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Abstract

Invasion of various tissues and vessels depends on distinct cellular structures involved in cell adhesion, initiation of tissue invasion, and degradation of the extracellular matrix (ECM). These structures are generally summarized under the term invadosomes, which in turn comprises the two major types of these specialized structures, i.e., podosomes and invadopodia. Podosomes are matrix-degrading adhesive structures formed by certain normal cells, such as macrophages and endothelial cells, and by invading cancer cells. The generation of podosomes strongly depends on protein kinase C-related signaling pathways. Podosomes can degrade ECM components through the shedding of wide array of proteases, specifically matrix metalloproteinases (MMPs). A special type of podosomes is invadopodia, which mediates basement membrane and tissue invasion of cancer cells. These protrusions are actin-based dynamic structures or "organelles" of transformed cells that are critically required for tumor cell invasion and extravasation. Tumor cells can extend invadopodia through the endothelial lining of vessels to the extravascular space prior to extravasation and metastatic growth.

Tissue Invasion: Invadosomes as Pacemakers of Invasion

Recent findings led to the identification of specialized cellular structures involved in adhesion, initiation of tissue invasion, and matrix degradation. These structures are generally summarized under the term invadosomes, which in turn contains the two major types of these structures, i.e., podosomes and invadopodia (Block et al. 2008). Podosomes and in particular invadosomes are characterized by the production of a wide array of enzymes that serve as histolytic factors that degrade tissues and specifically the extracellular matrix of tumors.

Podosomes

General Aspects

Podosomes ("feet bodies/particles") are matrix-degrading adhesive structures formed by invading normal cells, specifically macrophages, osteoclasts, and dendritic cell (Linder and Aepfelbacher 2003; Linder and Kopp 2005; Stylli et al. 2008; Symons 2008; Gawden-Bone et al. 2010; Murphy and Courtneidge 2011; Starnes et al. 2011; Schachtner et al. 2013). Podosomes or podosome rosettes also play a significant role in endothelial cell biology where they are involved in sprouty angiogenesis (Schlaepfer et al. 2004). Podosomes are induced by factors activating protein kinase C (Tatin et al. 2006), such as diacylglycerols and phorbol esters, and can, following their complete formation and activation, degrade EMC components through the shedding of proteases (Linder 2007). Podosomes are cylindrical cell protrusions located to the outer surface of the cell membrane, measuring up to 2 μm in diameter. Both podosomes and the similar invadopodia are actin-based structures that develop from the ventral cell membrane of cells in contact with a substratum. Podosomes carry the lipid membrane of the cell surface region from which they emerge (Yamaguchi and Oikawa 2010). In locomoting cells, podosomes are situated at the front border (leading edge) between lamellipodia and the lamellum. Podosomes have a central role in migration and invasion of matrix mediated by matrix degradation and therefore are important structures in inflammation and cancer. In contrast to invadopodia, which are small structures, podosomes grow to relatively large structures. Podosomes are usually visualized by phalloidin staining, this toxic cyclopeptide binding to filamentous actin/F-actin. In phalloidin or antibody staining, podosomes appear as isolated punctate structures on the ventral surface of cells. They are often localized behind the leading edge in case of podosomes, while invadopodia are more often clustered under the nucleus. Podosomes consist of a central core structure containing F-actin and actin regulators and a

peripheral ring structure (the podosome ring) showing integrins, vinculin, paxillin, and other proteins (Wernimont et al. 2008). In podosome rings, plectin, alpha-II spectrin, talin, and focal adhesion kinase are present, while these proteins are absent in invadopodia (Takkunen et al. 2010). In the course of the formation of a podosome ring, plectin accumulates at the early ring domain of the cell surface, whereby this deposition requires myosin contractility (Gad et al. 2008). In part of cells, including cancer cells, podosomes are clustered in the form of ringlike arrangements, the podosome rosettes. Rosette formation is strongly stimulated by Src kinases, protein kinase C, Rho family GTPases, ezrin, and certain integrins (review: Murphy and Courtneidge 2011). Formation of podosome rosettes is stimulated by ezrin interacting with cortactin and associated with adhesion of cells to fibronectin (Kocher et al. 2009). Furthermore, phosphorylation of moesin by Jun N-terminal kinase is important for podosome rosette formation (Pan et al. 2013a). Podosome rosette formation is stimulated by focal adhesion kinase (Pan et al. 2011) and by hepatoma-derived growth factor through the activation of the phosphatidylinositol 3-kinase/Akt pathway (Kung et al. 2012). Podosome rosette formation is suppressed by protein tyrosine phosphatase SHP2 (Pan et al. 2013b), and Src-induced rosette formation is inhibited by p53 via the upregulation of caldesmon (Mukhopadhyay et al. 2009).

