Inflammation fires up cancer metastasis

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Author: Bin-Zhi Qian

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Bin-Zhi Qian1, 2*
1 University of Edinburgh and MRC Centre for Reproductive Health, 2 Edinburgh Cancer Research UK Centre Queen's Medical Research Institute,
EH16 4TJ, Edinburgh, United Kingdom
*Correspondence to Bin-Zhi Qian, Binzhi.qian@ed.ac.uk

Bin-Zhi Qian PhD
Reader
Chancellor's Fellow & CRUK Career Development Fellow Edinburgh Cancer Research UK Centre & MRC University of Edinburgh Centre for Reproductive Health University of Edinburgh
Tel: +44 (0)131 2426765
E-mail: binzhi.qian@ed.ac.uk

Abstract: Metastatic disease is the major challenge of cancer that accounts for over 90% of total cancer lethality. Mounting clinical and preclinical data now indicate that inflammation, a potent immune and repair response, is indispensable for metastasis. In this review we describe our current understanding of how major inflammatory cells contribute to metastatic cascade with a focus on the primary tumour. We also discuss exciting new directions for future research and novel therapeutic approaches to tackle metastatic disease through targeting inflammation.

Keywords: metastasis; inflammation; cancer; immunology

Introduction

Inflammation is a response that an organism uses to resolve infection, tissue injury or other cellular stress, and to restore tissue function through repair mechanisms [1]. It is a sophisticated process involving extensive crosstalk among different immune cells as well as non-immune cells, such as epithelial cells, endothelial cells and fibroblasts. Unlike normal tissue, cancer involves continuous cell renewal and proliferation that induces persistent inflammation [2]. In fact, inflammation is observed in almost every cancer and is one of the hallmarks of cancer [3]. Cancer associated inflammation involves crosstalk between both malignant and nonmalignant cells through mediators (e.g. cytokines, chemokines and prostaglandins) in autocrine and paracrine manner [4]. Joint forces with genetic alteration, the inflammatory tumour environment eventually leads to tumor progression and metastasis [5]. For example, inflammatory response associated with epithelial cell senescence contributes significantly to transformation and carcinogenesis in the absence of p53 tumour suppressor gene, which can be inhibited with anti-inflammatory drugs [6]. Treatment with the anti-inflammatory drug dexamethasone also significantly suppressed cancer dissemination through suppression of epithelial to mesenchymal transition (EMT), a process epithelial cell uses to obtain migratory and invasive properties [7]. Thus, inflammation is an indispensable driver for cancer metastasis.

Mechanistically, tumour associated inflammation produces mutagenic factors (e.g. reactive oxygen species) that drive tumour initiation[5]. Tumour associated inflammation is a source of survival, growth and pro-angiogenic factors, as well as extracellular matrix (ECM)-modifying enzymes that facilitate angiogenesis, invasion and metastasis [8, 9]. Inflammation induced angiogenesis not only provides necessary nutrients for tumour growth, but also provides a 'highway' for tumour to escape from the

primary tumour site to start their journey of distal metastasis. Inflammation is also associated with suppression of anti-tumour immune responses. This leads to tumour escaping from host immune surveillance that is essential for almost all steps of metastatic tumour progression [10, 11]. This review will discuss major host cell types involved in inflammation and their contribution to cancer metastasis with a focus on the series of events that enables tumour cells to escape from the primary tumour including angiogenesis, ECM remodeling, immune suppression, invasion and intravasation (Figure 1).

Macrophages

Macrophages are powerful regulators of inflammation[12, 13]. They are often the most abundant immune cells infiltrating the tumour and their infiltration is associated with poor prognosis and treatment failure[14]. These tumour-associated macrophages (TAMs) play multiple roles in promoting cancer metastasis.

