Clin Exp Metastasis (2008) 25:171–181
DOI 10.1007/s10585-007-9130-6

REVIEW

The tumor cell–host organ interface in the early onset of metastatic organ colonisation

Peter Gassmann · Joerg Haier

Received: 15 June 2007 / Accepted: 15 November 2007 / Published online: 5 December 2007

Abstract Metastatic lesions are the leading cause of death among cancer patients. These lesions usually originate from clonal proliferation of single tumor cells dispersed from the primary tumor into the circulation which finally arrest in the capillary bed of distant organs. The microenvironment within the circulation of potential metastatic target organs provides a variety of pro- and anti-metastatic stimuli regulating the onset of organ colonisation by metastatic tumor cells. Mechanical shear stress, anoikis and cell mediated cytotoxicity within the microcirculation probably clear most circulating tumor cells. Adhesion, and eventually extravasation, are essential initial interactions of circulating tumor cells with distant organs and can provide escape from the cytotoxic environment within the circulation. Adhesion to the capillary wall is mostly controlled by the organ-specific availability of adhesion molecules on tumor cells, the endothelium, and the composition of the underlying extracellular matrix. The availability of pro-adhesive and pro-migratory paracrine signals provided by the organ specific microenvironment can further initiate the onset of metastatic organ colonisation. Tumor cell and microenvironment factors regulating survival within the microcirculation, adhesion and extravasation of tumor cells are highlighted in the review.

Keywords Metastasis · Organ selectivity · Microenvironment · Tumor cell adhesion · Extravasation

P. Gassmann (✉) · J. Haier
Molecular Biology Laboratory, Department of General Surgery, University Hospital Muenster, Waldeyerstrasse 1, 48149 Muenster, Germany
e-mail: Peter.Gassmann@ukmuenster.de

Introduction

Most patients dying from solid organ cancer are victims of metastatic cancer growth rather than local tumor progression. Lymph node and even more distant organ metastasis is the most relevant prognostic factor for patients with epithelial derived tumors and usually in other tumor entities. For example, UICC stage II colon cancer patients with locally limited tumor progression have a cancer-specific 5-year survival rate of ~75% or more while the cancer-specific 5-year survival decreases for UICC stage III patients with regional lymph-node metastasis to ~45% and for patients in UICC stage IV with distant organ metastasis to ~13% [1]. Similarly, although breast cancer is a much more heterogeneous disease the metastatic spread has the most important impact on patients' outcome [2]. The importance of hematogenous dissemination is also suggested by data showing that tumor cells in the blood or the bone marrow can have a strong prognostic impact [3].

During the progression of cancer disease, the colonisation of distant organs by circulating tumor cells marks the turning point from a localized, potentially curable disease, to a systemic, usually incurable disorder. At the same time, the growth of cancer metastasis appears not to be a matter of chance. Tumor cells usually show a remarkable preference to choose certain tissues and organs for formation of secondary tumor nodes [4]. For example, bones are the preferred metastatic sites for breast, certain lung and prostate cancer, but rarely a target for colorectal cancer. The adrenals are a typical metastatic target for small cell lung cancer but rarely affected by kidney cancer [5]. This organ distribution indicates that metastasis formation is a highly orchestrated, multi-step process rather than random proliferation at distant sites.

The whole process has been outlined in the literature as the 'metastatic cascade', a series of well defined interrelated steps leading to the formation of a clinically overt metastatic lesion. All of these steps must be completed, and failure of any step usually results in metastatic insufficiency [6]. Although most models or pathways of metastasis formation, respectively, use more or less linear follow-up of the cascade [7], this tumor progression should be considered as a network of mostly physiological processes occurring in a pathologic context. This network's control mechanisms of feedback loops and regulated steps left the physiological range of function. Some of these aspects will be discussed below. As a consequence dissection of single steps or mechanisms of metastatic progress, respectively, has to consider this problem and limits their applicability for individual human beíngs, which is a known problem in the clinical situation.

