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Review article

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Cancer-induced systemic pre-conditioning of distant organs: building a niche for metastatic cells

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Abstract

From their early genesis, tumour cells integrate with the surrounding normal cells to form an abnormal structure that is tightly integrated with the host organism via blood and lymphatic vessels and even neural associations. Using these connections, emerging cancers send a plethora of mediators that efficiently perturb the entire organism and induce changes in distant tissues. These perturbations serendipitously favour early metastatic establishment by promoting a more favourable tissue environment (niche) that supports the persistence of disseminated tumour cells within a foreign tissue. Because the establishment of early metastatic niches represents a key limiting step for metastasis, the creation of a more suitable pre-conditioned tissue strongly enhances metastatic success. In this Review, we provide an updated view of the mechanisms and mediators of primary tumours described so far that induce a pro-metastatic conditioning of distant organs, which favours early metastatic niche formation. We reflect on the nature of cancer-induced systemic conditioning, considering that non-cancer-dependent perturbations of tissue homeostasis are also able to trigger pro-metastatic conditioning. We argue that a more holistic view of the processes catalysing metastatic progression is needed to identify preventive or therapeutic opportunities.

Sections

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Introduction

An early event during tumour growth is the induction of an injury-like response in the affected organ and, through the early induction of a highly permeable vasculature, long-distance interactions with the rest of the body are established. The mediators of these long-distance interactions are an arsenal of factors produced directly by cancer cells or other cells in the tumour microenvironment (TME), but also mediated via a perturbed systemic immune response. This cancer-mediated perturbation, by its very nature, combines factors present during other physiological responses to pathogens, stress and injury[1]. Long-distance communication is mediated by tumour-derived exosomes[2], which have also been shown to contribute directly to global immunosuppression[3]. Together with other soluble factors, cancer initiates a broad alteration of the body's steady-state physiology. Besides the vascular network, tumours are integrated with the organism via innervation, which has been shown to profoundly influence the local TME[4]. Moreover, the hypothalamus, the brain region critical for maintaining homeostasis, can detect cancer-induced changes via receptors on afferent nerves, but also via the detection of circulating inflammatory signals[5]. These systemic effects can be induced by the neuroendocrine system upsetting the balance of many physiological parameters, such as glucocorticoid-dependent suppression of immune responses and disruption of glucose metabolism[5]. Importantly, not only are these changes found in advanced disease, but they can be initiated early, as demonstrated in a mouse model of non-metastatic breast cancer where tumour-induced hypothalamic perturbations drove altered systemic metabolism and sleep[6].

An additional early connection established by cancer-derived inflammatory mediators occurs in the bone marrow, where perturbation of haematopoietic progenitors leads to the production of abnormal cells of the myeloid and lymphoid lineages and offers a powerful source of systemic distal changes[7]. Other early changes are known to occur in the circulation, including the release of procoagulant factors, activating platelets, inflammatory cells and clot formation, which have implications for cancer progression. At late stages of disease, this can become a pathological condition itself, with cancer-associated venous thromboembolism and arterial thrombosis accounting for 20–30% of all first venous thrombotic events[8]. Exacerbated thrombosis represents a cause of morbidity and mortality for people with cancer, and a better understanding of the pathways involved is needed[8,9]. Collectively, these systemic perturbations grow and constantly influence each other as cancer persists, instigating a vicious self-amplified cycle connecting multiple organ systems and possibly ultimately contributing to complex syndromes, such as cachexia, which can itself cause death (Fig. 1).

The cancer-to-body connections established early, typically during the asymptomatic phase of cancer growth, can influence metastatic progression by inducing changes in distant organs. The seminal findings of Hiratsuka et al.[10] and Kaplan et al.[11] first demonstrated the existence of a cancer-mediated distant conditioning that enhanced metastatic outgrowth. Over the following years, a large body of work identified a huge variety of mechanisms by which metastatic efficiency is increased by such perturbations, specifically targeting organs where metastasis will occur, which were termed pre-metastatic niches (PMNs)[12,13]. Importantly, some mechanisms of cancer-induced conditioning will affect any organ, regardless of whether that organ will become the target of metastatic dissemination, and in doing so can contribute to driving the complex whole-body changes mentioned above, with the potential to be pathological and in themselves cause death[14]. This Review will focus on the perturbations mediated early on by cancer that have been shown to affect metastatic progression (Fig. 1). Understanding and interfering with the onset of this complex whole-body priming has the potential to reduce the chances of cancer progression and mortality.

PMN is an anticipation of the metastatic niche

Cancer-cell growth requires the generation of a tailored local tissue environment, which is evident from the fact that cancer cells are at all times embedded in an altered heterogeneous composite of different cell types. When cancer cells leave the primary tumour via the circulation, they have the potential to seed a range of organs along the circulatory network connecting the tumour with the rest of the organism, but their opportunity to home and grow will largely depend on the tissue environment that they find. There are certain inhospitable tissues, such as skeletal muscle, intestine, spleen, and kidney, that despite their large blood flow, rarely host metastatic growth[15] (Fig. 2a). What makes these tissues unfavourable for metastatic growth remains an important question that needs to be addressed to better understand the biology of metastasis. One speculative possibility is that these organs are potentially less susceptible to PMN formation. Nonetheless, driven by the need to discover novel therapeutic approaches, studies mainly focus on trying to understand cancer growth in organs often targeted for secondary relapse, such as lung, liver, bone and brain (Fig. 2a).

Metastatic cells disseminate from the primary tumour in the context of early cancer-dependent perturbations, which effectively represent the first step in the metastatic cascade. Of course, the magnitude of these perturbations is likely to positively correlate with the intrinsic metastatic potential of the tumour itself. Interestingly, the tissue perturbations reported to promote a pro-metastatic conditioning modulate each other and represent key features of tumour niches, such as immunosuppression, extracellular matrix (ECM) remodelling and stromal and vasculature activation[16]. Therefore, the key alterations of pre-metastatic conditioning increase the chance of metastatic colonization by anticipating, and therefore facilitating, the creation of the subsequent metastatic niche (Fig. 2b).

ECM remodelling

The ECM builds the three-dimensional infrastructure providing the biochemical, physical and mechanical characteristics of each organ. Although the core matrisome will contain the same type of components – proteoglycans, fibrous proteins (such as collagens), fibronectins, laminins and glycoproteins – the distinct physical characteristics of each organ is ensured by a tailored composition of these components. In addition, the presence of associated matricellular proteins (such as tenascin C, thrombospondin 1, periostin and osteopontin) influence the physio-chemical characteristics of the ECM. Cancer has a very different matrisome composition compared with the tissue of origin[17]. Similarly, within metastatic niches, key changes in the ECM are needed for cancer-cell growth[18,19]. Therefore, remodelling of the ECM of future metastatic organs is a core feature of pre-metastatic conditioning[20]. Primary-tumour-derived factors directly initiate crosstalk with resident cells at distant organs, leading to the restructuring of ECM as well as the instigation of immune-cell recruitment[21]. Conversely, the immune infiltrate can influence ECM composition. In pancreatic liver metastasis, the recruitment of granulin-secreting inflammatory monocytes activates resident stellate cells to release periostin and create a pro-fibrotic microenvironment[22].

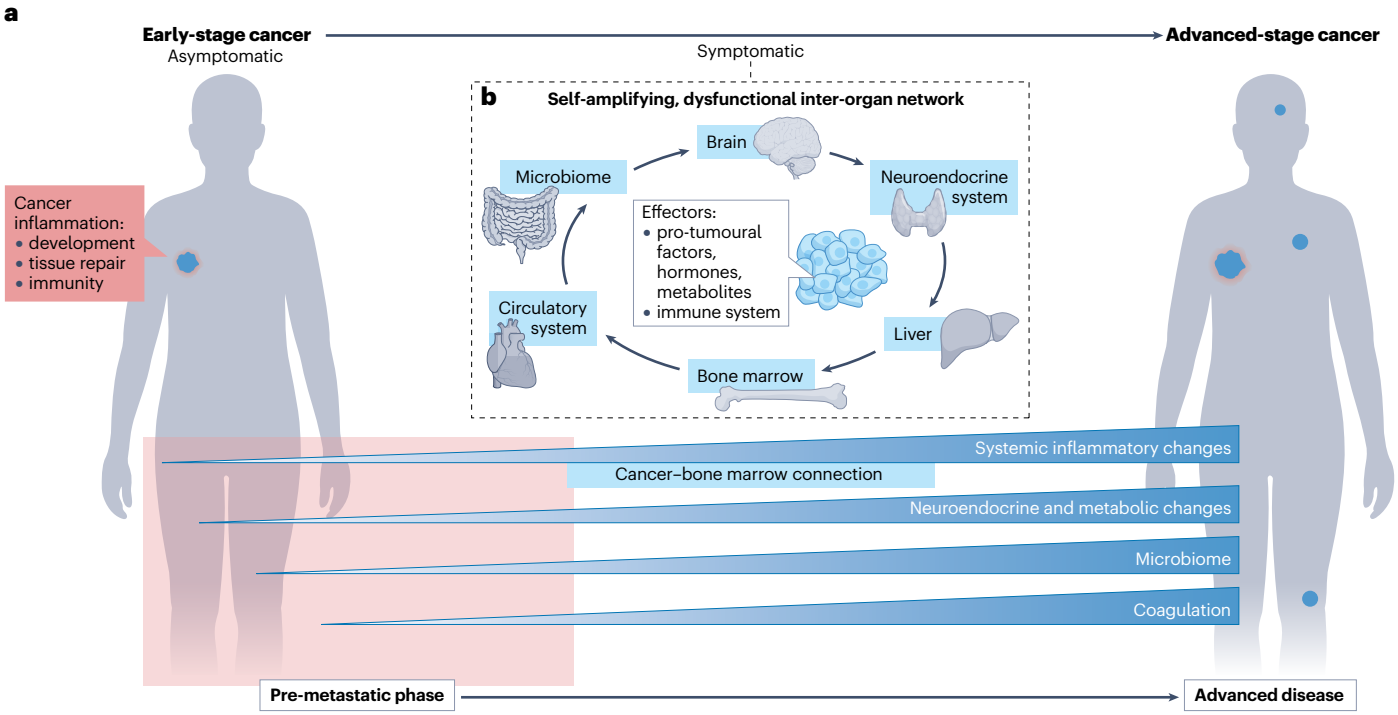


Fig. 1 | Cancer-to-body connections. Schematic representation illustrating the systemic perturbations induced by cancer, which initiate at early (asymptomatic) stages and intensify with disease progression to later stages of symptomatic disease. **a**, Already at early stages of cancer development, tumours trigger systemic effects owing to their intrinsic programme of inflammation, reactivation of developmental programmes and tissue repair and via the release of soluble factors and extracellular vesicles. These perturbations – such as systemic inflammatory changes, neuroendocrine and metabolic changes, as well as changes in the microbiome and coagulation – disrupt networks crucial for host physiology. When these systemic changes predispose distant organs for metastatic growth upon cancer-cell dissemination, these changed tissues are termed pre-metastatic niches. **b**, As cancer advances, these interconnected alterations establish a vicious cycle of progressive physiological disruption involving different organs, which in the very late stages of disease may contribute to complex syndromes such as cachexia and pathological thrombosis, ultimately leading to organ damage. Arrows represent the idea of multiorgan connections but do not correspond to any known specific interaction between organs nor to the order of disease onset and inter-organ signalling.

Immunosuppression

In addition to ECM-mediated changes in immune-cell recruitment, tumour-derived factors can modulate the immune landscape directly or via activation of other cells in the environment. Cancer-derived factors, such as vascular endothelial growth factor (VEGF), can directly activate cells residing at distant sites, such as endothelial cells, to drive vascular hyperpermeability, leading to cancer-cell recruitment[23]. Activated endothelial cells can also release prostaglandin E_2 (PGE_2), supporting a pro-inflammatory environment[24]. Moreover, VEGF acts not only on endothelial cells but also on recruited myeloid cells[25]. Similarly, ECM modulators, such as tissue inhibitor of metalloproteinases 1 (TIMP1), influence neutrophil recruitment in the liver and favour metastasis[26]. A key feature of cancer-mobilized innate cells from the bone marrow[7], see below, is immunosuppression. This includes the mobilization of both monocytes or macrophages and neutrophils, which represent the main cells responsible for suppressing T and natural killer (NK) cell responses against cancer cells[27]. Notably, the interaction between ECM changes and myeloid cells is bidirectional and often involves fibroblast activation[28].

Stromal activation

The activation of stromal cells is an early feature of the tissue niche around metastatic cells, and it is known to modulate their growth potential[29]. During pre-metastatic conditioning of distant organs, cancer-derived factors are reported to directly activate resident fibroblasts and induce the release of pro-inflammatory mediators[30]. Stromal cells are the main depositor of ECM molecules, and many of their pathophysiological activities are in turn controlled by mechanosensing[31]. Therefore, stromal activation in PMNs also has a direct effect on ECM components. For instance, stromal pericytes around the perivascular niche at distant sites were reported to produce a fibronectin-rich environment[32]. Moreover, melanoma-derived factors induce p38α kinase activation in lung fibroblasts, leading to both ECM remodelling and chemokine release driving neutrophil infiltration[33].

The effectors of PMNs

The mediators of PMNs differ in nature, but they can be either directly produced by the primary tumour or indirectly emerge from other organs under the cancer's influence (Fig. 2c). However, it is difficult to resolve these mediators over time as being either direct or indirect because, for example, bone-marrow-derived neutrophils can be triggered early and their actions effectively overlap with primary-tumour-derived factors in shaping PMNs. Both direct and indirect mediators will be discussed in detail below. To investigate these complex systemic interactions, preclinical animal models are considered the gold

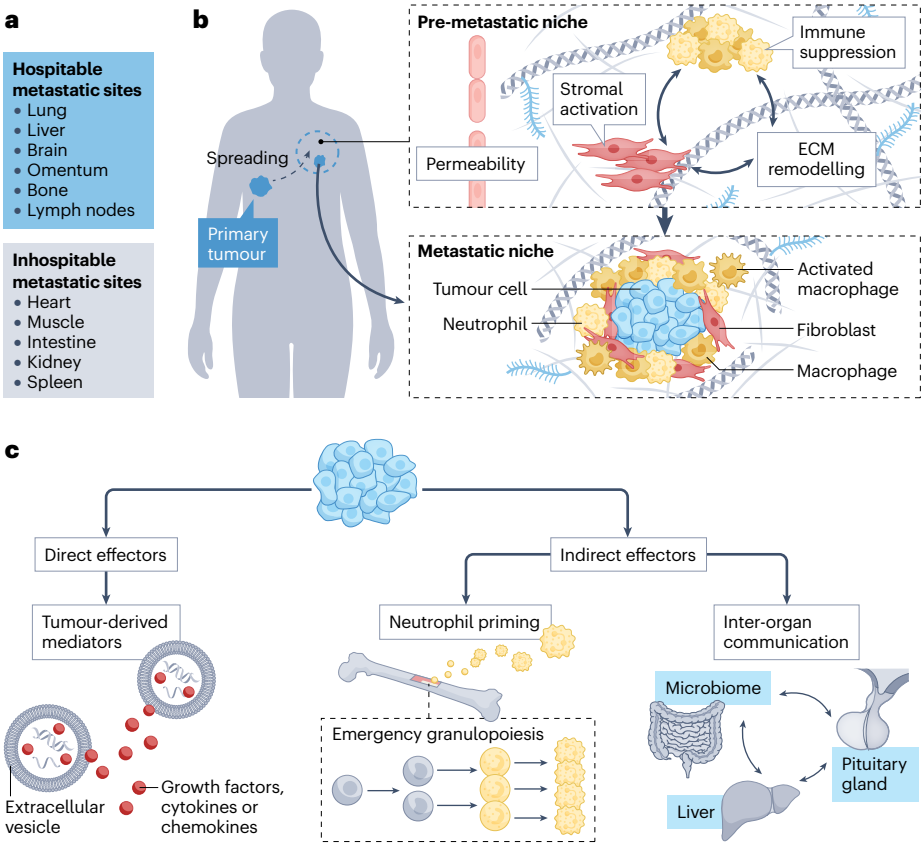


Fig. 2 | Cancer-derived pre-metastatic conditioning. a, List of organs where metastatic spread is usually found (blue box) as opposed to organs where metastases rarely occur (grey box). **b**, Primary tumours induce changes in distant organs, which are the key features of the metastatic niche. Therefore, the pre-metastatic niche is characterized, but to a lesser extent, by the same interconnected processes of stromal activation, immunosuppression and extracellular matrix (ECM) remodelling of the metastatic niche. **c**, Cancer cells can secrete soluble factors and extracellular vesicles (collectively termed tumour-derived mediators) that act directly on cells at a distant site and direct them to induce a pre-metastatic niche (direct effectors). In parallel, the primary tumour can induce changes that perturb distant organs more indirectly, such as inducing emergency granulopoiesis with consequent neutrophil priming as well as changes in the gut microbiome and systemic metabolism (indirect effectors).

standard. However, alternative modelling strategies are emerging from the bioengineering field, alongside some potential therapeutic approaches (Box 1).

Primary tumour-derived direct effectors

Tumour-derived mediators (TDMs) are crucial in the orchestration of PMNs and increase the chance of metastatic success. PMN-inducing mediators include exosome-derived proteins and other molecular signals, but also soluble molecules such as cytokines, chemokines, growth factors, free RNAs and metabolites. Indeed, free RNAs have also been shown to be taken up by NK cells, potentially enhancing their anti-metastatic activity[34]. Interestingly, non-cancer cells within the TME can also contribute to PMN formation. Salivary-adenoid-cystic-cancer-associated fibroblasts (CAFs) release exosomes that remodel the lung ECM at the PMN stage[35]. Below, we describe how the biology of key cell types is perturbed by TDMs during the formation of PMNs, on the basis of recent advances in our understanding of the field (Fig. 3 and Supplementary Table 1).

