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Innate and Acquired Immune Surveillance in the Post-Dissemination Phase of Metastasis

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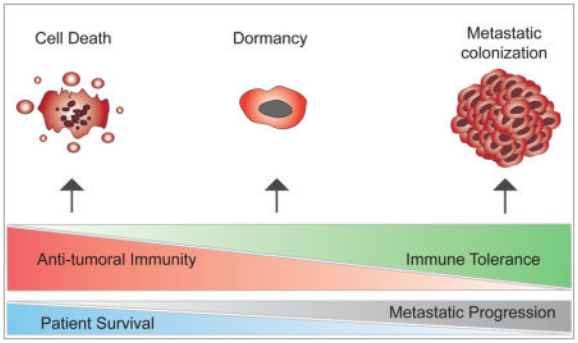
Abstract

Metastasis is responsible for the majority of death in cancer patients. Of the different steps in the metastasis cascade, the post-dissemination phase is perhaps one of the least understood. Many factors, both from the disseminated tumor cells (DTCs) and the microenvironment, impact the success of the metastatic outgrowth. In this article, we discuss the interactions between colonizing cancer cells and immune cells in the period between vascular arrest in a secondary organ and metastatic outgrowth. We address the ambiguity in the findings of current research regarding the role of immune cells in regulating the metastatic microenvironment, and their hand in determining cancer cell fate.

Graphical Abstract

During the post-dissemination phase of metastasis, cancer cells encounter a dynamic immune equilibrium which impacts patients' clinical outcomes, ranging from an anti-tumor immune response to constrain the metastatic spread to immune tolerance that promote metastatic colonization. Here we discuss the strategies that disseminated cancer cells develop to avoid immune attack and successfully generate metastatic colonies in distant organs.



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Keywords

Disseminated Tumor Cells; Immune evasion; Tumor dormancy; Metastasis-associated immune cells; patient-derived xenograft; organ-specific; Metastatic colonization; Extracellular matrix; Tumor microenvironment; Extracellular matrix

Introduction

Most cancer-associated deaths result from the development of metastasis rather than primary tumors [1, 2]. Traditionally considered a late-stage event in tumor progression, metastasis is the end result of a complex process known as the invasion-metastasis cascade, which enables cancer cells to acquire cellular traits, allowing them to travel from the primary tumor and migrate to distant tissues [3, 4]. Since many of the cancer cells that reach a distant organ have already been selected as therapy-resistant populations, once the metastatic colony is established, it is more difficult to treat the disease effectively. Thus, the major challenge in current clinical practice is understanding the mechanisms that cancer cells develop to successfully colonize distant organs.

Most available data about metastasis focus on the lungs as the site of dissemination, leaving much less known about other colonized organs, such as the bone, liver, and brain [4, 5]. Also, whether these mechanisms that promote or suppress metastasis are tissue-specific remain notably understudied. While intravenous and intra-cardiac injections of cancer cells have revealed that metastasis is a highly inefficient process at the cellular level, with an estimated survival of less than 0.01% [6–8], little is known about the necessary conditions and cellular programs that determine a successful metastatic outgrowth in a secondary organ. Since organ colonization is the last, and also rate-limiting, step of the metastasis cascade, we must direct our efforts to describe the cellular mechanisms contributing to successful colonization, and to identify both common and tissue-specific vulnerabilities to effectively design therapeutic interventions for already metastasized patients.

Shifting our paradigm from a cancer cell-centric view of disease progression to one more integrative and less reductionist has revealed the critical roles of the immune system, stromal cells, and components of the extracellular matrix (ECM) in triggering, promoting, and preventing tumor development [9, 10]. The combination of cellular components, ECM, and signaling molecules is defined as the metastatic microenvironment, which, in recent years, has been found to be an integral factor during organ colonization of disseminating cancers [4, 9, 11, 12].

Here, we summarize important advances in the understanding of the events that occur during extravasation and after parenchymal infiltration of a secondary organ during metastasis from solid carcinomas, emphasizing the interactions between DTCs and innate and acquired immune cells in the metastatic microenvironment. We discuss how the cancer cell-immune cell crosstalk impacts the metastatic outgrowth, what relevant questions remain unaddressed, and challenges in the field. We postulate that, despite the differences between cancer types and colonized organs, there are some overarching biological principles characterizing immune surveillance in the post-dissemination phase of metastasis.