The metastatic cascade is likely initiated by epithelial-mesenchymal transition (EMT) that enables stationary, polarized epithelial cells to migrate, invade surrounding tissues and eventually detach from neighbouring cells and their microenvironment [8]. Although the molecular bases of EMT have not been completely elucidated, several interconnected transduction pathways and a number of signalling molecules potentially involved have been identified. These include growth factors, receptor tyrosine kinases, Ras and other small GTPases, Src, beta-catenin and integrins, which are frequently or exclusively, related to cell adhesion and migration processes. Most of these pathways converge on the down-regulation of the epithelial molecule E-cadherin, an event critical in tumour invasion and a 'master' programmer of EMT [9–11]. This local invasion is usually followed by intravasation into blood and/or lymphatic vessels and dispersion of the tumor cells into the systemic circulation. Survival within the circulation and resistance to anoikis of single, circulating tumor cells or small cell clusters, enable the arrest of these cells within the microcirculation of potential metastatic target organs and eventually extravasation into their parenchyma [6, 13]. Tumor cells may then either be cleared by local defence mechanisms [12] or they escape these host defence mechanisms, sometimes entering a state of dormancy. Subsequently, surviving tumor cells can also undergo clonal proliferation and initiation of neo-angiogenesis to form clinically overt metastatic lesions [6, 13].

At least since James Ewing [14] challenged Stephen Paget's [15] 'seed-and-soil' concept in the early 1930s, the mechanisms of tumor cell arrest in distant organs is a matter of debate. Indeed, cancer cells dispersed from colorectal cancers, for example, draining via the potal vein into the liver likely give rise to liver metastases, later followed by lung metastases. Futhermore, examining autopsy data, Weiss et al. found an association of metastatic incidence and organ blood flow consistent with the mechanical hypothesis of metastatic pattern [16]. However, both hypotheses are not mutually exclusive. Tumor type specific distribution of metastatic growth cannot solely be explained by anatomical considerations of blood supply in most cases. An extraordinary example for the organ specific metastatic capacity comes from observations in women with peritoneal carcinomatosis from ovarian cancer, whose ascites has been surgically drained into the venous circulation. Although viable tumor cells gained access to the systemic circulation, autopsy studies revealed that lung metastasis (the first capillary bed the drained cells reached) were found only in a minority of patients. Furthermore, tumor cell deposits in the lung did not often develop into clinically relevant lung metastases [17, 18].

Virtually any step of the metastatic cascade, is potentially regulated in an organ specific manner. Some of these pathways may provide redundant routes for successful metastasis formation. From the basis of the traditional 'seed and soil' hypothesis, several concepts were developed to emphasize the organ specific character of different steps of the metastatic progression. The 'adhesion theory' stresses the role of organ specific adhesive interactions of tumor cells in the capillary bed of potential target organs. In analogy to the homing of leukocytes into specific organs and sites of inflammation by chemotactic migration, the evolution of the 'migration' or 'chemotaxis theory' was triggered by the discovery of chemokine receptor expression in tumor cells and their role for organ specific metastases formation [19]. Furthermore, the "growth factor theory" emphasises the organ specific availability of growth factors and their receptors supporting survival and proliferation of metastatic tumor cells colonizing distant organs.

We will further highlight the tumor cell–host organ interface with respect to cell adhesion and extravasation as very early, 'kick-off' events for the colonization of distant organs by circulating and metastasizing tumor cells.

Shear stress and other mechanical forces in the circulation

The circulation itself represents a highly toxic environment for disseminating tumor cells. Mechanical destruction of circulating tumor cells is the first line of defence in the host microenvironment acting against hematogenous cancer spread. Although even small tumors can release a large number of tumor cells into the circulation [20, 21] the vast majority of tumor cells are rapidly cleared from the circulation. Cancer cells circulating in the blood are subjected to intense mechanical stress by shear forces caused by blood flow. Especially in narrow capillaries required

sphere-to-cylinder shape-transformation is lethal to a majority of tumor cells [22–25]. The same holds true for the deformation within the microvasculature of contracting skeletal and heart muscle [26, 27].

These shear forces acting on tumor cells are very intense in small capillaries. At the same time this deformation of circulating cells within narrow capillaries enables intense contacts of the tumor cell surface's adhesion molecules with potential ligands at the capillary walls and tumor cell adhesion may be initiated. This is caused by enlarged contacting surface areas of deformed cells resulting in increased availability of cell adhesion molecules and longer time for the establishment of adhesive bonds. In addition, close contact between these cell adhesion molecules and their potential ligands at the microvessel surface enable binding of adhesion molecules with shorter extracellular domains, such as integrins with higher mechanical resistance, that also supports the formation of initial and/or stable interactions [28]. This is supported by the observation, that microtubules and actin filaments are involved in the regulation of initial adhesive steps during distant metastasis formation. Actin disruption with resulting enhanced deformability led to an increase in the numbers of adherent tumor cells similar to lymphocytes and monocytes [29, 30]. In contrast, disruption of microtubules with increased cellular stiffness inhibited early adhesive interactions between circulating tumor cells and host organ microvasculature [31].

