Metastasis: A Major Driver of Cancer Pathogenesis

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Abstract

Cancer is a multifactorial condition that originates from genomic alterations in the cells, which confer them the ability to evade various cellular regulations and proliferate incessantly. Furthermore, the accumulation of these mutations confers metastatic abilities to the tumor cells, which help them in contriving various features essential for invasion of the host tissues and evading immune surveillance and thus spreading to distant sites. Metastasis is a key phenomenon in cancer pathogenesis, which involves invasion of host tissue, escape into the blood vascular system, survival within the circulation, extravasation into the secondary sites, establishment of micrometastasis, and colonization. The tumor cells utilize various host cells and pathways to reach the pre-destined sites, also known as pre-metastatic niches (PMNs). The primary tumor is known to secrete various factors, which render the secondary metastatic sites hospitable for the arriving tumor cells. These tumor cells, in turn, invade the PMNs and either undergo dormancy or outgrow to develop secondary metastases. Since metastasis involves

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a cascade of events, it also offers attractive targets for therapeutic intervention. This chapter elaborates the series of events involved in metastasis initiation and progression along with the role of PMNs and various therapeutic approaches to target metastasis.

Keywords

Metastasis · Pre-metastatic niches · Cancer · Tumor cells · Extracellular matrix · Anti-cancer therapy

10.1 Introduction

The process of movement of primary tumor cells from their original site of growth to other distant sites or organs, where they colonize and establish secondary metastases, was termed as metastasis by Jean Claude Recamier in 1829 [1]. During metastasis, the tumor cells gain the ability to invade neighboring tissue, access the blood supply, and disseminate to distant organs [2, 3]. Today, metastasis is considered to be a major contributor to cancer related deaths. In fact, 90% of the cancer associated mortalities are attributed to metastasis following failure of surgical resection and chemotherapeutic approaches [4, 5]. Metastasis is a multi-step process, occurring in a defined pattern, which involves a variety of steps in a successive manner, including the invasion of the surrounding tissue, intravasation into the blood vessels, survival of cancer cells in the blood circulation, extravasation into the distant sites, adaptation in the new tumor microenvironment, and colonization (Fig. 10.1) [6, 7].

In fact, the formation of PMNs by the primary tumor cells itself lays the foundation for metastatic spread, thus justifying the words said by Paget, "When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil" [8]. Thus, the distant organs/sites (soil) which are occupied by the metastatic tumor cells (seed) are primed prior to the arrival of these cells by various factors secreted by the primary tumor itself, which render them conducive for the invading tumor cells to grow and colonize. The steps of a metastatic cascade are sequentially discussed below.

10.2 Invasion of the Surrounding Tissue

Invasion of a tumor into its malignant phenotype is the very fundamental step in metastasis. Normal cells in the body grow in a dynamic environment defined by the extracellular matrix (ECM) surrounding stromal layers. The ECM mainly comprises of collagen, fibronectin, proteoglycans, elastin, and laminins apart from water, proteins, and polysaccharides [9]. Whereas the tumor-associated stroma encompasses a heterogenous population of cells such as endothelial cells (ECs), fibroblasts, myofibroblasts, adipocytes, plethora of bone marrow-derived cells (BMDCs), and several immune cells including macrophages [10]. The ECM

