation, is now emerging into the research spotlight[8,9].

In some cases, the systemic interactions between tumour and host mimic and co-opt normal physiological processes, such as inflammation and wound healing. Indeed, the histopathological appearance of the TME of most carcinomas closely resembles that of inflamed and wounded tissues, a similarity that was noted a quarter of a century ago when tumours were described as "wounds that do not heal"[10]. These similarities explain why studies of other pathological processes, such as wound healing[11], inflammation[12–16] and organ fibrosis[17,18], have shed light on carcinoma pathogenesis. Importantly, however, the transient activation of stromal cells observed during wound healing contrasts with the behaviours of these cells in tumours, where stromal cell recruitment and activity persist throughout the course of tumour development[2,19,20].

In this Review, we discuss what is known about tumour–host interactions that reach beyond the boundaries of individual tumours to evoke systemic responses. So far, a handful of tumour-derived cytokines have been proven to act in a systemic fashion to affect distant tissues and, thereafter, to foster tumour growth. As this research field expands, this list is likely to grow longer. Here we examine how these tumour-derived factors and underlying pathophysiological processes play a part in nearly all aspects of cancer progression, starting with primary tumour growth and focusing particular attention on the growing body of evidence that tumour-driven systemic perturbations can also influence disease recurrence by governing some of the critical, rate-limiting steps in the metastatic process. Finally, we discuss how these emerging paradigms of systemic interactions may guide new areas of research on cancer pathogenetic mechanisms and therapeutic strategies designed to prevent disease relapse.

Tumour-driven systemic processes that affect primary tumour growth

Tumour cells secrete chemokines that act by recruiting various peripheral blood cells from the circulation into the TME. The repertoire of host circulating cells and the release of tumour-derived chemokines that recruit them into the primary TME remain areas of active investigation (reviewed in refs 1,2,21–25). These findings have given rise to the notion that the recruitment of many of the stromal cell types that are found within the TME of most primary adenocarcinomas (Fig. 1a) involves the release of tumour-derived factors that may also mobilize host cells from distant tissues, notably the bone marrow and spleen[26]. Ultimately, these systemic perturbations impinge on cancer progression when resulting circulating cells are recruited into the tumour-associated stroma (Fig. 1b and Table 1).

Tumour-derived factors that affect the bone marrow.

In the bone marrow, the binding of stromal-cell-derived factor-1α (SDF-1α, also known as CXCL12; expressed by bone marrow endothelium[27]) to its receptor CXCR4 (expressed by both human and mouse haematopoietic stem cells (HSCs)[28]) represents a critical axis in bone marrow retention and homing of haematopoietic stem and progenitor cells[29]. The inflammatory cytokine G-CSF (granulocyte-colony stimulating factor) is known to

antagonize this interaction by acting to either mobilize cells into the circulation or to prevent their homing back to the bone marrow[30]. Hence, G-CSF is a critical modulator of bone marrow haematopoietic progenitor cell mobilization and homing as a part of both normal homeostasis and inflammation[29,31–33].

Studies using mouse models of melanoma, lymphoma, lung carcinoma and mammary carcinoma have shown that tumour-derived G-CSF induces mobilization of tumour-supporting cells from the bone marrow into the circulation[34,35]. In one of these studies, certain haematopoietic progenitor cells, defined as $CD11b^{+}/Gr1^{+}$ myeloid cells, were altered in the bone marrow before their mobilization into the circulation[35], and when harvested directly from the bone marrow of tumour-bearing mice, expressed distinct sets of genes — including the G-CSF responsive gene, Bv8 prokineticin — known to regulate myeloid cell mobilization and angiogenesis[34]. Following their recruitment from the circulation into the TME, $CD11b^{+}/Gr1^{+}$ myeloid cells were found to facilitate tumour-associated angiogenesis and to render tumours refractory to inhibition by anti-VEGF (vascular endothelial growth factor) treatment[34].

Other work has demonstrated that tumour-derived, systemically acting osteopontin (OPN), an inflammatory cytokine, is necessary for the pro-tumorigenic function of bone marrow cells (BMCs) that are recruited into the TME of certain breast tumour xenografts[36,37]. In mice bearing the OPN-secreting tumours, but not in those with tumours that lack OPN expression, $Sca1^{+}/cKit^{-}/CD45^{+}$ haematopoietic BMCs are rendered pro-tumorigenic at the functional and molecular levels in the bone marrow before their mobilization into the circulation[37]. The tumour-supportive functions of $Sca1^{+}/cKit^{-}/CD45^{+}$ BMCs were discovered when they were mixed with otherwise-indolent breast tumour cells and injected into mice. It was observed that the BMCs from mice carrying OPN-secreting xenografts facilitated the growth of the indolent breast tumours, whereas the corresponding BMCs from cancer-free mice or mice bearing OPN-deficient xenografts did not[33].

Several other studies have revealed tumour-derived factors that are important systemic mediators of tumour angiogenesis through their effects on BMCs. Specifically, vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PlGF) trigger release of haemangiogenic BMCs (a collection of endothelial progenitor cells (EPCs) and VEGFR-1-positive haematopoietic cells) from the bone marrow into the circulation[23]. Following their recruitment to tumour sites, these haemangiogenic populations may promote tumour neovascularization[38], although the precise function of EPCs and whether they are necessary for promoting tumour blood vessel formation remain unresolved[39]. Cancer-associated fibroblasts (CAFs), which are often abundant in the TME of most carcinomas, have also been linked to tumour angiogenesis through systemic effects. CAFs were shown to release CXCL12 (SDF-1α) into the circulation in a breast tumour xenograft model[40]. Together with earlier results demonstrating that circulating CXCL12 mobilizes haematopoietic progenitor and stem cells from the bone marrow[41], this work led to the notion that CAF-derived circulating CXCL12 triggers the release of progenitor cells into the circulation, thus leading to their subsequent recruitment into the TME to promote angiogenesis.