Immune Surveillance During Metastasis

Because the establishment of a new colony in a distant organ is both the last and rate-limiting step of the metastatic cascade, it is accepted that only few cancer cells successfully reach this stage [6]. Those able to reach a secondary organ have three possible fates: i) elimination, ii) entry into a dormant state, iii) survival and proliferation (Fig. 1). Many studies agree that the majority of extravasated cancer cells in a secondary organ are eliminated by diverse mechanisms [3, 6–8, 13]. Of the surviving cells, some enter a period of latency/quiescence, awaiting conditions more favorable for proliferation [4, 8]. An even smaller portion of survivors go on to proliferate, eventually giving rise to a metastatic colony. In this context, both innate and adaptive immune cells play relevant roles that impact the cancer cell fate [9, 14]. Whether the immune cells act, as either promoters or suppressors of metastatic outgrowth, dictate cancer cell fate post-dissemination to a secondary organ. In recent years, most reports have focused on the metastasis-promoting role of immune cells. We discuss those mechanisms here, as well as those that the immune system exerts to suppress metastasis.

Metastasis-associated Macrophages (MAMs)

The roles of both resident and infiltrating monocytes/macrophages during cancer progression as key components of the tumor microenvironment have been extensively studied and discussed in recent years [14, 15]. It is accepted that a higher number of tumor-associated macrophages (TAMs) correlates with a poorer prognosis in patients and a reduced survival in mouse models of cancer [15, 16]. TAMs mechanistically have been associated with promoting important steps of cancer progression—angiogenesis, migration, suppression of the adaptive immune response, and limiting the efficacy of therapeutics [14, 15, 17–19]. However, much less is known about the role of these monocytes/macrophages during metastasis.

MAMs have been shown to act as metastatic promoters by increasing endothelial permeability. In a mouse model of pulmonary metastasis from breast cancer, chemokine ligand 2 (CCL-2) secreted by both cancer cells and the stroma preferentially recruited C-C chemokine receptor type 2 (CCR2+) inflammatory monocytes to metastatic sites, resulting in increased metastatic seeding and tumor outgrowth. Also, endothelial cells have been described as actively participating in the recruitment of CCR2+ monocytes via CCL2 secretion[20]. Anti-CCL2 treatment in mousee models of breast cancer has been shown to be effective; reciprocally, the discontinuation of anti-CCL2 treatment increases lung metastasis and accelerates mice death [21]. Interestingly, specifically ablating vascular endothelial growth factor (VEGF) in monocytes blocks metastatic seeding and tumor outgrowth, while the transfer of inflammatory monocytes results in preferential metastasis to the lung[22]. Along the same line, another study using a MMTV-PyMT mouse model, which spontaneously develops lung metastasis from mammary carcinoma, elegantly demonstrated that in an angiopoietin-1 receptor (TIE2)-mediated mechanism, MAMs enhance angiogenesis in metastatic foci. Notably, angiopoietin 2 (ANG2) inhibition markedly decreases both the number of lung metastatic foci and also the outgrowth of pre-established metastases [23]. An ANG2 blockade following resection of the primary tumor has a similar

effect—a reduction in metastatic burden via an antiangiogenic response in lung metastasis. [20]. Likewise, the expression of vascular cell adhesion molecule 1 (VCAM-1) by cancer cells results in the recruitment of MAMs to the lung. This interaction transmits anti-apoptotic signals to the cancer cells by activating the PI3K/Akt pathway[24]. MAMs also have a more complex role in promoting metastasis by cultivating a more fibrotic metastatic microenvironment, which serves to sustain the metastatic outgrowth. In a genetic mouse model of pancreatic ductal adenocarcinoma (PDAC), granulin secreted by MAMs in the liver induces the differentiation of resident hepatic stellate cells into periostin-secreting myofibroblasts, creating a metastatic microenvironment more favorable for outgrowth. Circulating monocytes isolated from PDAC patients express high levels of granulin [25]. Evidence of increased endothelial permeability, in conjunction with the development of a more fibrotic metastatic microenvironment, supports the idea of MAMs functioning in a pro-metastatic capacity, not only allowing for metastatic seeding but also nurturing colony development. In the near future, we anticipate a detailed characterization of pro-metastatic MAMs, with identification of specific phenotypes associated with cancer survival and cancer subtypes. We also expect the validation of many of these findings in more reliable *in vivo* approaches of studying cancer, such as patient-derived xenograft (PDX) models.

