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Cross-talk between tumors at anatomically distinct sites

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Running title: Cross-talk between metastatic tumors

List of abbreviations:

TME – Tumor microenvironment

PLR – paraneoplastic leukemoid reaction

GM-CSF/G-CSF – granulocyte-macrophage/granulocyte colony stimulating factor

IL – interleukin

TNF – Tumor necrosis factor

MDSC – myeloid derived suppressor cell

VEGF – vascular endothelial growth factor

DC – dendritic cell

EV – extracellular vesicle

EGFR – epithelial growth factor receptor

TCR – T cell receptor

NK – natural killer

Treg – regulatory T cell

FLT3L – FMS-like tyrosine kinase receptor ligand

SC - subcutaneous

Abstract

Cancer tissue is not homogenous, and individual metastases at different anatomical locations can differ from the primary tumor and from one another in both their morphology and cellular composition, even within an individual patient. Tumors are composed of cancer cells and a range of

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other cell types, which, together with a variety of secreted molecules, collectively comprise the tumor microenvironment. Cells of the tumor microenvironment can communicate with each other and with distant tissues in a form of molecular cross-talk to influence their growth and function. Cross-talk between cancer cells and local immune cells is well described, and can lead to the induction of local immunosuppression. Recently, it has become apparent that tumors located remotely from each other, can engage in cross-talk that can influence their responsiveness to various therapies, including immunotherapy. In this article, we review studies that describe how tumors systemically communicate with distant tissues through motile cells, extracellular vesicles and secreted molecules that can affect their function. In addition, we summarize evidence from mouse studies and the clinic that indicate an ability of some tumors to influence the progression and therapeutic responses of other tumors in different anatomical locations.

Introduction

Tumors in humans often spread to multiple different sites within one patient. All tissues of the body are connected through lymphatic and vascular systems, and systemic immune responses against tumors have been shown to impact distal tissues and tumors. Tumor cells and their associated cells, collectively known as the tumor microenvironment (TME), in one location can have a significant influence on the TME of distal sites. Various factors secreted from tumors, such as growth factors and tumor-derived extracellular vesicles (EVs), have been observed in the circulation (**Figure 1A and B**). Immune cell populations in peripheral blood and lymphoid organs are influenced by tumor cell derived factors, leading to systemic changes within the host (**Figure 1D**).

The impact of tumors on non-cancerous distal tissues is largely demonstrated in studies of the pre-metastatic niche, where secreted factors from a primary tumor create an environment within the pre-metastatic tissue conducive to tumor cell growth (**Figure 1C**). In addition, the term “abscopal effect” that was first used by Mole in 1953 in radiotherapy describes a phenomenon where local treatment of one tumor leads to regression of a distant tumor [1]. This suggests it is possible that tumors in different metastatic sites can influence each other during tumor development, progression and therapy. However, very few studies have investigated how tumors in different metastatic sites might impact each other. In this article, we review studies that consider the existing evidence on the concept of cross-talk between tumors in different anatomical locations (**Figure 1E**).

Systemic changes mediated by tumor cells

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Circulating factors from tumors

Tumor cells secrete various molecules including cytokines and growth factors that maintain the local microenvironment. These tumor molecules can also be released into the circulation where they can influence distant tissues. A clinical example of this comes from paraneoplastic leukemoid reaction (PLR) which describes a variety of hematological clinical disorders due to a non-hematolymphoid tumor. PLR has been reported in patients with a variety of cancers, including lung cancers, melanoma, mesothelioma, head and neck cancer and cancers of other origins [2]. The most commonly secreted cytokine by these tumors include granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), IL-1, IL-6 and TNF-α. In fact, GM-CSF is expressed by a number of tumor types constitutively, with one study reporting 23 of 75 human tumor lines producing GM-CSF [3]. These cytokines stimulate bone marrow myelopoiesis and inhibit myeloid cell differentiation that leads to accumulation of immature myeloid cells, which are called myeloid-derived suppressor cells (MDSCs) that suppress effector cell responses.