Macrophages potently promote tumour angiogenesis that contributes significantly to metastasis. Initial experimental evidence comes from in vivo studies using Polyoma middle T antigen (PyMT) onco-protein induced mouse mammary tumour model. In this model, macrophage deficiency through genetic ablation of colony stimulating factor 1 (CSF1), the major lineage growth factor, significantly inhibited angiogenesis [15] and distal metastasis [16, 17]. Part of the mechanism may act through macrophage derived angiogenic factors including vascular endothelia growth factor VEGF [18]. Transcription factor Ets2 in TAMs acted downstream of the CSF1 signaling that promote PyMT breast cancer lung metastases at least partly by promoting angiogenesis in the primary tumours [19]. Furthermore, macrophage derived Wnt7b is critical for angiogenic switch in the PyMT primary tumours and macrophage specific genetic depletion of which significantly inhibited lung metastasis [20]. In Lewis lung carcinoma model, interleukin 1 alpha (IL-1a) expressed by cancer cells can induce the recruitment of cyclooxygenase 2 (COX2)-expressing macrophages that in turn secretes inflammatory cytokines to promote tumor angiogenesis and metastatic progression [21]. Reciprocally, new blood vessels secrete angiopoietin 2 to recruit macrophages expressing TEK receptor tyrosine kinase (also known as Tie2) to further promote angiogenesis and tumour dissemination from the primary tumour [22]. IL-1b expression by myeloid cells has also been shown to induce VEGF expression in endothelial cells that promote angiogenesis, inflammation and tumour progression [23].

Macrophages also actively remodels extra-cellular matrix (ECM) through production of extra-cellular proteinases, such as MMPs and cathepsins. ECM remodeling together with the release of ECM binding cytokines promote angiogenesis, inflammatory cells infiltration and tumour cell invasion. For example, TAM derived cathepsin B and cathepsin S can promote cancer cell egress and angiogenesis [24]. Matrix metalloproteinase 9 (MMP9) derived from TAMs together with other myeloid cells is important for skin cancer progression [25]. In pancreatic islet cancer models, myeloid cell derived MMP2 and MMP9 modulate the ECM and release VEGF from ECM that enhances angiogenesis [26]. TAMs also promote tumour cell interaction with ECM through secretion of Secreted Protein Acidic and Rich in Cysteine (SPARC, also known as osteonectin). This interaction is dependent on tumour cell alpha(v)beta(5) integrin, which contribute significantly to tumour invasion and metastasis [27]. Interestingly, TAMs are able to modulate tumour cell integrin clustering and enhancing its adherence to extracellular matrix through the secretion of CCL18, which promotes invasion and metastasis [28]. Interaction with ECM can regulate macrophages' own function. Versican (VCAN), a extracellular matrix protein secreted by Lewis lung carcinoma cell, interact with Toll like receptor 2 and 6 on macrophages to induce expression of inflammatory cytokines IL6 and TNFa which is critical for tumour metastasis in lung[29]. Consistently, VCAN promotes macrophage infiltration and lung metastasis in a mouse model of invasive bladder cancer. Macrophage ablation in this model significantly decreased lung metastases and the levels of COX2 and inflammatory factors IL-6, CCL2

2

in the tumor microenvironment [30]. Together, these results indicate that the interaction among TAMs, tumour cells and ECM significantly promotes tumour cells escape from primary tumour.