Despite the number of studies documenting the pro-tumor effect of MAMs, they often have been observed eliciting an immune effector response, functioning to suppress metastasis rather than acting in the pro-metastatic role described above. For example, in the MMTV-PyMT model, Nr4a1+ patrolling monocytes reduce lung metastases by eliminating tumor cells in a CX3CR1-dependent manner, and inducing the recruitment of natural killer cells to the lung tumor microenvironment [26]. Using the selective class IIa histone deacetylase inhibitor, TMP195, a reduction in tumor burden and decrease in spontaneous pulmonary metastasis in a macrophage-dependent manner has been observed recently. The TMP195-activated macrophages are highly phagocytic and induce vasculature normalization in breast tumors [27]. Another study, using a mouse model of liver metastasis, demonstrates that, following an antibody-dependent cellular phagocytosis associated with monoclonal therapy, the tumor cells are rapidly recognized and arrested by resident macrophages [28].

As most studies focus on the lung metastasis as site of dissemination, little is known about the role of MAMs in other organs like the bone or brain. In a lung cancer model, the inhibition of monocyte/macrophages through clodronate encapsulated by liposomes resulted in a decrease in bone and muscle metastases [29]. Similarly, the forced CCL2 expression in a human prostate cancer cell line enhances bone metastasis associated with the recruitment of osteoclasts [30].

To this day, brain metastasis continues to have the worst prognosis of any cancer. Using a mouse model of brain metastasis from breast cancer, it has been proposed that cancer cells secrete high amounts of CCL2 i*n vivo* as a consequence of PTEN downregulation in cancer cells that have infiltrated the brain parenchyma, resulting in the recruitment of IBA1+ myeloid cells that reciprocally enhance the metastatic outgrowth [12]. However, several fundamental questions about brain metastasis progression remain unaddressed—in the central nervous system (CNS), still considered an immune privileged site protected from inflammatory damage, can monocytes or any other peripheral immune cells infiltrate the

brain parenchyma during brain metastasis; can microglia, considered to be resident macrophages of the CNS, acquire MAM's properties, coming to resemble peripheral macrophages; how does the presumed activation of microglia or infiltrated macrophages during brain metastasis impact the integrity and permeability of the blood-brain-barrier? Despite differences in ontology, microglia share many properties with the peripheral macrophages, specifically regarding their role as mediators of inflammation[31]. We therefore anticipate new insights about the crosstalk between DTCs and microglia, its impact in metastatic outgrowth, and further development into the function of MAMs in organs beside the lung.

Metastasis-associated neutrophils

The role of neutrophils has been intensely debated and explored in recent years, as there is evidence they can both promote and inhibit metastasis [32]. Several experiments demonstrate neutrophils exerting an anti-metastatic role. For example, in a spontaneous model of breast cancer with lung metastases and in experimental models of lung cancer, melanoma, fibrosarcoma, and pancreatic cancer, neutrophils that express the hepatocyte growth factor receptor (MET) exhibit a strong anti-metastatic effect. Mechanistically, the expression of MET is required for endothelial transmigration and cytotoxicity [33]. Furthermore, tumor-entrained neutrophils exert a potent anti-metastatic cytotoxic response in the lung through the secretion of reactive oxygen species. Notably, this study also establishes that tumor-secreted CCL2 is both necessary and sufficient for neutrophil entrainment and cytotoxic response, in contrast with the aforementioned pro-metastatic role of CCL2 [34]. However, other studies demonstrate conflicting results, featuring neutrophils acting in a pro-metastatic capacity. IL-7 produced by γδ T-cells induces the recruitment and expansion of neutrophils in spontaneous lung metastasis from breast cancer, promoting cancer survival and outgrowth by suppression of the cytotoxic response of CD8+ T cells [35]. Neutrophils have been postulated to be pioneer immune cells, infiltrating the metastatic niche at a very early stage of metastatic dissemination and supporting the formation of colonies of initiating breast cancer cells [11]. Neutrophils also initiate liver metastasis through the interaction of MAC-1 with ICAM-1 expressed in cancer cells [36]. In addition, neutrophils producing CXCR2 instigate liver metastasis in the PDAC model [37]. The various mechanisms by which neutrophils promote and suppress metastasis, and the fact that they are the most abundant circulating immune population, highlight the importance of placing our efforts into better characterizing the different phenotypes of neutrophils, not just in cancer models and metastasis, but also in normal tissues during homeostasis.