Another common tumor-secreted protein which has systemic effects is vascular-endothelial growth factor (VEGF). Increased plasma levels of VEGF in cancer patients correlates with poorer prognosis [4] and is thought to impact on dendritic cell (DC) differentiation [5]. Furthermore, arginase activity is higher in peripheral blood of gastric cancer patients and could potentially be involved in suppressing functions of circulating immune cells [6]. In each of these examples, tumor growth can result in an altered serum proteome which, can impact on distal tissues and alter the normal physiology of the host. Of course, many other proteins are secreted by tumor cells, but have no function in malignancy or transformation of distal tissues. Examples include elevated serum AFP (hepatocellular cancer), HCG (choriocarcinoma), PSA (prostate cancer), CEA (colorectal cancer), CA 125 (ovarian cancer) and CA 15-3 (breast cancer). Many of these proteins have been used for decades as biomarkers of tumor size indicating both tumor progression and response to therapy [7].

Extracellular vesicles

EVs are small membrane-encapsulated particles, derived from cells, which contain DNA, RNA and proteins representative of the host cells. EVs describe both exosomes and microvesicles which can mediate communication between cells, through their content, to modulate both the local and distal microenvironments. Exosomes are released from the cell

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by fusion of multivesicular endosomes with the plasma membrane whereas microvesicles are formed by budding off the plasma membrane [8]. Tumor-derived or tumor-associated EVs can exchange molecules from malignant or non-malignant cells within the TME to other cells throughout the body [9]. This communication can impact on signaling between the tumor and host, and can influence many aspects of tumorigenesis. Expression of ligands such as PD-L1, which can engage with receptors expressed by T cells to impair their function, have been identified on EVs. High levels of EV PD-L1 associate with clinical non-responders to anti-PD-1 therapy in metastatic melanoma [10].

EVs can be found in the blood and lymph through which they travel to distant tissues. A number of studies have demonstrated the influence of EVs on the pre-metastatic niche. Tumor-derived EVs have been shown to reprogram fibroblasts in pre-metastatic sites to generate an acidic microenvironment inhibitory for anti-tumor immune responses [11-13]. Epidermal growth factor receptor (EGFR)-expressing EVs secreted by gastric cancer cells enhance liver metastasis through induction of hepatocyte growth factor signaling in liver stromal cells [14]. Melanoma-derived EVs have been shown to induce vascular leakiness, allowing for increased accessibility for tumor cells into pre-metastatic sites [15]. In addition, tumor-derived EVs can also suppress monocyte maturation, leading to increased MDSCs, effectively increasing systemic tumor-mediated immunosuppression [16]. Thus, tumor derived EVs represent a form of communication from tumors to distal tissues that may potentially impact on distal TMEs and immune responses in other tumors.

Circulating cells

Various studies have focused on changes in the peripheral blood of cancer patients and pre-clinical cancer models. One study generated a novel system to match interactions across tissues to link pathways within primary tumors with changes in the systemic response in 173 breast cancer patients [17]. This study revealed that expression of genes in circulating blood cells are tightly linked to the genes in the primary tumors, and such gene expression patterns vary with breast cancer subtypes. Therefore, the RNA profiles of tumors can be indicative of systemic immune responses. A separate study of breast cancer patients identified changes in the peripheral blood immune cell profile between breast patients with or without lymph node metastasis [18].

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Indication of a systemic T cell response against cancer is evident from studies where T cells from peripheral blood of cancer patients can destroy tumor cells *in vitro* [19]. In addition, the presence of MDSCs in peripheral blood is associated with increased disease burden and negative prognosis in multiple solid tumors, presumably by infiltrating tumor sites, pre-metastatic niches and with their potential to inhibit circulating T cells [20, 21]. In ovarian cancer patients, the diversity in T cell receptor (TCR) clones within the circulation decreased during disease progression [22]. The diversity of peripheral TCR clones is decreased in lung and ovarian cancer patients compared to healthy controls, indicating that the presence of negatively impacts on T cells systemically[22, 23]. Intriguingly, during treatment with chemotherapy, the circulating T cell receptor (TCR) clonality is altered in various cancers, indicating a potential enhanced immune response that can be identified systemically in these cases [24, 25]. In breast cancer patients, increased diversity of the circulating TCR repertoire of $CD8^+$ T cells was associated with increased response to chemotherapy[25].Furthermore, a study in melanoma found that the combinatorial diversity evenness in the TCR repertoire pretreatment can be predictive of checkpoint blockade efficacy [26].