Fibroblasts

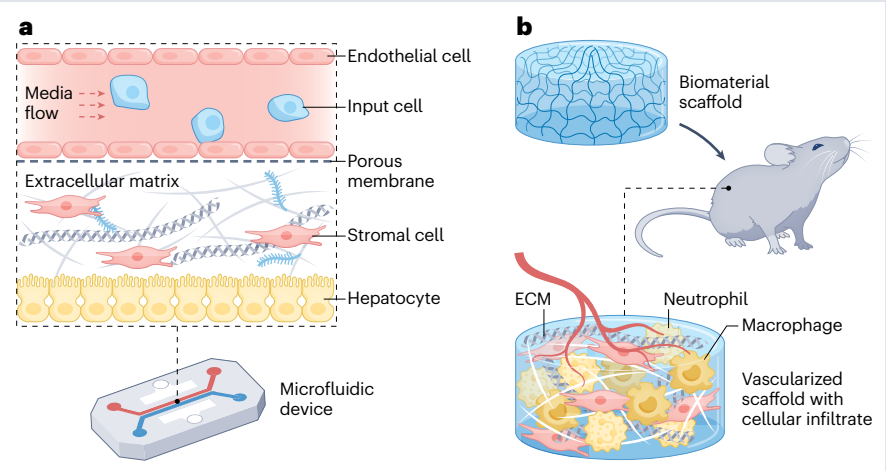
Fibroblast-dependent matrix remodelling is often observed in the PMN of several cancer types, and activation of p38α in lung fibroblasts of the PMN seems to be a conserved mechanism of action. Patients with metastatic melanoma exhibit high stromal p38α phosphorylation, which correlates with disease progression and poorer survival[33]. In pre-clinical models, mouse lung fibroblasts exhibit p38α phosphorylation upon exposure in vivo to metastatic melanoma TDMs but not when exposed to TDMs from their less metastatic counterparts[33]. As a result of p38α phosphorylation, the type I interferon receptor 1 (IFNR1) is inactivated, which is also observed to be the outcome of the action of pancreatic and mammary adenocarcinoma TDMs. Inhibition of IFNR1 was shown to lead to an increase in fibronectin deposition, expression of matrix remodellers, such as matrix metalloproteinase 9 (MMP9), and chemokine-dependent neutrophil recruitment[33].

Lung fibroblasts have also been shown to exhibit ECM remodelling properties after exposure to osteosarcoma-derived extracellular vesicles (EVs). Tumour-derived EVs containing transforming growth factor β1 (TGF-β1) convert lung fibroblasts into fibronectin-secreting myofibroblasts[36]. Breast-cancer exosomes containing caveolin-1 induce enhanced secretion of fibronectin and tenascin C from lung fibroblasts and thereby increase metastatic seeding into the organ[37]. The PMN-inducing exosomal cargo can also vary within the same tumour type depending on the mutational landscape. In pancreatic ductal adenocarcinoma (PDAC), exosomes from p53 gain-of-function mutated cancer cells alter integrin trafficking of lung fibroblasts, which remodel the type and quality of deposited ECM to support lung metastasis[38]. ECM remodelling is also a common feature in liver PMNs. Exosomes from highly metastatic colorectal cancer (CRC) cells activate hepatic stellate cells (HStCs) by direct transfer of the microRNA miR-181a-5p. This results in the release of suppressor of cytokine signalling 3 (SOCS3)-mediated inhibition of interleukin-6 (IL-6)–signal transducer and activator of transcription 3 (STAT3)

signalling, leading to a downregulation of tenascin C and an increase in fibronectin deposition from HStCs[39]. Similarly, PDAC exosomes containing the CD44 variant isoform 6 (CD44v6)–complement C1q binding protein (C1QBP) complex directly activate HStCs and induce liver fibrosis prior to tumour seeding[40]. Lastly, bone-marrow-derived cells (BMDCs) recruited to the PMN of lung-cancer-bearing mice release EVs that contain miR-92a, which targets SMAD7 in HStCs, resulting in TGFβ signalling and ECM deposition in the liver[41]. HStCs are mainly quiescent and require engagement with resident liver macrophages known as Kupffer cells for their activation[42]. Hence, most of the ECM remodelling in the liver occurs after activation of these resident immune cells.

Soluble factors can also trigger ECM remodelling by fibroblast activation. Recently, lysyl oxidase (LOX), long known to directly cross-link collagen fibres in pre-metastatic lungs[43], was also shown to induce stiffer ECMs in PMNs of hepatocellular carcinoma (HCC) by increasing fibronectin and MMP9 secretion from lung fibroblasts[44,45]. Finally, activin A (a soluble factor and a TGFβ ligand) is secreted by breast-cancer

Box 1 | Alternative models to study pre-metastatic niches



The complex inter-organ nature of pre-metastatic niches (PMNs) means that their characteristics and the mediators of their formation are best studied in mouse models. Nonetheless, advances in tissue-engineered microfluidic devices have created alternative in vitro approaches to modelling human organs, termed organ-on-a-chip (OoC; see Box 1 figure panel **a**). These systems rely on hydrogel structures and microfluidic devices that can be moulded according to precise geometries and mechanical properties. They have been used to model primary tumours, but also metastatic sites such as the liver, lung, brain and bone[225]. Kim et al.[226] created a microfluidic human liver-on-a-chip to mimic a PMN and functionally assessed breast-cancer-derived extracellular vesicles (EVs) isolated from patients with cancer. Platforms mimicking the pre-metastatic bone niche have also been reported. For instance, in a bio-printed bone-on-a-chip model, three interconnected niches were recapitulated in which the characteristics of the cells were analysed[227]. Similar bone mini-tissues created by embedding human osteoblasts, osteoclasts, bone-resident macrophages, endothelial cells and cancer cells into hydrogel have been designed to enable drug screening[228]. A key limitation of these organ-on-a-chip models is the lack of multiorgan connections. However, emerging multi-organ-on-a-chip (multi-OoC) platforms have begun to overcome this limitation. These platforms involve integrated body-on-a-chip devices in which organ-specific modules are interconnected. Over the past 5 years, many multi-OoCs have been developed, mainly for drug and metabolic screening but also for cancer research, in which a tumour-on-a-chip is connected to different OoCs[229]. Despite this progress, key challenges remain, from achieving coupling of the various OoCs to reflect physiological stimulations to whether OoCs are sufficiently complex to realistically reflect the in vivo environment.

The field of bioengineering has also provided approaches that interface biomaterials within the organism. These take the form of biomaterial scaffolds subcutaneously implanted into mice to mimic metastatic and non-metastatic organs for the study of cancer dissemination and growth (see Box figure panel **b**). A recent example of this approach showed that cancer-educated neutrophils adopt tissue-specific phenotypes in mice harbouring lung metastatic breast cancer. Here, cancer cells that disseminated to the endogenous lung were supported to grow by lung neutrophils, but in the exogenous scaffold, neutrophils pushed the cancer cells towards dormancy, highlighting that neutrophils have opposing functions in response to different local signals[230]. In a similar approach, the presence of biomaterial scaffolds was shown to systemically influence the immune environment of the primary tumour, which reduced its metastatic potential[231]. These implantable scaffolds can also be used to study extracellular matrix (ECM) proteins whereby ECM-coated scaffolds were shown to capture metastatic cells better than uncoated scaffolds. One can also use decellularized matrices from different pre-metastatic organs to study the effect of alteration of ECM proteins at PMNs[232].

Finally, biomaterials can be designed for therapeutic use. For instance, a sponge-like neutrophil membrane-coated nanosystem was shown to enhance antitumour immunity and limit PMN formation in the lung[233]. In a similar approach, ginsenoside RG3 liposomes loaded with the chemotherapy docetaxel, captured by circulating tumour cells via interaction with the glucose transporter 1 (GLUT1), inhibited metastatic niche formation by reversing the immunosuppressive microenvironment[234]. Nevertheless, some of these systems, like any nanoparticle approach, do not always successfully specifically target cancer cells. Looking forward, despite their limitations, progress in the engineering of niche-mimicking biomaterials provides a way to complement metastatic research using animal models and offers alternative opportunities for intervention.

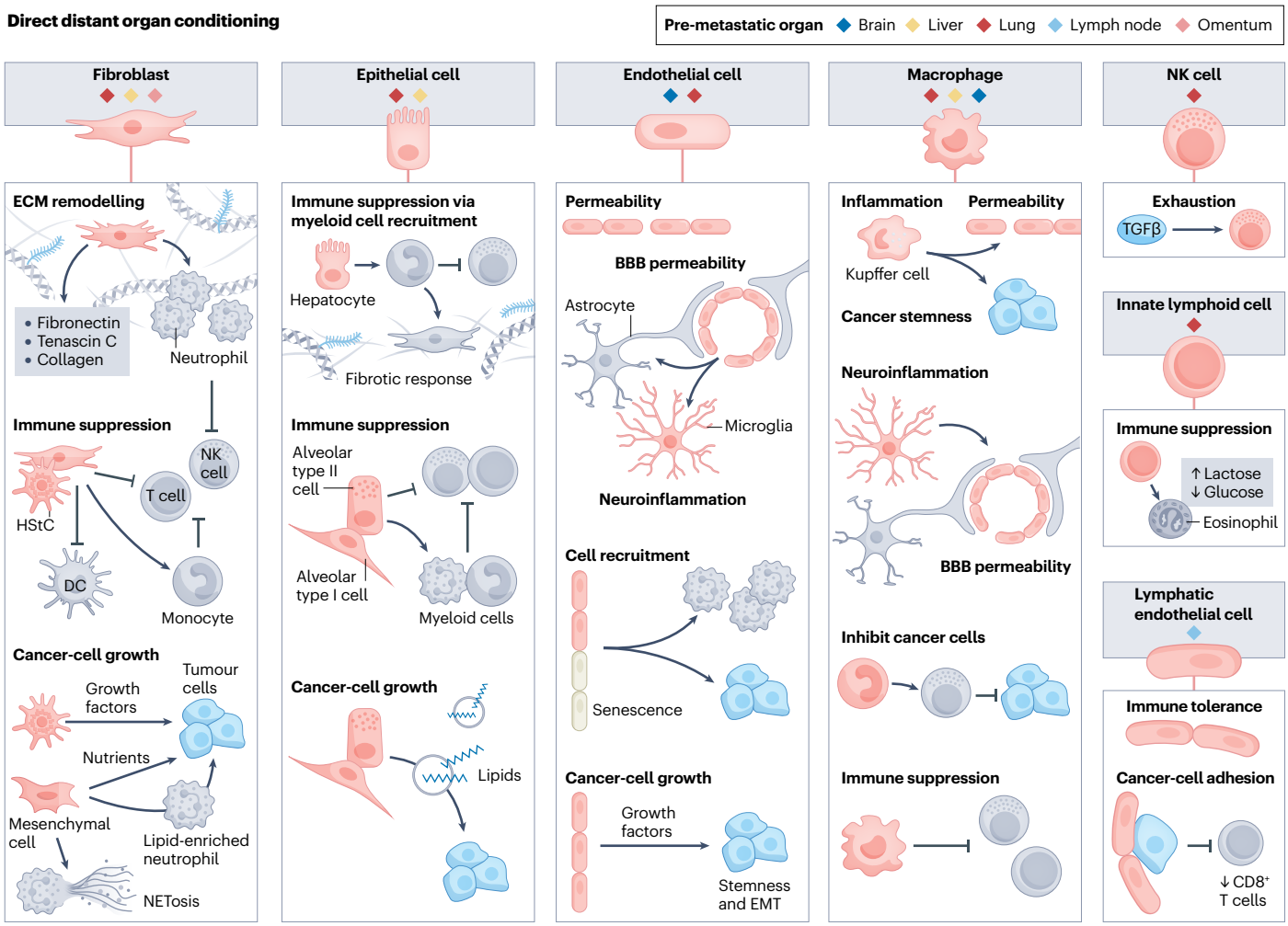


Fig. 3 | Direct distant organ conditioning. This schematic illustrates the main cell types directly modulated by tumour-derived mediators (TDMs) within pre-metastatic organs, and the biological mechanisms of pre-metastatic conditioning triggered by such cells. TDMs are released into the circulation and taken up by fibroblasts, epithelial cells, endothelial cells, innate lymphoid and natural killer (NK) cells, lymphatic cells and macrophages at the distant site before tumour-cell arrival. For each specific affected cell type, the indicated organs (see key) represent the sites where these cell populations have been shown to drive the pre-metastatic conditioning. Activation of fibroblasts at the distant site leads to extracellular matrix (ECM) remodelling via secretion of ECM proteins, immune suppression and a specific increase in cancer-cell growth upon arrival via the release of growth factors and nutrients. Epithelial cells conditioned by TDMs drive immune suppression of innate cells directly or via the recruitment of myeloid cells. They also increase the fibrotic response and cancer-cell growth. Endothelial cells mainly regulate organ permeability but can also promote cancer cell and immune cell recruitment as well as induce stemness by secretion of growth factors. Innate lymphoid cells and NK cells mediate immune suppression following conditioning from TDMs. Lymphatic cells have been shown to induce immune tolerance and cancer cell adhesion in response to TDMs. Lastly, tissue-resident macrophages, such as liver Kupffer cells, brain microglia and alveolar macrophages, as well as others, can remodel vessel and blood–brain barrier (BBB) permeability, promote or inhibit immune-cell activity, and drive cancer stemness upon cancer-cell arrival at the distant site. DC, dendritic cell; EMT, epithelial-to-mesenchymal transition; HStC, hepatic stellate cell; NETosis, neutrophil extracellular trap formation; TGFβ, transforming growth factor β. See also Supplementary Table 1.

cells, leading to a profibrotic gene expression programme in lung fibroblasts that results in increased collagen deposition[46].

Albeit less frequently, fibroblasts can also directly regulate immune-cell function. Following uptake of let-7-containing exosomes, secreted by LIN28B-expressing breast-cancer cells, lung fibroblasts in the PMN induce CXC-chemokine ligand 1 (CXCL1) and IL-6 expression and drive immune-suppressive neutrophil recruitment to the pre-metastatic site[47]. Breast-cancer cells also release IL-1β, which expands an immune-suppressive cyclooxygenase 2 (COX2)-expressing CD140A$^+$ lung adventitial fibroblast population. These fibroblasts produce PGE_2, which impairs dendritic cell and monocyte function[48]. In the liver PMN, TIMP-1 is the main factor driving immune suppression. TIMP-1, secreted by PDAC cells, activates HStCs via PI3K signalling, leading to neutrophil recruitment[49]. Recently, miR-181a-5p within EVs of highly metastatic CRC was shown to activate an immunosuppressive phenotype in HStCs by induction of inflammatory mediators, such as IL-6 and IL-8 (ref. 39).

Lastly, fibroblasts in PMNs regulate growth factor and nutrient availability, which directly supports tumour-cell fitness.

Gastric-cancer-derived exosomes containing epidermal growth factor receptor (EGFR), and CRC exosomes containing miR-221 and miR-222, induce hepatocyte growth factor (HGF) secretion from HStCs, which supports tumour-cell proliferation[50,51]. CRC-derived exosomal HSPC111 alters lipid metabolism in HStCs, which results in the accumulation of acetyl-coenzyme A (acetyl-CoA), leading to histone H3 lysine 27 (H3K27) acetylation and consequent increased CXCL5 expression and secretion. A CXCL5–CXC-chemokine receptor 2 (CXCR2) axis subsequently promotes liver metastasis[52]. Similarly, ovarian-cancer-derived exosomal miR-141 activates peritoneal fibroblasts by inducing Yes-associated protein (YAP)–transcriptional co-activator with PDZ-binding motif (TAZ)-mediated upregulation of the chemokine GROα (also known as CXCL1), which is released into the omentum to boost cancer-cell proliferation[53].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are emerging as a critical modulator of the PMN by way of regulation of the immune response. Their capacity to differentiate into fibroblasts, osteoblasts, chondroblasts, adipoblasts and pericytes magnifies their potential range of action and thus, the impact on metastatic spread[54]. Breast-cancer cells create an IL-1β-rich environment that instructs lung-resident CD140A$^+$ MSCs to store and deliver lipids via vesicles to other cells. This was shown to be mediated by hypoxia-inducible factor 1α (HIF-1α)-dependent expression of a lipid droplet-associated protein in MSCs. These MSC-derived lipid-laden vesicles are engulfed by tumour cells and NK cells, both supporting cancer-cell proliferation and impairing NK-cell function[55]. In addition, lung CD140A$^+$ MSCs induce the expression of inhibitory factors of adipose triglyceride lipase (ATGL), such as hypoxia-inducible lipid droplet-associated (HILPDA), CIDEC and G0/G1 switch protein 2 (G0S2) in neutrophils via soluble factors and cell–cell contact. The increased expression of repressors of ATGL results in an accumulation of intracellular lipids within these neutrophils, which, when transferred to breast-cancer cells, function as energy reservoirs that support cancer-cell survival and proliferation[56]. Finally, breast-cancer cells activate STAT6 signalling in lung MSCs, which triggers complement C3a upregulation and subsequent C3a receptor (C3aR)-dependent neutrophil recruitment and neutrophil extracellular trap (NET) formation[57].

Epithelial cells

Epithelial cells are the predominant cell population in many organs at risk of metastasis and are increasingly understood to have important roles in the formation of PMNs.

Hepatocytes. Recent work in PDAC and lung adenocarcinoma uncovered a pivotal role for hepatocytes in establishing liver PMNs. Lung-adenocarcinoma-derived EVs induce HGF expression in hepatocytes, facilitating invasion, migration and proliferation of cancer cells[58]. Stromal-cell-derived IL-6 in PDAC-bearing mice induces a STAT3-dependent hepatocyte response and release of serum amyloid A1 and A2 proteins (collectively known as SAA). This in turn leads to elevated circulating SAA levels in the mouse metastatic PDAC model, which is similarly seen in patients with PDAC and liver metastases. SAA promotes the infiltration of immunosuppressive myeloid cells and activates HStCs to trigger an inflamed and fibrotic liver PMN[59].