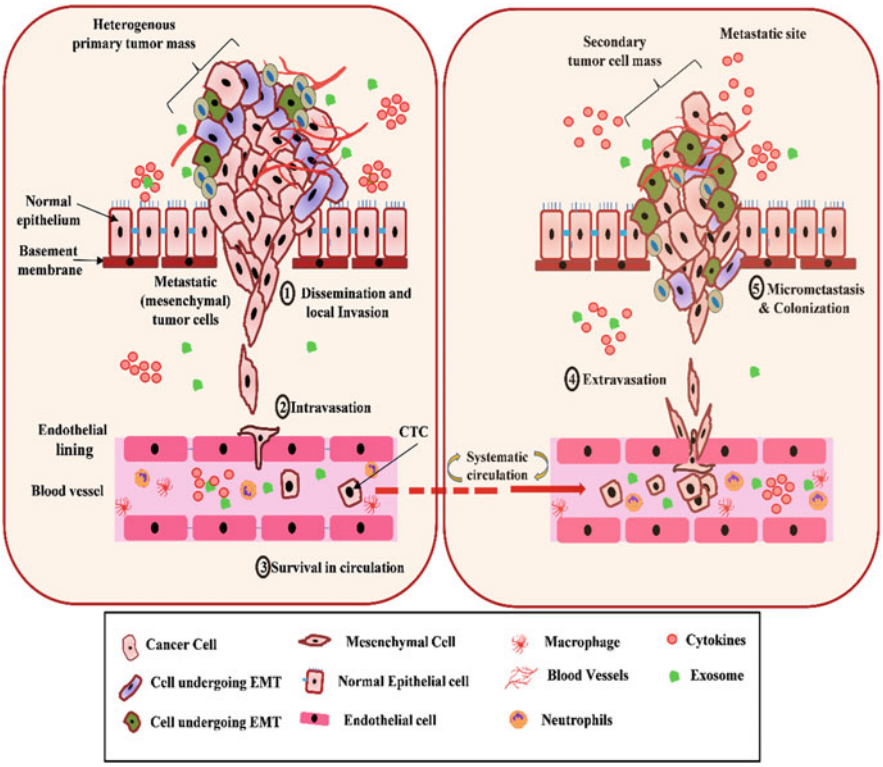

Fig. 10.1 The metastatic cascade: Metastasis encompasses a sequential occurrence of events, which ensues from invasion followed by the intravasation, survival in the circulation, extravasation to the distant metastatic sites, development of micrometastases, and colonization of the occupied sites. The role of various host cells in accomplishing each of these steps of this cascade is imperative

performs a key role in cell growth, morphogenesis, and plasticity of the parenchyma by providing a spatio-temporally regulated scaffold to the epithelial cells, thus maintaining the cell polarity. It is also responsible for providing essential bio-chemical and bio-mechanical signals or cues required for cellular differentiation and homeostasis, alteration of which is known to cause cancer [11–13]. The metastatic process initiates with the acquisition of invasive potential by the primary tumor cells, which then break free from the basement lining and move into the surrounding tissues, a phenomenon known as epithelial to mesenchymal transition (EMT) (Fig. 10.2) [14–16]. Various aspects of EMT are described in subsequent sections below.

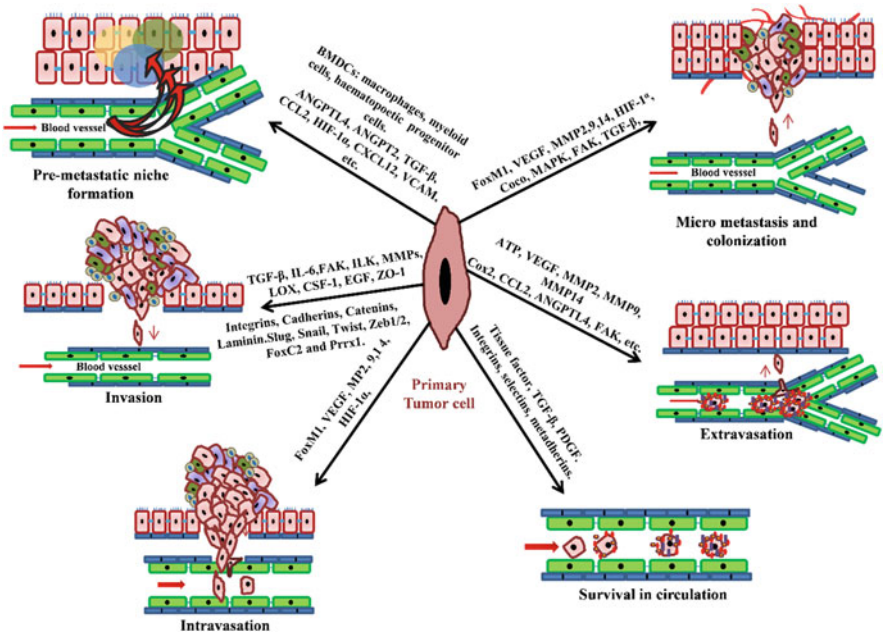

Fig. 10.2 Various factors regulate the metastatic cascade: Metastasis encompasses several sequential steps, which are regulated by the interplay among various signaling molecules released by the primary tumor cells and the host-derived factors. Several factors such as TGF-β, MMPs, etc. exhibit pleiotropic functions in metastasis

10.3 Epithelial to Mesenchymal Transition (EMT)

The tumor-associated stroma consists of a heterotypic population of cells, which resembles the inflammatory stromal configuration and is induced upon wound healing processes under normal physiological conditions. This modulated stroma then releases various signaling molecules such as interleukin-6, transforming growth factor (TGF)-β, WNT, etc. which assist the adjacent carcinoma cells to activate the silent EMT mechanism. EMT involves the conversion of normal epithelial cells to an invasive mesenchymal phenotype by modulating their apical-basal polarity [17–19]. These mesenchymal cells are characterized by enhanced invasive and migratory capabilities and display resistance to apoptosis.

Evasion of apoptosis upon detachment from the anchorage of the basement membrane, i.e. anoikis, is a key feature of invasive cells [20, 21]. Integrins, which mediate the cellular attachment to the ECM, play a major role in escaping anoikis. Among various forms of integrins, upregulation of $\alpha_5\beta_3$ integrin is important in this process [22–24]. It also stimulates the production of matrix metalloproteinase (MMP) 2, thus further enhancing metastasis [25]. Integrin associated signaling pathways subsuming focal adhesion kinase (FAK) and integrin linked kinase

(ILK) are also involved in the obstruction of anoikis [26–28]. Similarly, cadherins contribute critically in mediating cell–cell adhesion by forming intercellular complexes with catenins that link them to the cytoskeletal proteins. Thus, the loss of certain epithelial cell surface markers such as ZO-1, laminin, E-cadherin, which favor homotypic cell adhesion, and the upregulation of N-cadherin, which promotes heterotypic cell adhesion, lead to the dissolution of intercellular junctions favoring the mesenchymal phenotype [29]. This transition is facilitated by activation of various pleiotropic transcription factors, namely Slug, Snail, Twist, Zeb1/2, FoxC2, and Prrx1 [30, 31]. This allows the migrating tumor cells to cross the basement membrane as well as the ECM, and intravasate into the blood or lymphatic vessels either as single entities or as clumps [32].