A recent study investigated systemic immune responses in experimental mouse models. Spitzer *et al.* found multiple changes within lymphoid tissue and within the circulation of mice receiving effective immunotherapies during the priming and rejection phase of tumors [27]. In peripheral blood, there were increases in NK cells, DCs, activated B cells, naïve $CD4^+$ T cells, $CD90^{hi}$ T-helper cells and $CD8^+$ T cells expressing Ly6C and CD44, observed during the priming phase. During the rejection phase, there were substantial decreases in immune cell frequencies in the circulation likely denoting migration of immune cells into the tissues. However, many cell populations in the circulation at this time retained expression of Ki67, indicating potential ongoing expansion and maintenance of these cells.

Thus, changes in the TME and immunity against a tumor is not just confined to the tumor, and/or the tumor-draining lymph nodes, but can cause systemic immune dysfunction. In this light, a study of osteosarcoma found that T cells in the spleen of tumor bearing mice showed an exhaustion status [28]. In addition, there was an increase in the percent populations of Tregs and MDSCs in the spleens of the tumor bearing mice. In this model, treatment with anti-PD-L1 decreased T cell exhaustion and increased monocyte maturation. These data suggest that cancer induced systemic immune dysregulation should be considered and targeted during cancer treatment.

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Seed and soil hypothesis

In 1889 Stephen Paget proposed the seed and soil hypothesis, where metastatic spread depends on cross-talk between the cancer cells (the 'seed') and the organ microenvironment (the 'soil')[29]. This hypothesis has been built upon with clinical observations and murine models of cancer in which certain tumor types tend to metastasize to specific organs independent of vascularization, rate of blood flow or the number of tumor cells delivered.

Experimental data to support this hypothesis first came from a study of B16 murine melanoma cells which grow in the lungs when injected intravenously. It had been assumed that the explanation for this is trivial – that the melanoma nodules develop in the lungs because they lodge in the first capillary bed they encounter. However, B16 cells also grew in lung tissue, but not in renal tissue, that had been implanted intra-muscularly demonstrating that the tissue microenvironment is important in determining the site of metastasis [30]. Comparison of B16 and K-1735 melanoma cell lines injected into the internal carotid artery revealed differences in brain metastasis patterns, as they produced only meningeal or parenchymal growths, respectively [31]. This indicates different regions and microenvironments, even within the same organ, may support the seeding and growth of different tumor cell types.

Furthermore, establishment of a 'pre-metastatic niche' has now been identified as a precursor for metastasis. The pre-metastatic niche is defined as aberrant immune cells and extracellular matrix that initiate the transformation of a healthy microenvironment to one supportive of tumor cell growth. The first-described pre-metastatic niche found a role for $VEGFR1^{+}$ hematopoietic progenitor cells that formed cellular clusters in pre-metastatic sites before tumor cell arrival [32]. Blocking VEGFR1 function or removing these cells ablated the cellular clusters and decreased tumor metastasis. Various proteins such as fibronectin, collagen IV, tenascin, periostin and certain chemokines and cytokines can be aberrantly expressed by tumor-influenced stromal cells in distal tissues [33-37]. EVs from pancreatic cancer can establish pre-metastatic niches in the liver and promote liver metastasis [38]. Tumor derived EVs can also be taken up by Kupffer cells of the liver, which produce TGFβ and fibronectin to recruit bone marrow derived cells (BMDCs) that support metastasis [39].

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Cells attracted to the pre-metastatic niche include MDSCs, neutrophils, macrophages and regulatory T cells (Tregs) [33, 36, 40-45]. For example, a murine study of breast cancer demonstrated that granulocytic MDSCs were important for establishing a pre-metastatic niche [46]. Thus, it is well established that signals from the primary tumor can influence distal tissues and impact healthy organ microenvironments. It could be expected that tumors in different primary and metastatic sites can also influence each other in a similar manner.