Alveolar epithelial cells. Alveolar epithelial cells respond to injury and infection primarily via Toll-like receptor (TLR) signalling, to elicit innate immune responses, a mechanism exploited by tumour-derived EVs, loaded with RNA, which activate TLR3 signalling in alveolar type II (AT2) cells to drive TLR3-dependent chemokine production and neutrophil recruitment[60]. Similarly, breast-cancer EVs loaded with miR-200b-3p induce CC-chemokine ligand 2 (CCL2) production in AT2 cells, via direct targeting of PTEN[61]. Beyond regulating innate immunity, tumour-primed AT2 cells can suppress adaptive immunity because a pro-metastatic population of AT2 cells, characterized by high glutathione peroxidase 3 (GPX3), produces IL-10, which supports an immunosuppressive microenvironment by inhibiting the proliferation of CD4$^+$ T cells while enhancing the generation of regulatory T cells[62].

Interestingly, a recent study identified AT2 cell-dependent metabolic remodelling of the interstitial fluid in the lung PMN towards a composition that is rich in the lipid palmitate. This increased supply of palmitate drives pro-metastatic histone acetyltransferase KAT2A expression and nuclear factor-κB (NF-κB) signalling in metastatic cells. Thus, distal tumours influence the nutrient composition in the pre-metastatic site, creating an environment that promotes lung metastasis[63]. Palmitate metabolism regulates multiple immune and stromal cell types[64] and supports fatty acid receptor CD36$^+$ metastasis-initiating cells[65], suggesting that nutrient priming of the pre-metastatic niche may have widespread consequences for various niche cell types and contexts.

Vascular endothelial cells

Destabilized endothelial barriers have long been recognized as contributors to a pro-metastatic microenvironment in various PMNs. For instance, melanoma-derived factors upregulate angiopoietin 2, MMP3 and MMP10 in the premetastatic lung endothelium, which supports metastatic intravasation via endothelial junction disruption[66]. Many studies have identified a key role for tumour-derived exosomal factors in driving vascular permeability and metastasis. Mechanistically, these range from direct silencing of junctional components in the case of miRNA-containing EV transfer[67–69], to enzymatic products in EVs driving purinergic signalling in endothelial cells, resulting in loss of junctional β-catenin, vascular destabilization and metastasis[70]. Specific examples include breast-CAF-derived exosomes containing the long non-coding RNA SNHG5, which targets endothelial cells, leading to angiogenesis and vascular permeability[71]. Under homeostasis, lung endothelial cells maintain vessel integrity through high expression of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), acting as a barrier to metastatic colonization. In the pre-metastatic context, various tumour-derived factors, including VEGFA, placental growth factor (PIGF) and basic fibroblast growth factor (bFGF), repress TRAIL expression in endothelial cells, leading to elevated apoptosis, reduced vessel integrity, and the induction of adhesion molecules promoting immune and cancer cell recruitment[72]. Importantly, this suggests that the TRAIL pathway could be a potential target for therapeutic intervention in PMN formation. Furthermore, tumour-derived Notch ligands activate Notch signalling in endothelial cells, promoting senescence and expression of inflammatory cytokines and adhesion molecules. This cascade of events supports both neutrophil and tumour-cell recruitment[73].

Elevated angiogenesis in the distal microvasculature is a frequent hallmark of PMNs. For instance, primary HCC cells generate a lung PMN by enhancing the angiogenesis and permeability of vessels[74]. It should be noted that although enhanced angiogenesis and vascular remodelling are common features of PMNs, how these changes lead to a more receptive environment is yet to be determined.

Tumour-induced ECM alterations in the PMN also affect endothelial cells. Breast-cancer cells induce upregulation of tenascin C in the premetastatic lung, activating TLR4 on perivascular macrophages and modifying the lung endothelium, which respond by secreting various factors that support stemness, self-renewal and cell survival, fostering metastatic outgrowth[75]. Likewise, in the bone PMN, endothelial cells generate stemness-supporting vascular niches. Here, tumour-induced expression of E-selectin on endothelial cells promotes mesenchymal-to-epithelial transition and WNT signalling in cancer cells upon arrival within the niche[76]. The systemic microvasculature may serve as a source of factors that orchestrate the PMN. TDMs were shown to induce an organism-wide upregulation of leucine-rich α2-glycoprotein 1 (LRG1) in endothelial cells where elevated circulating LRG1 promotes the expansion of neural/glial antigen 2 (NG2)-expressing perivascular cells, facilitating lung metastasis[77].

Thanks to the blood–brain barrier (BBB), the neurovascular unit (NVU) poses a challenge for PMN formation in the brain. Increasing evidence suggests that the signals that govern PMN formation in the brain are distinct from other organs. Supporting this idea, cancer-derived exosomes from brain-tropic metastatic breast-cancer cells can successfully establish a brain PMN while exosomes from lung-tropic metastatic breast-cancer cells cannot[78]. These exosomes package high levels of proteins involved in normal brain physiology, such as cell-migration-inducing and hyaluronan-binding protein (CEMIP), a regulator of calcium signalling. CEMIP-containing exosomes are mainly taken up by endothelial cells, leading to disruption of vascular integrity along with pro-inflammatory cytokine production by perivascular microglia[78]. As an alternative strategy, TGFβ1-mediated non-small-cell lung-cancer exosomes containing the long non-coding RNA lnc-MMP2-2 downregulate the tight junctions of brain endothelial cells, increasing permeability[79]. In addition to the direct disruption of endothelial cell properties, tumour-derived exosomes disrupt the interaction between microglia and astrocytes, and induce inflammation, equally important for the establishment of brain PMNs[80]. Non-small-cell lung-cancer exosomes were shown to be taken up by endothelial cells, leading to the expression and release of dickkopf-1 (DKK1), which promoted astrocyte polarization towards supporting a pro-tumorigenic PMN[81]. Studies so far decoding the brain PMN have focused mainly on the cellular components of the brain. However, remodelling of the ECM is also likely to be a feature of the formation of brain PMNs.

Lymphatic endothelial cells

Remodelling of the lymphatic vasculature and cancer-cell accumulation in lymph nodes (LNs) has long been known to play a critical role in metastasis[82]. Recently, its importance has been extended to the PMN, as cancer cells at the LNs were shown to induce immune tolerance that renders distant tissues amenable to cancer cell colonization[83]. Little is known about the mechanisms of TDMs in PMN induction at LNs; however, recent evidence reports changes in adhesion and permeability of lymphatic vessels, both at LNs and at distant sites.

Cervical cancer cells were shown to induce periostin expression in LN fibroblasts which, in response to VEGFC, boosted lymphangiogenesis, and tumour-cell proliferation[84]. Melanoma-derived exosomes were shown to instruct LN-resident lymphatic endothelial cells, triggering vascular endothelial-cell adhesion molecule 1 (VCAM1)-dependent remodelling of the vasculature. Tumour-educated lymphatic endothelial cells also exhibit cross-presentation of EV-derived tumour antigens, with consequent apoptosis induction in antigen-specific $CD8^+$ T cells[85]. Furthermore, neural growth factor receptor (NGFR) present in melanoma exosomes activated MAPK in lymphatic endothelial cells initiating sprouting, proliferation, and increased tumour-cell adhesion to the lymph endothelia[86].

The role of lymphatic vessels in the PMNs of non-lymphoid tissues is much less well understood. Recently, this has been interrogated through a lympho-reporter mouse model, where whole-body lymphangiogenesis was monitored through VEGF receptor 3 (VEGFR3)-driven luciferase expression. It was demonstrated that while lymphangiogenesis within and around the primary tumour and within the tumour-draining LN was dispensable for metastasis, instead, tumour-induced systemic aberrant lymphangiogenesis in distal LNs and various organs, facilitated by tumour-derived midkine, was crucial for metastatic colonization[87].

Tissue-resident macrophages

Tissue-resident macrophages originate embryonically and have organ-specific roles that range from maintenance of tissue homeostasis to immunosurveillance. Multiple processes characteristic of these cells when manipulated can contribute to the formation of PMNs in various organs and so these cells are increasingly being recognized as important players in establishing PMNs.

Kupffer cells. Kupffer cells are the predominant macrophage population in the liver. Multiple studies indicate that various cancer types drive inflammatory phenotypes in Kupffer cells via transfer of diverse exosome cargos. CRC-derived exosomes, through their cargo miR-21, activate TLR signalling in Kupffer cells, leading to the upregulation of IL-6 and a pro-inflammatory microenvironment[88]. Moreover, angiopoietin-related protein 1 (ANGPTL1)-containing exosomes support the inflammatory activation of Kupffer cells, which in turn contributes to the destabilization of endothelial integrity via MMP9 release, supporting metastatic colonization[89]. Kupffer cells exert pro-metastatic functions through regulating adaptive immunity in the PMN. For example, phagocytic uptake of miR-135-containing CRC-derived EVs by Kupffer cells results in reduced serum levels of IL-2 and tumour necrosis factor (TNF) along with intrahepatic $CD4^+$ T cells[90].

Highlighting their important role in wound healing, Kupffer cells educated by gastric-cancer-released exosomes containing miR-151a-3p acquire an altered secretome and generate a stem-cell-permissive microenvironment supporting metastatic colonization[91]. The HGF–MET signalling axis is a key player in liver regeneration and gastric tumours activate HGF production in Kupffer cells via exosomal transfer of functional EGFR, leading to remodelling of the liver microenvironment[50]. Lastly, exciting recent work has identified monocyte-derived Kupffer cells as the predominant population in tissues following injury[92], but the potential contribution of cancer-primed monocytes in seeding monocyte-derived Kupffer cells in the liver PMN is yet to be explored.

Alveolar macrophages. Alveolar macrophages (AMs) are long-lived cells residing in lung alveoli and airways. In models of HCC lung metastasis, AMs are enriched in the metastatic lung in a CCL2-dependent manner. While CCL2-driven lung inflammation is a frequent hallmark of the lung PMN, it remains unclear whether these AM-driven effects precede metastatic colonization[93]. When compared with other populations of tissue-resident macrophages, AMs probably have a limited role in the initiation of the PMN. Their localization to the luminal surface of the alveolar space probably positions them unfavourably for exposure to tumour-derived factors. In the context of injury and infection,

the AM pool is bolstered by the recruitment of bone-marrow-derived monocytes that differentiate into AM-like cells termed recruited alveolar macrophages, but their importance in the premetastatic lung in the context of concomitant perturbed myelopoiesis is yet to be determined[94].

Microglia. Microglia are the predominant immune cell population in the brain, and recently applied single-cell technologies have unveiled a previously underappreciated diversity in microglial heterogeneity[95]. TDMs produced from cancer cells, which can metastasize to the brain, modulate signalling pathways that regulate neurotransmitter release, glia and microglia activation and are involved in neuroinflammation. Microglia can support metastatic outgrowth by generating an immunosuppressive PMN through the release of CXCL10, a factor also found to be upregulated in the metastatic niche and enhancing immunosuppression[96]. This is further supported in mouse models of breast cancer, where the injection of a BBB-permeable macrophage colony-stimulating factor 1 (CSF1) inhibitor, which dampens inflammatory responses in microglia, resulted in reduced intravasation of cancer cells and metastatic colonization[97].

Monocytes and macrophages

The role played by monocytes and monocyte-derived cells is intricate and complex and they can be pro- or anti-metastatic depending on the specific context. Nonclassical patrolling monocytes, primarily enriched in the lung vasculature, engage with early disseminating cancer cells by scavenging cancer-cell material and recruiting NK cells, ultimately preventing lung metastasis in multiple mouse models[98,99]. This is, in part, orchestrated by tumour-derived exosomes, which are taken up by monocyte progenitors in the bone marrow, promoting expansion of the anti-metastatic patrolling monocyte pool[100]. Conversely, tumour-derived tissue factor (TF)-induced thrombosis has been demonstrated to induce the formation of a lung PMN via monocyte recruitment. Recently, tumour-induced SAA signalling in lung monocytes and macrophages was shown to activate the expression of the arginine-modifying enzyme protein arginine deiminase (PADI), resulting in citrullination of lung fibrinogen deposits, thereby supporting lung PMN formation and cancer-cell recruitment[101]. These studies reflect a large body of literature, demonstrating a key role for inflammatory monocyte recruitment in establishing varied PMNs[93,102].

TDMs have a pivotal role in directing macrophage polarization towards pro-metastatic phenotypes. In gastric cancer and CRC, liver macrophages undergo polarization towards alternatively activated phenotypes following exosome-mediated delivery of miRNAs[103,104] and their immunosuppressive activity contributes to the establishment of the liver PMN. Moreover, macrophages in the lung PMN undergo expansion driven by tumour-derived exosomes whose damage-associated molecular pattern (DAMP)-containing cargo induces TLR2-dependent glycolytic metabolism; the resulting enhanced lactate production activates NF-κB signalling, which drives polarization towards a mixed M1–M2 immunosuppressive phenotype[105].

NK and other innate lymphoid cells

Innate lymphoid cells (ILCs) are highly heterogeneous with key roles in orchestrating innate immune processes. They are largely tissue-resident, functioning as immune sentinels with additional roles in tissue repair and are emerging as orchestrators of antitumour adaptive immunity[106]. For instance, in a melanoma mouse model, IL-33 was shown to activate ILC2 and suppress NK cells promoting immunosuppression[107]. Interestingly, IL-5 release from ILC2 in the lung PMN drives the recruitment of glycolytic eosinophils that establish a glucose-poor and lactate-rich local metabolic microenvironment to suppress antitumour immunity by NK cells[108].

NK-cell-mediated cytotoxicity is a core component of antitumour immune surveillance and a potent inhibitor of metastasis. Circulating tumour cells are highly susceptible to NK-cell attack and employ multiple mechanisms to subvert this via cluster formation, along with shielding by platelets, neutrophils and neutrophil-derived NETs[109]. Impaired NK-cell function is a common feature of PMNs and is induced, via a variety of strategies, leading to alterations in NK-cell recruitment, survival, proliferation, differentiation and tumoricidal function. NK cells constitute a substantial immune-cell population in the lung but in the context of the lung PMN, as discussed above, these cells develop a suppressed anti-metastatic function by cancer-primed infiltrating neutrophils and resident ILC cells[108].

Active TGFβ-signalling, a hallmark of PMNs, has profound effects on inducing NK-cell states reminiscent of an exhausted phenotype[110]. Multimodal characterization of NK cells from patients with metastatic breast cancer identified TGFβ-driven NK-cell dysfunction characterized by impaired interferon-γ (IFNγ) production, defective oxidative metabolism and reduced cytotoxicity, supporting the notion that TGFβ-induced NK-cell plasticity may contribute to defective NK-cell activity both systemically in the circulation and in the PMN[111]. Remarkably, tumour-derived TGFβ was demonstrated to induce conversion of NK cells into ILC1-like cells, with similar presentation of exhaustion markers and suppressed anti-metastatic activity[112].

Indirect effectors in systemic perturbation

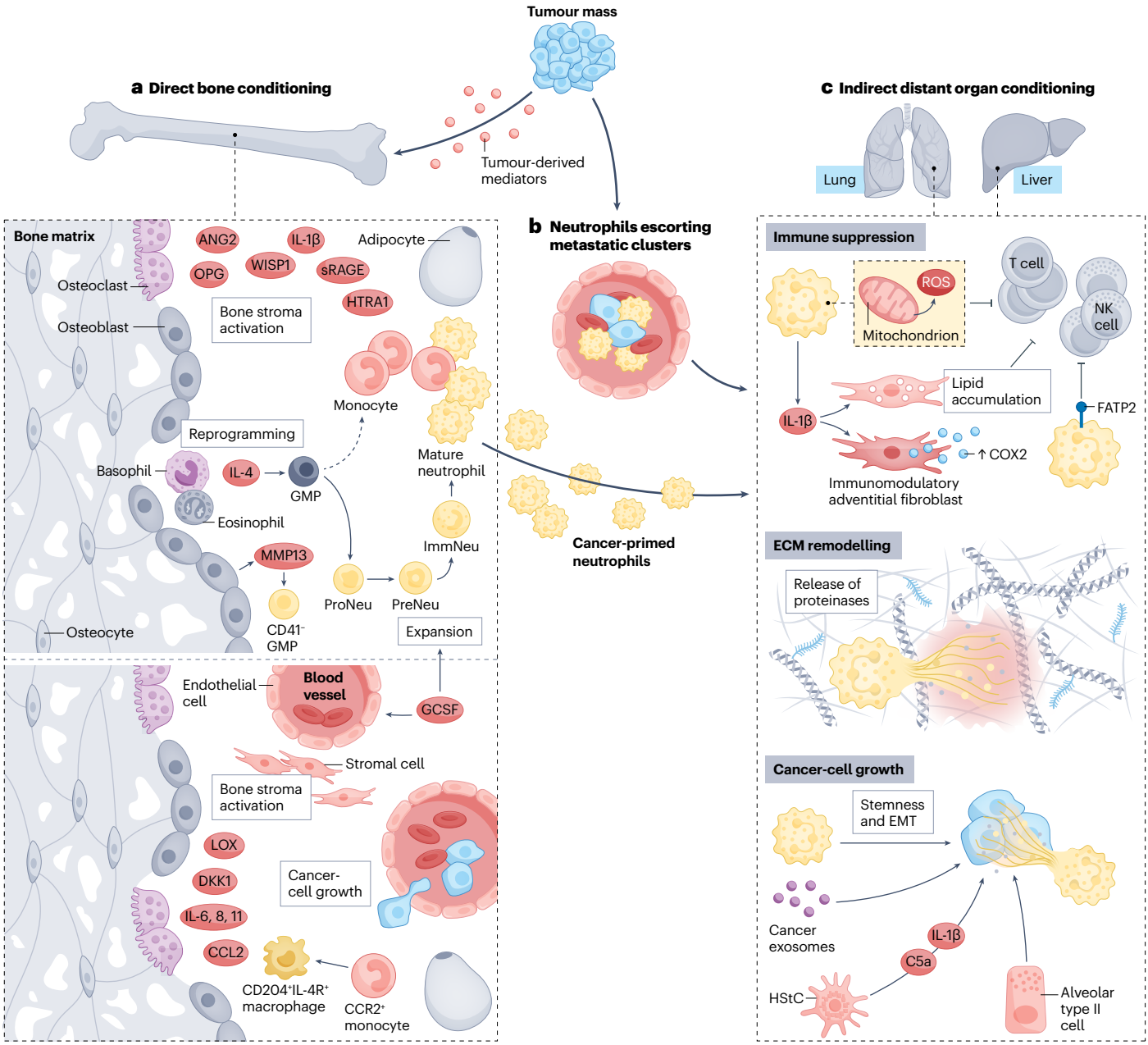
Platelets

Systemic platelet activation and elevated thrombosis are frequently experienced when widespread clotting contributes to organ dysfunction and morbidity. Platelets are recognized for their pro-metastatic functions through diverse mechanisms ranging from shielding circulating tumour cells to pro-angiogenic and immunoregulatory processes. They are important mediators of the formation of multiple PMNs[113]. Coagulation is initiated by TF, which triggers a proteolytic cascade leading to platelet activation, aggregation and thrombus formation. Tumour-derived TF and the ensuing platelet activation and microthrombus formation promote myeloid cell recruitment to the lung, leading to PMN formation[102]. Breast-tumour-derived EVs induce both systemic platelet activation and local activation within the PMN, which induces NETs and metastasis[114]. Moreover, cancer-activated platelets promote lung-endothelial-cell activation and melanoma-cell adhesion to lung endothelial cells[115].