Metastasis-associated Natural Killer (NK) cells

Other innate immune cells such as NK cells function in immune surveillance, vigilant for metastatic cells. There is a general consensus that NK cell cytotoxicity exerts a pivotal role against metastatic dissemination; indeed, an inverse correlation between metastasis and cytotoxic NK cell activity has been observed in renal [38], prostate [39], pancreatic [40], gastric [41], melanoma [42], breast [43], colorectal [44] and lung cancer patients [45]. Notably, the *in vivo* NK cell depletion by specific antibodies against NK cell receptors, results in increased metastatic burden in immunocompetent mice [46, 47]. Mechanistically, the acquisition of mesenchymal-associated traits by tumor cells during metastasis-invasion

cascade is also associated with upregulation of cell surface ligands recognizable by NK cell-activating receptors (NKARs) [48, 49]. Thus, disseminated tumor cells that escape from the immune effector response in primary tumors are recognized in circulation and metastatic sites by NK cells through the abnormal expression of ligands such as major histocompatibility antigen [50], E-cadherin [51], MIC-A/B [52], UL16 binding proteins [47], DNAM-1 ligand [53], and others [48]. Upon activation of NKARs (e.g., CD160, CD266, CD244, NK-p46, NK-p44 and NCR3, reviewed in ref. [48]), NK cells efficiently exerts the anti-metastatic activity by releasing effector mediators such as perforins [50], granzyme B [54], interferon gamma (IFNG) [55] and the expressing ligands of death receptors such as tumor necrosis factor-related apoptosis inducing ligand (TRAIL) and CD95L [48, 56]. Notably, the genetic inactivation of NKARs and/or NK cell effectors results in a metastasis-permissive microenvironment and increased metastatic burden; for example, the receptor NKp46 is necessary to mediate the cancer cell recognition and cell killing in mouse models of melanoma and lung cancer metastasis [57], and a similar finding has been observed in $CD266^{-/-}$ [53], perforin-$1^{-/-}$ [50], $TRAIL^{-/-}$[56] and $IFNG^{-/-}$ NK cells [55]. Taken together, the evidence indicates that NK cells exert a strong anti-metastatic response, and that a better understanding of the mechanisms that undergoes metastatic cells to avoid the NK cell recognition is crucial to developing successful therapeutic strategies.

Overall, the current dubiousness regarding the role of the innate immune system during the last step of metastatic dissemination—particularly MAMs and neutrophils—emphasizes the need to converge our efforts into better characterizing its roles and associated phenotypes. In the foreseeable future, we anticipate experimental evidence linking phenotypes of MAMs and neutrophils with metastatic fate to define the roles and functions of cellular plasticity more precisely, as well as the anatomical dynamics of circulating myeloid cells during cancer progression, with particular focus on disparities between early and late stages.

Metastasis-associated T cells

The infiltration of T cells is crucial to the tumor microenvironment, and has been extensively studied in primary tumors in diverse cancers [58]. As a general rule, a high grade of T-cell infiltration in tumors is associated with favorable prognosis in patients [14]. The notable success of checkpoint blockades (e.g., anti-PD, anti-PD-L1 or anti-CTLA4), particularly in melanoma and lung cancer, highlights the impact of the endogenous anti-tumoral T-cell response during cancer progression [59]. On this subject, a number of clinical trials have reported therapeutic activity of immune checkpoint inhibition in metastatic carcinomas [60–64]. The anti-metastatic effect of T cell activation has been documented—analysis in bone metastasis from breast carcinoma shows that cytotoxic CD8+ T cells, in an interferon-dependent manner, play a primary role in anti-metastatic defense [65]. A clinical prospective study with 31 lung cancer patients revealed that the levels of circulating cancer cells are positively correlated with bone metastasis, but negatively correlated with circulating T cell levels [66]. Similar conclusions arose from a study of 65 breast cancer patients, whose levels of circulating tumor cells correlate with a defective adaptive immune response [67]. Intriguingly, check-point inhibition in melanoma and lung cancer patients has been shown to be significantly effective in the clinical treatment of brain metastatic tumors [61, 68, 69]. It remains obscure if adaptive immune cells like T cells exert an anti-metastatic effector