Abscopal effects of localized radiation

A well-documented example of one tumor impacting on a distal tumor in metastatic cancer patients is the abscopal effect of local radiation - in rare cases, localized radiation therapy of one tumor is followed by regression of distant untreated tumor/s in an immune-dependent manner. The abscopal effect has been observed in melanoma [47], renal cell [48], breast [49], hepatocellular [50], non-small cell lung and thymic cancers [51]. Between 1969 and 2014, there were an estimated 46 case reports of the abscopal effect from radiation therapy [52].

The involvement of the immune system in abscopal responses has been demonstrated in mouse models. In a mouse fibrosarcoma model, the dose needed for 50% tumor control in T cell-deficient mice was 64.5 Gray compared with 30 Gray in immunocompetent mice, demonstrating the key role of the immune system [53]. In a bilateral mouse model of breast cancer, irradiation in one flank along with systemic delivery of FMS-like tyrosine kinase receptor 3 ligand (FLT3L) resulted in a T cell dependent delay in growth of both irradiated and non-irradiated tumors [54]. Another study using the Lewis lung carcinoma model observed control of lung metastases when footpad tumors were irradiated and the mice received systemic Flt3L [55].

Since the initial observations of abscopal responses, combined immunotherapy and radiation has increased the reports of abscopal responses. In a clinical trial combining radiotherapy with GM-CSF in patients with solid cancer, abscopal responses were observed in 30% of patients [51]. In melanoma, αPD-1 or αCTLA4/αPD-L1 in combination with radiotherapy also increased abscopal responses [56, 57].

Mechanistic studies on combined radio-immunotherapy have shown that cross-presentation by BATF3-dependent DCs, CD8 T cells and type I interferons are required for abscopal responses [58-61]. Radiation therapy is thought to enhance the release of tumor associated

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antigens and promote local promotion of inflammatory responses, especially stimulation of the innate immune system, which consequently leads to $CD8^+$ T cell priming by BATF3-dependent DCs and T cell circulation and homing to tumor sites [62, 63]. In summary, tumors in distal sites can influence each other, in the context of radiation therapy, whereby tumor destruction by radiation leads to enhanced anti-tumor immune responses that become systemic.

Abscopal responses to other localized therapies have been observed when they are combined with PD-1/PD-L1 inhibitors [27]. In the MMTV-PyMT mouse model, which produce spontaneous tumors in multiple mammary glands, only those tumors that were directly injected with a tumor-binding antibody therapy regressed. However, when combined with systemic anti-PD-L1, intra-tumoral injection resulted in regression of distal tumors, even though anti-PD-L1 alone did not bring about systemic immune responses. Another study, which utilized vascular-targeted photodynamic therapy in primary murine Renca kidney tumors, resulted in systemic immune responses against lung metastases, when administered alongside anti-PD-1/PD-L1 [64].

Cross-talk between tumors in different anatomical sites

Evidence from experimental models

As discussed so far, complex interactions occur between the tumor and host, and these interactions can have systemic consequences. Thus, it is reasonable to hypothesize that metastatic tumors in different anatomical sites are not completely independent entities and that connectivity between tumors could impact on tumor growth and response to therapy. The limited number of studies that have investigated this hypothesis to date are discussed in detail in the following section.

Studies into how tumors can affect each other's growth and response to immunity and therapy go back many years. In 1905, a study by Paul Ehrlich found that engrafted tumors exhibit a negative effect on each other. In this study, earlier implanted tumors inhibited the growth of tumors injected later and the inhibitory effect increased with the size of the first tumor [65]. Studies in anti-angiogenic therapies have observed a decrease in the growth of metastatic tumors by angiogenesis inhibitors, only when the primary tumor is present. The serum and urine of tumor bearing mice contained angiostatin which inhibits endothelial cell

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proliferation and was determined to be a systemic mediator of the effects in metastatic tumors in this study [66].