Shear stress, however, is not only a potentially lethal environmental condition for tumor cells. Shear forces and tension alone can induce functional reactions in circulating tumor cells, but also in leukocytes, platelets, or endothelial cells (EC) [32, 33]. For example, these mechanical forces can activate intracellular signalling cascades, such as focal adhesion kinase [31, 34]. Moreover, the organization and structure of cytoskeletal components, such as actin, can also be modified by external forces [35]. Since integrins appear to be directly involved in early steps of metastasis formation [41, 42], cell signalling and regulatory processes that modulate their affinity and/or avidity may therefore influence metastatic tumor cell adhesion or migration into host organs at ECM components [36].

Therefore, the tumor cells' balance between mechanical destruction and adhesion initiation by biophysical forces appears to be a regulatory mechanism for hematogenous cancer spread.

The role of tumor cell adhesion and migration for metastasis formation

Epithelial and mesenchymal cancer cells are usually adhesion dependent and their occurrence within the blood circulation can initiate anoikis, a special form of apoptosis due to the lack of adhesion. Therefore, anoikis limits the available 'circulation time' of cancer cells and their resistance to this process can act as an additional rate limiting factor within the metastatic cascade. The most effective way for a circulating tumor cell to escape this initiation of cell death is the establishment of adhesive interactions within metastatic target organs [37]. Importantly, tumor cell adhesion appears to be limited to the capillary bed of potential metastatic target organs with the suitable microenvironment for their survival whereas their adhesion to large vessel walls seems to be negligible in vivo (Fig. 1).

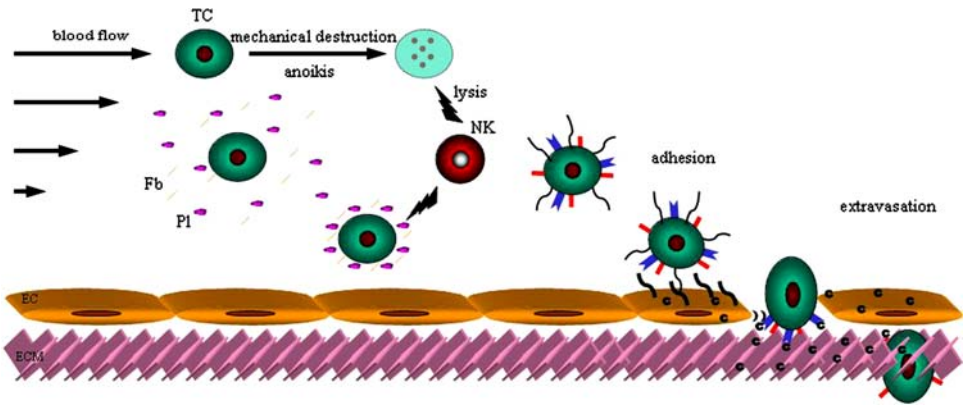

Fig. 1 The circulation provides a cytotoxic environment for metastasising tumor cells (TC). Circulating, non-adherent tumor cells may be destroyed by mechanical forces within the circulation or may undergo anoikis due to the lack of adhesive interactions. Platelets (Pl) and fibrin (Fb) associate with tumor cells and protect them against the attack of natural killer cells (NK) and may also facilitate adhesion to the endothelium. TC adhesion to the microvasculature may be initiated by adhesive interactions with endothelial cells (EC) mediated by sialylated selectin ligands, for instance, but can also take place by integrin mediated adhesion to the extracellular matrix (ECM), that may be directly accessible due to a fenestrated endothelial lining (e.g. liver) or can be exposed after TC induced retraction of EC. EC and ECM present chemotactic chemokines (C), inducing migration and extravasation of TC