Beyond the lung, cancer-primed platelets mediate tumour-to-bone communication and the formation of bone PMNs. Primary prostate cancer induces upregulation of thrombospondin 1 (TSP1) and TGFβ release from platelets, which represses osteoclast differentiation and promotes myeloid-cell recruitment and subsequent bone metastasis[116]. Intriguingly, in melanoma, platelets promote bone PMN formation by sequestering tumour-derived TGFβ and MMP1, which is shuttled to the bone to support remodelling of the bone microenvironment[117].

Neutrophils

Alongside their direct action on distant organs, TDMs can stimulate haematopoiesis and increase the mobilization of bone-marrow-derived inflammatory cells, which infiltrate distal organs and contribute to the formation of PMNs[11,118]. Neutrophils are the predominant



bone-marrow-derived cell; they rapidly enter the circulation and recruit to sites of tissue injury and infections. Over the past few decades, many studies have focused on neutrophil responses and their prominent roles as regulators of tumour progression and, despite their short-lived and non-proliferative status, neutrophil plasticity and functional diversity are now well recognized[7,119].

Generation of cancer-primed neutrophils. Neutrophils change their phenotype and functions in response to the local tissue environment and are dramatically altered upon exposure to the TME[120–122]. Importantly, their modulation in the context of cancer is initiated during their production in the bone marrow, which generates altered (cancer-primed) neutrophils that can be observed in both mice and humans[123,124]. The bone marrow environment in the context of cancer is profoundly perturbed: activation of granulopoiesis leads to the expansion of early progenitors, and the production of neutrophils results in an increased release into the circulation of heterogeneous primed neutrophils, including mature, immature and early neutrophil progenitors[125–127]. Interestingly, in certain cancer contexts, neutrophils are reported to be additionally produced from progenitors residing outside the bone marrow, in a process termed extramedullary granulopoiesis, which may contribute to their immunosuppressive functions[123,128]. The TDMs that induce neutrophil perturbations have been extensively reported. One key factor driving increased neutrophil production is granulocyte-colony-stimulating factor (GCSF), a major instigator of emergency granulopoiesis and reported to be

Fig. 4 | Bone-marrow conditioning in the local and distal formation of pre-metastatic niches. a, The top panel shows the generation of cancer-primed neutrophils, initiated by tumour-induced conditioning of the bone marrow and resulting in early activation of granulopoiesis, characterized by rapid expansion of early neutrophil progenitors and the production of a highly heterogeneous neutrophil population. Similarly, tumour-derived mediators (TDMs) induce aberrant expansion of monocytes. This process is facilitated by TDM-induced perturbation (some indicated in the figure) of the bone-marrow microenvironment, notably through bone-marrow–stromal activation-generating niches that support and shape myelopoiesis towards the generation of pathological populations of monocytes and neutrophils. The dashed arrow represents monocyte precursors not being shown. The lower panel shows that the same process of TDM-induced remodelling of the bone-marrow microenvironment leads to the generation of a metastasis-supportive bone pre-metastatic niche via the activation of osteoclasts and osteoblasts as well as bone vasculature remodelling. **b**, Neutrophils escort clusters of circulating tumour cells, enhancing their growth potential, and facilitate their subsequent extravasation at distant sites. **c**, Tumour-induced bone-marrow conditioning drives the production and systemic mobilization of cancer-primed neutrophils, which infiltrate distant organs and serve as key mediators of pre-metastatic niches, particularly in the lung and liver. Within these pre-metastatic niches, cancer-primed neutrophils exhibit broad phenotypic alterations, including changes in metabolism, pro-inflammatory signalling, proteolytic activity and neutrophil extracellular trap formation, known as NETosis. These alterations support their pro-metastatic conditioning by enabling immune suppression, extracellular matrix (ECM) remodelling, and the promotion of cancer-cell growth and stem-like characteristics directly or through the aberrant activation of tissue-resident cells. ANG2, angiopoietin 2; C5a, complement 5a; CCL2, CC-chemokine ligand 2; CCR2, CC-chemokine receptor 2; COX2, cyclooxygenase 2; DKK1, dickkopf-1; EMT, epithelial-to-mesenchymal transition; FATP2, fatty acid transport protein 2; GCSF, granulocyte-colony-stimulating factor; GMP, granulocyte–macrophage progenitor; HStC, hepatic stellate cell; IL, interleukin; IL-4R, interleukin 4 receptor; ImmNeu, immature neutrophil; LOX, lysyl oxidase; MMP13, matrix metalloproteinase 13; NK, natural killer; OPG, osteoprotegerin; PreNeu, preneutrophil; ProNeu, proneutrophil; ROS, reactive oxygen species; sRAGE, soluble receptor for advanced glycosylation end products; WISP1, WNT1-inducible-signalling pathway protein 1.

highly produced by cancer cells and the TME[118,129,130]. Recent studies have shown that osteogenesis-inducing TDMs, such as angiopoietin-2 (ANG2), WNT1-inducible-signalling pathway protein 1 (WISP1; also known as CCN4) and the receptor activator of NF-κB ligand (RANKL) decoy receptor osteoprotegerin (OPG; also known as TNFRSF11B), from early breast cancer remodel the bone-marrow MSC niche, which, alongside altered myelopoiesis, leads to the production of immunosuppressive monocytes and neutrophils[131]. Similarly, in the presence of non-small-cell lung cancer, the IL-4 derived from bone marrow basophils and eosinophils induced granulocyte-monocyte progenitors (GMPs) to transcriptionally reprogramme the development of immunosuppressive tumour-promoting myeloid cells[132]. Further changes in the bone-marrow niche were reported in a mouse model of pulmonary malignancy, where the presence of cancer cells in the lung activated osteocalcin-positive osteoblasts via tumour-associated soluble receptor for advanced glycosylation end products (sRAGE). This in turn promoted the expansion and mobilization of pro-tumorigenic sialic-acid-binding immunoglobulin-like lectin F (SIGLECF)-high neutrophils[133]. In mouse models of breast cancer characterized by p53 loss, tumour-associated macrophages were found to produce IL-1β, which induced the mobilization of neutrophils from the bone marrow to the lung to form PMNs[134]. Interestingly, the remote effect of cancer on myelopoiesis was shown to persist even after tumour removal. Cancer-derived serine protease HTRA1 on EVs was shown to target osteoprogenitors to induce expansion of GMPs via MMP13 upregulation and altered granulopoiesis[135]. This effect was also shown to endure after tumour resection and continued to negatively influence anticancer responses[135]. Thus, these tumour-to-bone-marrow connections drive the mobilization of cancer-primed myeloid cells, in particular neutrophils, fostering PMN formation in other organs (upper part of Fig. 4a).

Bone conditioning. The bone tissue also experiences tumour-induced changes that subsequentially support metastasis (lower part of Fig. 4a). These can occur, as reported for breast cancer, via the recruitment and retention of $CCR2^+$ monocytes, which undergo differentiation into $CD204^+IL\text{-}4R^+$ macrophages, which actively support the outgrowth of bone metastases[136]. However, resident cells in the bone that mediate altered myelopoiesis, such as osteoclasts[133] and other MSCs, also represent cellular components involved in the formation of bone PMNs[137]. This can proceed, for example, following conditioning by factors that increase osteoblastic differentiation[131]. Moreover, the recruitment of osteoclast precursors can support the formation of the bone PMN for metastatic breast cancer cells via the production of R-spondin-2-rich, RANKL-rich and leucine-rich repeat-containing G protein coupled receptor 4 (LGR4)-dependent WNT inhibitor DKK1[138]. Remarkably, GCSF, one of the key mediators of granulopoiesis occurring in the bone marrow and responsible for cancer-dependent neutrophil mobilization[7], was recently reported to have a haematopoietic-cell-independent role in directly remodelling the bone vascular endothelium[139], suggesting that a single factor has the potential to concomitantly drive local bone PMN formation alongside the induction of systemically mobilized cancer-primed neutrophils. Importantly, breast cancers release various factors (LOX, CCL2, IL-6, DKK1 IL-11 and IL-8) that activate osteoclastogenesis and bone resorption[37,131], to induce a pro-tumorigenic bone environment. This is a feature consistent with the clinical evidence that osteoporosis accelerates the progression of bone metastasis[140].

Cancer-primed neutrophils as mediators of PMNs. Neutrophils have been reported to directly support cancer-cell spread by escorting circulating tumour clusters enhancing their growth potential[141], as well as promoting their extravasation at metastatic sites[142] (Fig. 4b). Importantly, cancer-primed neutrophils can prime distant organs for metastasis (Fig. 4c). Furthermore, owing to their cancer-primed state, bone-marrow-derived neutrophils exhibit increased migration to both pre-metastatic and other tissues[143]. Importantly, this increased mobilization results in elevated neutrophil infiltration in distant organs, an important prerequisite for effective PMN formation[7]. The predominant pre-metastatic activity of cancer-primed neutrophils relates to immunosuppression. Cancer-primed neutrophils are reported to harbour altered metabolic activity that supports their immune-suppressive functions. These include upregulated fatty acid transport protein 2 (FATP2) mediating the uptake of arachidonic acid and synthesis of PGE_2 (ref. 144), or the ability to engage in oxidative mitochondrial metabolism maintaining high production of

reactive oxygen species (ROS)[145]. Recent studies have provided mechanistic insights into neutrophil–NK cell crosstalk. In mouse models of mammary lung metastasis, GCSF-dependent lung-infiltrating neutrophils elicit a potent anti-metastatic activity in NK-cell-deficient hosts, but a pro-metastatic activity in NK-cell-competent hosts[146]. Cancer-primed neutrophils have also been shown to exert a strong ROS-induced suppression of NK-cell cytotoxicity and tumoricidal effect ex vivo, and again demonstrating the high potency of NK cells in mediating metastatic control. Neutrophils in the premetastatic lung also indirectly suppress NK-cell cytotoxicity through stromal regulation. As mentioned earlier, preconditioned lungs show a specific expansion of immunomodulatory adventitial fibroblasts in response to neutrophil-derived IL-1β. These fibroblasts were found to reprogramme various myeloid populations in the PMN via COX2 upregulation and subsequent production of PGE_2, which results in suppression of T and NK cells[48]. Interestingly, the same inflammatory IL-1β signalling has been shown to induce lipid accumulation in mesenchymal lung cells, which inhibit NK cell function via the transfer of exosome-like particles[55].

An additional important pro-tumorigenic function of cancer-primed neutrophils is mediated by their high production of NETs, which enhance cancer-cell growth in PMNs[147,148]. Stromal and parenchymal tissue cells at the pre-metastatic stage can contribute to the recruitment and activation of cancer-primed, NET-forming neutrophils. Hepatic stellate cells in the pre-metastatic liver were polarized into an inflammatory cancer-associated phenotype, which promoted neutrophil infiltration and NET formation via the production of complement C5a and IL-1β[149]. As mentioned previously, the upregulation of complement C3 in lung MSCs, regulated by T_H2 cytokine–STAT6 signalling cascade, stimulates NETosis in infiltrating cancer-primed neutrophils[57]. Increased NETosis activity can also be triggered by oxalate, which accumulates in the lung PMN as a result of metabolic reprogramming of alveolar epithelial cells, which activates TLR3–interferon regulatory factor 3 (IRF3) signalling. Oxalate in the lung tissue induced NADPH oxidase activation in neutrophils, necessary for NETosis, which in turn accelerated metastatic colonization by breast cancer cells[150]. Tumour-secreted exosomes were also shown to directly contribute to the release of NETs in distal PMNs as well as in the vasculature, which has the added effect of promoting thrombosis known to support both PMN activity (see subsection 'Platelets') and cancer-associated pathological conditions[114,151].

The tumour-promoting effect of infiltrating neutrophils can be mediated by stimulation of (lympho)angiogenesis and ECM remodelling[152,153]. Under sustained tissue inflammation, ECM remodelling in PMNs was shown to be regulated by the proteolytic cleavage of laminin, orchestrated by the NET-associated proteins, neutrophil elastase and MMP9 (ref. 153). Neutrophils in PMNs can also directly influence the intrinsic metastatic features of cancer cells upon seeding either by enhancing their stemness potential[118] or by modulating their mesenchymal phenotype[154,155]. Cancer cells endow neutrophils with the ability to promote the EMT of cancer cells, by stimulating secretion of the EMT inducer FAM3C in a TGFβ1–SMAD2/3-dependent manner[156]. FAM3C recently emerged as a biomarker of disease progression and was found to be present in tumour-derived EVs, which could pre-condition distal organs[157].

Box 2 | Clinical evidence of pre-metastatic conditioning

The study of pre-metastatic changes in patients with cancer is limited by the difficulty of analysing organs free of metastatic disease. Nonetheless, clinical evidence of the pre-metastatic niche can be found in organs in which removal is part of clinical practice, such as the lymph nodes. A study that analysed draining lymph nodes of patients with bladder cancer demonstrated a clear association between the presence of the extracellular matrix (ECM)-associated protein tenascin C and metastatic progression[235]. Interestingly, this also positively correlated with the presence of cytokine-containing extracellular vesicles (EVs) in the urine of patients with cancer, providing evidence of both an ECM change in an organ free of metastasis and the systemic presence of a cancer-derived mediator of pre-metastatic niches (PMNs)[235]. In a recent study, clinical evidence of cancer-primed neutrophils, another potential mediator of PMNs, was reported in patients with asymptomatic early breast cancer[236]. The possibility of monitoring PMN mediators (such as exosomes, cancer-specific immune-cell populations or mediators in circulation) together with new technological advances in analysing cancer-derived EVs offer strong potential for early cancer diagnosis[237,238]. Additionally, whole-body imaging analysis could also be used to detect the presence of PMNs. For instance, in preclinical models, computed tomography (CT) images quantifying different parameters of the lung (such as volume and density) identified changes, thus allowing detection of lung PMNs in mice harbouring primary breast cancer[239]. In a retrospective study, CT radiomic features present in the liver were shown to predict metachronous liver metastasis within 24 months after surgical removal of primary rectal tumours, suggesting that changes in whole-organ PMNs could also be used clinically to predict early recurrence[240]. Similar evidence was provided in a retrospective study that predicted lung metastasis in patients with breast cancer[241].

A knowledge of PMNs has potential not only for early metastatic risk assessment but also for targeted interventions aimed at decreasing the risk of development of metastasis. As our mechanistic understanding of PMN formation grows, so too does the list of possible targets for anti-metastatic therapies. For this, a deeper understanding of the cancer-intrinsic drivers, such as oncogenic mutations, responsible for specific PMN priming will be essential. Moreover, while the majority of tumour-induced tissue perturbations generate pro-metastatic conditions, given the right context, anti-metastatic host responses in the cancer context also occur[154,242]. It is conceivable that if harnessed, these could also offer novel anti-metastatic therapeutic strategies.

Inter-organ communication

The systemic perturbations described above have mostly been reported in mechanistic studies using preclinical models, but their occurrence has also been described in patients with cancer (Box 2). Importantly, the conditioning that targets specific pre-metastatic sites also has the potential to trigger a cascade of events affecting multiple organs and resulting in alterations to overall body physiology (Fig. 5). Evidence for this comes from observed changes in body composition, particularly skeletal muscle, adipose tissue and bone, in patients with cancer. Not only does clinical monitoring of these changes have prognostic value but also precise detection of the changes means that more targeted approaches providing

nutritional support could be applied to patients with cancer[158]. Alterations in body composition can, at late stages of disease, lead to complex syndromes such as cachexia, where intricate metabolic imbalances become irreversible, leading to systemic wasting and contributing to mortality[159]. Moreover, alterations to metabolism and the immune system are constantly evolving and when tumours progress and metastases are established, additional systemic perturbations will occur, which may depend on the specific organ of metastatic spread. In the case of melanoma, clinical evidence indicates that patients stop responding to immunotherapy once they develop liver metastasis, and a study that mimicked this scenario in preclinical models did indeed find that liver metastases systemically deplete activated $CD8^+$ T cells by apoptosis through interaction with FAS ligand $(FASL)^+CD11b^+F4/80^+$ monocyte-derived macrophages within the liver[160]. This further exemplifies the constant evolution of the systemic interaction between cancer and the host, a phenomenon that at early stages might drive local perturbations in distant tissues but also represents a prelude to what, at late stages of disease, may cause a degenerative syndrome, a common cause of mortality.

