Pathogenic Features of Liver Metastasis: Mechanisms Involving Platelets, Tumor Stroma, Epithelial-Mesenchymal Transition, and the Premetastatic Niche

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Abstract

Homing of circulating cells to pre-metastatic niches of the liver and their subsequent growth to a metastasis requires a complex interaction between tumor cells and various normal cellular and matrix components of the future metastatic site. In the course of homing to endothelial surfaces of hepatic blood vessels and vascular invasion, tumor cells interact with platelets and induce platelet adhesion and aggregation. Tumor cell-induced thrombocyte aggregation facilitates early steps of metastasis through increased tumor cell arrest and formation of tumor cell emboli. Platelets participating in tumor cell aggregates promote cell adhesion and invasion and release growth factors for cancer cells. Following their exit from blood vessels, tumor cells engage in complex interactions with stromal cells. The stromal microenvironment profoundly influences growth and invasion of tumor cells in the metastatic site. Stromal cells interacting with tumor cells include cancer-associated fibroblasts and myofibroblasts, vascular cells, tumor-associated macrophages/TAMs, myeloid suppressor cells, and other cells of local immune responses. Cancer cells in turn constantly modulate the cellular composition of stroma, promote angiogenesis, and are subject to epithelial-mesenchymal transition.

Platelet Interactions, Platelet Aggregation, and the Formation of Tumor Metastasis

Introduction

In the course of vascular invasion and the associated endothelial cell damage, cancer cells having contact to streaming blood can induce platelet homing and thrombocyte aggregation. These thrombocyte aggregates, being in contact with the subendothelial space following endothelial cell loss, form a distinct niche for tumor cells that promotes growth and the formation of metastases. Tumor cell-induced platelet aggregation facilitates hematogenous metastatic spread by increasing the arrest of tumor cell clusters and tumor cell emboli in the microcirculation and is also involved in differential homing of platelet-tumor cell aggregates to distinct vascular beds (reviews: Honn et al. 1992; Tsuruo and Fujita 2008; Sharma et al. 2014). Generally, platelets can exert pro-metastatic effects. Platelet-tumor cell interactions are sufficient to prime tumor cells for subsequent metastasis, involving TGF-beta/Smad and NF-kB pathways via platelet-derived TGF-beta (Labelle et al. 2011). Platelets possess a complex granule proteome (Koseoglu and Flaumenhaft 2013) that contains numerous factors that can affect neoplastic cells. Through secretion of granule proteins, platelets modulate growth of tumor cells and the associated angiogenesis (Dovizio et al. 2014; Riedl et al. 2014). Thrombocyte alpha-granules of platelets also contain chemokines that can affect tumor cell behavior (Karshovska et al. 2013). In addition, platelets store laminins 411/421 and 511/521 in non-alpha- or dense-granule compartments and secrete these proteins via microvesicles (Pook et al. 2014).

Thrombocyte-Tumor Cell Interactions

It is known for long that patients with solid cancers can show elevated platelet blood counts in the absence of a paraneoplastic thrombocythemia. This thrombocytosis varies widely in its severity but may be associated with shorter patient survival (review: Buergy et al. 2012) and is associated with a higher metastatic load, e.g., in hepatocellular carcinoma. Elevated circulating thrombocytes enhance cancer cell migration and promote hematogenous metastasis in patients with lung cancer (Li et al. 2014). Neoplastic cells of solid cancers can undergo complex interactions with thrombocytes, whereby these interactions are capable to induce platelet aggregation favoring homing of cancer cells after intravascular spread (see below; Chang et al. 2009) or to affect the biological behavior of neoplastic cells, e.g., promoting their proliferation, cell-matrix adhesion, and/or invasive features. Cancer cells, also those of metastases, can internalize thrombocytes

or thrombocyte fragments (Panasci et al. 1980; Bhatia and Dey 2013), a process probably inducing complex signaling pathways mediated by platelet granule factors.

Platelets and Platelet Aggregates as Pacemakers of Metastatic Spread

In the setting of metastatic spread, thrombocytes play a pro-metastatic role involving several steps of the invasion and metastatic cascade (Karpatkin and Pearlstein 1981; Gasic 1984; Mehta 1984; Falanga et al. 2003; Borsig 2008; Erpenbeck and Schön 2010; Jain et al. 2010; Bambace and Holmes 2011; Gay and Felding-Habermann 2011). Interactions between platelets and tumor cells are important for metastatic spread and are mediated by adhesive receptors expressed by both partners of the interaction (Oleksowicz and Dutcher 1995). Thrombocytes promote the adhesion of spreading tumor cells to endothelial cell surfaces (Nierodzik et al. 1995), form aggregates that can store growth factors to be delivered to tumor cells, mediate access to the subendothelial space via collagen-induced viscous metamorphosis, slow down the streaming blood through induction of coagulation, induce a focal angiogenic response, and shield tumor cells from attack of host cells, in particular natural killer cells (Table 1; Yahalom et al. 1985; Eldor et al. 1987; Honn et al. 1992; Tsuruo and Fujita 2008; Gil-Bernabé et al. 2013; Reymond et al. 2013). Promotion of tumor angiogenesis by platelet products is an important mechanism that is not only dependent on VEGF and is the result of a combined action of several molecules that form the angiogenic payload of platelets (Battinelli et al. 2011; Sabrkhany et al. 2011; Radziwon-Balicka et al. 2012; Etulain et al. 2013). Platelet extracts induced growth, migration, and invasion in human hepatocellular carcinoma in vitro (Carr et al. 2014). Direct signaling between thrombocytes and tumor cells also induces epithelial-mesenchymal transition/EMT, an alteration that is critically involved in tumor metastasis (Labelle et al. 2011). Important steps in the process of platelet-induced tumor cell adhesion, homing, and transendothelial migration are mediated by P-selectin. P-selectin plays an important role in liver metastasis even in the absence of natural killer cell function (Coupland et al. 2012).