Very recent as well as historic work is still challenging the concept of specific tumor cell adhesion at the capillary system of distant metastasis target organs. Especially intravital fluorescence microscopy revealed conflicting results with respect to the underlying mechanisms of tumor cell arrest within the capillary bed of distant host organs. For example, mechanical arrest of rat colon carcinoma cells by size restriction within the liver was described using intra-vital fluorescence microscopy by different groups in murine models [38–40]. Using similar systems, other laboratories found specific tumor cell adhesion to capillary walls and particularly defined involved sets of adhesion molecules [41, 42]. For example, biological behaviour of fluorescence labelled colon carcinoma cells entering the hepatic microcirculation has been monitored by in vivo microscopy of the liver after injection into rats. Single tumor cells entering the sinusoids were found passing the microcirculation without any sign of mechanical arrest, but other tumor cells were able to establish stable adhesions at the sinusoidal capillary wall leaving a remaining perfused vessel lumen [43]. Similarly, integrin mediated adhesion of human HT1080 sarcoma cells to laminin-5, a component of the basement membrane underlining pulmonary endothelial cells [44], demonstrated specific interactions of these cells with pulmonary microvessels not requiring vessel occlusion [45].

In contrast, using different technical applications of intravital microscopy, various studies demonstrated initial arrest of melanoma, CHO, and colon carcinoma cells that appeared to be due to size restriction, based on measurements of cell and vessel diameters [38, 46, 47].

Since these investigations rely on the relationship between diameters of the microvessels and tumor cells, their deformability and biophysical factors, the choice of model systems may have severe impact on the observed cellular behaviour. For example, site of injection, number of tumor cells per blood volume, investigated animal species (rat, mouse, rabbit) compared to the origin of the tumor cells (human, rat, murine) and some technical aspects of the microscopic techniques can also severely impact intravital observations of circulating tumor cells.

Tumor cell interaction with blood components

Morphologic observations showed tumor cells closely associated with platelets arrested in the microvasculature and much evidence indicates that circulating tumor cells can also interact with leucocytes and/or the coagulation system. Early work from the 1970s and 1980s showed that platelet–tumor cell interaction can facilitate metastatic spread in vivo [48]. For example, genetically induced platelet dysfunction impaired experimental metastasis formation in a syngenic mouse model using Lewis lung carcinoma and B16-BL6 melanoma cells [49].

Specific adhesive systems seem to provide selective mechanisms for these interactions. The altered surface glycosylation is a common feature of carcinoma cells and notably in epithelial cancer cells with high expression of sialyl Lewis$^{a/x}$ as selectin ligands has been associated with poor prognosis [50, 51] suggesting a potential role of these cell adhesion molecules in the metastatic process. The adhesion of platelets and tumor cells seems to be mainly mediated by P-selectin and sialyl Lewis$^{a/x}$ on the tumor cells' surface, but other non-mucin ligands. Glycoproteins and integrin $\alpha_{IIb}\beta_3$ (GpIIb/IIIa) may also be involved [52, 53, 55]. While inhibition of P-selectin mediated adhesion of tumor cells and platelets impaired metastasis formation of syngenic MC-38 colon and Lewis lung carcinoma cells in a mouse model [46, 47] their adhesive interactions are not limited to these direct contacts.

The aggregation of platelets around tumor cells can also involve thrombin and fibrin. For example, addition of thrombin and activated platelets can stimulate adhesion of melanoma cells in mice with PAR-4 deficient platelets. Their platelets are usually unable to respond to thrombin resulting in a reduced ability to support melanoma metastasis [54]. Furthermore, the inhibition of platelet aggregation using heparin that potently inhibits P-selectin, or using the GpIIb/IIIa antagonist XV454 [55] can impair experimental metastatic spread of tumor cells. However, clinical trials using the anticoagulant Warfarin acting in a different, platelet independent way failed to improve patients' outcome. Interestingly in experimental settings platelet inhibition only reduced the number of metastatic lesions but did not affect organ distribution or size of the metastatic foci. Moreover, the anti-metastatic effect of platelet inhibition using heparin was limited to the initial 5 h after tumor cell inoculation [53]. This indicated that platelets are able to interfere with early events of organ colonization [46].

Activated platelets in concert with thrombin can also enhance melanoma tumor cell adhesion to EC and subendothelial matrix components like fibronectin and vitronectin [56, 57]. There is evidence that platelet derived 12(S)-HETE, a lipoxygenase metabolite of arachidonic acid, may promote tumor cell extravasation by induction of enhanced EC retraction, a prerequisite for tumor cell extravasation and escape from the toxic intravascular environment [58].