Macrophages have been shown to interact with tumour cells directly to promote their invasion into the surrounding tissue and intravasation. Using intra-vital imaging, Wyckoff and colleagues showed that cancer cells in PyMT tumours invade surrounding tissues together with TAMs [31]. In this process, cancer cells secrete CSF1 to promote TAM mobility. In turn, TAMs secrete epidermal growth factor (EGF) to activate the corresponding receptor on cancer cells that enhances their motility and invasive potential by increasing invadopodium formation and matrix degradation[32]. Mechanistically, CSF1 receptor (CSF1R) in macrophages activates Wiskott–Aldrich syndrome protein (WASP) to promote TAM migration towards CSF1-producing cancer cells and stimulates EGF release [33]. Tumour cell CSF1 production is dependent on steroid receptor co-activator 1 (SRC1) which when genetically deleted disrupts the paracrine signaling between tumour cell and TAMs. This significantly inhibited tumour cell invasion in PyMT tumours and subsequent lung metastasis without affecting primary tumour growth[34]. Interestingly, macrophage-tumour cell paracrine signaling can also be established through macrophage derived heregulin β1 (HRGβ1) and tumour cell derived CXCL12 that triggers tumour invasion [35]. In human breast cancer xenograft models, paracrine signaling of CCL18 and GM-CSF derived from macrophage and tumour cell respectively induces macrophage polarization, tumour cell migration and subsequent metastasis[36]. Recent studies also illustrated that macrophage secreted factors stimulate S100A8 and S100A9 expression in colon cancer cells that promoted their invasion and liver metastasis [37]. Thus, depending on tumour types, multiple signaling pathways can be hijacked by tumour cells to interact with TAMs to achieve invasion and metastasis.

Tumour cell intravasation has been reported to occur in association with perivascular TAMs in breast cancer models [38]. This seems to be associated with a micro anatomic structure within the tumour, which is composed of direct interacting macrophage, endothelia and invasive tumour cell (termed as 'tumour microenvironment for metastasis or TMEM') [39]. Regardless of clinical subtypes or tumour grade, TMEM abundance in breast cancer specimens correlates with tumour cell expression of the invasive isoform of MENA (an actin binding protein essential for chemotactic direction and invasion) [40]. This significantly potentiates EGF signaling in cancer cells [41] and promotes macrophage-induced intravasation of human breast cancer cells [39]. Using intra-vital microscopy, our recent studies indeed illustrated that the TMEM structure control tumour cell intravasation by transiently increase local vascular permeability in a VEGF dependent manner [42]. Importantly, the abundance of TMEM has been shown to predicate metastasis of ER+ breast cancer in a case control study with over 3700 patient samples [43]. Together, these data strongly indicate that tumour-macrophage crosstalk plays a central role in promoting tumour cell intravasation. Whether this mechanism is commonly used across different tumour types and whether TMEM can be used as prognostic marker for other cancers will be topics of great interests for future research.

The metastasis promoting function of TAM is tightly regulated by the inflammatory tumour microenvironment. TAM recruitment into tumour hypoxia area is partly mediated by neuropilin 1 (Nrp1), that binds to Semaphorin-3A (SEMA3A). Disruption of this signaling significantly suppresses the pro-angiogenic function of TAMs and inhibits tumour progression and lung metastasis [44]. Interleukin 1 receptor activation is observed in patients with renal cell carcinoma (RCC) and is essential for TAM phenotype and function in RCC xenograft models that promotes tumour angiogenesis and invasion [45]. Inhibitor of cyclooxygenase 2 (COX2) the enzyme that generates inflammatory factor prostaglandin, significantly suppresses VEGF expression in TAMs and inhibits breast cancer metastasis [46]. Furthermore,

TAM polarization can be skewed from a pro-tumorigenic to an anti-tumour phenotype by altering the signals in the tumour microenvironment. For example, overexpression of histidine-rich glycoprotein (HRG) can down-regulate placental growth factor (PlGF) expression and alter TAM polarization. This normalizes the leaky blood vessels and inhibits metastasis [47]. Inhibition of CSF1 receptor signaling alters TAM polarization in GEM models of Glioblastoma multiforme, which leads to dramatic tumour regression [48]. Together, these studies indicate that signaling pathways regulating TAM functions can be promising therapeutic targets to treat advanced tumour.