Several other bone-marrow-derived cell types, including a complex array of leukocytes, have been observed in tumour specimens from mice and human patients[42], and many of the mechanisms that control their recruitment from the circulation into the TME by tumour-derived chemokines have been uncovered[43]. Nevertheless, it is not yet clear whether these various immune cell types (or their precursors) are directly mobilized from distant reservoirs into the circulation by tumour-derived cytokines, or whether certain tumours may merely take advantage of the host cells that travel through the peripheral circulation as a part of normal physiologic homeostasis. Similarly, certain mouse models have revealed that some TME cells, such as mesenchymal stem cells[44,45], can have origins in the bone marrow, but whether cancers directly elicit their mobilization from that site is not known.

Tumour-derived factors that affect the spleen.

Populations of $CD11b^+/Gr1^+$ myeloid cells are significantly expanded in the bone marrow and spleens of cancer-bearing mice relative to cancer-free counterparts[46,47], and their numbers are also increased in the circulation of cancer patients compared with cancer-free subjects[48,49]. Experiments using mouse models of mammary carcinoma expanded on these observations by demonstrating that when $CD11b^+/Gr1^+$ myeloid cells were isolated from the spleens of mice bearing mammary tumours and were mixed with tumour cells before implantation, tumour growth and metastasis were enhanced[50]. In contrast, equal numbers of antigenically identical myeloid cells from the spleens of tumour-free mice failed to alter tumour progression[50]. In these experiments, the $CD11b^+/Gr1^+$ myeloid cells helped to promote metastasis, at least in part, by expressing functional matrix metalloproteinases. However, although the pro-metastatic myeloid cells were specifically recruited to mammary carcinomas, it was unclear how these tumours communicated systemically with the spleen to induce their mobilization into the circulation.

Later studies using a mouse model of lung adenocarcinoma development suggest that tumour-derived angiotensinogen, the precursor molecule to the circulating peptide hormone angiotensin II, can function as a modulator of tumour-supporting cells in the spleen. One of these studies revealed that the majority of tumour-associated macrophages and neutrophils were derived from progenitor $CD11b^+/Ly\text{-}6C^{High}$ monocytes and $CD11b^+/Ly\text{-}6G^{High}$ granulocytic cells respectively, and that both populations were increased in the spleens of tumour-bearing mice[51]. Subsequent work showed that elevated levels of circulating angiotensin II were necessary for amplifying self-renewing HSCs and macrophage progenitors in the spleen, but not in the bone marrow, of lung tumour-bearing mice[52,53]. These studies suggested that angiotensin II was tumour-derived, as expression of angiotensinogen was readily detectable in the lung tumour cells.

In support of the pre-clinical findings discussed above, elevated levels of many of these cytokines have been detected in primary tumour samples as well as in the plasma of patients bearing various cancer types, including colon carcinoma, melanoma, hepatocellular carcinoma and breast cancer, and have been positively correlated with metastatic progression[36,54–60]. As we discuss later, primary tumour-derived secreted factors may also have a profound impact on the outgrowth of disseminated metastatic colonies.

Circulating microvesicles.

The release of soluble cytokines into the circulation is not the only means by which primary tumours communicate with distant tissues. Tumour cells are known to extrude microvesicles, which are membrane-bound particles (including microparticles and exosomes ranging in size from 0.1–1 μm) that carry lipids, proteins, mRNAs and miRNAs[61]. Recent discoveries indicate that these tumour-derived microvesicles can modulate cancer progression by influencing the behaviour of host cells in distant tissues[62]. For example, exosomes derived from melanomas were proposed to 'educate' pro-metastatic progenitor cells in the bone marrow[63]. Likewise, renal-carcinoma-derived exosomes were found to promote angiogenesis in lung tumour metastases[64]. Additionally, a study of murine mammary carcinoma demonstrated that osteopontin, carried through the circulation by tumour-derived microparticles, was necessary to mobilize pro-angiogenic cells from the bone marrow[65]. Interestingly, in these experiments, the mammary tumours produced microparticles as a result of paclitaxel chemotherapy, which was consistent with the authors' clinical observations that circulating microparticle numbers were elevated in some cancer patients following chemotherapy.

Although microvesicles have attracted much attention and have even been suggested as targets for cancer therapy, their cellular sources, target tissues and various roles in tumour pathogenesis are only beginning to be uncovered. The importance of these particles in systemic signalling is supported by the finding that their circulating levels in tumour-bearing hosts seem to be higher than the levels observed in cell culture experiments where microvesicle-induced effects have been clearly observed[65].

Tumour-driven systemic processes that alter distant tissues before metastasis

Tumour metastasis can be portrayed as the end-product of a multi-step succession of events termed the invasion–metastasis cascade, which has been extensively reviewed elsewhere[66–69]. To disseminate, cancer cells from the primary tumour must first invade the local tissue parenchyma of the primary tumour and intravasate into nearby microvessels to enter into the circulation. Following haematogenous dissemination, tumour cells can be trapped in the microvessels of distant tissues, where they may exit the circulation via the process termed extravasation, to enter into the tissue parenchyma. The final step in this cascade, which we discuss in more detail later, is defined operationally as the acquired ability of micrometastatic deposits to form macroscopic metastases — a process often termed colonization. In some cases, primary-tumour-driven systemic processes that occur before metastasis have been found to dictate the site where subsequently disseminated cancer cells extravasate into tissue parenchyma (Fig. 2a and Table 1).

Initial evidence that the pre-metastatic tissues of tumour-bearing animals are altered in the presence of distantly located tumours came from studies using subcutaneously implanted murine melanoma and lung carcinomas[70,71]. This work indicated that tumour-derived VEGF-A, TGF-β and TNF-α induced changes in the lung microenvironment that subsequently made the lung tissue more competent at recruiting circulating $CD11b^+$ myeloid

cells in a VEGFR1-dependent manner. The same group showed that the extracellular matrix-remodelling metalloproteinase, MMP9, is expressed in the lungs both by resident endothelial cells and by recruited $CD11b^+$ cells, resulting in significantly more metastatic tumour cells being recruited to the lungs of tumour-bearing mice; they also showed that the metastasis-free lungs from cancer patients exhibit enhanced MMP9 expression[70].