Table 1 Effects of platelets on malignant neoplastic cells

Induction of platelet aggregation (via Aggrus/podoplanin-CLEC-2 pathway)
Promotion of adhesion to endothelial cells
Induction of tumor cell motility and migration
Vessel wall transmigration
Stimulation of tumor cell growth
Induction of epithelial-mesenchymal transition
Signaling of platelet-tumor cell interactions (in part through platelet internalization)
Induction of angiogenesis

Tumor Cells Can Promote Platelet Aggregation and Release of Microvesicles and Exosomes

Several tumor types have been shown to produce and secrete the platelet aggregation-inducing factor Aggrus, a protein also termed podoplanin. Aggrus is secreted by various tumors, including CRC (Kato et al. 2003). Aggrus released by tumor cells interacts with a platelet receptor termed CLEC-2, and the ligand-receptor binding induced thrombocyte aggregation (Takagi et al. 2013). Aggrus-induced aggregate formation plays an important role for the changes in blood rheology required for tumor cell homing in the microvascular bed (Jurasz et al. 2004). Platelet aggregates and thrombocyte-induced local blood coagulation cause slowdown of streaming blood in microvessels, enabling tumor cells to engage with endothelia and adhere to the inner vessel wall. In fact, platelet-derived Aggrus/podoplanin was shown to promote metastasis (Kunita et al. 2007; Suzuki-Inoue 2011; Fujita and Takagi 2012; Lowe et al. 2012). One mechanism of metastasis promotion by podoplanin involves an induction of tumor cell migration (Shen et al. 2010; Kunita et al. 2011), whereby serine moieties in the intracellular tail of podoplanin regulate cell motility (Krishnan et al. 2013). In addition, contacts between platelet aggregates

induced by tumor cells permit the transfer of granule and nongranule proteins of platelets and of exosomes to adjacent endothelial cells and tumor cells. Platelet-derived microvesicles or microparticles are important participants in intercellular communication and play a role in cancer progression (Varon and Shai 2009; Aatonen et al. 2012). Activated platelets secrete granule proteins and parallel release two types of membrane microvesicles, namely, simple microvesicles by surface shedding and more complex exosomes derived from multivesicular bodies and alpha-granules (Heijnen et al. 1999). Platelet-derived microvesicles (microparticles) possess membrane domains that contain adhesion molecules and diverse receptors and contain signal substances that can stimulate angiogenesis (Varon and Shai 2009) and tissue regeneration (Varon et al. 2012).

Platelet Mimicry of Cancer Cells

Certain cancer cell types acquire a geno-phenotype the closely resembles that of thrombocytes/platelets. Such tumor cells express megakaryocyte genes, including adhesion receptors alpha IIb beta 3, thrombin receptor and PECAM/Cd31, and/or platelet-type 12-LOX. These acquired expression patterns enable the cancer cells to activate the coagulation cascade. It is currently considered that these platelet-like features of cancer cells affect their capability to spread and metastasize (Timar et al. 2005).

The Metastatic Stromal and Vascular Environment of the Liver

Introduction

The liver is known to provide a tissual microenvironment that favors the establishment of metastases of various malignancies, but specifically carcinomas. Part of the tumor cells transported into the liver via the vascular system resists antitumor defense mechanisms and can adhere as viable cells to endothelium of blood vessels, chiefly endothelia of hepatic sinusoids. Here, they start to respond to growth factors produced and secreted by neighboring hepatocytes, perisinusoidal cells, and vascular cells. In the first step, this results in avascular micrometastases in periportal areas of liver lobules. The next step is characterized by stroma formation, a prerequisite for angiogenesis, because newly formed blood vessels depend on being embedded within a mesenchymal matrix with its specific extracellular matrix (ECM) proteins. Fibroblasts from portal tracts become cancer-associated fibroblasts (CAFs) as an important component of stroma, and stromal myofibroblasts are recruited from activated hepatic stellate cells and portal tracts. Together, these cells generate a "private" tumor microenvironment that has a pro-metastatic effect (Vidal-Vanaclocha 2008, 2011).

The Pro-metastatic Effect of Stromal Interactions

The stromal microenvironment profoundly influences many steps of cancer progression, including the ability of cancer cells to metastasize (the 'stromal factor'; Wernicke et al. 2011). Within stroma, influences of this distinct and complex microenvironment are mediated by bidirectional interactions between epithelial tumor cells and the neighboring stromal cells, these interactions referring to adhesion, migration, proteolysis, angiogenesis, homing strategies, epithelial-mesenchymal transition, immune escape mechanisms, and survival (reviews: Bogenrieder and Herlyn 2003; Orimo and Weinberg 2006).

What are the pathways leading to stromal formation in metastases? Early in the outgrowth phase of murine colorectal carcinoma micrometastases, hepatic Kupffer cells and fibroblasts are recruited and start to invade the metastatic nodules. These transitional metastases are connected by protrusions of fibroblast-rich tissues co-localized with collagen-rich matrix and CD31-positive cells. The latter step is characterized by the generation of a pro-angiogenic niche and the switch of a transitional metastasis to an established, vascularized metastasis (Higashi et al. 2002). Stromal components, including

fibroblasts, myofibroblasts, endothelial and other vascular cells, mesenchymal stem cells, granulocytes, and cells of the immune system, interact with carcinoma cells to promote growth, invasion, and metastasis (reviews: Li et al. 2007; Aharinejad et al. 2009; Finger and Giaccia 2010; Pietras and Ostman 2010; Udagawa and Wood 2010). Stroma-derived growth factors and cytokines produced by stromal-resident lymphoid cells and macrophages activate autocrine and paracrine oncogenic signaling pathways, which in turn promote proliferation or spread of epithelial cancer cells. Stromal cell can produce matrix metalloproteinases (MMPs) which are known to operate within the invasion cascade. However, whereas MMP-9 is upregulated in primary CRCs, it is expressed mainly by macrophages in the invasion zone of hepatic metastases and there generally less expressed than in primary tumors (Illemann et al. 2006). Both mesenchymal cells and macrophages are active in the procoagulative environment of tumors, coagulation factors such as fibrinogen and thrombin affecting tumor cell growth and differentiation. Components of stromal cells may also promote the locomotor and migratory activity of carcinoma cells. The intermediate filament protein, vimentin, a constituent of mesenchymal cells, is an AKT1 target mediating motility and invasion (Zhu et al. 2011a). Factors regulating epithelial-mesenchymal transition (EMT) affect the metastatic process. The developmental transcription factor, Six1, induces EMT in dependence of TGF-beta signaling. Six1 is a critical mediator of the switch in TGF-beta signaling from tumor-suppressive to tumor-promotional activity, the TGF-beta type I receptor being the target of Six1 and a critical effector of Six1-induced TGF-beta signaling and EMT (Micalizzi et al. 2010).

Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) seem to regulate many aspects of tumorigenesis and cancer spread (reviews: Orimo and Weinberg 2006; Cirri and Chiarugi 2012). Stromal fibroblasts in CRC metastases originate from resident fibroblasts and create an inflammatory microenvironment characterized by TNF-alpha-mediated upregulation of IL-8 via nuclear factor kappaB (Mueller et al. 2007). Colorectal cancer-associated fibroblasts represent a genetically distinct population of stromal cells (Mrazek et al. 2014). Activated CAFs residing in tumor stroma are a source of growth factors for carcinoma cells, factors promoting angiogenesis and lymphangiogenesis, cytokines mediating tumor immunity, and factors involved in epithelial-mesenchymal transition (Räsänen and Vaheri 2010). Primary CAFs from colorectal liver metastases express several inflammatory, tumor-enhancing factors, including IL6 and monocyte-chemoattractant protein (MCP)-1. Both factors are induced by TNF-alpha, which also upregulates ICAM-1. A similar reaction pattern was found for liver-resident, non-tumor-associated fibroblasts (Mueller et al. 2010), which may therefore constitute a cell type playing a role in the generation of a pro-metastatic stroma. The stroma of carcinomas exerts an influence on angiogenesis and antiangiogenesis and by this affects the development of metastases. The growth of metastases is dependent on the growth of blood vessels into the tumor mass. The extracellular matrix of the stroma and its specific proteins, including basement membrane laminin, fibronectin, and tenascin, is a source of both pro-angiogenic factor activation and endogenous angiogenesis inhibitors, such as endostatin (review: Nyberg et al. 2008). Multicellular spheroids of murine colorectal cancer cells mimic micrometastases and their growth pattern activates the pro-angiogenic phenotype of the carcinoma cells (Valcarcel et al. 2008). Antiangiogenic effects and hypoxia-dependent signaling pathways are counteracted by semaphorin 3A produced by cancer cells in metastases (Maione et al. 2012).

Lymphangiogenesis in Hepatic Metastasis: Does It Play a Role?

For the metastatic spread of cancer cells, generation of a lymph vessel network (lymphangiogenesis) plays a crucial role. A dynamic lymph vessel system has an active role

in metastatic dissemination, and metastasizing tumor cells are capable to synthesize and secrete factors that promote lymphangiogenesis. In a mouse model of breast cancer, tumor cells produced the homeodomain-containing transcription factor SIX1, which induces lymphangiogenesis and metastasis via upregulation of VEGF-C (Wang et al. 2012a).

Interactions of Metastatic Carcinoma Cells with Hepatic Stellate Cells (HSC)

As stroma plays a significant role in homing and growth of carcinoma metastasis, cells potentially producing stroma in the liver are of specific interest. Apart from fibroblasts and myofibroblasts in portal tracts and vessel walls, the only cell type of the liver capable of producing extracellular matrix is the hepatic stellate cell (HSC). We have shown that HSCs can interact and form tight adhesions with hepatocytes during the early regeneration phase of the normal rat liver (Mabuchi et al. 2004a, b), suggesting that HSCs can form a epithelial-mesenchymal interactome in the liver. By the use of a nude mouse model, it was demonstrated that intrasplenically injected colon carcinoma cells migrated into the space of Disse and underwent proliferation, in close association with hepatocytes and HSCs. At 14 days, HSCs were accumulated around the emerging small tumor mass and showed transformation into alpha-SMA-positive myofibroblasts. The growing colon carcinoma cells produced PDGF-AB, enhancing proliferation and migration of HSCs, while HSCs produced PDGF-AB, HGF, and TGF-beta and could augment proliferation of carcinoma cells, suggesting complex bidirectional interactions between metastasizing carcinoma cells and activated HSCs (Shimizu et al. 2000). This interaction may result in an "amplification loop" to further metastatic growth in the liver (review: Kang et al. 2011). The transition from HSCs to myofibroblasts in pro-metastatic hepatic stroma is regulated by the fibrillar collagen receptor discoidin domain receptor 2 (DDR2). Downregulation of DDR2 promotes myofibroblast transition and predisposes hepatic tissue to colorectal carcinoma metastasis in mice (Badiola et al. 2011).

Stroma-Associated Inflammatory and Immunologic Effector Cells Control Metastasis Formation: TANs, TAMs, Myeloid-Derived Suppressor Cells (MDSCs), Myeloid Angiogenic Cells (MACs), and Lymphocytes

The stroma of many tumors contains leukocytic infiltrates/inflammatory cells which are instrumental in immune reactions that either inhibit tumors or produce factors that stimulate growth and metastasis. An inflammatory microenvironment induced by myeloid cells is key alteration for promoting tumor invasion and metastatic spread (Grugan et al. 2012; Capece et al. 2013; Smith and Kang 2013; Keskinov and Shurin 2014). A specific role is attributed to tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and myeloid-derived suppressor cells/MDSCs. The presence of TAMs and TANs has been linked to poor clinical outcomes in solid tumors, as these cells can switch from a tumor-suppressing to a tumor-promoting phenotype (review: Alphonso and Alahari 2009). TANs can play a role in tumor cell detachment (tumor cell individualization as a prerequisite for motility and migration), have a pro-angiogenic activity, and secrete MMP-9 playing a role in tumor invasion (Benson et al. 2012).