The migratory process involves the mechanical modulation of ECM by contraction and protrusion of the cells accompanied by degradation of the ECM by various proteases. Although the degradation of the ECM is the most common mode of migration of tumor cells, a protease independent mechanism is also known [33]. This mode involves the formation of invadopodia (actin-rich projections of cancer cells), which utilize protrusive and contractile forces to make their way through the ECM, indeed depending on the plasticity of the ECM components [33–35]. The role of macrophages in the initial stages of metastasis is also noteworthy. They have been shown to assimilate along the endothelium of blood vessels adjacent to the site of inflammation, and these macrophages secrete epidermal growth factor (EGF), which drives the chemotactic movement of tumor cells towards the vasculature as observed in breast cancer models [36]. The tumor cells exhibit EGF receptors on their surface and also secrete colony stimulating factor 1, which draws the macrophages and instigates them to secrete EGF and vice versa, thus forming a closed paracrine loop among themselves. This paracrine signaling results in modulation of the actin cytoskeleton in both tumor cells as well as macrophages, thus leading to the development of invadopodia in the migrating tumor cells and podosomes in macrophages.

The protease dependent mechanism followed by the migrating cells involves secretion of various MMPs responsible for the breakdown of several proteins involved in maintaining the integrity of the basement membrane and associated cellular parenchyma [37, 38]. The MMPs are also called as matrixins, and they belong to the metzincin superfamily of zinc-endopeptidases, which specifically cleave a variety of ECM components by proteolysis. Apart from the MMPs, other prominent members of this superfamily include A Disintegrin and metalloproteinases (ADAMs) and A Disintegrin and metalloproteinases with thrombospondin motifs (ADAMTS). MMPs are further categorized on the basis of their substrates into Collagenases, Gelatinases, Stomelysins, Matrilysins, Membrane-type MMPs, and other MMPs [37]. These MMPs cleave and degrade their respective substrates, thus facilitating the alteration of the ECM.

Moreover, the rapidly proliferating tumor mass also develops hypoxic conditions towards its core due to lack of proper blood supply, thus generating hypoxic conditions. Hypoxia mediated upregulation of lysyl oxidase (LOX) is also known to activate FAK and integrins, which further drive actin polymerization in the

invadopodia, thus enhancing the migration of these cells. The exploration of LOX functioning in breast cancer cells uncovered its essential role in recruiting various MMPs, viz. MMP 2, MMM 9, and MMP 14, thus potentiating the tumor cell motility [39]. Therefore, the cancerous cells invade through the ECM, cross the basement membrane, reach the nearest blood or lymphatic vessel, and proceed to intravasation.

10.4 Intravasation

The process of entering the lymph or blood vessels by the locally invasive cancer cells is known as intravasation, which marks the second step in the metastatic cascade. There are two known modes of dissemination of cancer cells: the hematogenous spread, which occurs via the blood vessels, and the lymphatic spread, which proceeds via the lymphatic system. Hematogenous spread of the carcinogenic cells is the most common mode of transmission in metastasis [4]. In order to intravasate, the presence of blood vessels in proximity to the tumor cells is mandatory. The tumor cells therefore induce neo-angiogenesis by secreting various chemokines, which induce the generation of nascent blood vessels. This vasculature generated by neo-angiogenesis is prone to leakage due to lack of basement membrane and unorganized perivascular layers. These haphazardly formed blood vessels thus lead to the irregular supply of nutrients and oxygen to the rapidly proliferating tumor mass. Additionally, these mal-developed vessels provide various growth factors and cytokines to the tumor-associated matrix but their leakiness also leads to a poor blood supply to the core of the developing tumor, thus rendering it hypoxic. Various transcription factors that are responsive to low availability of oxygen are thus activated, which bestow the tumor cells with the ability to survive these oxygen deficient conditions. One such key protein is the hypoxia inducible factor (HIF1α). HIF1α further activates various subordinate genes involved in angiogenesis and invasion such as Forkhead Box M1 (FOXM1) and vascular endothelial growth factor (VEGF), etc. [40]. FOXM1 is an oncogenic transcription factor that controls the expression of several downstream genes regulating metastasis. In fact, FOXM1 is also known to transcriptionally regulate VEGF, MMP 9, etc. [41]. VEGF is the most potent angiogenic factor involved in the production of new blood vessels [42]. Besides VEGF, activation of MMPs such as MMP 2, 9, and 14 further aggravates the invasive nature of the carcinoma cells [38]. MMP 9 leads to the release of the sequestered VEGF, thus making it available to bind to its receptor VEGF-R, which enhances the generation of defective endothelial blood vessels. Thus, the interplay between these various molecules leads to intravasation of the invasive tumor cells into the blood circulation, resulting in circulating tumor cells (CTCs). These CTCs upon survival within the blood vessels migrate into the distal target organs and form micrometastases (Fig. 10.2).