A study using the same mouse models of subcutaneously implanted metastatic melanoma and lung carcinoma showed that tumour-derived VEGF-A and PlGF could mobilize $VEGFR1^+$ BMCs, which subsequently localized not only to primary tumour sites, but also to the lungs before dissemination of tumour cells from the primary site[72]. At the same time, lung fibroblasts upregulated expression of fibronectin at these sites, thus facilitating recruitment of $VEGFR1^+/\alpha_4\beta_1$-$integrin^+$ [72], These sites within the lung tissue were termed pre-metastatic niches[72], and were locations where disseminated cancer cells could eventually be detected. However, it was unclear whether other sites within the lung could also provide microenvironments favouring the foundation and outgrowth of metastases, or whether $VEGFR1^+$ cells are necessary for the formation of these specific niches[73]. Results from more recent studies have uncovered additional tumour-derived factors and mechanisms by which myeloid cells accumulate in pre-metastatic lung tissue to influence the subsequent recruitment of disseminated metastatic cells from a variety of primary tumour types (reviewed in ref. 74). For example, a study of breast cancer human xenografts and syngeneic mouse models indicated that accumulation of tumour-secreted lysyl oxidase (LOX) recruits bone-marrow-derived myeloid cells that establish a pre-metastatic niche in the lungs[75].

Since the first descriptions of pre-metastatic niches, more circulating tumour-derived factors that alter lung tissue have been identified, including the inflammatory cytokine MCP1 (monocyte chemotactic protein 1; also known as CCL2)[76] and the proetoglycan versican (VCAN)[77]. At present, the direct targets of these tumour-derived factors (for example, bone marrow cells or host cells in the distant tissue that is the eventual site of metastasis) are not clear[78]. The role of these factors in normal physiological processes might provide clues to this unanswered question. For example, mobilization of inflammatory monocytes is thought to be modulated by MCP-1 and its receptor, CCR2 (ref. 79).

In contrast to the tumour-supportive lung microenvironments described above, one study demonstrated that certain poorly metastatic primary breast tumours inhibit the growth of future metastases by establishing ‘anti-metastatic niches’ in the lungs[80]. In this study, primary breast tumours secreted the cytokine prosaposin into the circulation, resulting in enhanced expression of thrombospondin, an anti-angiogenic factor, in distant lung fibroblasts.

The currently available information about pre-metastatic niches leaves open two important questions. First, although experimental metastasis models have demonstrated pre-metastatic niches in organs such as adrenal glands[77], liver[81] and lymph nodes[82], it is not yet clear whether such perturbations are most frequently observed in the lung because it is simply the most-studied site in experimental metastasis models, or whether it is an organ that is particularly predisposed to inflammation. The potentially unique status of the lungs is suggested by a recent report demonstrating that allergy-induced inflammation caused the

lungs to serve as a target tissue for metastasis[83]. Second, as many cancer patients experience bone metastases (particularly those with metastatic breast or prostate cancer[84]), and as most patients display disseminated tumour cells in the bone marrow even at early stages of disease[85,86], it is plausible that similar tumour-supportive niches are also formed in the bone marrow. The fact that various cancer types can elicit tumour-specific systemic effects in the bone microenvironment from a distance (as discussed previously) lends some support to this notion.

A recent study suggests that these considerations are worth further exploration: in a mouse model of arthritis, the systemic inflammatory effects significantly increased breast-cancer-associated metastases to both lungs and bones in arthritic compared to non-arthritic mice[87]. The pre-metastatic lungs of arthritic mice were highly inflamed, and use of an anti-interleukin (IL)-17 antibody significantly reduced inflammation and metastatic burden in both lungs and bone.

Tumour-driven systemic processes that affect metastatic colonization

The final step in the metastatic cascade involves metastatic colonization — the outgrowth of micrometastatic deposits into overt tumours. Colonization in itself is often viewed as a series of obstacles that disseminated tumour cells must overcome to form macroscopic metastases, such as: remodelling the extracellular microenvironment, gaining access to local trophic growth factors, avoiding immune attack, acquiring a blood supply and forming a tumour-supportive TME (ref. 66). The vast majority of extravasated tumour cells are unable to form a successful tumour and thus remain dormant and eventually disappear[88,89]. Hence, metastatic colonization is thought to be the rate-limiting step in the successful generation of metastases; indeed, some studies have demonstrated that far fewer than 1% of disseminated tumour cells succeed in forming a macrometastatic growth[85,86].

In certain cases, as we discuss in detail below, disseminated tumour cells that would otherwise remain dormant can succeed in colonizing distant tissues in response to changes in the host systemic environment triggered by a distantly located tumour (Fig. 2b and Table 1). Thus, the critical determinants of whether or not a population of disseminated tumour cells succeeds in generating clinically significant metastases may include not only the intrinsic properties of the cancer cells themselves but also the state of the host environment, including both the local tissue microenvironment and the systemic physiological environment (Fig. 3).

Impact of systemic regulation of immune function on metastatic colonization

Early experimental models of fibrosarcoma suggested that certain aggressively growing tumours attenuate the anti-tumour immune response of the host, thereby creating a tumour-permissive systemic environment[90]. In these studies, certain fibrosarcoma cells were found to grow well in immune-deficient mice but were frequently rejected in immune-competent mice. However, these fibrosarcoma cells could grow aggressively and form tumours with short latency when implanted into immune-competent mice bearing already-established fibrosarcomas at distant sites, suggesting immune tolerance in this class of tumour-bearing

hosts. A more recent example of this mechanism of systemically induced immunological tolerance comes from work using the transgenic *HER2/neu* model of mouse mammary carcinogenesis[91].

Research using the 4T1 mouse model of murine mammary adeno-carcinoma revealed that tumour-derived G-CSF mobilized neutrophils into the circulation, which played a pro-metastatic role by creating an immunosuppressive microenvironment at metastatic sites[92]. However, the influence of this pro-metastatic mechanism on the success of lung colonization by 4T1 mouse breast cancer cells remains unresolved in light of other work that used the same mouse model to show that although tumour-derived G-CSF induced neutrophil mobilization into the circulation, these neutrophils instead played an anti-meta-static role[93]. Specifically, mammary-tumour-derived CCL2 rendered G-CSF-mobilized neutrophils cytotoxic, such that after accumulating in the lungs, they inhibited metastatic colonization. Such cytotoxic tumour-entrained neutrophils were also found in the peripheral blood of breast cancer patients before surgical resection, but not in cancer-free individuals[93]. It is possible that the particular cell-surface markers used to characterize and isolate neutrophil populations in these studies account for the differences in observed outcomes. Insights into these considerations are provided by experiments showing that among the $Gr1^+$ cells that were recruited to the premetastatic lungs, the monocytic and not the neutrophil subpopulation contributed to metastatic colonization[94]. These findings point to the fact that the heterogeneity and plasticity of certain haematopoietic populations, particularly neutrophils, are an important consideration when studying tumour-modulating systemic events.