Biogenesis and Morphogenesis of Podosomes

Podosomes contain a complex set of proteins making part of the actin-based engine, including actin, myosin IIA, the Arp2/3 complex, N-WASP, cortactin, gelsolin, and cofilin. For the generation of podosomes, actin cytoskeleton remodeling through Arp2/3-mediated actin polymerization and dynamic microtubules are required (Linder et al. 2000; Snyder et al. 2011; van den Dries et al. 2013). Rapid and spatially restricted remodeling of the actin cytoskeleton is a crucial step in the initiation of podosome formation. The site of first appearance is a surface microdomain where actin-containing stress fibers and focal adhesions intersect (Kaverina et al. 2003). Certain actin-associated proteins are involved in this process. A central role is played by the Arp2/3 pathway, whereby the Arp2/3 complex promotes actin assembly and competes with caldesmon in this function (Morita et al. 2007). Other actin-associated protein comprises Src-cortactin (Luxenburg et al. 2006; Clark et al. 2007), WASP (Tsuboi 2007), caldesmon, and paxillin (Badowski et al. 2008). Caldesmon has an important role in podosome biogenesis and function. Ectopic expression of caldesmon reduces the number of both podosomes and invadopodia (Yoshio et al. 2007). Furthermore, the actin-mediated morphogenesis of podosomes is modulated by integrins located at the podosome site. Integrin-linked kinase/ILK, located in an area surrounding the actin-rich podosome core, regulates podosome maturation (Griera et al. 2014). WASP (Wiskott-Aldrich syndrome protein) is an adaptor protein critical for podosome formation (Dovas et al. 2009) and operates in conjunction with the WASP-interacting protein/WIP. WIP is responsible for the stability and localization of WASP to sites of actin assembly in podosomes (Chou et al. 2006; Garcia et al. 2012) and is involved in ruffle formation (Banon-Rodriguez et al. 2013). WASP also interacts with the F-BAR domain protein, FBP17, a protein that promotes actin nucleation (Tsujita et al. 2013). Integrins can prevent the Src-induced cell rounding, but cannot impair the formation of podosomes (Huveneers et al. 2008).

It is suggested that an actin-microtubule cross talk in the cytoskeleton is critical for the morphogenesis of podosomes. There is evidence that protrusion of the podosome depends on the activity and function of the microtubule-associated kinesin motor component, KIF1C (Kopp et al. 2006). In early sites of podosome formation, vimentin deposition colocalizes at the stress fiber-focal adhesion interface, and plectin colocalizes with vimentin. Plectin is an important protein in cytoskeleton organization (Wiche 1998). Apart

from well-known members of the actin assembly engine, podosomes also contain other proteins, such as the cytoplasmic scaffold protein Tks5 (synonym: Fish), which accumulates in podosomes under stimulation by Src. The presence of Trk5 in podosomes is required for cell invasion (Courtneidge et al. 2005). In the process of podosome formation, Tks5 recruits AFAP-110, p190RhoGAP, and cortactin, essential for podosome morphogenesis (Crimaldi et al. 2009). The early morphogenesis of podosomes is preceded by the formation of cell surface ruffles at the dorsal surface of cells. Ruffle formation is associated with morphogenesis of podosomes and depends on an interaction between palladin and the receptor tyrosine kinase, Eps8, this interaction promoting assembly of the actin cytoskeleton (Goicoechea et al. 2006). Palladin is a protein that promotes podosome formation and assembly (Goicoechea et al. 2009), but it also regulates cell and ECM interactions via maintenance of a normal actin cytoskeleton architecture (Liu et al. 2007). Podosome size and number are regulated in macrophages by the Rho GTPase effector PAK4, a member of the p21-associated kinase family, and its regulator alphaPIX (PAK-interacting exchange factor), two factors which induce highly localized changes in actin dynamics (Gringel et al. 2006).