10.5 Survival in the Circulation

Upon entering the blood circulation, the majority of the CTCs die, either due to the stress of blood flow or due to the immune destruction. Thus, only 0.01% of the circulating cells survive to form secondary metastases even though tumor cells shedding into the vasculature provide an ample number of tumor cells to intravasate [43, 44]. Altogether, they spend a short time in transit through the blood vessels and usually get trapped into the first capillary bed which they encounter [45]. Prior to their entrapment, the CTCs encounter a plethora of cells in the circulation such as platelets, natural killer cells (NK cells), and various bone marrow cells during their travel to secondary metastatic sites. The CTCs are able to undergo remarkable changes in their nuclear and overall shape to fit into the capillaries [46]. They acquire various features that enable survival in the host circulation, such as loss of various immunogenic markers from the cell surface and elevated expression of certain immune-suppressive markers, thus enabling them to evade apoptosis mediated by NK cells and circulating macrophages [47]. The CTCs express tissue factor (TF) as well as P-selectin ligands on their surfaces, which lead to interaction and activation of platelets, respectively, while instigating coagulation as well [48, 49]. Platelets are known to play a critical role in the survival of CTCs in the circulation as their depletion by genetic manipulation or pharmacological inhibition in metastatic tumor models greatly reduces metastasis [50]. Stimulation of platelets by the CTCs also serves as a source of TGF-β, which suppresses the immunolytic ability of NK cells by diminishing the NKG2D receptor. TGF-β is also reported to act in concert with the platelets to induce the activation of nuclear factor kappa B (NF-κB) pathway in the CTCs, thus sustaining their EMT phenotype. The secretion of platelet derived growth factor by platelets is also known to enhance their survival in circulation [51–53]. Apart from this, the interaction of platelets with the CTCs forms a physical shield over them forming tumor-platelet emboli, which helps them escape the immune surveillance. The CTCs draw similar benefits from the neutrophils present in the circulation, for example, the formation of neutrophil extracellular traps (NETs), which are known to entangle the tumor cells in circulation, thus enhancing their survival and providing them apt surface to adhere to the endothelial cells and extravasate [54]. Formation of tumor-host cell emboli mediated via interactions of CTCs and immune cells not only prevents the metastasizing cells from immune destruction but also helps them to reach the destined secondary sites and extravasate. Apart from passive trapping of the tumor emboli into the capillaries, the adherence ability of these complex structures is also found, which enables them to adhere to vessels of larger than the capillary diameter. This active adhesion is mediated by various adherence molecules such as integrins, selectins, and metadherins, which are also contributed by the interacting platelets, leukocytes, and other stromal fibroblasts [55–59]. Therefore, CTCs survive the circulation and get blocked in the capillary beds, where they extravasate into the metastatic site and form micrometastases.

10.6 Extravasation

Following the course of the bloodstream, the CTCs either get arrested in the capillary beds within few minutes after entering the circulation due to the capillary diameter restriction or adhere to the EC surface mediated by various adhesion and cell signaling mechanisms. Extravasation is similar to intravasation, which requires the CTCs to cross the endothelial barrier and this phenomenon is referred to as transendothelial migration (TEM) [60]. Most of these extravasated cells then migrate to the PMNs but only a few survive and proceed to micrometastasis and colonization whereas most of them are destroyed by immune cells. While the tumor cell-platelet emboli arrest at the endothelial lining, the activated platelets release adenine nucleotides (viz. ATP), which interact and activate the P_2Y_2 receptors on the ECs. This interaction leads to downstream activation of protein kinase C and causes unlocking of the endothelial barrier [61]. As mentioned earlier, the interaction of CTCs with various cells in the blood circulation as well as the endothelium leads to the secretion of various other chemokines such as VEGF, MMPs, cyclooxygenase 2 (COX2), and C-C motif ligand 2 (CCL2). These chemokines alter the integrity of the vascular membrane, thus facilitating extravasation [60, 62]. Similarly, the lung tumor and stromal cells secrete CCL2 which recruits CCR2+ monocytes that facilitate extravasation [63, 64]. Furthermore, secretion of TGF-β by the CTCs is also known to stimulate secretion of Angiopoietin-like 4 (ANGPTL4), and promote vascular permeability in breast carcinoma cells [65, 66]. Most of these factors are also implicated in the formation of PMNs as well as facilitation of invasion and intravasation, thus implying the pleiotropic nature of these molecules in metastasis.