The role of platelets in the metastatic network, however, is not limited to proadhesive processes. A very effective innate defence mechanism of potential metastatic host organs against their colonization are Natural Killer (NK) cells that can effectively clear tumor cells arrested in capillaries by lysis following close physical contact [59]

(see below). Aggregating platelets and fibrin meshworks can form a potent shield around metastasizing tumor cells that seems to prevent this contact with NK cells and, therefore, early clearance of the tumor cells within the microvasculature of host organs [46, 60].

For arrest in the capillary bed of target organs tumor cells can also 'hijack' polymorphnuclear neutrophils (PMNs) to enhance their metastatic capacity. Many tumor cells express inter-cellular adhesion molecule-1 (ICAM-1) to a certain extent enabling them to adhere to PMNs during their presence in the blood circulation. In vitro this heterotypic cell adhesion promoted tumor cell arrest to EC due to indirect recruitment of PMNs' adhesion molecule repertoire. For example, C8161 melanoma cells, deficient of sLe^X or other sialylated glycoproteins, express ICAM-1. Using heterotypic adhesion via ICAM-1 and β2-integrins these cells can recruit PMNs' E-selectin ligands for indirect adhesion to ECs [60–62]. Additionally, co-cultured PMNs also promoted transendothelial migration of tumor cells In vitro [63], a process influenced by shear forces of fluid flow as well [62]. Furthermore, human LS180 colon carcinoma cells express mucin-type sialylated proteins enabling heterotypic adhesion to ECs, platelets and leukocytes via E-, P- and L-selectins, respectively [64, 65]. P-selectin and L-selectin deficient mice were less susceptible to experimental metastasis from LS180 colon carcinoma cells than wild-type mice [53].

Natural killer cells (NK) and Kupffer cells (KC) in the liver

Discovered in rat liver in the 1970s [66], natural killer cells (Pit cells) have proven to lyse many types of tumor cells in vitro and to reduce metastasis formation in vivo. NK cells are found in the liver, blood and bone marrow. Upon challenge by melanoma cells, NK cells have been found to redistribute to liver and lung. After tumor cell injection an 80% increase in the number of NK cells in the lung was observed within 60 min that normalized after 210 min. [67]. Similar results with a somewhat longer time interval were reported for liver NK cells upon colon cancer challenge [68]. NK cells obviously act through different pathways to eliminate tumor cells in host organs. They were shown to induce apoptosis in rat colon carcinoma cells by the perforin/granzyme pathway following granule exocytosis [69, 70] or the FAS/FAS-L pathway [71] in vitro within a few hours. But recently also perforin and interferon-gamma independent elimination of melanoma cells was demonstrated in vivo [67]. It has been known for a while, that NK cell activity can reduce liver and lung metastasis from melanoma and Lewis lung carcinoma cells in mice by acting during extravasation and/or the early post-extravasation period [72]. For example, Timmers et al. [12] showed that Pit cell activity cleared the majority of intravascularly located colon carcinoma cells reaching the liver within 6 h. Grundy et al. [67] described the elimination of the majority of injected cells in mice lungs in vivo within the initial 60 min. at which most NK cells were present within the lungs. In these, and in other studies [73, 74], NK cell elimination was associated with increased metastases formation.

Kupffer cells (KC), liver residing macrophages located within the sinusoids, were also observed in close contact with NK cells and tumor cells [12]. They also exhibit efficient cytolytic activity against tumor cells in vitro [75, 76], but are also an important sources of chemotactic mediators for tumor cell extravasation (see below). For example, KC depletion resulted in reduced metastasis formation in the liver in a syngenic murine colon carcinoma model [77].

NK cells and KC seem to act synergistically in this first line defence mechanism. The contribution of the single cell population to tumor cell elimination seems to be target dependent [12, 73]. On the other side, these cells can be utilized by circulating tumor cells for initial steps of metastasis formation pointing to a bivalent role of KC and NK cells.