Another study used mathematical modelling to investigate dynamic behavior and interactions between tumor and immune cells at various metastatic sites, with or without therapy [67]. Simulation of T cell recruitment in lung and breast tumors was assessed in isolation, and upon metastatic seeding after 200 days, aimed at analyzing T cell redistribution and immune cell population dynamics between the two sites, and to model the effect of surgery or radiation. This mathematical modelling revealed that a proportion of the T cells activated in the breast were recruited to the metastatic site. A larger fraction of circulating immune cells traffic through the pulmonary circulation and therefore have a greater chance of extravasation into the lung. The authors hypothesized that this would result in increased primary tumor growth, given the relocation of tumor reactive T cells to the lungs and estimated a 30% reduction in lung tumor size when a secondary breast tumor is seeded. Thus, this study provides a simulation and mathematical model for interconnectivity between existing tumor sites, which is based on assumptions from redistribution of T cells and systemic immunity in various tumor studies and other mathematical models of tumor growth.

A study by our laboratory was the first to demonstrate the influence of one tumor on immunotherapy responses to tumor located in a distant anatomical site [68]. Using the Renca kidney cancer model, in which subcutaneous (SC) tumors were responsive and orthotopic kidney tumors resistant to a triple antibody (trimAb) therapy, this study assessed therapy responses in mice simultaneously implanted with SC and kidney tumors. When mice had only contralateral SC tumors, responses to trimAb therapy were sustained. However, when mice had one SC tumor and one kidney tumor, growth of the SC tumor was accelerated with therapy, indicating that the Renca kidney tumor was inhibiting the response of the SC tumor.

In exploring a possible mechanism, we determined that M2 macrophages, which are commonly found in Renca kidney tumors increased in number in SC tumors when a kidney tumor was also present. The increase in M2 macrophages was accompanied by a decrease in T and NK cell numbers and cytotoxicity within the SC tumors. Furthermore, CCL2 blockade or systemic macrophage depletion using Clodrolip improved therapy responses in SC tumors when kidney tumors were present. As there were no soluble factors identified to mediate the suppressive effects, we hypothesized that M2 macrophages generated within the suppressive

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kidney tumor could traffic to the SC tumor, where they suppressed immune responses and decreased the therapeutic response.

A more recent study investigated the efficacy of dual checkpoint blockade (αPD-1/αCTLA4) on melanoma brain metastases [69]. Taggart *et al* found that an extracranial tumor (SC, in their model) had to be present for αPD-1/αCTLA4 to be efficacious against intra-cranial tumors. Mice implanted only with intra-cranial B16 melanoma cells responded poorly to αPD-1/αCTLA4, whereas those bearing both intra-cranial and SC tumors had enhanced survival and decreased growth of both extra- and intra- cranial tumors. When an extracranial tumor was present, intra-cranial tumors had enhanced infiltration of immune cells and particularly, $CD8^+$ T cells, bone marrow-derived macrophages and brain microglia. The beneficial effect of an extracranial tumor was abolished when mice were depleted of $CD8^+$ T cells and NK cells. Furthermore, $CD44^+CD62L^-$ effector $CD8^+$ T cells were increased in the peripheral blood of mice with extracranial disease and transfer of these cells from spleens of αPD-1/αCTLA4 treated mice demonstrated enhanced homing into intracranial tumors compared with the same cell population from spleens of treatment-naive mice. The authors also demonstrated that this enhanced homing may be due to enhanced T cell trafficking determinants on intracranial blood vessels when extracranial tumors were present.

Interestingly, further evidence in support of immune cross-talk between tumors can be found in studies utilizing neoadjuvant therapy [70]. In this approach, mice bearing both primary breast tumors and lung metastases were treated with immunotherapy prior to surgical removal of the primary. Mice undergoing neoadjuvant therapy survived longer, with decreased primary recurrence and progression of lung metastases, compared with mice undergoing surgery followed by adjuvant immunotherapy. The presence of the primary tumor during immunotherapy enabled a more pronounced tumor-specific T cell response that subsequently impacted on tumor relapse and metastatic formation.