Metabolic homeostasis

EVs are part of the inter-organ communication maintaining metabolic homeostasis. They have roles in many physiological processes via the delivery of bioactive cargos[161]. Specifically in the context of cancer, EVs delivering miR-122 were reported to induce alterations in O-linked *N*-acetylglucosamine (O-GlcNAc) protein modifications in muscle, affecting protein homeostasis and causing muscle dysregulation in a mouse model of breast cancer[162]. Similarly, the same miRNA was reported to target metabolic homeostasis in the pancreas. Here, breast-cancer-produced EVs containing miR-122 suppressed glycolysis and ATP-dependent insulin exocytosis from pancreatic β-cells, leading to loss of whole-body glycaemic control, with increased glucose production and decreased glucose tolerance, resulting in fasting hyperglycaemia[163]. Recent work, using mouse models of melanoma and osteosarcoma, has shown how the fatty acid cargo of tumour-derived EVs can induce Kupffer cells in the liver to express TNF, which suppresses hepatocyte fatty acid metabolism to generate a pro-inflammatory fatty liver microenvironment[164]. Intriguingly, this study also found that this EV-dependent liver perturbation enhanced the side effects of chemotherapy, such as bone marrow suppression and cardiotoxicity[164], suggesting that tumour-induced metabolic reprogramming of the liver causes systemic effects in other organs. Moreover, the miRNA cargo of breast-cancer-derived EVs, namely miR-204-5p, was reported to target white adipose tissue (WAT) and activate hypoxia-inducible factor 1A (HIF1A), which in turn induces leptin signalling and promotes lipolysis and white adipose tissue browning, thus reducing fat mass[165]. Syngeneic transplant mouse models of cancer were also shown to induce increased innervation in WAT, which induced browning via β-adrenergic activation of adipocytes. This effect was shown to be mediated by IL-4 dependent macrophage activation[166]. Given that EV-mediated crosstalk between adipose tissue and other organs under physiological and other pathological conditions is well established[161], alterations in adipose mass in the context of cancer have the potential to have additional systemic consequences.

The gut microbiome

The gut microbiome is the most abundant symbiotic microbial population in the body and profoundly influences organismal homeostasis

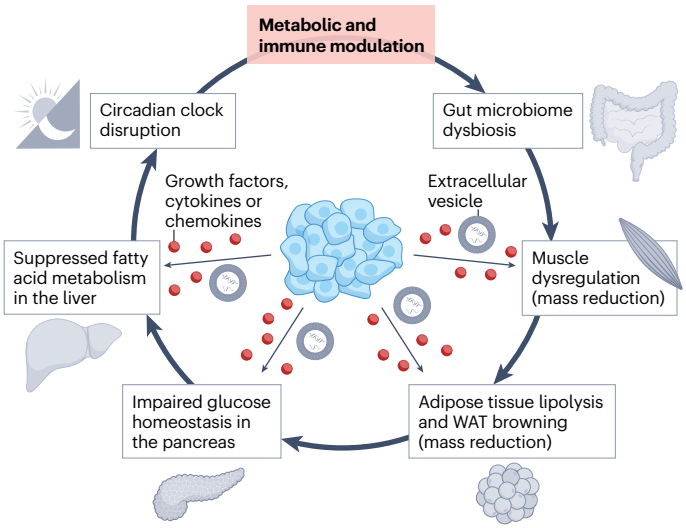


Fig. 5 | Multi-organ and multi-system interactions between tumours and the host. Tumours influence multiple organs and systems either directly through tumour-derived mediators (TDMs) (with associated growth factors, cytokines, chemokines and extracellular vesicles), or indirectly via disruption of circadian rhythms and gut dysbiosis. These interactions lead to distal organ preconditioning, which, in isolation, initially perturbs specific organ functions. However, these physiological systems are interconnected primarily through systemic modulation of metabolism and the immune system, which will have repercussions on multiple organ systems. This widespread physiological disruption can initially manifest as pro-metastatic conditioning in early stages and may eventually progress to degenerative syndromes. WAT, white adipose tissue.

via vitamin and metabolite production[167,168]. An impaired gut microbiota, a condition known as dysbiosis, can contribute to many diseases. Equally, pathological conditions, including cancer, can induce dysbiosis[169]. The link between the microbiome and the immune system is also well known; indeed, germ-free mice exhibit a deficiency in their immune system as well as control of neutrophil heterogeneity that results from ageing[170,171]. The crosstalk between cancer and the gut microbiome via changes in the immune system is best exemplified by its impact on the response to immune checkpoint blockade[172,173]. Alterations to the composition of the gut microbiome can also result in altered host metabolism, with repercussions for energy availability and muscle function[174]. Cumulative evidence on the interplay between cancer and the gut microbiome has led to the idea of fine-tuning a patient's microbial composition to increase the efficacy of cancer treatment[175].

Circadian rhythms

The circadian clock is responsible for maintaining a healthy physiology and its disruption is also linked to cancer, with disruption of different molecular clock components reported to either promote or counteract tumorigenesis[176]. Again, the interaction between cancer and the circadian clock appears to be reciprocal. For instance, lung adenocarcinoma was reported to inhibit rhythmic hepatic insulin signalling, which consequently led to a decrease in glucose sensitivity as well as changes in lipid metabolism via the rewiring of circadian transcription in the liver[177]. Equally, the metastatic behaviour of cancer cells was shown to be profoundly influenced by circadian rhythm hormones such as melatonin, testosterone and glucocorticoids[178].

Cancer-independent preconditioning

Cumulative evidence of non-cancer-related systemic perturbations that mimic features of cancer-induced pro-metastatic conditioning suggests a bidirectional interaction between cancer and its host. For example, neutrophils can acquire pro-tumoural functions in the context of tissue injury[121], pathological conditions, such as stress[179,180] and inflammatory diseases, associated with obesity and smoking[153,181,182]. Similarly, the same mediator reported to be involved in the formation of liver PMNs, SAA, also plays a part in exacerbating liver inflammation associated with nonalcoholic fatty liver disease (NAFLD) and ethanol-induced liver injury and cirrhosis[183,184]. Collectively, these studies, support the idea that cancer dependent pre-conditioning hijacks and simultaneously brings together mechanisms of systemic alteration present in multiple disorders thereby creating novel, complex pathophysiological states.

Stress-induced preconditioning

Stress is known to greatly perturb the physiological state and was recently shown to induce broad perturbations in the bone marrow[185]. Indeed, chronic stress was shown to increase bone metastasis via the activation of osteoblasts[186], but also to induce mobilization of perturbed myeloid cells[179]. Disseminated cancer cells can more effectively colonize the lungs of mice exposed to chronic unpredictable mild stress (CUMS) because it elevates systemic glucocorticoid levels, leading to increased pulmonary recruitment of immunosuppressive myeloid cells via the CXCL1–CXCR2 axis[187]. In mice, stress hormones induced by physical restraint can induce the release of pro-metastatic neutrophils, which increase the chance of metastatic cell reactivation from dormancy[180]. In a recent study, CUMS was shown to create a PMN in the lung by increasing fibronectin deposition, reducing T-cell presence and increasing the infiltration of neutrophils. Importantly, these neutrophils, which express the glucocorticoid receptor, when stimulated by stress-induced glucocorticoids, were reported to alter their circadian rhythm, which potentiated their ability to release NETs. Intriguingly, these features mimic the characteristics of cancer-primed neutrophils, as this study showed that, when mice harbour primary carcinomas, chronic stress did not further change the expression of their ageing markers[179]. In certain cases, CUMS can also induce the recruitment of myeloid cells from an extramedullary site, the spleen, to induce a lung PMN[187]. In mouse models of ovarian- and lung-cancer dormancy, stress hormones indirectly mediated a fibroblast growth factor (FGF)-dependent reactivation of quiescent tumour cells, via the accumulation and release of oxidized lipids from stress-activated S100A8/A9^{+} neutrophils[180]. These studies support the notion that distant changes to a tissue can, at least in part, be regulated by the nervous system, and whether cancer can also induce similar perturbations in distal organs via activation of the nervous system is an area that remains to be explored.

Ageing-induced conditioning

Ageing is also a potent physiological process that induces tissue changes predisposing to metastatic growth[188,189]. Ageing is often characterized by a state of chronic low-grade inflammation and cellular senescence[190] whereby ageing-associated dysregulated systemic inflammation can affect neutrophils. Neutrophils can facilitate tissue colonization by circulating tumour cells, by functionally compromising vascular endothelial junctions, thereby increasing circulating tumour-cell extravasation[181]. However, neutrophils in aged mice show reversed trans-endothelial migration patterns, whereby neutrophils lose directional motility in circulation and accumulate in vascular endothelium in inflamed lungs[191]. This phenomenon increases vascular leakage and therefore could increase CTC extravasation in aged venules. In addition, in the bone marrow, the origin of myeloid priming, alterations typical of ageing induce a steady-state myeloid-biased haematopoiesis[192]. Collectively, the changes driven by ageing, which include changes in inflammation, in the tissue stroma and in the ECM, are naturally driving the key determinants of cancer-induced pre-metastatic conditioning (Fig. 2) and mechanistically support the link between ageing and cancer risk[193].

Diet- and lifestyle-induced conditioning

Other physiological changes can influence metastatic progression in similar ways. A diet rich in fat is reported to induce changes in the lung similar to that of a cancer-induced PMN through the accumulation of palmitic acid[63], as well as the mobilization of dysfunctional neutrophils increasing vascular permeability[181,194]. This phenomenon was observed in mouse models of diet-induced obesity and was associated with obesity-mediated neutrophil reprogramming, causing an increased production of ROS and NETosis[181]. A high-fat diet also causes an increase in fatty acid release from adipocytes in the omental PMN, favouring the establishment of metabolic crosstalk with ovarian cancer cells and promoting metastatic progression, as well as inducing systemic changes in myeloid cells via alteration of the intestinal microbiome[195,196]. Moreover, certain diets rich in capsaicin, found in chili peppers, were shown to disrupt gut barrier integrity leading to bacterial entry into the liver with consequences for bile acid metabolism, which drove natural killer T (NKT) cell recruitment, inducing a liver PMN[197]. Conversely, systemic changes induced by dietary restriction were also shown to perturb the bone marrow environment and optimize immunological memory, supporting the idea that dietary interventions could be used to positively control immunity[198,199].

Smoking is well known to have pro-carcinogenic effects in the lung, but more recently both nicotine and lipopolysaccharide (LPS) contaminants in smoke were reported to induce a lung PMN by modulation of neutrophil activities[153,182]. Exposure of lung PMNs to nicotine also induced EMT in and increased the metastatic colonization potential of cancer cells, by promoting secretion of the pro-tumour neutrophil-related factor lipocalin 2 (LCN2)[182]. Equally, the beneficial effects of exercise were linked to metabolic reprogramming of the stroma, an increase in T-cell activity, and potential induction of a niche pre-conditioning that counteracts metastasis via the release of muscle-derived EVs[200–202]. Interestingly, mild cold exposure was shown to activate brown adipose tissue, which induced metabolic alterations that decreased blood glucose and inhibited primary tumour growth[203], suggesting that knowledge of the mechanisms of both cancer-dependent and cancer-independent PMN formation could lead to novel therapeutic interventions.

Other variables of the physiological state

We must also consider that additional variables might be relevant, but also represent confounding factors that indirectly influence lifestyle, making the identification of causalities challenging. This is the case for variables such as ancestry or sex that might correlate with variations in lifestyle. Nevertheless, there may also be clear biological differences in these variables that equally need to be taken into account, such as the well recognized differences in immune responses between men and women, but also the reported sex biases in cancer incidence, spectrum and outcomes as well as sex differences in the

onset of systemic syndromes such as cachexia[204–206]. Similarly, ethnic disparities in the severity of pancreatic-cancer-related cachexia have also been reported[207].

Therapy-induced conditioning

Considering that systemic anticancer therapies impose substantial alterations on the body as well on the TME[16], it is perhaps not surprising that they also induce a distant preconditioning that favours metastatic progression. Chemotherapy has been reported to enhance metastasis in many ways. For instance, cytotoxic drugs were reported to increase levels of cancer-derived EVs enriched in annexin A6, which promoted NF-κB-dependent endothelial cell activation and $LY6C^{+}CCR2^{+}$ monocyte expansion in the pre-metastatic lung[208]. Systemic chemotherapy was also reported to selectively drive NETosis in the lung and kidney. Here, the NETs were able to promote the therapeutic resistance of cancer cells in the lung via activation of TGFβ as well as contribute to kidney damage[209]. Chemotherapy was also shown to activate complement signalling in CAFs, which triggered immunosuppression via myeloid cell recruitment to metastatic sites[210]. In another study, multi-dose gemcitabine was reported to induce reactive myelopoiesis, increasing monocyte production but also generating pro-metastatic lung interstitial macrophages via upregulation of coagulation factor X[211]. Additionally, a side effect of radiation exposure in healthy lungs was shown to be an efficient priming of the organ for metastatic growth of different tumour types. This effect was mediated by the accumulation of radiation-primed neutrophils that, via degranulation, drove NOTCH pathway activation in the alveolar cells, which subsequently increased the metastatic potential of cancer cells to the post-irradiated lung[121].

Are PMNs stochastic or deterministic?

The shared mechanisms between cancer-independent and cancer-dependent preconditioning of distal tissues suggests that cancer might induce the formation of PMNs by hijacking more general physiological whole-body responses. Moreover, that the same or similar mediators are involved in PMN formation and in the extensive inter-organ connections that occur upon metastasis, raises the question of whether PMNs are stochastic or deterministic phenomena resulting from a wider disruption of host physiology. The aggressive potential of cancers is, like any other biological process, largely governed by serendipitous processes that are positively selected to increase the chances of growth, dissemination and successful metastasis. Therefore, the pre-metastatic conditioning induced by systemic perturbations could be viewed as general alterations in the organism physiology that, in sites targeted by cancer cells, increase their chance of growth. When PMNs are induced via indirect mediators like systemic mobilization of myeloid cells, or primary-tumour-derived factors that activate resident cells in multiple organs, it is unclear whether their impact is restricted to sites subsequently targeted for metastatic growth. It is conceivable that multiple organs are affected independently of metastatic dissemination. In this regard, pre-metastatic conditioning could be viewed as a more stochastic property of a wider physiological change. Moreover, if these perturbations are stochastic, they could, in some organs, generate tissue states with anti-metastatic properties. This phenomenon has been poorly investigated so far. However, analysis of circulating neutrophils has uncovered their previously underappreciated extensive heterogeneity[212] and despite their more common pro-metastatic behaviour, in certain contexts, they are reported to kill disseminated tumour cells, limiting metastatic spread[213,214]. Furthermore, the type of systemic changes induced may depend on the properties of cancer cells themselves and the ability to efficiently induce PMNs may be an inherited property of a more aggressive cancer programme. Indeed, syngeneic transplant mouse models showed that myeloid cells systemically primed by aggressive breast-cancer cells could restore the metastatic ability of cells otherwise unable to evade immune control[214].

The fact that certain organs are frequent sites of metastasis but others, despite being accessible due to extensive vascularization, very rarely host secondary tumour growth (Fig. 2a), raises the question of whether all organs are equally targeted by tumour-induced conditioning. In the case of EVs as mediators of PMNs, the specificity in targeting certain tissues challenges the idea that PMN formation is stochastic and points to a deterministic model for metastatic tropism. Indeed, the compatibility between the specific integrin complexes of EVs and the ECM components of the secondary niche is a major selective pressure for metastatic spread. Moreover, exosomes were shown to preferentially fuse with specific resident cells in certain organs through specific integrin-mediated interactions[215]. This organotropism of EVs is a frequent observation; for instance, runt-related transcription factor 2 (RUNX2) in colorectal cancer regulates the release of EVs enriched in integrin beta-like 1, which are able to activate fibroblasts via NF-κB signalling. However, these EVs were shown to accumulate specifically in liver and lung fibroblasts, and, to a lesser extent, in those of brain and bone[30]. Similarly, PDAC exosomes preferentially accumulate in the liver where they activate hepatic stellate cells and induce liver fibrosis, increasing organ stiffness and collagen density[40]. This preconditioning changes the properties of the target site and experimentally, conditioning with exosomes from lung-tropic tumours can induce a lung PMN that subsequently allows metastasis from bone-tropic tumour cells, which normally would not be retained in this organ[215]. This piece of evidence attests to the power of PMN changes in driving metastatic tropism. Nonetheless, despite the complex process of cargo selection during exosome biogenesis, the integrins that mediate specificity in PMN formation would be produced and present on the cancer cell producing the exosome[216]. Therefore, pre-conditioning that is tightly dependent on the properties of the cancer cells probably represents a way of supporting metastatic organ tropism.

However, the control of metastatic tropism is multifactorial and is not necessarily determined by the cancer-cell-intrinsic properties alone, as demonstrated by soluble mediators characteristic of certain physiological states, which can cause pre-metastatic conditioning, which in turn mediates metastatic tropism. For instance, in the brain, oestradiol (E2) levels were reported to induce increased production of brain-derived neurotropic factor (BDNF) in astrocytes, which leads to the activation of tropomyosin kinase receptor B (TRKB) on cancer cells and thereby increases the seeding efficiency of brain metastasis[217]. This could explain in part why breast-cancer brain metastases are more common in younger females[218]. The most likely scenario is that PMN formation is a product of a combination of both stochastic and deterministic processes, which occur simultaneously and may differ in their contribution depending on the stage of disease and cancer type.