response within the brain parenchyma or in perivascular spaces. Some preliminary insight comes from a recent study using a dual anti-angiogenic (anti-ANGPT2 and anti-VEGF) blockade therapy in mouse models of metastatic breast cancer, pancreatic neuroendocrine tumor and melanoma. Notably, this treatment increased the extravasation and accumulation of T cells in tumors with reduced incidence and burden of lung metastasis [70]. In the same line, intra-vital imaging during first hours of lung colonization by pioneering melanoma cells identified a subset of lung resident CD103+ dendritic cells (DCs) as direct suppressors of metastatic seeding [71]; notably, CD103+ DCs have been identified as potent antigen presenting cells and crucial for mounting an effector T-cell immune response in tumor microenvironment [72].

In contrast to the anti-metastatic role of T cells described above, immune-tolerant T cells are exploited by cancer cells to alter the tumor microenvironment, allowing for evasion of T cell recognition and metastatic outgrowth. Although the immunosuppressive activity of CD4+ CD25+ T regulatory cells (Treg) has not been described in detail in metastasis, association between Tregs and incidence of metastasis has been reported in studies in which cancer cells hijack the immune system to induce tolerance to immunogenic DTCs. Indeed, a clinical study from non-small lung carcinoma observed an increased percentage of circulating Tregs in patients with metastatic tumors compared with non-metastatic [73] -similar associations have been described in breast cancer [74], colorectal carcinoma metastasis [75] and hepatocellular carcinoma [76]. Moreover, the expression of oxygen-sensing prolyl-hydroxylase (PHD) proteins on T-cells promote Treg induction and restrain the CD8+ T-cell function in lung, generating a permissive microenvironment for pulmonary metastasis from melanoma [77]. Interestingly, reduced levels of miR-34a induced by TGF-β signaling results in enhanced secretion of CCL2 that the promotes the recruitment of Tregs, favoring metastatic seeding in liver and lung [78]. Finally, transcriptomic analysis of highly metastatic subtypes of renal carcinoma documented an immunosuppressive microenvironment characterized by markers as FoxP3, IL-10, TGF-β and the T cell immunosuppressive molecule PD-L1 [79].

Although the T cell-dependent mechanisms involved in metastasis remain understudied, the available evidence allows speculation that T cells play important roles in the metastatic cascade and that DTCs must orchestrate immunosuppressive mechanisms to evade T cell recognition. The success of therapies that amplify antigen-specific T cell responses against primary tumors in experimental models and patients offers promising therapeutic opportunities to treat metastatic tumors. Advances in T cell engineering and development of more reliable immunocompetent mouse models for metastasis should reveal important insights that can be exploited to further therapeutic manipulation.

Control of Metastatic Dormancy by Inflammatory Cells

Many cancer patients suffer metastasis relapse several years after therapy and surgeries of primary tumors. Indeed, breast cancer metastases are detected up to 20 years post-surgical removal of the primary tumor, with similar findings reported for prostate cancer and melanoma. These observations suggest that some undetectable, slow-cycling DTCs and/or micrometastatic lesions remain dormant for long periods of time as a consequence of their

inability to proliferate and give rise to metastatic outgrowth. Due to technical limitations, it is difficult to get results demonstrating that metastatic tumors derive from pre-existing dormant DTCs, as it is not feasible to monitor DTC awakening and reactivation after years, possibly decades. Despite the clinical relevance of DTC dormancy, at present very little is known about the mechanisms that control DTC's entry to and exit of dormancy.