Evidence from human cancers

There is increasing evidence for tumors in different metastatic sites influencing each other in human cancers. Evaluation of 371 patients with metastatic melanoma treated with high-dose IL-2 revealed that cutaneous and subcutaneous melanoma metastases were more responsive than visceral metastases [71]. Interestingly, patients with both cutaneous/subcutaneous and visceral metastases had an overall response rate of 17%, whereas patients with only

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cutaneous/subcutaneous metastases had on overall response rate of 50%, supporting the notion of visceral metastases having a negative impact on therapy response.

Data presented at the 2017 American Society of Clinical Oncology meeting reported that metastasis to the liver in melanoma patients was associated with reduced αPD-1 response [72]. The authors recapitulated these findings in the B16 melanoma mouse model, in that mice with liver and SC tumors were unable to achieve SC tumor clearance upon treatment with αPD-1, whereas 30% of mice with SC tumors alone achieved tumor rejection. Interestingly, the presence of liver metastases from an unrelated MC38 tumor line did not impact on SC tumor rejection, suggesting a tumor- or antigen-specific process. Although neither study controlled for the possibility that visceral/liver metastases signify more aggressive or progressive disease, these studies suggest that in humans, metastatic tumors situated in specific organs can have an influence on the overall response to therapy.

Recent results from human trials of immune checkpoint blockade in the neoadjuvant setting support the observations in mice described above [73, 74]. Patients with melanoma or glioblastoma undergoing neoadjuvant checkpoint blockade had better outcomes than patients receiving adjuvant checkpoint blockade, with increased time to progression and increased overall survival. Enhanced systemic immune responses were observed in some patients receiving neoadjuvant therapy, supporting the interpretation that, despite a larger tumor burden, the presence of the primary tumor during checkpoint blockade led to an increased T cell response against the remaining unresectable malignant disease.

Concluding remarks

Given the complexity of cancers, with metastases to various organs, and the ability of tissues to communicate across very distinct anatomical sites, it is not surprising that tumors might also affect each other's progression and responses to therapy. Tumors at different sites can differ in their immune composition, and the immune system is made up of a diverse variety of motile cells and secreted molecules that have the potential to move throughout the body. In addition, other cell types within tumors, including malignant cells, can also produce a variety of molecules and particles, many of which presumably remain to be identified, that may influence other tissues and tumors remotely.

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In this review, we have described studies supporting the concept of cross-talk between tumors, which can impact on the growth of metastases in various sites in the body and their response to various therapies, including immunotherapy (**Figure 1**). In some instances, cross-talk can clearly lead to a reduced response to therapy at certain sites, but there are also instances where tumors can become more responsive to therapy. With further advancement of this field, it may be possible to identify tumors that, based on their histological origin and anatomical site, might have a positive or a negative impact on the response to therapy. In at least some limited instances, it may be feasible to consider excising tumors at certain specific sites, or subjecting them to localized radiotherapy, in order to enhance the patient's overall response and prolong survival.

Figure Legend

Figure 1: Mechanisms of cross-talk of tumors with distal tumors and tissues. The presence of a tumor in one location results in systemic changes and can impact on distal tumors in other locations. **A)** Tumor-derived EVs and tumor-secreted proteins from malignant and non-malignant cells within the tumor microenvironment (TME), along with cells from the TME, can be released into the circulatory and lymphatic systems. **B)** The consequent changes in the molecular and cellular composition systemically have been detected in cancer patients compared to healthy individuals, and patients before, during and after treatment with various anti-cancer therapies. This highlights that events happening within the TME have an impact on the entire host. **C)** and **D)** Distant healthy tissues are impacted by secreted factors from the primary tumor which can disrupt the extracellular matrix and promote local immunosuppression in order to create the pre-metastatic niche (C) and impact on the composition and production of immune cells within lymphoid organs (D). For example, GM-CSF secreted by tumor cells can increase production of myeloid derived suppressor cells (MDSCs) from the bone marrow. **E)** The impact of one tumor on other distal tumors has recently been investigated in a limited number of studies. It seems that tumors can exhibit both positive and negative effects on each other, especially in the context of immunotherapy responses. For example, murine studies indicate that the presence of a primary tumor can enhance the generation of tumor specific T cell responses in metastatic tumors upon treatment with immunotherapies. Other studies suggest that immunosuppressive cells, such as M2 macrophages, that are generated in one tumor can traffic to, infiltrate and exhibit local immunosuppression in distal tumors thus dampening immunotherapy responses.