Future perspectives and conclusions

As discussed in Box 2, clinical evidence of premetastatic conditioning is emerging and an understanding of these processes from the preclinical studies discussed in this Review could lead to novel targeted approaches. Indeed, therapies could potentially be developed to target many of the TDMs described here that induce PMNs (Supplementary Table 1). However, this would probably represent a limited approach because its efficiency would depend on how heavily a

Glossary

Adipoblasts
Specialized cells of the adipose tissue derived from mesenchymal stem cells that function as precursors of adipocytes.

Bone resorption
Process by which osteoclasts dissolve the minerals in bone and break down the matrix.

Cachexia
Complex multiorgan syndrome causing wasting of the body.

Chronic unpredictable mild stress
(CUMS). Animal model of depression and stress characterized by exposure to a combination of mild and randomly administered sources of stress such as food and water deprivation, tilting of the cage, physical restraint and forced swimming. The purpose of this model is to mimic the stress in daily human life.

Citrullination
Process by which the amino acid arginine is converted into citrulline by post-translational modifications catalysed by peptidyl arginine deaminases, also referred to as deamination.

Decellularized matrices
Extracellular matrix from biological origins that have been processed to remove their cellular components to obtain a scaffold of the site-specific extracellular protein composition.

Degranulation
Action carried out by specialized cells that is characterized by the release of intracellular granules.

Granulopoiesis
Haematological process whereby granulocytes — namely neutrophils, eosinophils and basophils — are produced. This process is enhanced under certain inflammatory contexts and termed emergency granulopoiesis.

Hyperglycaemia
High levels of blood glucose in the absence of external glucose sources (such as food) during periods of fasting.

Lipolysis
Metabolic process to mobilize energy via the hydrolysis of triglycerides into glycerol and free fatty acids.

Long non-coding RNA
RNA sequences usually of about 200 nucleotides that are not translated into proteins.

Lymphangiogenesis
Physiological process for the formation and growth of new lymphatic vessels from pre-existing ones.

Matrisome
Chemical and biophysical composition of the extracellular matrix.

Microbiome
The microbiota naturally living in the human body at a given location or habitat. The term usually used in the context of the intestine is 'gut microbiome'.

Microglia
Resident macrophages of the nervous system.

Myelopoiesis
Biological process for the formation of all myeloid cells (such as monocytes and granulocytes) from undifferentiated bone marrow progenitor cells.

Myofibroblasts
Specialized type of activated fibroblast, usually characterized by the expression of α-smooth-muscle actin and exhibiting a smooth-muscle (spindle) morphology.

Neurovascular unit
(NVU). Anatomical structure that provides integrity and regulates the blood–brain barrier. Composed of cerebral vascular cells and surrounding neurons, glia and extracellular matrix.

Neutrophil extracellular trap
(NET). An extracellular network of decondensed DNA and proteases from neutrophils, usually formed in the context of pathogens. The neutrophil specific process of NET release is known as NETosis.

Omentum
A multi-layered specialized tissue of the peritoneum.

Osteoblasts
Specialized cells originating from the monocyte lineage in the bone marrow whose function is to synthesize bone tissue.

Osteoclast
A specialized cell originating from the monocyte lineage in the bone marrow whose function is to break down bone tissue.

Osteoclastogenesis
The biological processes involved in bone degradation including osteoclast differentiation and bone resorption.

Pancreatic β-cells
Neuroendocrine pancreatic cells responsible for insulin production.

Purinergic signalling
Extracellular signalling mediated by purine nucleotides, such as ATP.

Thromboembolism
Vascular obstruction due to the formation of a blood clot.

Thrombosis
Formation of a blood clot.

White adipose tissue
(WAT). The most abundant type of adipose tissue involved in energy storage, endocrine communication and insulin sensitivity.

White adipose tissue browning
Metabolic adaptation to increased thermogenic demand characterized by the development of brown adipose tissue or the conversion of white adipocytes into beige adipocytes.

given cancer relies on a specific mediator. In the context of complex tissue-wide or organism-wide interactions, more effective therapeutic approaches would need to target the key processes that are activated and are common among different tumour types and metastatic sites. For instance, the reprogramming of the myeloid compartment is a key process to induce immunosuppression (Fig. 4), and some experimental approaches have been reported to revert this myeloid priming to drive whole-body conditioning and generate antitumour effects. As an example, reprogramming monocyte plasticity offers a potential opportunity for therapeutic intervention. Low-dose combinatorial therapy with epigenetic modulatory drugs has been shown to disrupt monocyte-induced PMN formation. This approach downregulates CCR2 receptor expression on cancer-primed monocytes, steering them away from an immunosuppressive phenotype and reducing post-surgery metastasis in mouse models of lung adenocarcinoma[219]. In another proof-of-concept study direct engineering of myeloid cells to express IL-12 was able to reverse immunosuppression and drive antitumour immunity[220]. Remodelling of the vasculature, another key event in PMN formation, is also a potential target for intervention. For instance, a fusion protein consisting of the cytokine LIGHT and a vascular-targeting peptide (LIGHT–VTP) was used to normalize vascular integrity and peri-vascular ECM deposition and in turn efficiently

suppressed lung metastasis and sensitized established lung metastases to immune checkpoint inhibition[221]. Cancer-derived EVs represent one of the main TDMs of pre-metastatic conditioning, and interfering with EV uptake at the target site could represent a potent and broad way of blocking distant conditioning. In a preclinical melanoma model, where uptake of exosomes is facilitated by the downregulation of IFNR1 and cholesterol 25-hydroxylase (CH25H) in diverse healthy tissue cell types including those of the lung, treatment with the anti-hypertensive drug reserpine halted this downregulation and suppressed tumour-derived EV uptake, thereby blocking lung PMN formation[222].

As discussed previously, cancer-dependent conditioning induces similar perturbations to other physiological changes, which boost metastatic progression. This offers the opportunity to reduce cancer-dependent priming by repurposing drugs that are already in use for other pathologies. For instance, targeting stress-related mediators, which we now know have profound influence on neutrophil pro-tumorigenic priming, by using beta blockers has been reported in patient cohorts to reduce breast-cancer progression[223,224]. Similarly, a high-fat diet is a potent inducer of pro-metastatic conditioning and so tailored and balanced dietary interventions could be implemented as part of a metastasis-prevention therapy. Looking forward, we believe that an increased knowledge of both cancer-dependent and cancer-independent conditioning will provide a platform for the implementation of targeted therapies as well as behavioural interventions in patients with cancer to limit cancer progression.

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References

1. Greten, F. R. & Grivennikov, S. I. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity* **51**, 27–41 (2019).
2. Kalluri, R. & McAndrews, K. M. The role of extracellular vesicles in cancer. *Cell* **186**, 1610–1626 (2023).
3. Chen, G. et al. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. *Nature* **560**, 382–386 (2018).
4. Gysler, S. M. & Drapkin, R. Tumor innervation: peripheral nerves take control of the tumor microenvironment. *J. Clin. Investig.* **131**, e147276 (2021).
5. Francis, N. & Borniger, J. C. Cancer as a homeostatic challenge: the role of the hypothalamus. *Trends Neurosci.* **44**, 903–914 (2021).
6. Borniger, J. C. et al. A role for hypocretin/orexin in metabolic and sleep abnormalities in a mouse model of non-metastatic breast cancer. *Cell Metab.* **28**, 118–129.e5 (2018).
7. Hedrick, C. C. & Malanchi, I. Neutrophils in cancer: heterogeneous and multifaceted. *Nat. Rev. Immunol.* **22**, 173–187 (2021).
8. Canonico, M. E. et al. Venous thromboembolism and cancer: a comprehensive review from pathophysiology to novel treatment. *Biomolecules* **12**, 259 (2022).
9. Hisada, Y. & Mackman, N. Cancer-associated pathways and biomarkers of venous thrombosis. *Blood* **130**, 1499–1506 (2017).
10. Hiratsuka, S. et al. MMP9 induction by vascular endothelial growth factor receptor-1 is involved in lung-specific metastasis. *Cancer Cell* **2**, 289–300 (2002).
11. Kaplan, R. N. et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* **438**, 820–827 (2005).
Along with Hiratsuka et al. (ref. 10), this pioneering study demonstrates the ability of cancer cells to create a hospitable environment at distant sites prior to tumour-cell dissemination.
12. Peinado, H. et al. Pre-metastatic niches: organ-specific homes for metastases. *Nat. Rev. Cancer* **17**, 302–317 (2017).
13. Patras, L., Shaashua, L., Matei, I. & Lyden, D. Immune determinants of the pre-metastatic niche. *Cancer Cell* **41**, 546–572 (2023).
14. Boire, A. et al. Why do patients with cancer die? *Nat. Rev. Cancer* **24**, 578–589 (2024).
15. Crist, S. B. & Ghajar, C. M. When a house is not a home: a survey of antimetastatic niches and potential mechanisms of disseminated tumor cell suppression. *Annu. Rev. Pathol. Mech. Dis.* **16**, 409–432 (2021).
16. de Visser, K. E. & Joyce, J. A. The evolving tumor microenvironment: from cancer initiation to metastatic outgrowth. *Cancer Cell* **41**, 374–403 (2023).
17. Cox, T. R. The matrix in cancer. *Nat. Rev. Cancer* **21**, 217–238 (2021).
18. Malanchi, I. et al. Interactions between cancer stem cells and their niche govern metastatic colonization. *Nature* **481**, 85–89 (2011).
19. Oskarsson, T. et al. Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. *Nat. Med.* **17**, 867–874 (2011).
20. Patras, L., Paul, D. & Matei, I. R. Weaving the nest: extracellular matrix roles in pre-metastatic niche formation. *Front. Oncol.* **13**, 1163786 (2023).
21. Deasy, S. K. & Erez, N. A glitch in the matrix: organ-specific matrisomes in metastatic niches. *Trends Cell Biol.* **32**, 110–123 (2022).
22. Nielsen, S. R. et al. Macrophage-secreted granulin supports pancreatic cancer metastasis by inducing liver fibrosis. *Nat. Cell Biol.* **18**, 549–560 (2016).
23. Hiratsuka, S. et al. Endothelial focal adhesion kinase mediates cancer cell homing to discrete regions of the lungs via E-selectin up-regulation. *Proc. Natl Acad. Sci. USA* **108**, 3725–3730 (2011).
24. LIU, S. et al. Vascular endothelial growth factor plays a critical role in the formation of the pre-metastatic niche via prostaglandin E2. *Oncol. Rep.* **32**, 2477–2484 (2014).
25. Hiratsuka, S. et al. Primary tumours modulate innate immune signalling to create pre-metastatic vascular hyperpermeability foci. *Nat. Commun.* **4**, 1853 (2013).
26. Seubert, B. et al. Tissue inhibitor of metalloproteinases (TIMP)-1 creates a premetastatic niche in the liver through SDF-1/CXCR4-dependent neutrophil recruitment in mice. *Hepatology* **61**, 238–248 (2015).
27. Veglia, F., Sanseviero, E. & Gabrilovich, D. I. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat. Rev. Immunol.* **21**, 485–498 (2021).
28. Qi, Y., Zhao, T., Li, R. & Han, M. Macrophage-secreted S100A4 supports breast cancer metastasis by remodeling the extracellular matrix in the premetastatic niche. *BioMed. Res. Int.* **2022**, 9895504 (2022).
29. Martin, Y. et al. Mesenchymal cancer cell–stroma crosstalk promotes niche activation, epithelial reversion, and metastatic colonization. *Cell Rep.* **22**, 2456–2469 (2015).
30. Ji, Q. et al. Primary tumors release ITGBL1-rich extracellular vesicles to promote distal metastatic tumor growth through fibroblast-niche formation. *Nat. Commun.* **11**, 1211 (2020).
31. Moretti, L., Stalfort, J., Barker, T. H. & Abebayehu, D. The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. *J. Biol. Chem.* **298**, 101530 (2022).
32. Murgai, M. et al. KLF4-dependent perivascular cell plasticity mediates pre-metastatic niche formation and metastasis. *Nat. Med.* **23**, 1176–1190 (2017).
33. Gui, J. et al. Activation of p38α stress-activated protein kinase drives the formation of the pre-metastatic niche in the lungs. *Nat. Cancer* **1**, 603–619 (2020).
34. Tomita, T. et al. Extracellular mRNA transported to the nucleus exerts translation-independent function. *Nat. Commun.* **12**, 3655 (2021).
35. Kong, J. et al. Extracellular vesicles of carcinoma-associated fibroblasts creates a pre-metastatic niche in the lung through activating fibroblasts. *Mol. Cancer* **18**, 175 (2019).
36. Mazumdar, A. et al. Osteosarcoma-derived extracellular vesicles induce lung fibroblast reprogramming. *Int. J. Mol. Sci.* **21**, 5451 (2020).
37. Wang, Y. et al. Tumor-derived Cav-1 promotes pre-metastatic niche formation and lung metastasis in breast cancer. *Theranostics* **13**, 1684–1697 (2023).
38. Novo, D. et al. Mutant p53s generate pro-invasive niches by influencing exosome podocalyxin levels. *Nat. Commun.* **9**, 5069 (2018).
39. Zhao, S. et al. Highly-metastatic colorectal cancer cell released miR-181a-5p-rich extracellular vesicles promote liver metastasis by activating hepatic stellate cells and remodelling the tumour microenvironment. *J. Extracell. Vesicles* **11**, e12186 (2022).
40. Xie, Z. et al. Exosome-delivered CD44v6/C1QBP complex drives pancreatic cancer liver metastasis by promoting fibrotic liver microenvironment. *Gut* **71**, 568–579 (2022).
41. Hsu, Y.-L. et al. Bone-marrow-derived cell-released extracellular vesicle miR-92a regulates hepatic pre-metastatic niche in lung cancer. *Oncogene* **39**, 739–753 (2020).
42. Ju, C. & Tacke, F. Hepatic macrophages in homeostasis and liver diseases: from pathogenesis to novel therapeutic strategies. *Cell. Mol. Immunol.* **13**, 316–327 (2016).
43. Erler, J. T. et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. *Cancer Cell* **15**, 35–44 (2009).
44. Wu, S. et al. Matrix stiffness-upregulated LOXL2 promotes fibronectin production, MMP9 and CXCL12 expression and BMDCs recruitment to assist pre-metastatic niche formation. *J. Exp. Clin. Cancer Res.* **37**, 99 (2018).
45. Wu, S. et al. The pathological significance of LOXL2 in pre-metastatic niche formation of HCC and its related molecular mechanism. *Eur. J. Cancer* **147**, 63–73 (2021).
46. Cohen, N. et al. Breast cancer-secreted factors promote lung metastasis by signaling systemically to induce a fibrotic premetastatic niche. *Cancer Res.* **83**, 3354–3367 (2023).
47. Qi, M. et al. Lin28B-high breast cancer cells promote immune suppression in the lung pre-metastatic niche via exosomes and support cancer progression. *Nat. Commun.* **13**, 897 (2022).
48. Gong, Z. et al. Lung fibroblasts facilitate pre-metastatic niche formation by remodeling the local immune microenvironment. *Immunity* **55**, 1483–1500.e9 (2022).
49. Grünwald, B. et al. Pancreatic premalignant lesions secrete tissue inhibitor of metalloproteinases-1, which activates hepatic stellate cells via CD63 signaling to create a premetastatic niche in the liver. *Gastroenterology* **151**, 1011–1024.e7 (2016).
50. Zhang, H. et al. Exosome-delivered EGFR regulates liver microenvironment to promote gastric cancer liver metastasis. *Nat. Commun.* **8**, 15016 (2017).
51. Tian, F. et al. Exosome-delivered miR-221/222 exacerbates tumor liver metastasis by targeting SPINT1 in colorectal cancer. *Cancer Sci.* **112**, 3744–3755 (2021).
52. Zhang, C. et al. Cancer-derived exosomal HSPC111 promotes colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts. *Cell Death Dis.* **13**, 57 (2022).
53. Mo, Y. et al. Tumor-secreted exosomal miR-141 activates tumor–stroma interactions and controls premetastatic niche formation in ovarian cancer metastasis. *Mol. Cancer* **22**, 4 (2023).