TAMs form a major component of tumor stroma, consist of several functionally different subsets, and originate from distinct circulating monocytes that home to the tumor microenvironment (Movahedi et al. 2010). But accumulation of TAMs in stroma is also accomplished by in situ proliferations of TAMs in tumors (Tymoszuk et al. 2014). Local accumulation of monocytes differentiating into TAMs is promoted by the TGF-beta superfamily member, Nodal, which is an embryonal morphogen that is upregulated in numerous tumors (Wang et al. 2014a). The interaction of stromal cells with TMAs results in differential macrophage programming in the tumor microenvironment (Ruffell et al. 2012). TAMs are

major players in the tumor microenvironment and exert a strong influence on progression and metastatic spread of cancer (Hao et al. 2012; Galdiero et al. 2013). In the course of tumor progression, TAMs and their hematogenous precursors, the monocytes, are actively recruited into tumor tissue, and particularly its stroma. In their interaction with tumor and stromal cells, TAMs can undergo several functional changes. Whereas classical M1 macrophages are engaged in inflammatory responses, antitumor immunity, and antigen clearance, alternative M2 macrophages are active in anti-inflammatory reactions, wound healing, stroma formation, and tumor progression (reviews: Chanmee et al. 2014; Van Overmeire et al. 2014). TAMs most closely resemble polarized class two macrophages/M2 and are cells that markedly modulate the composition and function of tumor microenvironments (Mantovani et al. 2002). TAMs have upregulated expression of CD206 and CD163 markers of alternative activation but do not have increased expression of classically activated macrophage markers, CCR2 and CCR5. Monocytes as precursors of M2 TAMs are recruited to metastatic sites by distinct homing mechanisms. A major ligand facilitating monocyte accumulation is P-selectin glycoprotein ligand-1/PSGL-1 (Hoos et al. 2014).

The interaction of TAMs with tumor cells is mediated by adhesion molecules and glycosaminoglycans. Hyaluronan synthase HAS2 stimulates the interaction between cancer cells and TAMs and promotes tumor progression and metastasis (Okuda et al. 2012). The interactome of TAMs, lymphoid cells (mainly T cells), and myeloid-derived suppressor cells is active in pro-angiogenic reactions and the preparation of homing vascular surface facilitating tumor cell and platelet adherence and cancer cell transmigration (reviews: Labelle and Hynes 2012; Smith and Kang 2013).

M2 TAMs exhibit a distinct functional profile characterized by the (stimulated) production of a wide array of factors. Activated TAMs can produce a host of cytokines that can modulate tumor cell behavior and affect stromal cell production function. TAMs strongly express interleukin receptor-associated kinase (IRAK)-M, a serine/threonine kinase that is a potent negative regulator of Toll-like receptor signaling (Kobayashi et al. 2002). In tumors, IRAK-M is induced by TGF-beta1 from stromal cells and regulates tumor growth (Standiford et al. 2011). TGF-beta1 plays a central role in myeloid cell regulation (Pang et al. 2013). TAMS can secrete matrix metalloproteinases (MMPs), including MMP-9, whereby differentiation-related expression of MMP depends on an interaction of the ECM component, laminin.-5, with monocytes (Kamoshida et al. 2014). TAMs produce oncostatin M and VEGF (Benson et al. 2012). Tumor-infiltrating monocytes/macrophages produce and secrete the innate immune response mediator, human beta-defensin-3, a factor that inhibits cancer cell migration through downregulation of metastasis-associated 1 family, member 2 (MTA2 9 expression (Uraki et al. 2014)). TAMs are involved in the progression of HCC, as M2 type macrophages can modulate the composition of HCC stroma and modify immunosuppressive functions of immune effector cells (Shirabe et al. 2012). In HCCs, TAMs can promote a stem cell-like property of cancer cells through TGF-beta1-induced epithelial-mesenchymal transition (Fan et al. 2014), a mechanism that favors a metastatic phenotype. TAMs can also induce the expression of the macrophage receptor, CD163, in malignant cells, thus resulting in some sort of "induced receptor sistership". CD163 expression in a subpopulation of cancer cells may constitute a phenotypic shift associated with epithelial-mesenchymal transition, increased invasion, and a metastatic phenotype (Maniecki et al. 2012). Part of TMAs are involved in the promotion of angiogenesis (Owen and Mohamadzadeh 2013). These specialized cells are termed myeloid angiogenic cells (MACs). MACs are in part Tie-2 expressing monocytes and significantly contribute to angiogenesis and vascular repair through paracrine mechanisms as they lack the capacity to differentiate into endothelial cells (Chambers et al. 2013). Experimental selective ablation of TAMs with MAC features suppresses angiogenesis and metastatic tumor spread (Lin et al. 2013). MAC-induced angiogenesis depends on the expression of the myeloid cell receptor LRP1/

CD91 that regulates monocyte recruitment and VEGF availability in tumors (Staudt et al. 2013).

In addition to TAN and TAM, myeloid-derived suppressor cells (MDSCs) play a significant role in the function of tumor microenvironment, tumor progression, and metastasis (reviews: Schmid and Varner 2012; Brandau et al. 2013; Diaz-Montero et al. 2014). MDSCs are bone marrow-derived myeloid cells that are recruited to tumors, where they are transformed to potent immunosuppressive cells, which, however, also have functions other than blunting immune reactions (reviews: Mantovani et al. 2009; Dumitru et al. 2012; Schmid et al. 2012; Diaz-Montero et al. 2014). Apart from their role in mediating immunosuppression via strong inhibition of antitumor immune reactions produced by T cells, MDSCs strongly stimulate tumorigenesis, tumor growth, and metastasis (Umansky and Sevko 2013), probably by modulating the cellular composition of stroma in pro-metastatic niches. MDSCs enhance the stemness of cancer cells by inducing micron-101 and suppressing the corepressor CtBP2 (C-terminal binding protein-2, a protein that directly targets stem cell core genes resulting in cancer cell stemness and an invasive and metastatic phenotype (Cui et al. 2013)). The function of MDSCs is regulated by microRNA-155. Downregulation of the miR enhances the recruitment and function of MDSCs in the tumor microenvironment (Wang et al. 2014d).