Systemic effects on angiogenesis at metastatic sites

Studies of a form of pro-angiogenic signalling that takes place between pairs of distantly located tumours (a process that was termed systemic instigation[36]) revealed different mechanisms of systemic influence on metastatic colonization[23,89,95]. One set of experiments using xenografted cell lines and primary tumour specimens from patients with luminal breast cancer or clear cell renal cell carcinoma showed that platelets act as a long-range delivery system between aggressively growing tumours and otherwise-indolent clusters of tumour cells at distant sites[96]. In this study, certain human luminal breast cancers (LBCs) mobilized proangiogenic $VEGFR2^+$ BMCs from the bone marrow and secreted proangiogenic cytokines that were taken up by circulating platelets. When otherwise-indolent breast tumour cells or primary renal cell carcinoma specimens, which were unable to undergo angiogenesis or proliferate on their own, were implanted at sites distant from these LBC tumours, pro-angiogenic BMCs and platelets converged on them, promoting their growth into highly vascularized, rapidly proliferating tumours. In these experiments, circulating platelets produced by mice bearing the human LBC tumour xenografts were found to carry bioactive human cytokines, which included VEGF, TGF-β1, PDGF-BB, PlGF, IL-6 and CXCL1, among others[96]. This finding is in agreement with earlier studies demonstrating that platelets are capable of taking up factors secreted by breast tumour cells *in vitro*[97] and glioma and prostate tumour cells *in vivo*[98]. Although this work showed that the cognate receptors for some of these signalling molecules were activated within the TME (ref. 96), it has not yet been established conclusively that the bioactive cytokines acquired in

primary tumours by the platelets are delivered to distantly located nests of tumour cells. Thus, although a large body of literature has described the importance of platelets during tissue remodelling and wound healing[99], the selective release of platelet bioactive cargo[100] and the ability of platelets to help cancer cells to metastasize[101], their role as conveyors of systemic signals is only beginning to be appreciated. In contrast to these pro-angiogenic systemic mechanisms, early studies using mouse cell lines and human tumour cell line xenografts indicated that certain primary tumours can suppress the outgrowth of distant metastases by secreting anti-angiogenic factors, such as endostatin and angiostatin[102].

Systemic promotion of the metastatic tumour microenvironment

As described, certain triple-negative breast cancers release OPN into the circulation to render haematopoietic cells in the bone marrow protumorigenic[36]. These activated BMCs were capable of travelling not only to primary tumours, but also to otherwise-indolent tumours at distant sites, and to weakly metastatic disseminated tumour cells in the lungs, thereby acting as the primary mediators of systemic instigation. Subsequent research demonstrated that these pro-tumorigenic BMCs secreted elevated levels of the growth factor granulin (GRN)[103] in the marrow before their mobilization as well as within the tumour microenvironment following their recruitment to microscopic nests of tumour cells[37,104]. After entering the TME, GRN activated resident mam-mary fibroblasts, causing them to adopt a CAF phenotype associated with expression of pro-inflammatory and matrix-remodelling genes that further support tumour progression[37]. A complementary study using a mouse model of squamous skin carcinogenesis demonstrated that CAFs expressing many of the same factors (including CXCL2, IL-6, IL-1β, IL-8, Cox-2, CCL2 and CXCL3) promoted the recruitment of circulating inflammatory cells to the tumour site[105]. Ultimately this sequence of events results in the outgrowth of malignant tumours with highly desmoplastic stromata.

Alterations in the TME by distant tumours may also be reflected in the spectrum of mitogenic and trophic factors that neoplastic cells harvest from their nearby environment. Specifically, systemic signals released by aggressively growing breast tumour xenografts caused the formation of a tumour-supportive microenvironment enriched in epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) at distant anatomical sites where clusters of otherwise-indolent tumour cells already resided[104]. These indolent tumour cells were only able to form proliferating tumours when both EGF and IGF-1 were made available to them as a result of systemic instigation, which was prevented by treating the mice with a combination of EGFR and IGF-1R inhibitors.

A recent report has exposed CAFs as a previously unrecognized source of systemic instigation of disease progression through gene expression analyses of micro-dissected normal and cancer human prostate tissue that revealed significant upregulation of growth/differentiation factor 15 (GDF15; also known as macrophage inhibitory cytokine-1, MIC-1), a member of the TGF-β family of growth factors, in the cancer-specific TME relative to the normal tissue stroma[106]. CAFs derived from a mouse model of prostate carcinoma, as well as normal fibroblasts in which GDF15 was ectopically expressed, promoted tumour growth when directly admixed with otherwise-indolent prostate carcinoma cells and implanted into

mice[106]. Elevated plasma levels of GDF15 that had been previously observed in certain cancer patients[107] and in the experimental mice being studied[106] prompted further experiments that demonstrated GDF15-expressing CAFs implanted into one site in the mice promoted the outgrowth of distantly implanted, indolent prostate cancer cells. Although the underlying assumption of these findings is that the disseminated prostate tumour cells benefit from the effects of circulating GDF15 due to its effect on cell proliferation and migration, the direct target(s) of GDF15 in this systemic promotion of metastatic colonization remain unknown.

Metastatic colonization of the lung was also recently reported to occur as a result of systemic instigation in an experimental xenograft model of oesophageal cancer, for which IGF-II (insulin-like growth factor-II) is necessary[108]. In this study, an IGF-II-secreting oesophageal tumour xenograft could significantly enhance the growth of a distantly implanted tumour, as well as promote metastatic colonization of cancer cells that had disseminated to the lungs. Treating the mice with the IGF-I/IGF-II receptor inhibitor cixutumumab had significant suppressive effects on tumour growth and metastasis. Although the direct target of primary-tumour-derived systemic IGF-II is assumed to be the disseminated tumour cells due to the effects of IGF-II on AKT-dependent tumour cell survival, this hypothesis was not unequivocally proven.