Tumor cell–endothelial cell interactions

Initial arrest and attachment of circulating tumor cells in the secondary organs are believed to be crucial events for hematogenous metastasis, but the actual processes under living conditions remain a matter of debate. The adhesion of microvascular ECs and circulating tumor cells represents an initiating event of organ colonisation. As blood vessels are generally lined with endothelial cells, circulating tumor cells, similar to leukocytes, can utilize endothelial cell specific adhesion molecules, such as selectins or intercellular adhesion molecules (ICAM's), to interact with these cells before they touch the underlying basement membrane in the further course of extravasation. For example, the expression of ICAM-1 on pulmonary endothelial cells after stimulus and subsequent binding of neutrophils is a first step leading to lung injury. A similar process may dictate the binding of tumor cells to the pulmonary endothelium during metastasis formation [78]. Hence, also endothelial cell surface molecules may play a role in organ-specific settlement of tumor cells [36]. For example, inhibition of tumor cell adhesion to endothelial cells by anti-TF (Thomson–Friedenreich factor) resulted in increased survival in a mouse model for spontaneous breast cancer metastases without impairing tumor cell proliferation [79].

Real-time intravital microscopy analysis of circulating tumor cells revealed a very rapid arrest in sinusoidal vessels near terminal portal venules within 0.4 s after cell injection, but in contrast to leucocytes, no evidence of a "rolling"-like movement along EC surfaces was observed for various tumor entities [43, 80]. In addition, other authors reported that adhesion of colon cancer cells to sinusoidal endothelial cells of the liver was never observed. Instead, ECs retracted rapidly and interactions were observed only between cancer cells and hepatocytes [40, 81]. Microscopic studies revealed trans-endothelial tumor cell projections indicating interactions of these cells with underlining extracellular matrix. Furthermore, tumor cells can induce apoptosis of endothelial cells, but also increase their E-selectin surface expression, in turn, facilitating further tumor cell adhesion to the endothelium [82]. These functional in vivo studies demonstrate that adhesive interactions of tumor cells and ECs likely initiate organ colonisation, but have a more transient character. There are obviously not morphologic correlations for these functional, transient events. In addition, several reports indicated that tumor cells can induce production of cytotoxic nitric oxide (NO) by endothelial cells and thereby functioning as a host organ defence mechanism [83].

The interactions between circulating tumor cells and ECs are influenced by many other factors that are beyond the scope of this review. The organ specific distribution and characteristics of the latter cells, however, are undoubted determinants or, at least, important cofactors for the successful colonization of distant host organs during metastasis formation [84].

Tumor cell–matrix interactions

Interactions of cells, both tumor cells and host tissue cells, with the extracellular matrix (ECM) play a pivotal role in many of the aforementioned phenomena of tumor progression, such as anchorage-(in)dependent growth, any step of the metastatic cascade/network and angiogenesis [85]. Cellular contacts with the ECM are mediated via various cell adhesion molecules [86], among which are integrins, members of the immunoglobulin superfamily, cadherins [87], and membrane-bound proteoglycans, such as syndecans and glypicans [88].

Besides quantitative modulation of the expression of a number of cell adhesion molecules, qualitative alterations of their activity and affinity can provide oncogenic mechanisms for the aquisition of aggressive (metastatic) phenotypes and prediction of the metastatic pattern [89].

Integrin-mediated interactions of tumor cells with ECM components appear to be among the most important determinants for organ-specificity of the metastatic process and are sometimes referred to act as oncogenes or tumor suppressor genes [90, 91]. The expression of various integrins is altered on tumor cells compared to normal tissue cells [92]. However, it is not clear whether this "integrin switch" in primary tumor cells is a consequence or a cause of malignant transformation. Nevertheless, several experimental data corroborate the view, that certain integrins, such as $\alpha 5\beta 1$ [93], indeed may change the growth behaviour, neoangiogenesis and anchorage independent survival (anoikis) of normal cells and therefore act as oncogenes or tumor suppressor genes. Some of these transformed functions are directly or indirectly related to the metastatic process. However, none of the integrins is currently considered as a metastasis supressor gene in contrast to the cell adhesion molecules E-cadherin that is involved in EC interactions (see below) [94].

One way in, which integrins interfere with metastasis, is their regulatory effect for tumor cell motility. For example, the integrins $\alpha 2\beta 1$ and $\alpha 3\beta 1$ seem to play a role in oncogenic transformation and metatasis formation [95, 96]. Contradictory results about their involvement may be explained by the dual role of integrins with impaired cell adhesion at the primary site and requirement of new ECM–tumor cell interactions for colonization of distant organs. Furthermore, integrins allow tumor cells to settle in tissues with an ECM composition different to their home tissue [97, 98].