Other myeloid cells
Neutrophils. Neutrophils may contribute to metastatic disease. Elevated neutrophil number in blood is associated with increased metastasis risk of many solid tumours [49]. A large-scale meta-analysis indicated that intra-tumoural neutrophil-related gene signature is associated with poor prognosis [50]. Indeed, a recent study showed that neutrophil infiltration in a genetically engineered mouse model of melanoma enhanced tumour migration and invasion resulting in distal metastasis. This neutrophil infiltration was mediated by high mobility group protein B1 (HMGB1) derived from the ultraviolet UV-damaged keratinocytes, which illustrated a novel mechanism of UV induced inflammation in melanoma metastasis [51]. Consistently, granulocytic immature myeloid cells overexpressing S100A9 proteins, a key inflammation regulator, have been shown to promote tumour formation in models of skin cancer [52]. Neutrophils recruited by tumour-derived CXCL15 have been shown to promote lung metastasis in a xenograft model of intrahepatic cholangiocarcinoma [53]. Together these data indicate that neutrophils may promote tumour progression and escape from primary tumour with the models tested.

Of note, neutrophils in the distal metastatic organ have been shown to have either pro- or anti- metastatic functions [54-57]. This suggests that the phenotype and function of neutrophils are tightly regulated by specific environmental factors [58]. Further studies are required to test the role of neutrophils in primary tumour across different cancer types and if their anti-metastatic function can be elicited by altering signal from the inflammatory microenvironment.

Myeloid derived suppressor cells (MDSCs) MDSCs have been defined as CD11b+Gr1+ immature myeloid cells that have the potential to inhibit immune response [59, 60]. Direct evidence that MDSCs promote metastasis was initially shown in the PyMT mouse mammary tumour model [61]. In this study, abrogation of TGFβ signaling in tumour cells leads to chemokine CXCL5 expression and MDSC recruitment which promote tumour cell invasion through MMPs. Recent studies indicate the recruitment of MDSCs may be also mediated by G-CSF expression in cancer cells dictated by mTOR signaling [62]. However, MDSCs are a heterogeneous population of cells with distinct morphology and cell surface expression of the lymphocyte antigens LY6C and LY6G. The subsets are termed monocytic MDSCs (CD11b$^+$Ly6C^{hi}Ly6G^{low} cells) and granulocytic MDSCs (CD11b+LY6ClowLY6G+ cells) [63]. Essentially, the cell surface markers of monocytic MDSCs and granulocytic MDSCs are identical to monocytes and neutrophils. Both subsets in mice suppress immune effector cell function by nitric oxide synthase (iNOS) and arginase 1 [63]. Furthermore, monocytic MDSCs have been shown to give rise to granulocytic MDSCs [64]. Thus caution needs to be excised to dissect the contribution of each population and mature macrophages that can be derived from monocytes to metastasis in various tumour models.

Lymphocytes
T cell T cell is a type of lymphocyte that matures in thymus and characterized by T cell receptor expression. It contains many subsets. CD8+ cytotoxic T cell (CTL) is the subset that plays a central role in cell-mediated immunity. Its cytotoxicity is also key to anti-tumour immune surveillance that would inhibit every step of

cancer metastasis. CTLs are usually suppressed in advanced cancers and re-activation of their function is the focus of current immune therapy that exhibited great promises in treating metastatic cancer [65].