Other systemic processes for consideration

Early considerations of cancer as a systemic disease raised the question of whether the observed manifestations of systemic involvement were an integral part of tumour development or whether they were nothing more than epiphenomena of malignancy — paraneoplastic conditions that had little, if any, effect on tumour growth. Recent results however, suggest that conditions that were once thought to be paraneoplastic syndromes may, in ways that are still unclear, directly benefit the tumours that generated them. The evidence in these cases is still equivocal. The frequently observed dysfunctional immune responses[109] and neuropathies[110] in cancer patients may well support the expansion of established tumours through mechanisms that remain poorly resolved. More detailed mechanistic understanding has emerged from studies of the pathologic elevation of circulating platelet counts, termed thrombocytosis, which is observed in patients and is associated with reduced patient survival[111,112]. A recent study of an ovarian cancer experimental model revealed certain mechanisms by which cancer-associated thrombocytosis occurs: hepatic thrombopoietin (TPO) synthesis was enhanced in response to elevated ovarian carcinoma-derived IL-6 in the circulation. This circulating TPO impinged on bone marrow megakaryocytes, resulting in acceleration of the rate of platelet production[112] (Fig. 1b). Moreover, therapeutic targeting of platelets using an anti-platelet antibody resulted in reduced tumour growth and angiogenesis in experimental mice, and tumour-derived IL-6 and hepatic TPO were linked to thrombocytosis in a large cohort of ovarian cancer patients.

The various systemic mechanisms by which incipient tumours can progress to a malignant state in response to systemic instigation raise the question of whether other systemic states exist in which neoplastic disease progression can be modulated in the absence of an

instigating tumour. For example, epidemiological evidence indicates that obesity contributes to heightened incidence of multiple cancer types[113,114]. Pre-clinical evidence exists in support of the idea that systemic changes associated with pregnancy can affect the outgrowth of incipient breast tumours[115]. Finally, a number of studies suggest that the as-yet-undefined systemic effects of surgery can trigger outgrowth of dormant metastases[116,117].

Clinical implications and future perspectives

The realization that cancer is often, if not invariably, a systemic disease suggests that a variety of therapeutic interventions could be designed to inhibit or interdict the signalling mechanisms that underlie systemic changes in cancer patients. Although strategies targeting primary malignancies have improved markedly, there are no cures for metastatic disease, which remains the underlying cause of death for the majority of cancer patients. If a broad spectrum of metastases are eventually found to depend on systemic signalling, a new avenue of therapy development would be opened, as, in theory, the relevant systemic signals travelling through the circulation should be more susceptible to interdiction (for example, by a small-molecule inhibitor or neutralizing antibody) than the paracrine and juxtacrine signals that operate within the interstices of solid tumours.

Independently of their vulnerability to intervention, these systemic signalling mechanisms hold implications for various types of existing cancer therapies and treatment modalities. For example, recombinant G-CSF is often administered to bone marrow donors, transplant patients and some cancer patients undergoing myelosuppressive chemotherapy, with the intention of mobilizing their haematopoietic stem and progenitor cells into the circulation[118]. However, as discussed earlier, pre-clinical evidence indicates that G-CSF mobilizes into the circulation BMCs that are capable of promoting disease progression both at the primary tumour site and in the metastatic setting. Active investigation into the clinical use of haematopoietic growth factors, such as G-CSF and a related haematopoietic stimulating factor, GM-CSF, is ongoing.

Anti-angiogenic therapies, which are used in the oncology clinic, serve as a second example. A compelling pre-clinical study showed that when tumour-free mice were treated with anti-angiogenic therapy, plasma levels of a number of the systemic tumour-promoting factors enumerated earlier (including VEGF, SDF-1α, G-CSF and OPN, among others) were elevated in a dose-dependent fashion compared with those of untreated mice, implying that these treatments used to inhibit tumour growth might actually promote it[119]. Similarly, other pre-clinical studies have shown that certain chemotherapies and anti-VEGF treatments promote mobilization of cells from the bone marrow that are capable of enhancing tumour growth[120–122].

Findings such as these have caused some to propose that host ‘systemic conditioning’ provides an explanation for why certain patients are predisposed to the outgrowth of certain cancers, as in the case of radiation treatment[123], or to disease relapse, as in the case of certain chemotherapies[124]. At present it is difficult to know whether or not these treatments, which are designed to benefit cancer patients, may instead stimulate tumour growth.

The ability to identify tumours that are capable of eliciting a host systemic response as well as tumours that can respond to changes in the host systemic environment will carry significant implications for future risk stratification strategies. For example, testing tumour tissues for their ability to alter the systemic environment in pre-clinical models may allow for more accurate identification of patients with a high likelihood of future relapse. Ultimately, the goal of such studies is to devise tests that will allow oncologists to more accurately identify patients who may benefit from specific adjuvant therapies at a time when the progression to overt metastatic disease can still be prevented or at least significantly delayed.

The potential for defining a tumour-specific systemic environment is also leading to a search for biomarkers of malignancy. The studies described above suggest that systemic cellular and molecular signals play a role in driving malignancy, and that a better understanding of these signals may lead to the development of sensitive prognostic tests. For example, recent evidence supports the idea that an increased ratio of circulating neutrophils versus lymphocytes, previously known to be an indicator of systemic inflammation, seems to function as an outcome determinant in patients with various types of cancer, particularly advanced colon and pancreatic cancers, and that this ratio can be used to predict survival and stratify treatment[125–127]. Recently, the neutrophil-tolymphocyte ratio used in combination with elevated platelet count was found to be predictive of the future clinical course of colorectal cancer[128]. The Glasgow Prognostic Score, which measures circulating C-reactive protein and albumin, is another measure of systemic inflammation that has been in use for over a decade and has independent prognostic value for cancer patients in a variety of clinical scenarios[129].

These types of measurements would seem to represent the tip of a far larger iceberg: as the list of tumour-derived cytokines, unique circulating pro-tumorigenic haematopoietic cells and platelets and tumour-derived cell-free particles such as microvesicles expands, so will the opportunities to discover novel biomarkers that are highly useful for patient diagnosis and prognosis.