The employment of various bone marrow-derived cells (BMDCs) further aids in extravasation by inducing the expression of several cell surface markers on both the ECs as well as the CTCs. For example, the recruited neutrophils are known to induce expression of selectins, integrins, intercellular adhesion molecules (ICAM 1) on the ECs as well as the tumor cells, thus favoring cellular interactions [67]. These interactions, in turn, facilitate the movement of CTCs from the endothelial lining towards the PMNs. In fact, the expression of β1 integrin and FAK helps in forming filopodium like protrusions, which are required for the invasion of vascular endothelium. Apart from the common mechanism of TEM, CTCs have also been reported to skip the conventional mode of extravasation and proliferate in the vascular lumen itself, thus disrupting the endothelial barrier by the shear stress of proliferating tumor mass [55]. Interestingly, in 2016, Strilic et al. reported a previously unknown mechanism of extravasation in lung metastasis, wherein CTCs were shown to elicit controlled necrosis (necroptosis) in the ECs, thus disrupting the endothelial membrane [68].

10.7 Micrometastasis and Colonization

Certain sites in the human body are predisposed to metastatic growth. This predisposition also leads to organotropic metastasis in cancer, for example, the prostate tumor cells metastasize preferably to bone while cancer of breast colonizes bone, liver, brain, and lungs whereas colorectal cancers mostly metastasize to the liver. This propensity of various cancers to disseminate to various distant organs relies on the receptive environment provided by the PMNs.

10.8 Pre-metastatic Niche (PMN)

The primary tumor is known to send off certain chemokines (collectively known as secretome) to induce the formation of pre-metastatic niches at distant sites, thus enabling the disseminated tumor cells to colonize those tissues easily (Fig. 10.2). These factors stimulate the establishment of a suitable microenvironment in distant sites/organs that are amicable to the growth of secondary metastases prior to the arrival of metastasizing cells [8, 69, 70] (Fig. 10.2). This suitable microenvironment is also known as PMN. These PMNs are formed as a consequence of combined systemic efforts of the tumor secretome and extracellular vesicles derived from tumors. These secreted factors support a cascade of events culminating in the establishment of PMNs. Formation of anomalous blood vessels is the foremost event followed by modification of the local cell milieu and recruitment of various other cells such as BMDCs subsuming macrophages, myeloid cells, and hematopoietic progenitor cells to the target site which, in turn, attract the CTCs to the PMNs.

Tumor derived factor such as EGFR ligand epiregulin, COX2, MMP 1, MMP 2, MMP 9, ANGPTL4, VEGF-A, etc. are well observed to aggravate the loss of integrity of blood vessels in breast cancer [71]. These factors lead to the activation of FAK, which leads to disruption of inter-cellular connections among the ECs, thus facilitating the metastasis in breast cancer [62]. In fact, the activation of MMP 9 leads to the release of various sequestered cytokines, such as stromal cell-derived factor 1, which serves as a chemoattractant for CTCs [70]. The secretion of TGF-β is also reported to provoke the expression of ANGPTL4 and angiopoietin 2 in breast and lung tumor cells, respectively, thus increasing the permeability of blood vessels [65, 72]. Moreover, the secretion of chemokines such as CCL2 by both the tumor and stromal components leads to the recruitment of various BMDCs, which assist the CTCs in the process of extravasation as well as the formation of PMNs. CCL2 acts as a powerful chemoattractant for macrophages, NK cells, monocytes, and T-lymphocytes, thus functioning as a primary mediator of PMN formation and the metastatic colonization in various cancers [63, 73–75]. Apart from recruiting these cells, in order to promote an inflammatory environment in the PMNs, CCL2 is also known to suppress the immune ability of NK cells in breast cancer and melanoma models by hampering their maturation, thus shielding the CTCs from NK cell mediated destruction [76]. Another common regulator of inflammatory cues in

PMNs is the S100 family of proteins. They act both intracellularly and extracellularly to mediate the cross-talk between stromal cells and tumor cells during the configuration of PMNs. In the lung PMNs, expression of these S100 proteins on the endothelium layer is known to be instigated by various tumor secreted factors such as TGF-β, VEGF-A, TNF, and CD11b + myeloid cells [73, 77]. Similarly, HIF1 is also a crucial protein involved in the formation of PMN in various cancers [39, 78]. Studies encompassing breast cancer have demonstrated the increment in the shedding of extracellular tumor vesicles in a HIF dependent manner [79].

Apart from the chemokines secreted by tumor cells, extracellular vesicles (EVs) secreted by the tumor cells also play a substantial role in not only the establishment of PMNs but also carrying out metastasis. Tumor secreted EVs have been shown to carry genetic material (DNA and RNA), micro RNAs, proteins, and metabolites (fats and small metabolites), thus promoting PMN formation and disease progression [80, 81]. Surprisingly, tumor cells are known to exhibit amplified ability to secrete EVs, which is, in turn, boosted by hypoxic conditions [69, 79]. Various exosomes derived from the primary tumors display adhesion molecules on their surface such as integrin, which bind to ECM components and lead to the development of organotropic PMNs favoring organ-specific metastasis.