Interactions of Carcinoma Cells with Hepatic Blood Vessel Cells and Vascularization of Metastases

Successful growth of metastases requires the generation of a stroma harboring blood vessels produced in the setting of tumor-induced angiogenesis. The mode of neovascularization of metastases originating from various tumors varies itself considerably, suggesting an "individualized" mode of angiogenesis. A corrosion case study of 22 livers with multiple metastases from different primary neoplasms showed the development of an individual pattern of vascularization in all metastases. The majority of metastase displayed a distinct blood supply by branches of the hepatic artery and portal vein branches, whereby all metastases of the same liver showed an identical vascularization pattern (Strohmeyer et al. 1986). Intra- and peritumoral connections between vessels fed by the arteries and portal vein branches are mediated by sinusoidal connections (Nikfarjam et al. 2003). Also a Microfil injection study in human autopsies with liver metastases showed both an arterial and portal mode of vascularization, although the hepatic artery mode was more important (Lin et al. 1984). Injection studies of human liver metastases exhibited a highly abnormal mode of vascularization, never imitating the normal angioarchitecture of the liver (Strohmeyer et al. 1987). Gelatine-injected specimens of human hepatic metastases also revealed that vascularized micrometastases in the vicinity of macrometastases are more common than anticipated from routine preparations (Haugeberg et al. 1988). A gamma camera imaging study of colorectal hepatic metastases revealed that more than twice as much of test substrate was delivered per volume of tumor relative to liver by the hepatic artery as by the portal vein (Ridge et al. 1987). Portal vein blood played a minor role in a rat model of liver metastases (Archer and Gray 1989). In a murine model, blood feeding metastases was distributed from arteries to capillaries of the metastasis center, from where it flowed to a superficial venous network and then further to hepatic veins (Voboril 2005).

In a murine hepatic metastasis model, sinusoidal endothelial cells are activated by interaction with colon carcinoma cells. These activated endothelial cells display an increased expression of mannose receptor (ManR) and ManR-mediated endocytosis. This effect depends on a two-step mechanism: (1) release of COX-2-dependent IL-1 stimulating factors by LFA1-expressing C26 cells in response to ICAM1, which is expressed by activated sinusoidal endothelial cells and (2) widespread upregulation of ManR in endothelia through tumor cell-induced IL-1. ICAM-1-induced tumor COX-2 decreases antitumor activity during hepatic metastasis through Il-1-induced ManR in endothelial cells, ManR therefore constituting a common mediator

for the pro-metastatic effect of Il-1, COX-2, and ICAM-1 (Arteta et al. 2010).

Features of Hepatic Parenchyma That Can Promote Metastatic Growth

Ischemia/reperfusion injury to liver parenchyma can accelerate the outgrowth of preestablished colorectal micrometastases (van der Bilt et al. 2005). With increasing ischemia times, tissue necrosis, and ischemia/reperfusion injury-accelerated tumor growth in mice increased, and in this murine model, outgrowth of micrometastases was further increased by increasing the age of the mice and steatosis of the livers (van der Bilt et al. 2008).

Actions of miRNAs in the Tumor Stroma

In breast cancer metastases, it has been found that miRNA-31 inhibits metastatic growth through the pleiotropic suppression of pro-metastatic target genes that include integrin alpha(5), radixin, and RhoA (Valastyan et al. 2010). Heparanase, a potent protumorigenic and pro-metastatic enzyme which is produced by stromal cells, is targeted and suppressed by miRNA-1258 (Zhang et al. 2011). Epigenetic alterations of miRNA deregulation are common in various tumors. Enhancer of zeste homolog 2 (histone H3 lysine 27 trimethylating enzyme), frequently upregulated in malignancies, epigenetically silences multiple tumor suppressor miRNAs to promote liver cancer metastasis (Au et al. 2012).

Pathogenic Features of Liver Metastases: Epithelial-Mesenchymal Transition (EMT)

Introduction

Epithelial-mesenchymal transition (EMT) is a major process involved in the construction of tissues in early stages of ontogenesis. There, EMT is characterized by the internalization of epithelial cells to give rise to mesodermal/mesenchymal tissues. To arrive at this result, epithelial cells must undergo dramatic changes, including the disconnection of junctions, undergoing polarization and shape change to become migrating cells, and altering cell surface adhesion molecule complements (the "adhesome"). Specifically, distinct expression patterns of integrins are involved in EMT, described as an integrin adhesome (Zaidel-Bar et al. 2007; Zaidel-Bar and Geiger 2010; Winograd-Katz et al. 2014). Other adhesion platforms involved in EMT generation comprise the cadherin adhesome (Zaidel-Bar 2013) and dystroglycan adhesome (Bello et al. 2014). EMT in cancer is characterized by dysregulation of several molecules that comprise, apart from adhesion molecules, intermediate filament proteins, calcium-binding proteins, and transcription factors. Tumor cells in EMT show loss of E-cadherin expression, upregulation of vimentin, induction of alpha-SMA, and expression of Snail1 and Snail2/Slug (Maeng et al. 2014). Typically, cells engaged in EMT fail to express E-cadherin, an important adhesin. The dissolution of the E-cadherin-mediated adherens junction is an important early step in EMT in epithelial malignancies. Downregulation of E-cadherin is accomplished by the action of several transcription factors forming a hierarchical system. Initial transcriptional inducers of EMT are Snail1 and Snail2/Slug, which lead to the activation of ZEB family members, TCF3, TCF4, Twist, Goosecoid, FOXC1, FOXC2, H-Ras, CD44, claudin-1, TGF-beta1, and TNF-alpha. Upregulation of Snail2/Slug and FOXC2 by either Snail1 or Twist does not depend in TGF-beta1 signaling (Taube et al. 2010; Hugo et al. 2011; Qin et al. 2012; Xu et al. 2012; Suh et al. 2013; Caja and Vannucci 2014; Liu et al. 2014b; Okabe et al. 2014). Slug (or now Snail2) is a transcriptional repressor of E-cadherin and is a downstream target of SPARC/osteonectin (Fenouille et al. 2012). Twist1, a basic helix-loop-helix protein transcription factor involved in EMT both in ontogenesis and cancer, is regulated by phosphoregulation (Firulli and Conway 2008) and stabilized by autophagy deficiency via