CD4+ T helper (Th) cells are highly heterogeneous in regulating inflammation. Earlier studies characterized two major populations of Th cells: Th1 and Th2 characterized by expression of Type 1 cytokine (e.g. interferon-gamma, IFN_γ, tumor necrosis factor-alpha, TNF_a and interleukine-2, IL-2) and Type 2 cytokine (e.g. IL4, IL10) respectively. Th1 response activates CTLs and other cytotoxic cells, thus is being used in clinical trials of cancer immunotherapies including therapeutic vaccines[66]. In contrast, Th2 cell activity leads to humoral immunity and inflammation that may promote tumour progression[67]. Via IL4 expression, CD4+ T helper cells have been shown to induce alternative activation of TAMs and secretion of EGF that directly promote tumour invasion and egress from primary tumour [68]. This IL4 expression may also be responsible for the expression of Cathepsins [24] and CCL18 [28] in TAMs that promote tumour progression and invasion. CD4+ T helper cells contain several subsets. Regulatory T cells (or Treg cells) are the subset characterized by expression of Forkhead box P3 (Foxp3) transcription factor and their potent function in suppressing inflammation and immune response [69]. Suppression mechanisms employed by Tregs are thought to contribute significantly to the inhibition of T-cell immunity to tumour-associated antigens, which is prerequisite for cancer metastasis[70, 71]. IL-17–producing CD4+ T cells, also known as Th17 cells, are a pro-inflammatory subset involved in autoimmune and inflammatory disorders [72]. Th17 mediated inflammation promoted tumour initiation in multiple models of skin carcinogenesis [73, 74]. Human CD25^{high} Th17 cells are highly infiltrated in human breast cancers with poor clinical outcome where these cells seem to suppress CTL mediated anti-tumour immunity [75]. Interestingly, breast cancer induced systemic inflammation can activate IL17 expression that promotes spontaneous metastasis through granulocyte colony-stimulating factor (G-CSF)-dependent neutrophil activation and immune suppression[54]. IL17 has also been shown to promote colorectal tumorigenesis[76, 77]. However, IL17 has also been reported to inhibit tumour growth through T cell dependent mechanisms[78]. The abundance of IL17 expressing cells in colon cancer patient samples has recently been shown to be associated with improved survival potentially through recruitment of cytotoxic CD8+ T cells [79]. Of note, there are other types of T helper cells that are being characterized recently, such as γδ T cells, Th9, Th22, follicular T helper cells etc. Their roles in inflammation and cancer are just starting to be realized [80, 81] while their role in metastasis is still illusive. Further studies should focus on dissecting the positive or negative roles different T helper cell populations in metastasis in different tissue environment and tumour stages.

B cell Cells of B lymphocyte lineage have been shown to promote or inhibit inflammation [82-84]. B cells may contribute to squamous carcinogenesis by alternatively activating macrophages via immune complex deposition[85] and by suppressing T-cell–mediated antitumor response[86]. Several recent studies illustrated important roles of B-lymphocytes in tumour progression and therapy responses in pancreatic cancer models [87-89]. Gunderson and colleagues demonstrated that B cells mediated inflammation induces TAM alternative activation and tumour progression of advanced PDAC in an Fc receptor gamma (FcRγ) dependent manner[89]. In early pancreatic neoplasia, B cells are required to support tumour growth through IL35 production[88]. B1 cells are considered to be a type of innate immune cells of B cell lineage that produce the majority of natural antibodies against infections. Interestingly, Lee and colleagues reported an increase of CD43$^+$IgM^{hi}CD5$^-$ B1 cells in mouse pancreatic neoplastic lesions. This subset of B1-cells seems to be controlled by oxygen-sensing mechanisms since pancreatic specific ablation of HIF1α further expand these cells and promote PDAC initiation[87]. Given the potent function of B cells in above discussed studies, it is likely that further studies may illustrate how B cell mediated inflammation may contribute directly to cancer metastasis.

Innate lymphoid cells (ILCs) ILCs are a group of innate immune cells that belong to the lymphoid lineage but do not respond in an antigen-specific fashion[90]. ILCs can be categorized based on their cytokine production and dependent transcription factors into three groups (1-3), mirroring the nomenclature of T cell subsets[91]. Group 1 ILCs including ILC1 and Natural Killer (NK) cells are characterized by expression of Th1 cytokines, typically IFN$_\gamma$. Group 2 ILCs express Th2 cytokines including interleukin-4 (IL4), IL5 and IL13. Group 3 ILCs are able to produce Th17 associated cytokines IL17 and IL22. Thus, these cells have specific functions in the inflammatory response in different organs [92].