Facilitated by the PMNs, the extravasated cells then enter the secondary site, which is usually distant and has a different microenvironment as compared to the primary tumor site. Most of these cells persist as single disseminated tumor cells (DTCs) in the foreign tissue and either die or enter a state of dormancy, which eventually are either eliminated by the immune system or develop successful metastases [71, 82]. This period of dormancy can last up to days, weeks, or even years depending upon the availability of supportive signals and proliferative microenvironment. The state of dormancy is activated when the disseminated tumor cells fail to adapt to the new microenvironment or by the over-powering anti-proliferative signals in the secondary tissue or even by the failure to induce angiogenesis [83]. The patients who develop such dormant DTCs are designated to have minimal residual disease and are on the verge of greater risk of metastatic relapse. The dormant DTCs instigate certain signaling mechanisms to sustain in a quiescent state, such as the activation of AKT and SRC pathways by secretion of CXCL12 by the stroma in the metastatic niche. Upon metastasis to the bone, breast cancer cells have been shown to set off pro-survival mechanisms in response to CXCL12 secreted by the bone parenchyma [84]. These pro-survival pathways enable the DTCs to evade TRAIL-induced apoptosis as well as resist anoikis by further expressing tyrosine kinase receptor (TrkB) or by stimulating the non-canonical WNT pathway mediated by WNT2 [85]. The failure to interact with the ECM, and thus sensing the mitogenic cues also results in the induction of dormancy. For example, the DTCs undergo dormancy when they fall short to interact with the β1 integrin, which leads to the failure in stimulating the FAK mediated proliferative signaling [86–88]. Various such chemical interactions among the ECM and DTCs are also reported to induce a cell cycle exit into the G_0 phase, thus inducing a state of suspended growth [89]. The emergence of these indolent DTCs definitely requires favorable signals, which is distinct in different cancers. For example, the gain of

VCAM1 expression can activate the metastases of bone, by binding to the $\alpha_4\beta_1$ integrin receptor on the osteoclast progenitor cells, thus initiating colonization [90]. Similarly, the micrometastases in the lungs breakout of dormancy by expressing coco, which is an inhibitor of the bone morphogenetic protein (BMP) signaling thus potentiating metastatic colonization. These gains of function in the dormant metastatic cells indicate a low-level proliferation of the cells, which seems to be inevitable for the survival of DTCs. Acquisition of pro-proliferative signaling, mediated by MAP kinase, FAK, TGF-β, etc. is also known to enhance the colonization process as well [91].

10.9 Targeting Metastasis: Opportunities and Challenges

Metastasis is a highly unpredictable event, almost leading to the culmination of cancerous growth, making it certainly difficult to treat the cancer patients due to widespread mutations acquired by the metastasizing cells [92, 93]. Since metastasis is the major contributor to cancer related mortality, targeting metastasis provides a vast window of possibilities in dealing with cancer. However, by the time metastasis is detected in cancer patients, it has already spread to distant sites, which makes it a daunting target to follow [94]. Moreover, the involvement of various host cells, thus forming a heterogenous population that initiates and sustains metastasis is another major hurdle in pharmacological targeting of the metastatic cascade. Genetic instability forms the basis of neoplastic growth and the accumulation of these mutations with time makes it difficult to control metastasis. Increasing genetic instability confers the tumor cells with unprecedented variations which not only allow them to evade immune checkpoints but also survive under unfavorable conditions. Nevertheless, analysis of the metastatic cell karyotype and single cell studies have shown that these cells can originate from a single tumor cell potentiated by genetic variations [95, 96].

Since metastasis consists of a series of events, blocking the progression of any of these steps can be crucial in stopping it. While dealing with cancer metastasis, the majority of the therapies target the rapidly proliferating cells and associated mechanisms. Various anti-metastatic approaches have been enlisted below in Table 10.1. However, since the DTCs are known to be crucial purveyors of metastatic growth and relapse, specific approaches to target them should also be employed to obtain the recurrence-free survival of cancer patients. Different approaches to target metastasis have been employed, such as the inhibition of invasion promoting MMPs, thus curbing metastasis. The role of platelets in assisting CTCs to survive and extravasate has also garnered attention, thus the drugs targeting platelets have also been utilized against metastasis, although they do not reduce pre-existing lesions [115]. Following the entry into the blood, the CTCs have been proposed as markers of metastasis; however, these cells can also be targeted to prevent the establishment of metastases. With the advent of various techniques for isolating the CTCs from patient blood samples including the FDA approved Cellsearch® platform, various approaches to target them have been deployed

Table 10.1 Various inhibitors targeting different target molecules or pathways being used in treatment of metastatic cancer