54. Alvarez, M. V., Gutierrez, L. M., Correa, A., Lazarowski, A. & Bolontrade, M. F. Metastatic niches and the modulatory contribution of mesenchymal stem cells and its exosomes. *Int. J. Mol. Sci.* **20**, 1946 (2019).
55. Gong, Z. et al. Lipid-laden lung mesenchymal cells foster breast cancer metastasis via metabolic reprogramming of tumor cells and natural killer cells. *Cell Metab.* **34**, 1960–1976.e9 (2022).
56. Li, P. et al. Lung mesenchymal cells elicit lipid storage in neutrophils that fuel breast cancer lung metastasis. *Nat. Immunol.* **21**, 1444–1455 (2020).
57. Zheng, Z. et al. Lung mesenchymal stromal cells influenced by Th2 cytokines mobilize neutrophils and facilitate metastasis by producing complement C3. *Nat. Commun.* **12**, 6202 (2021).
58. Jiang, C. et al. Extracellular vesicles promotes liver metastasis of lung cancer by ALAHM increasing hepatocellular secretion of HGF. *iScience* **25**, 103984 (2022).
59. Lee, J. W. et al. Hepatocytes direct the formation of a pro-metastatic niche in the liver. *Nature* **567**, 249–252 (2019).
60. Liu, Y. et al. Tumor exosomal RNAs promote lung pre-metastatic niche formation by activating alveolar epithelial TLR3 to recruit neutrophils. *Cancer Cell* **30**, 243–256 (2016). **This key study identifies epithelial cells as active regulators of immune responses in the context of tumour-induced PMN formation.**
61. Gu, P. et al. Breast tumor-derived exosomal microRNA-200b-3p promotes specific organ metastasis through regulating CCL2 expression in lung epithelial cells. *Front. Cell Dev. Biol.* **9**, 657158 (2021).
62. Wang, Z. et al. Tumor-polarized GPX3+AT2 lung epithelial cells promote premetastatic niche formation. *Proc. Natl Acad. Sci. USA* **119**, e2201899119 (2022).
63. Altea-Manzano, P. et al. A palmitate-rich metastatic niche enables metastasis growth via p65 acetylation resulting in pro-metastatic NF-κB signaling. *Nat. Cancer* **4**, 344–364 (2023). **This key study demonstrates how distal tumours shape the metabolic microenvironment of the PMN through increased local production of palmitate to support subsequent metastatic growth.**
64. Zhang, S., Lv, K., Liu, Z., Zhao, R. & Li, F. Fatty acid metabolism of immune cells: a new target of tumour immunotherapy. *Cell Death Discov.* **10**, 39 (2024).
65. Pascual, G. et al. Targeting metastasis-initiating cells through the fatty acid receptor CD36. *Nature* **541**, 41–45 (2017).
66. Huang, Y. et al. Pulmonary vascular destabilization in the premetastatic phase facilitates lung metastasis. *Cancer Res.* **69**, 7529–7537 (2009).
67. Zhou, W. et al. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. *Cancer Cell* **25**, 501–515 (2014).
68. Fang, J. et al. Hepatoma cell-secreted exosomal microRNA-103 increases vascular permeability and promotes metastasis by targeting junction proteins. *Hepatology* **68**, 1459–1475 (2018).
69. Zeng, Z. et al. Cancer-derived exosomal miR-25-3p promotes pre-metastatic niche formation by inducing vascular permeability and angiogenesis. *Nat. Commun.* **9**, 5395 (2018).
70. Duan, S., Nordmeier, S., Byrnes, A. E. & Buxton, I. L. O. Extracellular vesicle-mediated purinergic signaling contributes to host microenvironment plasticity and metastasis in triple negative breast cancer. *Int. J. Mol. Sci.* **22**, 597 (2021).
71. Zeng, H. et al. Cancer-associated fibroblasts facilitate premetastatic niche formation through lncRNA SNHG5-mediated angiogenesis and vascular permeability in breast cancer. *Theranostics* **12**, 7351–7370 (2022).
72. Riera-Domingo, C. et al. Breast tumors interfere with endothelial TRAIL at the premetastatic niche to promote cancer cell seeding. *Sci. Adv.* **9**, eadd5028 (2023).
73. Wieland, E. et al. Endothelial Notch1 activity facilitates metastasis. *Cancer Cell* **31**, 355–367 (2017).
74. Mao, X. et al. Nidogen 1-enriched extracellular vesicles facilitate extrahepatic metastasis of liver cancer by activating pulmonary fibroblasts to secrete tumor necrosis factor receptor 1. *Adv. Sci.* **7**, 2002157 (2020).
75. Hongu, T. et al. Perivascular tenascin C triggers sequential activation of macrophages and endothelial cells to generate a pro-metastatic vascular niche in the lungs. *Nat. Cancer* **3**, 486–504 (2022).
76. Esposito, M. et al. Bone vascular niche E-selectin induces mesenchymal–epithelial transition and Wnt activation in cancer cells to promote bone metastasis. *Nat. Cell Biol.* **21**, 627–639 (2019).
77. Singhal, M. et al. Temporal multi-omics identifies LRG1 as a vascular niche instructor of metastasis. *Sci. Transl. Med.* **13**, eabe6805 (2021).
78. Rodrigues, G. et al. Tumour exosomal CEMIP protein promotes cancer cell colonization in brain metastasis. *Nat. Cell Biol.* **21**, 1403–1412 (2019).
79. Wu, D. et al. TGF-β1-mediated exosomal lnc-MMP2-2 increases blood–brain barrier permeability via the miRNA-1207-5p/EPB41L5 axis to promote non-small-cell lung cancer brain metastasis. *Cell Death Dis.* **12**, 721 (2021).
80. Doron, H., Pukrop, T. & Erez, N. A blazing landscape: neuroinflammation shapes brain metastasis. *Cancer Res.* **79**, 423–436 (2018).
81. Gan, D.-X. et al. Lung cancer cells-controlled Dkk-1 production in brain metastatic cascade drive microglia to acquire a pro-tumorigenic phenotype. *Front. Cell Dev. Biol.* **8**, 591405 (2020).
82. Stacker, S. A. et al. Lymphangiogenesis and lymphatic vessel remodelling in cancer. *Nat. Rev. Cancer* **14**, 159–172 (2014).
83. Reticker-Flynn, N. E. et al. Lymph node colonization induces tumor-immune tolerance to promote distant metastasis. *Cell* **185**, 1924–1942.e23 (2022).
84. Gillot, L. et al. Periostin in lymph node pre-metastatic niches governs lymphatic endothelial cell functions and metastatic colonization. *Cell Mol. Life Sci.* **79**, 295 (2022).
85. Leary, N. et al. Melanoma-derived extracellular vesicles mediate lymphatic remodelling and impair tumour immunity in draining lymph nodes. *J. Extracell. Vesicles* **11**, e12197 (2022).
86. García-Silva, S. et al. Melanoma-derived small extracellular vesicles induce lymphangiogenesis and metastasis through an NGFR-dependent mechanism. *Nat. Cancer* **2**, 1387–1405 (2021).
87. Olmeda, D. et al. Whole-body imaging of lymphovascular niches identifies pre-metastatic roles of midkine. *Nature* **546**, 676–680 (2017).
88. Shao, Y. et al. Colorectal cancer-derived small extracellular vesicles establish an inflammatory premetastatic niche in liver metastasis. *Carcinogenesis* **39**, 1368–1379 (2018).
89. Jiang, K. et al. Exosomal ANGPTL1 attenuates colorectal cancer liver metastasis by regulating Kupffer cell secretion pattern and impeding MMP9 induced vascular leakiness. *J. Exp. Clin. Cancer Res.* **40**, 21 (2021).
90. Sun, H. et al. Hypoxia-inducible exosomes facilitate liver-tropic premetastatic niche in colorectal cancer. *Hepatology* **74**, 2633–2651 (2021).
91. Li, B. et al. miR-151a-3p-rich small extracellular vesicles derived from gastric cancer accelerate liver metastasis via initiating a hepatic stemness-enhancing niche. *Oncogene* **40**, 6180–6194 (2021).
92. Li, W., Yang, Y., Yang, L., Chang, N. & Li, L. Monocyte-derived Kupffer cells dominate in the Kupffer cell pool during liver injury. *Cell Rep.* **42**, 113164 (2023).
93. Güç, E. & Pollard, J. W. Redefining macrophage and neutrophil biology in the metastatic cascade. *Immunity* **54**, 885–902 (2021).
94. Aegerter, H., Lambrecht, B. N. & Jakubzick, C. V. Biology of lung macrophages in health and disease. *Immunity* **55**, 1564–1580 (2022).
95. Mrdjen, D. et al. High-dimensional single-cell mapping of central nervous system immune cells reveals distinct myeloid subsets in health, aging, and disease. *Immunity* **48**, 380–395.e6 (2018).
96. Guldner, I. H. et al. CNS-native myeloid cells drive immune suppression in the brain metastatic niche through Cxcl10. *Cell* **183**, 1234–1248.e25 (2020).
97. Klemm, F. et al. Compensatory CSF2-driven macrophage activation promotes adaptive resistance to CSF1R inhibition in breast-to-brain metastasis. *Nat. Cancer* **2**, 1086–1101 (2021).
98. Hanna, R. N. et al. Patrolling monocytes control tumor metastasis to the lung. *Science* **350**, 985–990 (2015).
99. Chen, T. & Zhao, L. Patrolling monocytes inhibit osteosarcoma metastasis to the lung. *Aging* **12**, 23004–23016 (2020).
100. Plebanek, M. P. et al. Pre-metastatic cancer exosomes induce immune surveillance by patrolling monocytes at the metastatic niche. *Nat. Commun.* **8**, 1319 (2017).
101. Han, Y. et al. Citrullinated fibrinogen–SAAs complex causes vascular metastagenesis. *Nat. Commun.* **14**, 4960 (2023).
102. Gil-Bernabé, A. M. et al. Recruitment of monocytes/macrophages by tissue factor-mediated coagulation is essential for metastatic cell survival and premetastatic niche establishment in mice. *Blood* **119**, 3164–3175 (2012).
103. Zhao, S. et al. Tumor-derived exosomal miR-934 induces macrophage M2 polarization to promote liver metastasis of colorectal cancer. *J. Hematol. Oncol.* **13**, 156 (2020).
104. Qiu, S. et al. Gastric cancer-derived exosomal miR-519a-3p promotes liver metastasis by inducing intrahepatic M2-like macrophage-mediated angiogenesis. *J. Exp. Clin. Cancer Res.* **41**, 296 (2022).
105. Morrissey, S. M. et al. Tumor-derived exosomes drive immunosuppressive macrophages in a pre-metastatic niche through glycolytic dominant metabolic reprogramming. *Cell Metab.* **33**, 2040–2058.e10 (2021).
106. Ruf, B., Greten, T. F. & Korangy, F. Innate lymphoid cells and innate-like T cells in cancer—at the crossroads of innate and adaptive immunity. *Nat. Rev. Cancer* **23**, 351–371 (2023).
107. Long, A. et al. Type 2 innate lymphoid cells impede IL-33-mediated tumor suppression. *J. Immunol.* **201**, 3456–3464 (2018).
108. Schuijs, M. J. et al. ILC2-driven innate immune checkpoint mechanism antagonizes NK cell antimetastatic function in the lung. *Nat. Immunol.* **21**, 998–1009 (2020).
109. Chan, I. S. & Ewald, A. J. The changing role of natural killer cells in cancer metastasis. *J. Clin. Investig.* **132**, e143762 (2022).
110. Lazarova, M. & Steinle, A. Impairment of NKG2D-mediated tumor immunity by TGF-β. *Front. Immunol.* **10**, 2689 (2019).
111. Slattery, K. et al. TGFβ drives NK cell metabolic dysfunction in human metastatic breast cancer. *J. Immunother. Cancer* **9**, e002044 (2021).
112. Gao, Y. et al. Tumor immunoevasion by the conversion of effector NK cells into type 1 innate lymphoid cells. *Nat. Immunol.* **18**, 1004–1015 (2017).
113. Braun, A., Anders, H.-J., Gudermann, T. & Mammadova-Bach, E. Platelet–cancer interplay: molecular mechanisms and new therapeutic avenues. *Front. Oncol.* **11**, 665534 (2021).
114. Leal, A. C. et al. Tumor-derived exosomes induce the formation of neutrophil extracellular traps: implications for the establishment of cancer-associated thrombosis. *Sci. Rep.* **7**, 6438 (2017).
115. Lucotti, S. et al. Aspirin blocks formation of metastatic intravascular niches by inhibiting platelet-derived COX-1/thromboxane A2. *J. Clin. Investig.* **129**, 1845–1862 (2019).
116. Kerr, B. A. et al. Platelet TSP-1 controls prostate cancer-induced osteoclast differentiation and bone marrow-derived cell mobilization through TGFβ-1. *Am. J. Clin. Exp. Urol.* **9**, 18–31 (2020).

117. Kerr, B. A., McCabe, N. P., Feng, W. & Byzova, T. V. Platelets govern pre-metastatic tumor communication to bone. *Oncogene* **32**, 4319–4324 (2013).
118. Wculek, S. K. & Malanchi, I. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. *Nature* **528**, 413–417 (2015).
119. Quail, D. F. et al. Neutrophil phenotypes and functions in cancer: a consensus statement. *J. Exp. Med.* **219**, e20220011 (2022).
120. Giese, M. A., Hind, L. E. & Huttenlocher, A. Neutrophil plasticity in the tumor microenvironment. *Blood* **133**, 2159–2167 (2019).
121. Nolan, E. et al. Radiation exposure elicits a neutrophil-driven response in healthy lung tissue that enhances metastatic colonization. *Nat. Cancer* **3**, 173–187 (2022).
122. Ballesteros, I. et al. Co-option of neutrophil fates by tissue environments. *Cell* **183**, 1282–1297.e18 (2020).
123. Alshetaiwi, H. et al. Defining the emergence of myeloid-derived suppressor cells in breast cancer using single-cell transcriptomics. *Sci. Immunol.* **5**, eaay6017 (2020).
124. Veglia, F. et al. Analysis of classical neutrophils and polymorphonuclear myeloid-derived suppressor cells in cancer patients and tumor-bearing mice. *J. Exp. Med.* **218**, e20201803 (2021).
125. Zhu, Y. P. et al. Identification of an early unipotent neutrophil progenitor with pro-tumoral activity in mouse and human bone marrow. *Cell Rep.* **24**, 2329–2341.e8 (2018).
126. Evrard, M. et al. Developmental analysis of bone marrow neutrophils reveals populations specialized in expansion, trafficking, and effector functions. *Immunity* **48**, 364–379.e8 (2018).
127. Dinh, H. Q. et al. Coexpression of CD71 and CD117 identifies an early unipotent neutrophil progenitor population in human bone marrow. *Immunity* **53**, 319–334.e6 (2020).
128. Bao, Y. et al. Extramedullary hematopoiesis secondary to malignant solid tumors: a case report and literature review. *Cancer Manag. Res.* **10**, 1461–1470 (2018).
129. Casbon, A.-J. et al. Invasive breast cancer reprograms early myeloid differentiation in the bone marrow to generate immunosuppressive neutrophils. *Proc. Natl Acad. Sci. USA* **112**, E566–E575 (2015).
130. Coffelt, S. B. et al. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* **522**, 345–348 (2015).
131. Gerber-Ferder, Y. et al. Breast cancer remotely imposes a myeloid bias on haematopoietic stem cells by reprogramming the bone marrow niche. *Nat. Cell Biol.* **25**, 1736–1745 (2023).
132. LaMarche, N. M. et al. An IL-4 signalling axis in bone marrow drives pro-tumorigenic myelopoiesis. *Nature* **625**, 166–174 (2024).
This key study provides important mechanistic insight into myelopoiesis in cancer, including the identification of an IL-4-dependent axis within the bone marrow that directs GMP fate towards the production of monocytes and macrophages imprinted with immunosuppressive phenotypes, thus offering novel routes to potential therapies.
133. Engblom, C. et al. Osteoblasts remotely supply lung tumors with cancer-promoting SiglecF high neutrophils. *Science* **358**, eaal5081 (2017).
134. Wellenstein, M. D. et al. Loss of p53 triggers Wnt-dependent systemic inflammation to drive breast cancer metastasis. *Nature* **572**, 538–542 (2019).
This important study demonstrates how tumour-intrinsic heterogeneity, notably cancer cell p53 status, has important implications for the generation of pro-metastatic systemic inflammatory responses.
135. Hao, X. et al. Osteoprogenitor–GMP crosstalk underpins solid tumor-induced systemic immunosuppression and persists after tumor removal. *Cell Stem Cell* **30**, 648–664.e8 (2023).
136. Ma, R.-Y. et al. Monocyte-derived macrophages promote breast cancer bone metastasis outgrowth. *J. Exp. Med.* **217**, e20191820 (2020).
137. Sanmartin, M. C. et al. Bone marrow/bone pre-metastatic niche for breast cancer cells colonization: the role of mesenchymal stromal cells. *Crit. Rev. Oncol. Hematol.* **164**, 103416 (2021).
138. Yue, Z. et al. RSPO2 and RANKL signal through LGR4 to regulate osteoclastic premetastatic niche formation and bone metastasis. *J. Clin. Investig.* **132**, e144579 (2022).
139. Yip, R. K. H. et al. Mammary tumour cells remodel the bone marrow vascular microenvironment to support metastasis. *Nat. Commun.* **12**, 6920 (2021).
140. Chen, H.-M., Chen, F.-P., Yang, K.-C. & Yuan, S.-S. Association of bone metastasis with early-stage breast cancer in women with and without precancer osteoporosis according to osteoporosis therapy status. *JAMA Netw. Open* **2**, e190429 (2019).
141. Szczerba, B. M. et al. Neutrophils escort circulating tumour cells to enable cell cycle progression. *Nature* **566**, 553–557 (2019).
142. Chen, M. B. et al. Inflamed neutrophils sequestered at entrapped tumor cells via chemotactic confinement promote tumor cell extravasation. *Proc. Natl Acad. Sci. USA* **115**, 7022–7027 (2018).
143. Patel, S. et al. Unique pattern of neutrophil migration and function during tumor progression. *Nat. Immunol.* **19**, 1236–1247 (2018).
144. Veglia, F. et al. Fatty acid transport protein 2 reprograms neutrophils in cancer. *Nature* **569**, 73–78 (2019).
145. Rice, C. M. et al. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. *Nat. Commun.* **9**, 5099 (2018).
146. Li, P. et al. Dual roles of neutrophils in metastatic colonization are governed by the host NK cell status. *Nat. Commun.* **11**, 4387 (2020).
147. Yang, L. et al. DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25. *Nature* **583**, 133–138 (2020).
This study offers key mechanistic insights into how cancer cells detect and actively respond to NETs within the PMN, enhancing their migration, adhesion and metastatic colonization.
148. Lee, W. et al. Neutrophils facilitate ovarian cancer premetastatic niche formation in the omentum. *J. Exp. Med.* **216**, 176–194 (2018).
149. Li, C. et al. FGF19-induced inflammatory CAF promoted neutrophil extracellular trap formation in the liver metastasis of colorectal cancer. *Adv. Sci.* **10**, 2302613 (2023).
150. Zeng, Z. et al. HAO1-mediated oxalate metabolism promotes lung pre-metastatic niche formation by inducing neutrophil extracellular traps. *Oncogene* **41**, 3719–3731 (2022).
151. Su, X. et al. Tumour extracellular vesicles induce neutrophil extracellular traps to promote lymph node metastasis. *J. Extracell. Vesicles* **12**, 12341 (2023).
152. Zhang, Q. et al. ETV4 mediated tumor-associated neutrophil infiltration facilitates lymphangiogenesis and lymphatic metastasis of bladder cancer. *Adv. Sci.* **10**, 2205613 (2023).
153. Albrengues, J. et al. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science* **361**, eaao4227 (2018).
154. Castaño, Z. et al. IL-1β inflammatory response driven by primary breast cancer prevents metastasis-initiating cell colonization. *Nat. Cell Biol.* **20**, 1084–1097 (2018).
155. Stehr, A. M. et al. Neutrophil extracellular traps drive epithelial–mesenchymal transition of human colon cancer. *J. Pathol.* **256**, 455–467 (2022).
156. Wang, Y. et al. Neutrophils promote tumor invasion via FAM3C-mediated epithelial-to-mesenchymal transition in gastric cancer. *Int. J. Biol. Sci.* **19**, 1352–1368 (2023).
157. Thuya, W. L. et al. FAM3C in circulating tumor-derived extracellular vesicles promotes non-small cell lung cancer growth in secondary sites. *Theranostics* **13**, 621–638 (2023).
158. Wang, J., Tan, S., Gianotti, L. & Wu, G. Evaluation and management of body composition changes in cancer patients. *Nutrition* **114**, 112132 (2023).
159. Ferrer, M. et al. Cachexia: a systemic consequence of progressive, unresolved disease. *Cell* **186**, 1824–1845 (2023).
160. Yu, J. et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat. Med.* **27**, 152–164 (2021).
161. Hu, S., Hu, Y. & Yan, W. Extracellular vesicle-mediated interorgan communication in metabolic diseases. *Trends Endocrinol. Metab.* **34**, 571–582 (2023).
162. Yan, W. et al. Cancer-cell-secreted miR-122 suppresses O-GlcNAcylation to promote skeletal muscle proteolysis. *Nat. Cell Biol.* **24**, 793–804 (2022).
163. Cao, M. et al. Cancer-cell-secreted extracellular vesicles suppress insulin secretion through miR-122 to impair systemic glucose homeostasis and contribute to tumour growth. *Nat. Cell Biol.* **24**, 954–967 (2022).
164. Wang, G. et al. Tumour extracellular vesicles and particles induce liver metabolic dysfunction. *Nature* **618**, 374–382 (2023).
This landmark study uncovers how tumour-derived EVs disrupt broader host physiology by inducing systemic metabolic alterations through EV-mediated perturbations of hepatocyte function.
165. Hu, Y. et al. Cancer-cell-secreted miR-204-5p induces leptin signalling pathway in white adipose tissue to promote cancer-associated cachexia. *Nat. Commun.* **14**, 5179 (2023).
166. Xie, H. et al. An immune-sympathetic neuron communication axis guides adipose tissue browning in cancer-associated cachexia. *Proc. Natl Acad. Sci. USA* **119**, e2112840119 (2022).
167. Fan, Y. & Pedersen, O. Gut microbiota in human metabolic health and disease. *Nat. Rev. Microbiol.* **19**, 55–71 (2021).
168. Lynch, S. V. & Pedersen, O. The human intestinal microbiome in health and disease. *N. Engl. J. Med.* **375**, 2369–2379 (2016).
169. Yonekura, S. et al. Cancer induces a stress ileopathy depending on B-adrenergic receptors and promoting dysbiosis that contributes to carcinogenesis. *Cancer Discov.* **12**, candisc.0999.2021 (2021).
170. Zhang, D. et al. Neutrophil ageing is regulated by the microbiome. *Nature* **525**, 528–532 (2015).
171. Mazmanian, S. K., Liu, C. H., Tzianabos, A. O. & Kasper, D. L. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122**, 107–118 (2005).
172. Matson, V. et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* **359**, 104–108 (2018).
173. Routy, B. et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science* **359**, 91–97 (2018).
174. Hawley, J. A. Microbiota and muscle highway—two-way traffic. *Nat. Rev. Endocrinol.* **16**, 71–72 (2020).
175. Park, E. M. et al. Targeting the gut and tumor microbiota in cancer. *Nat. Med.* **28**, 690–703 (2022).
176. Qu, M. Molecular crosstalk between circadian clock and cancer and therapeutic implications. *Front. Nutr.* **10**, 1143001 (2023).
177. Masri, S. et al. Lung adenocarcinoma distally rewires hepatic circadian homeostasis. *Cell* **165**, 896–909 (2016).
This study identifies the circadian rhythm as a biological process affected by cancer cells (specifically lung cancer cells) within the primary tumour and the consequent disruption of liver metabolism.
178. Diamantopoulou, Z. et al. The metastatic spread of breast cancer accelerates during sleep. *Nature* **607**, 156–162 (2022).