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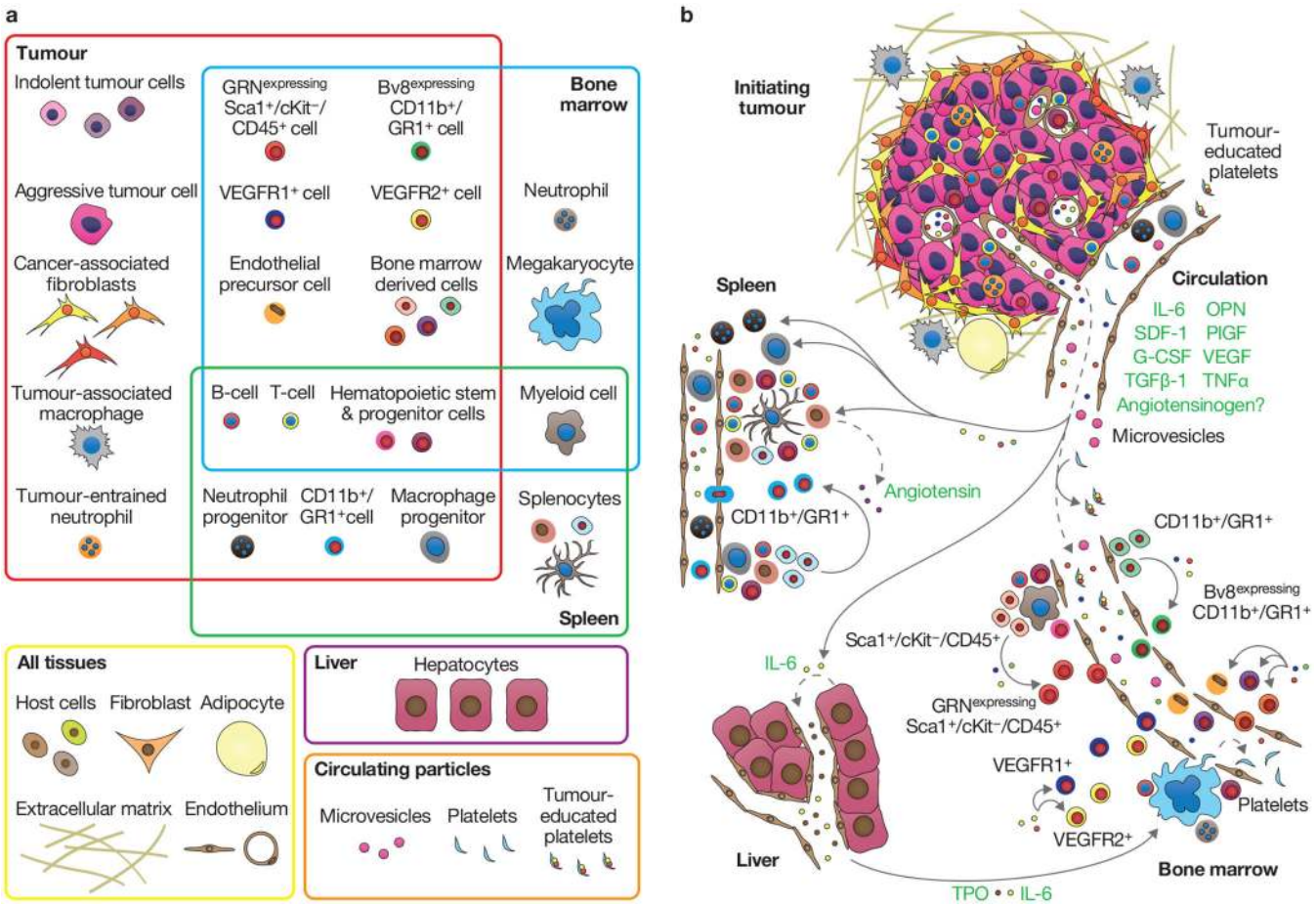

Figure 1.

Composition of local and systemic tumour environments. (**a**) Cell types that comprise tumour tissues and play a role in cancer pathogenesis are depicted, including cancer cells, normal host cells and tumour-derived and/or -entrained cells. Some of the cells that operate within the tumour microenvironment originate from distant sources, including bone marrow and spleen; these cells are represented in areas of overlap between the indicated tissues. Also represented are other normal tissue cells, circulating cells and cell-free particles that are known to be modulated in response to malignancy. Some groups of cells (for example, bone-marrow-derived cells) are illustrated as a collection of differently coloured objects to represent their heterogeneity. This illustration also serves as a key to Figs 2 and 3. (**b**) Some of the tumour-derived cytokines (green text and differently coloured small particles) and microvesicles that are known to play a necessary role in mobilizing tumour-supportive host cells from tissues at distant anatomical sites. In some cases, these host cells are rendered pro-tumorigenic even prior to their mobilization. In most cases, the precise mechanism of action of these tumour-derived cytokines is not completely understood. Ultimately, these tumour-driven systemic events facilitate the growth of the initiating tumour. Solid arrows indicate activation or translocation of cell types and molecules; dashed arrows represent secretion of molecules.