S. No.	Name	Target molecule/ pathway	Clinical Status	References
1.	Bevacizumab (monoclonal antibody)	VEGF/angiogenesis	Approved by FDA for resistant ovarian cancer, glioblastoma, cervical cancer, colorectal cancer, metastatic lung cancer, and renal cancer	[97–102]
2.	Denosumab (monoclonal antibody)	Receptor activator of nuclear factor kappa-B ligand/osteoclast activation	Approved by FDA for glioblastoma, metastatic lung cancer, colorectal and renal cancer. Also approved for cervical, colorectal, and resistant ovarian cancer	[103, 104]
3.	Cetuximab (monoclonal antibody)	EGFR	Metastatic colorectal carcinoma, non-small cell lung cancer (NSCLC), and head and neck cancer	[105]
4.	Gefitinib/ Erlotinib (small molecule)	EGFR/downstream receptor tyrosine kinase pathway	Approved by FDA for metastatic NSCLC	[106]
5.	Dasatinib (small molecule)	SRC/ABL kinase	Approved by FDA for chronic myeloid leukemia (CML) and resistant acute leukemia (AL)	[107]
6.	Olaparib (small molecule)	Poly (ADP ribose) polymerase	Approved by FDA for metastatic breast cancer	[108]
7.	Lutetium Lu 177dotate (radioactive compound)	Somatostatin receptor	Approved by FDA for neuroendocrine tumors (GEP-NETs)	[109]
8.	Abiraterone acetate (hormone drug)		Approved by FDA for castration resistant prostate cancer in combination with prednisolone	[110]
9.	Abemaciclib (small molecule)	CDK4/CDK6	Approved by FDA for metastatic breast cancer	[111]
10.	Brentuximab vedotin (antibody drug conjugate)	CD30 antigen	Approved by FDA for classical Hodgkin's lymphoma in combination with chemotherapy	[112]
11.	Osimertinib (small molecule)	EGFR	Approved by FDA for metastatic NSCLC	[113]
12.	Trastuzumab deruxtecan (monoclonal antibody-drug conjugate)	Human epidermal growth factor receptor 2 (HER2)	Approved by FDA for unresectable and metastatic HER2 positive breast cancer	[114]

[116–118]. Since the diagnosis of cancer in its earliest stages is not possible, targeting the formation of PMNs does not sound to be a confident option. Surgical resection of primary tumors definitely reduces the tumor cell load as well as the clonal variants in the host body; however, a holistic approach, which can target multiples facets of metastasis simultaneously, seems to be the best option for now.

10.10 Role of Natural Compounds in Targeting Metastasis

Targeting metastasis in anti-cancer research has proved to be an effective approach to curb cancer. However, the use of anti-metastatic agents is associated with several adverse outcomes. Surgical removal of tumor is also not possible in every carcinogenic scenario, for instance, in leukemia. Similarly, radiotherapy also has its own limitations and cannot be used everywhere as a generalized anti-cancer approach. In such scenario, the use of natural compounds against metastasis has proven itself a boon for cancer patients. Recent years have witnessed a spike in the use of natural compounds in treating cancer, and this is further aided by the fact that utilization of natural compounds is considered safer with no or lesser side effects than any other anti-cancer approach. Therefore, a variety of natural anti-metastatic agents are being currently used against cancer. A few of recently used anti-cancer natural compounds are listed below in Table 10.2.

10.11 Conclusion and Future Perspectives

Metastasis is a life-threatening phenomenon, which is initiated by the primary tumor cells and it subsequently marks distant organs for the development of secondary tumors by forming PMNs. Although this cascade has been acknowledged as the basis of most cancer related deaths for several years, the precise mechanisms and molecules involved in the spatio-temporal regulation of this cascade are still incompletely understood. However, the active involvement of the host cells and chemokines with the tumor cell milieu has garnered considerable attention and appreciation in recent years. The utilization of host-derived factors and cellular components for metastatic dissemination demonstrates a remarkable interaction among the primary tumor cells and the metastatic niches. Additionally, the rebel nature of metastatic cells not only allows them to successfully evade the host immune system but also utilize it for their own propagation and survival. These characteristics also bestow these cells with the ability to resist various therapeutic agents targeting cancer. Thus, metastasis stands as a major challenge for the scientific community today in dealing with cancer and necessitates in-depth research in the coming years. Although a plethora of studies have shed light on various happenings that lead to the origin of primary tumors and subsequent establishment of clinically detectable metastases, still a lot of effort is needed to comprehend the cues leading to the initiation of metastasis and subsequent colonization of distant metastatic sites. Further dissection of the microenvironment alterations and

Table 10.2 Various natural compounds, their chemical class, source, molecular targets, and type of cancer where they are used