179. He, X.-Y. et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment. *Cancer Cell* **42**, 474–486.e12 (2024).
This landmark study reveals the impact of chronic stress, an inevitable aspect of a cancer diagnosis, on the tissue microenvironment, highlighting how stress-induced glucocorticoids induce pro-metastatic neutrophil phenotypes, notably NETosis, to create a pro-metastatic tissue microenvironment.
180. Perego, M. et al. Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils. *Sci. Transl. Med.* **12**, eabb5817 (2020).
181. McDowell, S. A. C. et al. Neutrophil oxidative stress mediates obesity-associated vascular dysfunction and metastatic transmigration. *Nat. Cancer* **2**, 545–562 (2021).
182. Tyagi, A. et al. Nicotine promotes breast cancer metastasis by stimulating N2 neutrophils and generating pre-metastatic niche in lung. *Nat. Commun.* **12**, 474 (2021).
183. Zhao, J. et al. Interorgan communication with the liver: novel mechanisms and therapeutic targets. *Front. Immunol.* **14**, 1314123 (2023).
184. Li, D. et al. Hepatocytes derived increased SAA1 promotes intrahepatic platelet aggregation and aggravates liver inflammation in NAFLD. *Biochem. Biophys. Res. Commun.* **555**, 54–60 (2021).
185. Severe, N. et al. Stress-induced changes in bone marrow stromal cell populations revealed through single-cell protein expression mapping. *Cell Stem Cell* **25**, 570–583.e7 (2019).
186. Campbell, J. P. et al. Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. *PLoS Biol.* **10**, e1001363 (2012).
187. Zheng, Y. et al. Chronic psychological stress promotes breast cancer pre-metastatic niche formation by mobilizing splenic MDSCs via TAM/CXCL1 signaling. *J. Exp. Clin. Cancer Res.* **42**, 129 (2023).
188. Fane, M. E. et al. Stromal changes in the aged lung induce an emergence from melanoma dormancy. *Nature* **606**, 396–405 (2022).
189. Turrell, F. K. et al. Age-associated microenvironmental changes highlight the role of PDGF-C in ER+ breast cancer metastatic relapse. *Nat. Cancer* **4**, 468–484 (2023).
This important study uncovers a key role for ageing-associated changes to the tissue microenvironment in regulating the metastatic dormancy of breast cancer.
190. di Micco, R., Krizhanovsky, V., Baker, D. & d'Adda di Fagagna, F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat. Rev. Mol. Cell Biol.* **22**, 75–95 (2021).
191. Barkaway, A. et al. Age-related changes in the local milieu of inflamed tissues cause aberrant neutrophil trafficking and subsequent remote organ damage. *Immunity* **54**, 1494–1510.e7 (2021).
192. Nishi, K. et al. Age-associated myeloid biased hematopoiesis depends on relative decrease of short-term hematopoietic stem cell. *Blood* **134**, 2481 (2019).
193. López-Otín, C., Pietrocola, F., Roiz-Valle, D., Galluzzi, L. & Kroemer, G. Meta-hallmarks of aging and cancer. *Cell Metab.* **35**, 12–35 (2023).
194. Quail, D. F. et al. Obesity alters the lung myeloid cell landscape to enhance breast cancer metastasis through IL5 and GM-CSF. *Nat. Cell Biol.* **19**, 974–987 (2017).
195. Ladanyi, A. et al. Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. *Oncogene* **37**, 2285–2301 (2018).
196. Qiu, M. et al. Modulation of intestinal microbiota by glycyrrhizic acid prevents high-fat diet-enhanced pre-metastatic niche formation and metastasis. *Mucosal Immunol.* **12**, 945–957 (2019).
197. Cheng, P. et al. Capsaicin shapes gut microbiota and pre-metastatic niche to facilitate cancer metastasis to liver. *Pharmacol. Res.* **188**, 106643 (2023).
198. Collins, N. et al. The bone marrow protects and optimizes immunological memory during dietary restriction. *Cell* **178**, 1088–1101.e15 (2019).
199. Collins, N. & Belkaid, Y. Control of immunity via nutritional interventions. *Immunity* **55**, 210–223 (2022).
200. Sheinboim, D. et al. An exercise-induced metabolic shield in distant organs blocks cancer progression and metastatic dissemination. *Cancer Res.* **82**, 4164–4178 (2022).
201. Gomes-Santos, I. L. et al. Exercise training improves tumor control by increasing CD8+ T-cell infiltration via CXCR3 signaling and sensitizes breast cancer to immune checkpoint blockade. *Cancer Immunol. Res.* **9**, 765–778 (2021).
202. Darkwah, S. et al. Potential roles of muscle-derived extracellular vesicles in remodeling cellular microenvironment: proposed implications of the exercise-induced myokine, irisin. *Front. Cell Dev. Biol.* **9**, 634853 (2021).
203. Seki, T. et al. Brown-fat-mediated tumour suppression by cold-altered global metabolism. *Nature* **608**, 421–428 (2022).
204. Xiao, T. et al. Hallmarks of sex bias in immuno-oncology: mechanisms and therapeutic implications. *Nat. Rev. Cancer* **24**, 338–355 (2024).
205. Dunford, A. et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. *Nat. Genet.* **49**, 10–16 (2017).
206. Zhong, X. & Zimmers, T. A. Sex differences in cancer cachexia. *Curr. Osteopor. Rep.* **18**, 646–654 (2020).
207. Permuth, J. B. et al. Racial and ethnic disparities in a state-wide registry of patients with pancreatic cancer and an exploratory investigation of cancer cachexia as a contributor to observed inequities. *Cancer Med.* **8**, 3314–3324 (2019).
208. Keklikoglou, I. et al. Chemotherapy elicits pro-metastatic extracellular vesicles in breast cancer models. *Nat. Cell Biol.* **21**, 190–202 (2019).
209. Mousset, A. et al. Neutrophil extracellular traps formed during chemotherapy confer treatment resistance via TGF-β activation. *Cancer Cell* **41**, 757–775.e10 (2023).
210. Monteran, L. et al. Chemotherapy-induced complement signaling modulates immunosuppression and metastatic relapse in breast cancer. *Nat. Commun.* **13**, 5797 (2022).
211. Wu, C. et al. Reactive myelopoiesis and FX-expressing macrophages triggered by chemotherapy promote cancer lung metastasis. *JCI Insight* **8**, e167499 (2023).
212. Sagiv, J. Y. et al. Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. *Cell Rep.* **10**, 562–573 (2015).
213. Gershkovitz, M. et al. TRPM2 mediates neutrophil killing of disseminated tumor cells. *Cancer Res.* **78**, 2680–2690 (2018).
214. Piranlioglu, R. et al. Primary tumor-induced immunity eradicates disseminated tumor cells in syngeneic mouse model. *Nat. Commun.* **10**, 1430 (2019).
215. Hoshino, A. et al. Tumour exosome integrins determine organotropic metastasis. *Nature* **527**, 329–335 (2015).
This landmark study uncovers how organ specificity of metastases can be generated by tumour-intrinsic mechanisms involving release of exosomes with organ-homing properties determined by the matched integrin expression and ECM make-up of target tissues.
216. Lee, Y. J., Shin, K. J. & Chae, Y. C. Regulation of cargo selection in exosome biogenesis and its biomedical applications in cancer. *Exp. Mol. Med.* **56**, 877–889 (2024).
217. Contreras-Zárate, M. J. et al. Estradiol induces BDNF/TrkB signaling in triple-negative breast cancer to promote brain metastases. *Oncogene* **38**, 4685–4699 (2019).
218. Heitz, F. et al. Cerebral metastases in metastatic breast cancer: disease-specific risk factors and survival. *Ann. Oncol.* **22**, 1571–1581 (2011).
219. Lu, Z. et al. Epigenetic therapy inhibits metastases by disrupting premetastatic niches. *Nature* **579**, 284–290 (2020).
This important study demonstrates how epigenetic therapies can be leveraged to reprogramme pro-metastatic cancer-primed myeloid cells and prevent PMN formation.
220. Kaczanowska, S. et al. Genetically engineered myeloid cells rebalance the core immune suppression program in metastasis. *Cell* **184**, 2033–2052.e21 (2021).
This groundbreaking study demonstrates how the inflammatory characteristics of the PMN can be harnessed to develop an engineered myeloid-cell-based therapy that reprogrammes the tissue microenvironment through targeted cytokine production and effectively reverses PMN formation. It offers proof-of-concept for using cell-based therapies to deliver therapeutic cargo into the PMN to prevent metastasis.
221. He, B. et al. Remodeling of metastatic vasculature reduces lung colonization and sensitizes overt metastases to immunotherapy. *Cell Rep.* **30**, 714–724.e5 (2020).
222. Ortiz, A. et al. An interferon-driven oxysterol-based defense against tumor-derived extracellular vesicles. *Cancer Cell* **35**, 33–45.e6 (2019).
223. Barron, T. I., Connolly, R. M., Sharp, L., Bennett, K. & Visvanathan, K. Beta blockers and breast cancer mortality: a population- based study. *J. Clin. Oncol.* **29**, 2635–2644 (2011).
224. Spera, G. et al. Beta blockers and improved progression-free survival in patients with advanced HER2 negative breast cancer: a retrospective analysis of the ROSE/TRIO-012 study. *Ann. Oncol.* **28**, 1836–1841 (2017).
225. Piccolo, N. D. et al. Tumor-on-chip modeling of organ-specific cancer and metastasis. *Adv. Drug Deliv. Rev.* **175**, 113798 (2021).
226. Kim, J. et al. Three-dimensional human liver-chip emulating premetastatic niche formation by breast cancer-derived extracellular vesicles. *ACS Nano* **14**, 14971–14988 (2020).
227. Aleman, J. & Skardal, A. A multi-site metastasis-on-a-chip microphysiological system for assessing metastatic preference of cancer cells. *Biotechnol. Bioeng.* **116**, 936–944 (2019).
228. Colombo, M. V. et al. Engineering the early bone metastatic niche through human vascularized immuno bone minitissues. *Biofabrication* **13**, 035036 (2021).
229. Picollet-D'hahan, N., Zuchowska, A., Lemeunier, I. & Gac, S. L. Multiorgan-on-a-chip: a systemic approach to model and decipher inter-organ communication. *Trends Biotechnol.* **39**, 788–810 (2021).
230. Wang, J. et al. A synthetic metastatic niche reveals antitumor neutrophils drive breast cancer metastatic dormancy in the lungs. *Nat. Commun.* **14**, 4790 (2023).
231. Aguado, B. A. et al. Biomaterial scaffolds as pre-metastatic niche mimics systemically alter the primary tumor and tumor microenvironment. *Adv. Healthc. Mater.* **7**, e1700903 (2018).
232. Aguado, B. A. et al. Extracellular matrix mediators of metastatic cell colonization characterized using scaffold mimics of the pre-metastatic niche. *Acta Biomater.* **33**, 13–24 (2016).
233. Xia, C. et al. Sponge-like nano-system suppresses tumor recurrence and metastasis by restraining myeloid-derived suppressor cells-mediated immunosuppression and formation of pre-metastatic niche. *Acta Biomater.* **158**, 708–724 (2023).
234. Xia, J. et al. Versatile ginsenoside Rg3 liposomes inhibit tumor metastasis by capturing circulating tumor cells and destroying metastatic niches. *Sci. Adv.* **8**, eabj1262 (2022).
235. Silvers, C. R., Messing, E. M., Miyamoto, H. & Lee, Y.-F. Tenascin-C expression in the lymph node pre-metastatic niche in muscle-invasive bladder cancer. *Br. J. Cancer* **125**, 1399–1407 (2021).
236. Ramessur, A. et al. Circulating neutrophils from patients with early breast cancer have distinct subtype-dependent phenotypes. *Breast Cancer Res.* **25**, 125 (2023).
237. Liu, Z. et al. Liquid biopsy in pre-metastatic niche: from molecular mechanism to clinical application. *Front. Immunol.* **13**, 958360 (2022).
238. Penders, J. et al. Single particle automated Raman trapping analysis of breast cancer cell-derived extracellular vesicles as cancer biomarkers. *ACS Nano* **15**, 18192–18205 (2021).

239. Li, R. et al. Computed tomography reveals microenvironment changes in premetastatic lung. *Eur. Radiol.* **31**, 4340–4349 (2021).
240. Liang, M. et al. Whole-liver enhanced CT radiomics analysis to predict metachronous liver metastases after rectal cancer surgery. *Cancer Imaging* **22**, 50 (2022).
241. Qi, Y. et al. Radiomics analysis of lung CT image for the early detection of metastases in patients with breast cancer: preliminary findings from a retrospective cohort study. *Eur. Radiol.* **30**, 4545–4556 (2020).
242. Granot, Z. et al. Tumor entrained neutrophils inhibit seeding in the premetastatic lung. *Cancer Cell* **20**, 300–314 (2011).

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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