Integrins not only transmit signals from the ECM into the cells and vice versa, but also provide important anchorage points for the cells. They are the basis for static cell adhesion, contraction of the pericellular ECM and cell migration [99]. Primary tumors can scatter single cells as well as cell clusters [20], that also may dissociate under flow physiologic flow [100]—a condition that can influence their ability and mode of cell motility. As opposed to the mostly integrin-mediated fibroblast-type of migration with formation of filopodia and lamellipodia, tumor cells can also migrate independently of integrins, resulting in an amoeboid type of migration [101]. Similar to the protozoic amoeba, these cells migrate through the meshwork of ECM-molecules, without establishing firm adhesions or getting in close contact to them [102]. However, the role and extent of amoeboid motility has been investigated for primary tumor progression in skin chambers and in vitro [103], but not in metastatic target organs.

As the liver sinusoids contain fenestrated endothelial layers circulating tumor cells may directly contact the ECM of the Dissés space, a potential mechanisms for liver tropism for metastatic colonization by many tumor entities [104]. Liver metastasis formation may therefore be possible by direct integrin-mediated interactions of tumor cells with the stromal liver ECM [41, 42]. For example, investigating adhesive and invasive interactions of circulating

human colon carcinoma cells within the hepatic microvasculature by intravital fluorescence microscopy our group could show that their adhesion within the liver sinusoids appears to be mediated not only by the selectin ligand sialyl-Lewis$_a$ (sLe$_a$) but also by the integrins $\alpha6\beta1$ and $\alpha6\beta4$ [41]. Furthermore, $\alpha v\beta5$ and $\alpha v\beta6$ seem to be of paramount importance for this metastatic tumor cell adhesion [42]. In contrast, for the subsequent extravasation and invasive migration into the liver parenchyma, the $\alpha2\beta1$ integrin, but also the integrins $\alpha1\beta1$ and $\alpha6\beta4$, appear to be necessary, whereas inhibition of αv-integrins did not affect this step of metastasis within the liver [41, 42].

For CHO cells $\alpha v\beta3$ integrins may function to promote extravasation in the liver through a process possibly mediated by vitronectin produced by this organ [105]. Melanoma cells seem to prefer $\alpha v\beta3$ integrin-mediated cell adhesion when colonizing lymph nodes [106] Mediating adhesion and migration on ECM components of the bone, this integrin may also govern the metastatic colonization of bones as a specific target for metastases of breast and prostate carcinoma [107–109].

Not only tumor cells have an altered expression of cell adhesion molecules, but also the stromal ECM of metastatic sites usually differs from the one surrounding the primary tumor and that of healthy host organs. Corresponding to the specific expression of binding molecules at tumor cell surfaces the composition of ECM components in different potential host organs can determine the availability of adhesive interactions as prerequisites for metastatic colonization. For example, various types of the collagen family, different laminins, fibronectin and vitronectin provide adhesive ligands in an organ-specific matter [88, 110]. Additionally, soluble matrix proteins, such as osteopontin [111, 112], hyaluronectin [113] or sialoprotein [114], among others, can also participate in these adhesive interactions. Additionally, the stroma contains a variety of paracrine factors, such as growth factors, cytokines and hormones, many of which are associated with ECM molecules and are released from their storage sites by highly regulated cleavages of the ECM molecules that can be initiated by metastasizing tumor cells. Both the growth factors and the ECM components which regulate their availability result in a very specific microenvironment for every tissue. Thus, not only haptotactic but also chemotactic cues may account for the tissue-specific metastasis formation. For example, the bone marrow stroma-derived ECM molecule osteonectin acts chemotactically on breast and prostate cancer cells, both of which commonly metastasize in bone, but is not chemotactically functional on tumor cells which do not colonize bones [115].

In the liver, fibronectin and type IV collagen appear to provide the matrix for initial tumor cell arrest, whereas type I collagen that branches from the space of Dissé between hepatocytes in the liver parenchyma seems to act as guide for colon and hepatocellular carcinoma cell extravasation (unpublished data). In contrast, for early arrest of HT1080 cells in the pulmonary vasculature interactions of $\alpha3\beta1$ integrins with laminin-5 in exposed basal membranes can provide both a molecular and structural basis for cell arrest during pulmonary metastasis [116].