S. no.	Compound	Class	Source/Name	Molecular target(s)/	Type of cancer studied	Reference (s)
1	Evodiamine	Alkaloid	Plant/*Evodia rutaecarpa*	NFκB, MMP2, pERK1/2	Breast, colon, lung, melanoma and nasopharyngeal cancer	[119–123]
2	Hirsutine	Alkaloid	Plant/*Uncaria rhynchophylla*	MMP2/9, NFκB, ROCK1/PTEN/PI3K/GSK3β.	Breast cancer, lung cancer	[124–126]
3	Naringenin	Flavonone	Plant/citrus fruits.	VEGF, MMP2/9, AKT, mTOR, TGF-β.	Breast cancer, lung cancer, prostate cancer, pancreatic cancer	[127–131]
4	Genistein	Isoflavonone	Plant/*Genista tinctoria*	FLT4, MMP2/9, FAK, NFκB, ERK/PI3K/AP1	Lung cancer, prostate cancer, hepatocellular carcinoma	[132–135]
5	Myricetin	Flavonoid	Plant/*Myrica nagi*	MMP2/9, STAT3, PIM1/CXCR4, PI3K	Breast, cholangiocarcinoma, colon, esophagus prostate cancer, pancreatic cancer, medulloblastoma	[136–140]
6	Silibinin	Flavonoid	Plant/*Silybum marianum*	MMP2, vimentin, NFκB, Zeb1, SLUG, TGF-β	Lung cancer, prostate cancer, bladder carcinoma	[141–143]
7	Delphinidin	Anthocyanidin	Plant/ pigmented fruits and vegetables	ERK/p38MAPK, MMP9, NFκB, EGFR	Colorectal cancer, osteosarcoma, breast cancer, hepatocellular cancer	[144–147]
8	Shikonin	Naphthoquinone	Plant/ *Lithospermum erythrorhizon*	Integrin b1, ERK1/2, MMP2/9, GSK3β/β-catenin, RIP1/3, SIRT2	Prostate cancer, breast cancer, lung cancer, osteosarcoma, colorectal cancer	[148–151]
9	Sulforaphane	Isothiocyanate	Plant/ cruciferous vegetables	MMP2/9, pERK, MMP9, GSK3β/β-catenin, EGFR, TRAIL, BCl2/X_L and MCL1, COX2/MMP2/9/SNAIL/ZEB1	Lung cancer, prostate cancer, skin cancer, breast cancer, bladder cancer	[152–158]
10	Curcumin	Curcuminoid	Plant/*Curcuma longa*	NFκB, AP1, STAT3, MMP2/9, FAK, HLJ1	Breast cancer, lung cancer, prostate cancer	[159–161]

11	Paclitaxel	Diterpene	Plant/*Taxus brevifolia*	Tubulin, Aurora kinase/cofilin1	Breast cancer, lung cancer, glioblastoma, gastric cancer	[162–165]
12	Camptothecin	Alkaloid	Plant/ *Camptotheca acuminata*	DNA topoisomerase I	Ovarian cancer, colorectal cancer, lung cancer, pancreatic cancer, gastric cancer	[166–169]
13	Actinomycin D	Glycopeptide	Bacteria/ *Streptomyces* sp.	RNA polymerase I	Rhabdomyosarcoma, testicular cancer, Ewing's sarcoma, ovarian cancer, lung cancer, pancreatic cancer	[170–173]
14	Bleomycin	Glycopeptide	Bacteria/ *Streptomyces verticillus*	DNA strands	Squamous cell carcinomas, Hodgkin's lymphomas, and testicular tumor	[174–176]
15	Doxorubicin	Anthracyclines	Bacteria/ *Streptomyces peucetius*	Bcl2/Bax, topoisomerase I and II.	Breast cancer, acute lymphocytic leukemia, Kaposi's sarcoma	[177–180]
16	Vinblastine	Alkaloid	Plant/ *Catharanthus roseus*	Tubulin	Breast cancer, renal cell carcinoma, melanoma, lung cancer	[181–185]
17	Cytarabine	Anti-metabolite	Marine animal/ *Tectitethya crypta*	DNA replication	Acute myeloid leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma	[186–190]
18	Trabectedin	Alkylating agent	Marine animal/ *Ecteinascidia turbinata*	FUS-CHOP, IL-6, p-glycoprotein.	Liposarcoma, leiomyosarcoma	[191–193]
19	Brentuximab vedotin	Antibody drug conjugate	Marine/ *Dollabella auricularia*	CD30 antigen	Hodgkin's lymphoma	[194]

(continued)

Table 10.2 (continued)

S. no.	Compound	Class	Source/Name	Molecular target(s)/	Type of cancer studied	Reference (s)
20	Salinosporamide A	Bicyclic g-lactone b-lactam	Bacteria/ *Salinispora tropica*	NFκB, MMP9	Multiple myeloma and mantle cell lymphoma	[195–197]
21	Quercetin	Flavonoid	Plant/ cruciferous vegetables	MMP 2/9	Melanoma, oral cancer	[198]
22.	Carnosol	Polyphenol	Plant/ *Rosmarinus officinalis*	MMP 2/9	Melanoma	[199]
23.	Gambogic acid	Xanthonoid	Plant/*Garcinia hanburyi*	MMP 2/9	Adenocarcinoma, breast cancer	[200]

host-tumor interplay will not only allow us to understand the early events involved in metastasis but also will assist us to formulate specific and better therapeutic modalities against it.

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