Cancer cell dormancy is thought to be mediated—at the very least—by poor vascularization and continuous pressure enforced by the immune system. We may speculate that, as the dormant DTCs in patients must to be protected from immune attack, the inflammatory cells function in the induction, maintenance, and exit of DTC dormancy in the post-dissemination phase of metastasis. Accordingly, the role of immune cells in DTC dormancy has been documented in a mouse model of fibrosarcoma that develops spontaneous lung metastasis in immune-deficient nude mice, but not in immunocompetent mice until a period of 24 months. The depletion of CD8+ and/or CD4+ T cells after 5 months of primary tumor excision in the immuno-competent group promotes the awakening of DTCs and pulmonary metastatic outgrowth [80]. In another study, using a spontaneous mouse model of melanoma in which the tumor cells disseminate early during tumor progression to visceral organs and remain dormant for long periods of time, the specific ablation of CD8+ T cells induces the acceleration of re-activation, and proliferation of DTCs with subsequent development of visceral tumors [81]. These valuable data imply that both CD4+ and CD8+ T-cells are necessary and sufficient in these experimental models to maintain the dormancy of DTCs and also, considering the long periods of latency, likely induce the development of immunological memory.

As a prerequisite to developing a successful metastatic outgrowth is the ability of DTCs to develop a tumor, it has been proposed that the cancer stem cells (CSC) fit with the criteria of tumor initiation capacity—slow cycling, long-lived, and well protected against immune attack. In human breast CSC, LCOR (nuclear receptor co-repressor) is a direct functional target of miR-199a. The expression of miR199a significantly increases the tumor initiation capacity in a ER(-) PDX mouse model. In experimental metastasis to lung, liver and kidney, the LCOR overexpression suppresses metastatic outgrowth and negatively regulates the stem cell capacity by sensitizing CSC to IFN-γ response, the interferon signaling known to be a critical anti-metastatic immune surveillance by CD8+ T cells and macrophages [65, 82]. Recent data from experimental models of lung, brain, kidney and liver metastasis from breast and lung cancer, show that the slow-cycling DTCs evade immune attack by NK cells through the downregulation of various cell-surface NK activators. This quiescent immune evasive state is enforced by an autocrine inhibition of the Wnt pathway [47].

While these data illustrate that the immune system can exert a tight control of dormancy in DTCs, further studies are needed to identify the immune-mediated mechanism of dormancy, especially the strategies that display dormant DTCs to be protected of immune attack for long periods of time. The fact that the current anti-cancer therapies do not target dormant DTCs generates a clinical challenge highlighted by the poor prognosis of disseminated cancers, and advances in this area could provide valuable information to specifically target dormant DTCs, or avoid the development of metastatic outgrowth in asymptomatic patients after primary tumor resection.

Concluding Remarks

The significant progress made in recent years with immunotherapies that enhance the immune attack against tumors highlights the importance of the immune system as a key factor during cancer progression. Disseminated carcinoma cells must develop strategies to avoid immune attack. Most of the current knowledge about cancer immune surveillance comes from studies in primary tumors, however, metastatic cells can acquire mutations and progress independently after dissemination from primary sites. Therefore, we should ask if current data from primary tumors are sufficient to infer molecular analysis to develop successful immunotherapies against metastatic tumors. Currently, most of the metastatic cancer remains incurable. In this context, key questions remain to be addressed—which immune cell types are the critical regulators of a successful metastatic outgrowth; what is the impact of the mechanisms of immune evasion of DTCs in the incurability of metastasis; how do organ-specific immune responses determine the DTCs' fate; which immune mechanisms are turned-on or turned-off to allow awakening from dormancy in metastatic sites?

A major challenge in the future is developing more reliable preclinical models of metastasis that resemble the immune surveillance seen in cancer patients. Also, deeper characterization of the heterogeneity that metastasis-associated innate and acquired immune cells display is necessary to understand the functional implications of immune phenotypes. We speculate that in the near future, single-cell proteomic and transcriptomic analysis of human metastatic tumors will provide new insights, leading to new opportunities to treat already metastasized patients and develop new experimental models of cancer progression.