A hallmark of malignant tumor cells is their ability to penetrate tissue barriers including distant organ sites which are otherwise cell-impermeable, especially the basement membrane. However, although differences between various organs may be related to metastatic patterns these processes are not specific for secondary tumor colonization. The role of various proteases for invasive phenotypes is beyond the scope of this review and reviewed elsewhere [117, 118].

Chemokines regulate tumor cell "homing"to metastatic sites

Chemokines are small, pro-inflammatory cytokines that are involved in a variety of immune reactions including infection, inflammation, and tissue repair [119]. In addition, they play a significant role in trafficking of several cell types during embryogenesis [120]. First data on chemokine receptor expression on epithelial cancer cells came from Youngs et al. [121] when they initially described chemotactic response of human breast cancer cells to a variety of chemokines and from Müller et al. [19] when this group first demonstrated in vivo that the functional expression of the chemokine receptors CXCR4 and CCR7 governed experimental breast cancer metastasis to lung and lymph nodes. For example, human MDA-MB 231 breast cancer cells respond to the CXCR4-ligand CXCL12 (SDF-1α) by directed migration (chemotaxis) and this ligand is highly expressed in typical breast cancer metastatic sites like lung, liver, and lymph nodes. Subsequently CXCR4 revealed to be the most prominent chemokine receptor on solid cancer cells but other receptors, such as CCR6, CCR7, or CXCR3, have also been associated with the organ selectivity of cancer metastasis formation in different models and clinical observations [122].

Chemokines can exhibit multiple actions on tumor cells. Via expression of their receptors cancer cells can mimic, in part, lymphocyte behaviour [123, 124]. For example, CXCR4 has been demonstrated to be relevant for the outgrowth of syngenic CT26 colon carcinoma micrometastases rather than the colonization of the mouse liver [125]. In contrast, Cardones et al. [126] showed that CXCR4 inhibition can impair lung metastasis formation of melanoma cells only when administered in the early phase

of organ colonization. In a similar way, the colonization of the liver by mouse plasmocytoma cells appears to be regulated by the chemokine receptor CCR6 [127].

Upon chemokine stimulation small cell lung cancer cells (SCLC) exhibit facilitated adhesion to bone marrow stoma cells by integrin activation, chemotaxis and matrix invasion [124]. For example, CXCL10 significantly up-regulated invasion-related properties in colon carcinoma cells. This chemokine promoted MMP-9 expression and induced cell adhesion to and migration at laminin-1 [122]. In breast cancer cells activation of CXCR4 resulted in phosphorylation of focal adhesion kinase (FAK) and RAFTK/PyK2, key signalling proteins that interact with Src and PI3-kinase during cell adhesion and migration, among others. These signalling events can result in increased adhesion to endothelial cells or matrix components, such as fibronectin, and they can mediate tumor cell invasion via secretion of degradative enzymes, such as MMP-2 and MMP-9 [128, 129].

In metastatic target organs chemokines are presented in various ways with usually organ specific patterns of ligand availability. Organ specific ECs and tissue related macrophages, such as Kupffer cells in the liver, appear to be the most important sources of the chemokines that can mediate metastasis formation within various organs. For example, bone marrow stroma cells are dominant sources of CX CL12 that mediates integrin activation, adhesion and migration of various tumor cells through bone marrow endothelium [124, 130]. Lymphatic endothelial cells that express CCL21 as ligand for the chemokine receptor CCR7 seem to be responsible for metastasis formation of mouse melanoma cells to regional lymph nodes after injection into the footpad [131]. In addition to endothelial cells lining the capillary wall of target organs, chemokines can also be presented to circulating tumor cells by extracellular matrix components, such as fibronectin, where these ligands can be immobilized comparable to other paracrine factors (e.g. growth factors). At least in T-cells, this type of chemokine presentation induces cell polarization and migration events even without the establishment of a concentration gradient [132]; similar mechanisms can be also assumed for tumor cells.

Conclusion

The adhesive interactions between metastasizing tumor cells and potential target organs have to be considered as important and rate-limiting parts of the tumor progression processes that finally result in the formation of distant metastases. This interface is involved in a number of various steps acting in a concert and mostly relying on each other. Therefore, we suggest to consider the metastatic process more as a network than a straight cascade. The intense effort to understand this network has brought some clinically relevant novelties, such as anti-integrin treatment [133] or chemokine targetting [134], among others. The complexity and interrelationships between the various aspects of the metastatic process, however, are still only partially understood and may require improvements of the models used for their investigation.

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