NK cells are distinct from other ILCs by their potent cytotoxic activity that lyses target cell directly via production of perforin, granzyme B and pro-inflammatory cytokines like IFN$_\gamma$. The identification of their anti-tumour role dates back several decades ago[93]. In tumour, NK cells also lyse tumour cells through activation of T cell function and /or antibody-dependent cell-mediated cytotoxicity. Thus, NK cell actively inhibit almost every step of tumour metastasis. For example, recent studies indicate that NK cells keep breast and lung cancer cells in quiescence in multiple metastatic organs [94]. The cytotoxic functions of NK cells are often suppressed by tumour cells and tumour microenvironment[95] including myeloid cells[63] and Tregs[96, 97]. Of note several approaches are being tested in clinic trials to re-activate NK cells to treat late stage or metastatic tumours. Similar to T cell checkpoint blockade therapies, antibody (Lirilumab) blocking of NK cell inhibitory receptors Killer-cell immunoglobulin-like receptors (KIRs) is currently being tested in clinical trials (ClinicalTrials.gov Identifier: NCT01714739). Inhibition of the TAM (Tyro3, Axl and Mer) tyrosine kinase receptors in NK cells may also potentiate their anti-metastatic potential[98]. Adoptive transfer of human NK cells pretreated cytokine cocktail of IL-12, IL-15 and IL-18 is currently being tested in patients with acute myeloid leukemia (ClinicalTrials.gov Identifier: NCT01520558). Autologous transfer of genetically-engineered NK cells with chimeric antigen receptor (CAR) are being explored to direct NK cell cytotoxicity more specifically toward cancer cells [99]. Thus, it is with hope that reactivation of anti-metastasis activity of NK cells can soon lead to clinical benefit in the near future.

Data on the role of other ILC populations in tumour are just emerging and indicating both tumour promoting and suppressing potentials of different populations. ILC1s have been reported to suppress tumour development in PyMT mouse mammary tumour models [100]. ILC2s have been shown to promote mammary tumour growth through IL-13 production and recruitment of myeloid cells and Tregs [101]. ILC3 cells are involved in the homeostasis of gastrointestinal tract and suppression of bacteria-induced inflammation through IL-17 and/or IL-22 secretion. In contrast, in inflammatory bowel disease, ILC3 derived IL-17 enhances the inflammatory response [102]. ILC3 derived pro-inflammatory cytokines can improve tumour progression in preclinical models of colon cancer and hepatocellular carcinoma [103]. ILC3 cells are also involved in the development of human non-small cell lung cancer by modulating the tumour microenvironment [104]. Thus innate lymphoid cells may play important roles in the inflammatory environment of cancer metastasis.

Mesenchymal cells
Inflammation research has largely been focusing on immune cells in the past. Recent studies indicate that cells of mesenchymal origin, most notably mesenchymal stem cells (MSCs) and fibroblasts are important regulators of inflammatory response [105, 106]. MSCs have potent immune suppressive functions through multiple mechanisms including inducible nitric oxide synthase (iNOS), indolea- mine 2,3-dioxygenase (IDO), PGE2, IL-10, hemeoxygenase-1 (HO-1), programmed cell death 1 ligand 1 (PD-L1) and IL-6[107]. For example, human MSCs can inhibit dendritic cell differentiation and pro-inflammatory cytokine expression[108]. MSC derived PGE2 can inhibit DC maturation, reprogram macrophages to release IL10,

and switch the Th1 response to a Th2 response [109]. MSCs can also recruit immune suppressive macrophages to promote tumour growth through CCL2 secretion [110].

As the most abundant mesenchymal cells in tumour, cancer associated fibroblasts (CAFs) share many features as fibroblasts involved in wound healing and actively modulate tumour microenvironment[111]. CAF mediated inflammatory response can promote macrophage recruitment, angiogenesis and tumour progression in an NF-kB signaling dependent manner in skin cancer models [112]. CAF derived pro-inflammatory factors have also been shown to promote breast cancer progression [113]. Furthermore, MSCs and CAFs can promote metastasis through direct interaction with tumour cells. For example, bone marrow derived MSCs can be recruited by CXCL16/CXCR6 chemokine signaling into prostate cancer in vivo and differentiate into CAFs. These CAFs in turn promote prostate tumour cell invasion and metastasis through production of CXCL12 [114, 115] and CCL5 [116]. Consistently, CAFs can promote colorectal cancer cell intravasation and distal metastases through the secretion of stanniocalcin 1 (STC1) [117]. Future research is needed to better understand the direct interaction of MSC and its progenies with immune cells in modulating the inflammatory environment in cancer metastasis.