binding of SQSTM1 to Twist1 in order to prevent autophagosomal Twist1 degradation (Qiang and He 2014). A negative regulator in EMT-related TGF-beta signaling is Smurf2, a protein that interacts with the HCV viral protease NS3-4A (Verga-Gérard et al. 2013). The factors activated by the master EMT inducers Snail1 and Slug have themselves distinct targets that mediate their effects in the EMT molecular pathway. For example, ZEB1 has the collagen receptor tyrosine kinase, discoidin domain receptor 1/DDR1 as its transcriptional target, whereby ZEP1 downregulates DDR1 and contributes to an invasive cancer cell phenotype (Koh et al. 2014). Twist1, having a central role as an effector for EMT induction, can also induce endothelial transdifferentiation of cancer cells through a Jagged1-Krüppel-like factor/KLF-4 signaling axis (Chen et al. 2014a). A further transcription factor involved in EMT and metastasis I a cytotoxic T-lymphocyte agonist epitope of brachyury. EMT is also regulated by the Wnt/beta-catenin signaling cascade, which is activated in the setting of EMT by stromal cell-derived factor 1/SDF-1 and its receptor, CXCR4 (Hu et al. 2014). EMT induced by TNF-alpha requires stabilization of Snail1 mediated by Akt/GSK-3beta signaling, GSK-3beta being a Wnt signaling component (Wang et al. 2013a). EMT can be induced by extravasated platelet aggregation, one critical molecular being CD42b coexpressed with Snail1 (Miyashita et al. 2014).

In addition to factors promoting EMT, there are pathways counteracting EMT generation, and it may be anticipated that failure of such inhibitory pathways in tumors might be involved in metastasis. Protocadherin 9, frequently lost in HCC, inhibits EMT and cell migration through activation of the Wnt signaling component, GSK-3beta (Zhu et al. 2014). EMT can be repressed expression of SMAR1 which represses Snail2/Slug transcription and inhibits E-cadherin degradation in cancer cells (Adhikary et al. 2014). SMAR1 is a nuclear protein involved in chromatin homeostasis that binds to nuclear matrix attachment regions/MARs, regions crucial for proper periodic chromatin arrangement.

Epithelial-Mesenchymal Transition as a Metastasis-Promoting Alteration in Cancer

EMT plays a central role in the generation of a proinvasive tumor microenvironment and metastatic spread of cancer (reviews: Chaffer and Weinberg 2011; Jing et al. 2011; Meng and Wu 2012; Jung et al. 2015). EMT provides cancer cells with migratory, invasive, stroma interactive, and stem cell properties that enable them to disseminate and settle at remote sites. Advanced cancer stage and metastatic spread in HCC are associated with a typical EMT-related cellular alteration, i.e., downregulation of E-cadherin (Zhai et al. 2014). Abnormal expression of EMT-related proteins in HCC, i.e., loss of E-cadherin and overexpression of vimentin and S100 proteins, is correlated with an aggressive metastatic phenotype of this tumor (Zhai et al. 2014). EMT in HCC is related to hepatitis virus infection, viral proteins promoting EMT pathways by various mechanisms (Wang et al. 2014d). For example, HCV-induced expression of osteopontin, a pro-metastatic phosphoprotein overexpressed in HCC, is associated with EMT via the activation of the GSK-3beta signaling pathway (Iqbal et al. 2013).

EMT promoting invasion and metastatic spread in cancers, including liver cancer, is induced by aberrant expression of various pro-EMT factors. Metastasis in HCC is strongly promoted by overexpression of the pro-EMT transcription factor, Snail2/Slug (Sun et al. 2014). TGF-beta1 plays a central role in EMT induction and metastasis in HCC (Reichl et al. 2012). TGF-beta1, which induces EMT in HCC, is induced in these tumors by tumor-associated macrophages/TAMS which also promote cancer stem cell-like features in HCC cells (Fan et al. 2014). Tumor-derived secretory clusterin, a protein involved in the regulation of TGF-beta1-Smad3 signaling, facilitates HCC metastasis via induction of EMT (Wang et al. 2012b). Another member of the TGF-beta family of proteins, bone morphogenetic protein-9/BMP-9, also induces EMT in HCC (Li et al. 2013). Upregulation of hepatocyte growth factor/HGF promotes