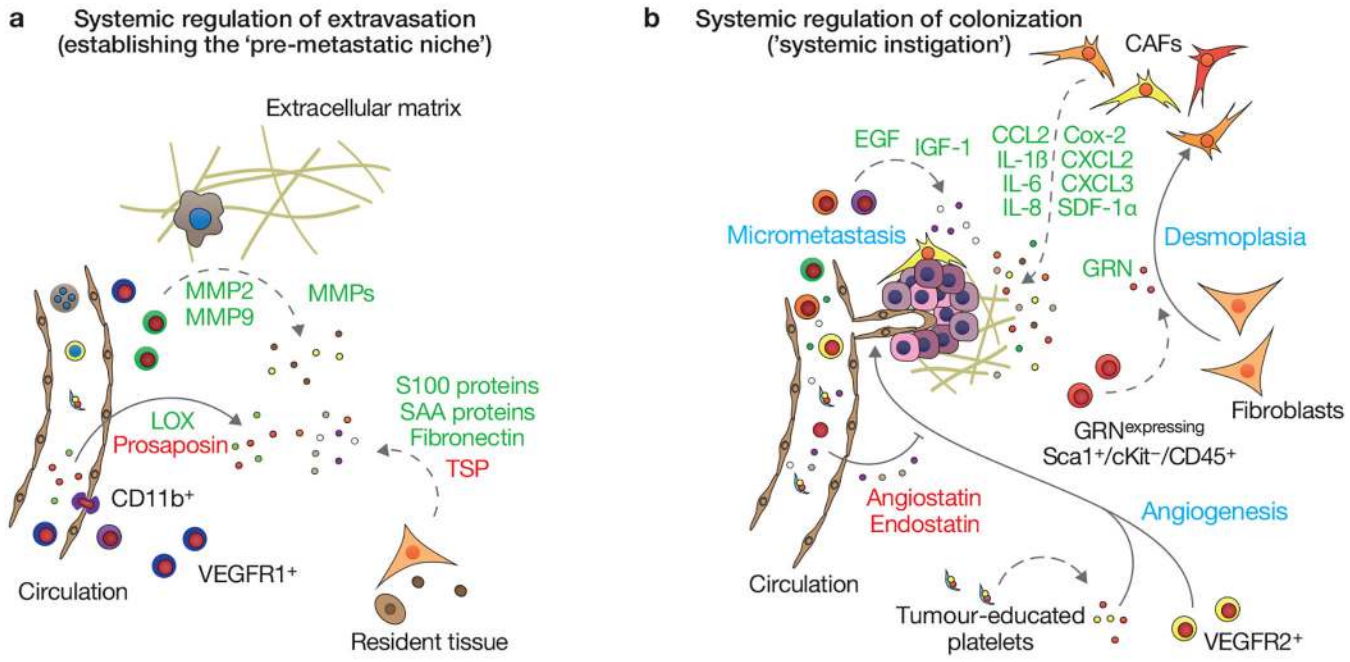

Figure 2.

Mechanisms of systemic regulation of metastatic tumour cell extravasation and colonization. (**a**) 'Pre-metastatic niches' are thought to form as a consequence of tumour-derived systemic factors that alter the tissue parenchyma of organs at distant sites, for example by extracellular matrix remodelling and activating resident tissue fibroblasts, as well as mobilizing bone-marrow-derived cells that subsequently incorporate into the parenchyma of these tissues. These niches are thus amenable to recruitment and extravasation of circulating metastatic tumour cells. Importantly, some tumour models have also revealed inhibitory factors that accumulate at pre-metastatic sites. (**b**) Circulating factors and bone-marrow-derived cells can affect disseminated micrometastases that would otherwise remain indolent, thus promoting their subsequent colonization into macroscopic metastases. For example, some reports have demonstrated promotion of vascularization by recruitment of pro-angiogenic bone-marrow-derived cells and platelets. Conversely, primary-tumour-derived anti-angiogenic factors have been reported to inhibit outgrowth of distant metastases. Other reports have revealed molecular mechanisms by which metastatic colonization is promoted by bone-marrow-derived cells that directly promote tumourcell proliferation and/or activation of tissue fibroblasts. Processes that affect colonization are represented in blue text, pro-tumorigenic factorsare represented in green text, and tumour inhibitory factors are shown in red text. Solid arrows indicate activation or translocation of cell types and molecules and dashed arrows represent secretion of molecules. For labelling key of cell types, see Fig. 1a.

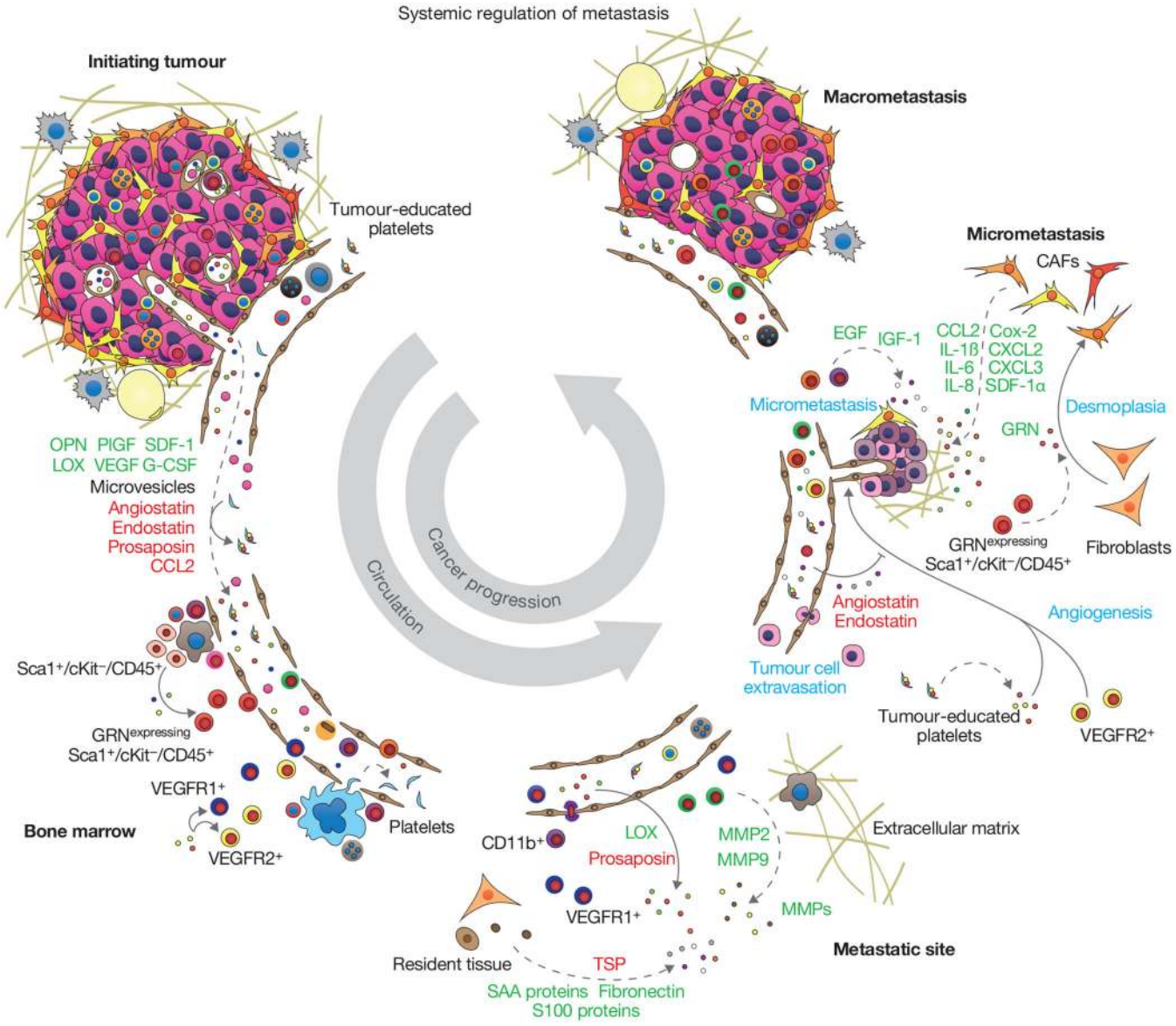

Figure 3.