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Abbreviations

ANG2	angiopoietin 2
CCL-2	chemokine ligand 2
CCR2	C-C chemokine receptor type 2
DTCs	disseminated tumor cells
ECM	extracellular matrix
MAMs	metastasis-associated macrophages
NK	natural killer
NKARs	NK cell-activating receptors
PDAC	pancreatic ductal adenocarcinoma
PDX	patient-derived xenograft

TAMs	tumor-associated macrophages
TRAIL	tumor necrosis factor-related apoptosis inducing ligand
VCAM-1	vascular cell adhesion molecule 1
VEGF	vascular endothelial growth factor

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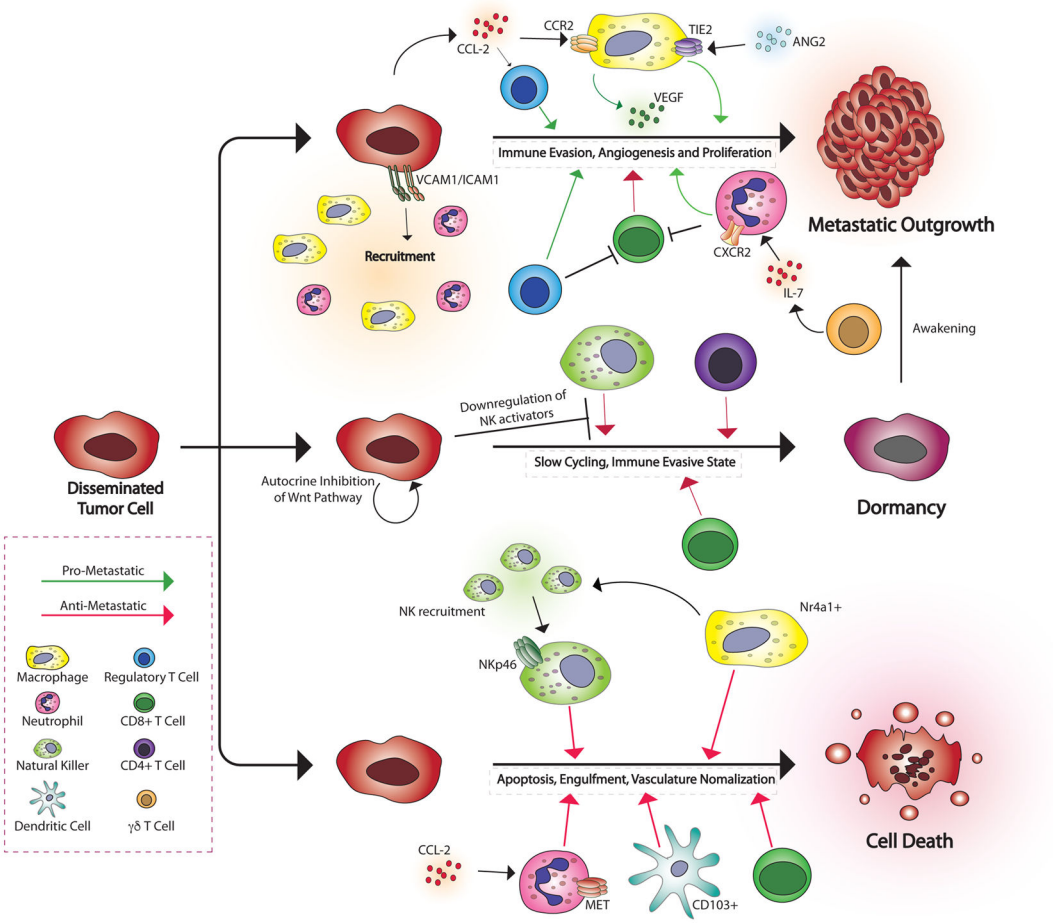

Figure 1. Impact of immune surveillance in the fate of disseminated tumor cells (DTCs)

Depicted here is a cancer cell endowed with tumor forming ability facing the post-dissemination phase of metastasis. Once circulating cancer cells reach a secondary organ, cellular components of both the innate and acquire immune system play key roles in fate determination of DTCs. Most of the DTCs are eliminated primary by the immune attack. A small portion of the DTCs that survive go on to proliferate, giving rise to a metastatic tumor. For this purpose the DTCs exploit the immunosuppressive and pro-angiogenic properties of immune phenotypes as a mechanism of colonization. Some of the surviving DTCs enter a period of latency, awaiting conditions more favorable for proliferation. These slow cycling DTCs can develop immune-evasive states to confront the continues pressure enforced by the immune system. For abbreviations and further details, see the text.