carcinogenesis and EMT in HCC through Akt and COX-2 pathways, whereby HGF causes loss of cell surface E-cadherin (Ogunwobi and Liu 2011). Expression of the Hedgehog signaling effector, Gli1, in HCC promotes EMT, invasion, and metastasis (Chen et al. 2014b). ZEB1, a second rank effector of EMT-inducing factors, reduces E-cadherin expression in HCC cells and increased expression of N-cadherin and vimentin, promoting EMT and metastasis in HCC (Zhou et al. 2012). Forkhead box Q1/FOXQ1, a master regulator of tumor metastasis, promotes HCC metastasis by transactivating the EMT inducer ZEB2 (Xia et al. 2014). Loss of expression of functional p53 in HCC is correlated with EMT via regulation of the beta-catenin signaling pathway (Wang et al. 2013b). Downregulation of lipocalin-22 by TGF-beta1 is associated with Tist1 expression and EMT in HCC (Wang et al. 2013b). Stress-activated protein kinase (SAPK)-interacting protein1 or SIN1 which is a key regulator of Akt is overexpressed in HCC and promotes metastasis via induction of EMT (Xu et al. 2013). Activated Wnt/beta-catenin signaling enhances hypoxia-induced EMT in HCC via crosstalk with hypoxia inducing factor-1alpha signaling (Zhang et al. 2013b). Hypoxia and hypoxia-inducible factor-1alpha as such induce EMT in HCCs through activation of Snail1 (Zhang et al. 2013c). EMT-related upregulation of hypoxia-inducible factor-1alpha induces the transcription factor PROX1, resulting in HCC metastasis (Liu et al. 2013). Sirtuin 1/SIRT1, a protein implicated I telomere maintenance and growth in HCC, can mediate EMT in these neoplasms by GSK-3beta/beta-catenin signaling (Chen et al. 2013). Metastasis of HCC induced by EMT is promoted by elevated expression of myeloid differentiation factor 88/MyD88, a protein interacting with p85, a regulatory subunit of phosphoinositide 3-kinase/PI3-K, causing Akt activation, subsequent GSK-3beta phosphorylation, and stabilization of the pro-EMT factor Snail1 (Jia et al. 2014). HCC expresses mortalin, a member of the HSP70 heat shock protein family involved in stress response regulation. Overexpression of mortalin is associated with EMT, angiogenesis metastasis in HCC (Yi et al. 2008; Chen et al. 2014c). In HCC, EMT is induced metadherin, a protein known to increase metastasis in these tumors (Zhu et al. 2011b). In various cancer types, including HCC, EMT as a mechanism involved in metastasis is modulated through the expression of members of a calcium-binding family, the S100 proteins. S100 proteins are critically involved in tumor cell-stromal cell interactions, promotion of EMT, and the generation of a proinflammatory tumor microenvironment promoting invasion and spread (Lukanidin and Sleeman 2012). Induction of EMT by S100A4 is regulated by the Sonic Hedgehog-Gli1 signaling pathway, whereby the Hedgehog effector Gli1 modulates S100A4 expression via cis-acting elements (Xu et al. 2014). S100A4 induces migration and invasion in HCC cells through the induction of an NF-kappaB-dependent MMP-9 signal (Zhang et al. 2013d). In HCC, abnormal expression of EMT-related S100A4 is correlated with an aggressive tumor biology (Zhai et al. 2014). The metastasis-associated protein S100A4 induces a network of inflammatory cytokines that activate stromal cells to have protumorigenic features (Bettum et al. 2014). In addition to S100A4, a second S100 protein can induce EMT, i.e., S100A2, acting through functional interaction with Smad3 which is enhanced in the presence of high calcium and TGF-beta activity (Naz et al. 2014). In HCC, ectopic expression of metastasin, a further calcium-binding protein, induces typical EMT with decreased E-cadherin and upregulation of vimentin via upregulation of SNAI1 (Zheng et al. 2013). Several EMT-associated proteins are regulated by BTB/POZ domain-containing protein 7/BTBD7 in HCC (Tao et al. 2013). In cancers, EMT is connected with the induction of an inflammatory microenvironment that plays a role both in favoring invasion and spread and tumor control by immune mechanisms. TGF-beta1 contributes to an inflammatory niche through promotion of immune cell homing and switching the phenotypes of tumor-infiltrating immune cells (Fuxe and Karlsson 2012).

Regulation of Epithelial-Mesenchymal Transition

EMT as a motor of the metastatic pathway is regulated by several mechanisms that control expression of pro- and anti-EMT factors. Numerous factors are regulated by epigenetic promoter methylation, with a complex EMT-related or even EMT-specific DNA methylome. EMT factors are controlled by microRNAs. MiR-29c mediates EMT in human CRC metastases via modulation of beta-catenin signaling (Zhang et al. 2014a). MiR-424-5p can reverse EMT in HCC by targeting the beta-catenin inhibitor, ICAT (Zhang et al. 2014b). MiR-122 triggers EMT and suppresses HCC cell motility, migration, and invasion via targeting RhoA (Wang et al. 2014b). Downregulation of microRNA-30a in HCC facilitates migration and invasion through promotion of EMT (Liu et al. 2014a). This miR can, however, also inhibit EMT via targeting the pro-EMT factor Snail1/Snai1, an effect circumvented by its downregulation in cancers (Kumarswamy et al. 2012). MicroRNA-26b inhibits EMT by targeting USP9X, a protein which in turn affects EMT through Smad4 and the TGF-beta signaling pathway (Shen et al. 2014). MicroRNA-148a suppresses EMT and metastasis of HCC by targeting Snail signaling (Zhang et al. 2014c). MiR-491 is involved in the regulation of HCC metastasis by blocking EMT via increase of surface E-cadherin expression (Zhou et al. 2013). Overexpression of microRNA-106b promotes cell migration and metastasis in HCC via promoting EMT via overexpression of the RhoGTPases, RhoA, and RhoC (Yau et al. 2013). Micro-RNA-490-3p modulates HCC cell growth and EMT by targeting endoplasmic reticulum-Golgi intermediate compartment protein 3/ERGIC3 (Zhang et al. 2013). The invasive and metastatic behavior of HCC is suppressed by microRNA-612 which inhibits EMT (Tao et al. 2013). Metastasis regulated by EMT is also subject to modulation by long noncoding RNAs that affect transcriptional and posttranscriptional steps in synthesis of critical factors (Serviss et al. 2014). A long noncoding RNA activated by TGF-beta promotes the invasion-metastatic cascade in HCC (Yuan et al. 2014).