Tumour-driven pathophysiological processes underlying cancer progression. Tumour-mediated events are depicted in space and time in a counter-clockwise fashion beginning with the initiating tumour. Although this cascade of events is represented in a unified fashion, it is clear that tumours from different cancer types employ different systemic tumour-promoting mechanisms that thus far seem to be context- and tissue-specific. In some cases, initiating tumours secrete cytokines into the circulation that cause mobilization of haematopoietic cells from distant organs; these cells can then contribute to pre-metastatic niche formation and/or promote metastatic colonization. In other cases, initiating-tumour-derived cytokines seem to directly affect growth of metastatic colonies at distant anatomical sites. In yet other cases, initiating-tumour-derived cytokines can be carried by circulating microvesicles or platelets, which serve as transporters of these cytokines to distant tissues or metastatic sites. Processes are represented in blue text, pro-tumorigenic factors are

represented in green text, and tumour inhibitory factors are shown in red text. Solid arrows indicate activation or translocation of cell types and molecules and dashed arrows represent secretion of molecules. For labelling key of cell types see Fig. 1a.

Table 1

Summary of known tumour-derived factors that act systemically

Initiating source	Systemic factor	Distant target tissue	Effect on initiating tumour	Effect on pre-metastatic tissues	Effect on disseminated tumours
T	G-CSF	Bone marrow: myeloid cells[34,122]; endothelial progenitor cells[122]	Promote angiogenesis[34,122]; Confer resistance to angiogenesis inhibitors[31]	Promote[92] or inhibit[93] metastatic seeding in lung	Promote[94] or inhibit[93] metastatic colonization
T	VEGF-A	Bone marrow: haemangiogenic cells[38]; myeloid cells[38,71]; VEGFR1$^+$ cells[71–73] Lung: tissue parenchyma[70]	Promote angiogenesis[38]	Upregulate chemotactic proteins and activate MMPs in lung; BMDCs form pre-metastatic niches[70–73]	
T	PIGF	Bone marrow: haemangiogenic cells[38]; VEGFR1$^+$ cells[72] Lung: tissue parenchyma[72]	Promote angiogenesis[38]	Upregulate chemotactic proteins; activate MMPs; BMDCs form pre-metastatic niches[72]	
S (CAFs)	SDF-1	Bone marrow: endothelial progenitor cells[39–41]; haematopoietic progenitor cells[41]	Promote angiogenesis[40]		
C, MV	OPN	Bone marrow: HPCs[36,37]; endothelial progenitor cells and myeloid cells[65]	Promote proliferation, invasion and angiogenesis[65]		Promote metastatic colonization[36]; Aid formation of metastatic TME[36,37,95]
T	ANG-II	Spleen: myeloid cells[50]; monocytes, granulocytes[51]; HSCs, monocytes, neutrophils[52]	Promote tumour growth and metastasis[50–53]		
T, U	TGF-β	Bone marrow: myeloid cells[71] Lung: tissue parenchyma[70,71]		Remodel lung parenchyma to promote pre-metastatic niche formation[71]	
T, U	TNF-α	Bone marrow: myeloid cells[71] Lung: tissue parenchyma[70,71]		Remodel lung parenchyma to promote pre-metastatic niche formation[71]	
C	LOX	Lung: tissue parenchyma[75]		Recruit myeloid cells to form pre-metastatic niche[75]	
C	MCP-1	Lung: tissue parenchyma[76]		Recruit BMDCs; form niche; suppress NK cells[76]	
C	Versican	Bone marrow: myeloid cells[77]		Promote niche formation[77]	
C	Prosaposin	Lung: tissue parenchyma[80]		Inhibit angiogenesis to form anti-metastatic niche[80]	
C	Endostatin	Disseminated tumours: TME[102]			Inhibit angiogenesis[102]
C	Angiostatin	Disseminated tumours: TME[102]			Inhibit angiogenesis[102]
S (CAFs)	GDF15	Disseminated tumours: tumour cells	Promote migration and invasion[106]		Promote survival, proliferation[106]

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Initiating source	Systemic factor	Distant target tissue	Effect on initiating tumour	Effect on pre-metastatic tissues	Effect on disseminated tumours
C	IGF-II	Disseminated tumours: tumour cells	Promote proliferation and survival[108]		Promote survival, proliferation[108]
T	Various	Circulating platelets: granule content[96–98]			Release contents to aid vascularization and tumour growth[96,97]
MV, P	Various	Bone marrow: HPCs[63,65] Lung: tissue parenchyma[63,64]	Recruit BMDCs to mediate tumour growth, angiogenesis and chemotherapeutic resistence[65]	Promote vascular leakiness in lung; 'educate' pro-angiogenic BMDCs[63,64]	Promote vascularization[65]
T	Unidentified	Bone marrow: $VEGFR2^{+}$ pro-angiogenic cells[96]			Promote vascularization[96]

Shown are tumour-derived factors that act to affect: (1) the initiating tumour from which they were derived; (2) distant tissues before metastatic dissemination; or (3) colonization and progression of disseminated micrometastases at distant anatomical sites. C, cancer cells; S, stromal cells; CAF, cancer-associated fibroblast; T, tumour tissue (specific cellular source unspecified); MV, tumour-derived microvesicles; P, tumour-modulated platelets; U, detected in circulation in cancer-specific manner but source undetermined; BMDC, bone-marrow-derived cell; HSC, haematopoietic stem cell; HPC, haematopoietic progenitor cell; TME, tumour microenvironment; ND, not determined.

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