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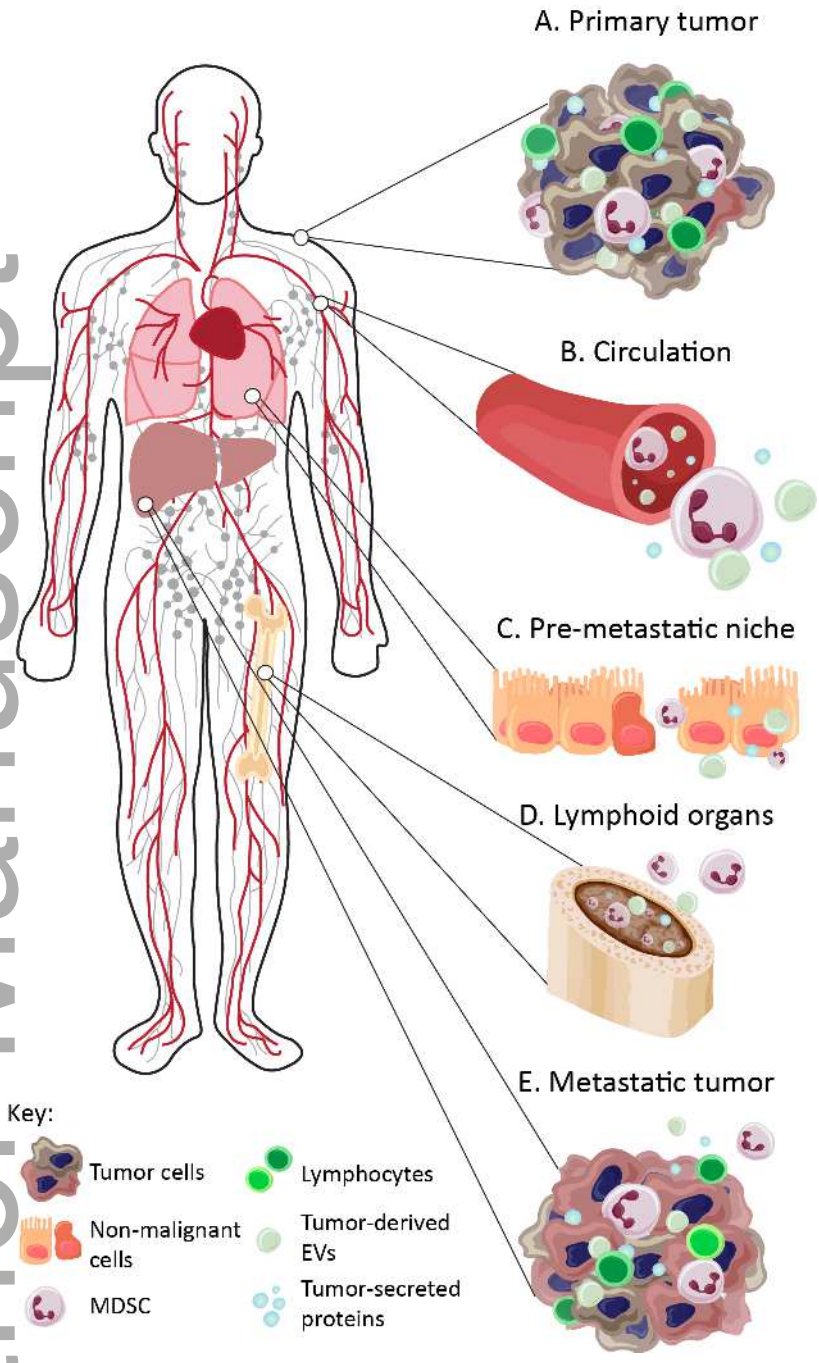
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