The Concept of the Pre-metastatic Niche

Introduction

The establishment of a microenvironment that favors homing and growth of cancer cells is a critical condition for the generation of metastasis. The biogenesis of metastases requires a distinct tumor cell-host organ interface in early phases of the metastatic process (Gassmann and Haier 2008). The cellular basis for this pathway of metastasis has been reviewed (Oppenheimer 2006) and has resulted in the concept of the pre-metastatic niche (pre-MN). A pre-MN is defined as a distinct variant of microenvironment that is induced in target organs of metastasis and facilitates homing, adhesion, growth, invasion, and survival of metastatic tumor cells (Kaplan et al. 2006; Perelmuter and Manskikh 2012; Zoccoli et al. 2012). In this sense, the pre-MN is a structure that precedes, and eventually anticipates, the generation of a metastasis, a novel concept for the understanding of a metastasis cascade. Also for the liver, which is a major metastasis-susceptible organ, a pre-or pro-metastatic microenvironment has been discussed (review: Vidal-Vanaclocha 2008).

The Cellular Preparation of the Pre-metastatic Niche

It was demonstrated that bone marrow-derived cells/BMDC home to the pre-MN via the action of adhesion molecule and chemokine signaling, and there establish clusters that precede the arrival of even single metastasizing cancer cells. Interaction of these BMDC with local cells promotes the upregulation of several factors that will be important for cancer cell growth, including signaling chemokines, stromal differentiation factors, and angiogenic factors (review: Kaplan et al. 2006). Bone marrow-derived myeloid progenitor cells can induce mesenchymal-epithelial transition/MET in remote tissues (Gao et al. 2012b).

Cancer Progenitor/Stem Cells in a Pre-metastatic Niche

Cancer stem cells are thought to possess distinct tissue and cell selection capabilities allowing them to home to a pre-MN (Malanchi et al. 2011). In their interaction with microenvironmental structures, cancer stem cells are not a fixed set of cells but rather a flexible population of cells that can differentiate to typical tumor cells and revert to a stemlike state. There is strong evidence that this switching is regulated by interactions with mesenchymal cells of the niche (Fessler et al. 2013), these cells themselves being programmed to later become true stromal cells, including cancer-associated fibroblasts and myofibroblasts. Within a pre-MN, cancer stem cells dwell in some sort of a "CSC niche" which controls their self-renewal, differentiation, and departure for other niches (Borovski et al. 2011).

Cross-Talk Between Tumor Cells and Elements of the Pre-metastatic Niche

In addition to several classes of stem cells that can prepare the pre-MN, differentiated tumor cells themselves interact in a complex manner with elements of the pre-MN. The interaction with cells of the pre-MN can induce genetic and epigenetic alterations in the homing tumor cells, changes that can themselves promote a metastatic phenotype of the cancer cells (Carlini et al. 2011). The offspring of tumor cells that have undergone such pre-MN-induced changes may be primed to transfer these acquired changes to other potential metastatic sites, eventually to induce novel pre-MNs. On the other hand, tumor cells that have settled in the niche can prime the further development of cells active in the niche (Deng et al. 2012) and induce the evolution of the pre-MN to a complete and active, vascularized stroma (the concept of induced stromal progression).

Programming of the Pre-metastatic Niche by Exosomes

The mechanisms as to how homing cells induce resident cells to become a pre-metastatic microenvironment and then a tumor stroma and an angiogenic field are still not well known. It is assumed that direct contact of homing bone marrow-derived cells and cancer stem cells and differentiated tumor cells with tissue can elicit a differentiation switch of mesenchymal and vascular cells in situ. On the other hand, exosomes delivered by tumor cells and harboring genetic information or signaling molecules can drive pre-MN formation (Alderton 2012). Exosomes contain membrane anchors that allow them to attach to target cells in a niche, to deliver their information cargo (Pant et al. 2012). Exosomes released from melanoma cells and transported to sentinel lymph nodes prepare these nodes for metastasis through remodeling of the lymphonodular microenvironment (Hood et al. 2011). Exosomes released from malignant cells, e.g., melanoma cells, can also educate noncancer progenitor cells toward a pre-metastatic phenotype through the action of the receptor tyrosine kinase Met (Peinado et al. 2012). For this pathway to work, certain conditions must be present in resident cells to interact with exosomes, such as expression of the CD44v6 isoform of CD44, this factor assembling a soluble matrix for exosomes to allow cell embedding and growth (Jung et al. 2009).

Programming the Pre-metastatic Niche by Soluble Factors from Progenitor Cells and Tumor Cells

Apart from direct interaction with future stromal cells and release of exosomes, tumor cells can also secrete various factors that "prepare" the future niche, and in particular its endothelial cells, for cancer cell homing. Such secreted factors include vascular endothelial growth factors, TGF-beta and TNF-alpha. These molecules can elicit the release of secondary signal substances from the

niche, e.g., the chemokines S100A8 and S100A9 (Rafii and Lyden 2006). The latter two chemokines are also produced by macrophages, including those located in pre-MNs (Maru 2007). Proteins of the S100A family, including S100A4, are metastasis-associated proteins (Hemandas et al. 2006). Myeloid progenitor cells from the bone marrow can secrete the proteoglycan, which is capable to regulate remote microenvironments to become of pre-MN (Gao et al. 2012a). Carcinoma cells secreting vascular endothelial growth factor C into lymph, draining the cancer, can induce characteristic changes in locoregional lymph nodes, including an increase in lymphatic vessels and the induction of high endothelial venules, before the arrival of tumor cells (Chung et al. 2012).

Counteracting the Function of the Pre-metastatic Niche

There are several mechanisms that may abolish the generation and functions of pre-MN. Mesenchymal cells and endothelial cells in certain tissues and organs may be refractory to pre-MN-inducing cells and factors, being one explanation why certain tissues are only seldom involved by metastases, e.g., skeletal muscle. Tumor cells having settled and grown in the area of the pre-MN can later destroy this microenvironment (Bidard et al. 2008), rendering it non-functional. A third mechanism depends on the formation of tumor-entrained neutrophils (TENs), cells that circulate in the blood as a response to malignancies but are absent in healthy subjects. TENs inhibit metastatic seeding by blunting the function of pre-MNs via secretion of hydrogen peroxide (Granot et al. 2011).

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