Of note, both MSCs and CAFs have been shown to promote tumour metastasis through their potent function in ECM remodeling. For example, MSCs have been shown to promote invasion of ovarian cancer cells through MMP2 and MMP9[118]. CAF is a rich source of MMPs that promote ECM remodeling and tumour cell invasion [119]. CAF have also been shown to generate mechanical pressure together with paracrine signaling that potently promote tumour invasion and metastasis [120]. These activities have been reviewed extensively recently [111] and are mostly independent of inflammation thus go beyond the scope of current review.

Conclusion

In general, inflammatory response has been hijacked by tumour cells to serve as a driving force for tumour metastasis. However, various inflammatory cells have anti-tumour potentials that can be elicited by modulation of the cytokine environment and/or signaling pathway within these cells. This provides an attractive therapeutic strategy to effectively treat advanced cancer alone or in combination with existing therapeutic modalities. Of note, even in aggressive tumours, only minority of cancer cells are migratory as revealed by intra-vital imaging studies across multiple tumour models [121, 122]. This may be partly caused by tumour cell plasticity[123] and intrinsic heterogeneity[124]. However, mounting evidence now indicates that the inflammatory tumour microenvironment is also heterogeneous which may be associated with heterogeneous tumour cell behavior [122]. For example, cells that undergo EMT have been show to reside preferentially in the perivascular region [125]. Local ECM composition and macrophage association have been shown to determine tumour cell motility in vivo [126]. Thus heterogeneity of the inflammatory tumour environment may significantly contribute to cancer metastasis at single- or multiple-cell level. Future studies characterizing this microenvironmental heterogeneity are warranted to illustrate novel mechanisms of cancer metastasis and inspire effective new therapies to eradicate this deadly disease.

Conflict of Interest statement
The authors declare that there are no conflicts of interest.

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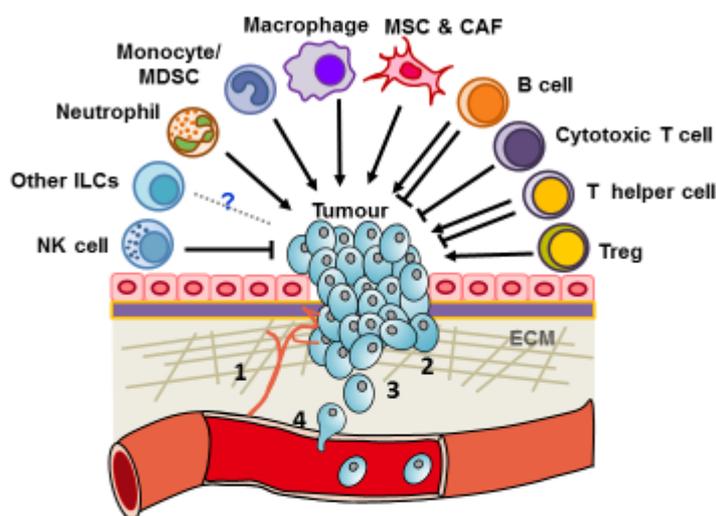
Figure 1. Inflammatory stroma in cancer egress from primary tumour: For haematogenous metastasis, the initial rate-limiting steps that allow cancer cells to escape from the primary site include (1) angiogenesis, (2) extracellular matrix (ECM) remodeling, (3) invasion and (4) intravasation. These processes are facilitated (-->) or inhibited (--I) by variety of stromal cell types involved in regulating tumour inflammation. NK cell: natural killer cell; ILC: innate lymphoid cell; MDSC: myeloid derived suppressor cell; MSC, mesenchymal stem cell; CAF: cancer associated fibroblast; Treg: regulatory T cells.

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