Podosome Functions

Podosomes are dynamic mechanosensors that sense torsional tractions underneath the podosome rings, whereby interactions between myosin tension and actin dynamics are essential for podosome regulation (Collin et al. 2008). Podosomes play an important role in the degradation of extracellular proteins. Podosomes express sets of proteases that hydrolyze several proteins and glycoproteins of the ECM. In dendritic cells, protrusive podosomes employ MMP-14 for matrix degradation and endocytosis (Gawden-Bone et al. 2010). Fully developed podosomes operate within a network of stimulatory and inhibiting factors. Podosome-mediated degradation of basement membrane collagen is induced by TGF-beta (Rottiers et al. 2009). Other proteins known to modulate podosome function are the Cdc42 regulators. Cdc42 GTPase-activating protein/CDC42GAP regulates podosome-associated cell motility through mediation of extracellular signal-related kinase/ERK activity (Szczur et al. 2006).

Invadopodia

General Aspects

There are several structures at the cell surface that are specialized in creating distinct intercellular and cell-matrix adhesions. A long-known example is the focal adhesion, which contains clusters of transmembrane integrin receptors which are tethered at one end to the ECM and at the other end to stress fibers of the actin network. A second adhesion structure which is critically involved in cancer invasion is the invadopodia.

Selected References (Gimona and Buccione 2006; Weaver 2006; Yamaguchi et al. 2006; Gimona et al. 2008; Stylli et al. 2008; Albiges-Rizo et al. 2009; Buccione et al. 2009; Saltel et al. 2011; Bravo-Cordero et al. 2012; Klemke 2012; Sibony-Benyamini and Gil-Henn 2012; Yamaguchi 2012; Génot and Gligorijevic 2014; Paz et al. 2014).

Invadopodia mediate basement membrane and tissue invasion of cancer cells and are characterized by the integration of several cytoskeletal processes that involve modulation of contractile forces and mechanotransduction (Lohmer et al. 2014; Tokui et al. 2014). Invadopodia are actin-based protrusions or "organelles" of transformed cells and tumor cells that form distinct cell-matrix adhesion sites. Invadosomes are critically required for cancer cell extravasation. In the course of intravascular spread of tumor cells, these cells can, after homing to distant endothelial surfaces, extend invadopodia through endothelium into the extravascular space prior to their extravasation and metastatic growth (Leong et al. 2014).

Invadopodia share several features with podosomes, but are morphologically different from podosomes, as they have a different structure, occur in larger numbers, and are more active in their capability to degrade matrix (Tolde et al. 2010; Artym et al. 2011). Adhesion rings surround invadopodia, a feature shared with podosomes (Branch et al. 2012). Typical invadopodia are smaller than podosomes and occur in larger numbers per cell. They measure from 0.1 to 0.8 μm in diameter and can reach a length of 2 μm or more. Invadopodia can form clusters around membrane invaginations close to the site of the Golgi complex.

Molecular Composition and Biogenesis of Invadopodia

Similar to podosomes, invadopodia possess a complex microfilament machinery regulating F/G-actin switching mediated by a now impressive number of actin-associated proteins, including N-WASP, cortactin, tensin, formins, Src kinases, the Arp2/3 complex, paxillin, cofilin, and gelsolin (Gimona 2008; Albiges-Rizo et al. 2009). Invadopodia are constructed of an N-WASP-dependent branched actin network and a Rho GTPase Cdc42-based pathway involved in invadopodial-membrane protrusion (Albiges-Rizo et al. 2009). The actin network of invadopodia, which contains cortactin, is regulated by a multimolecular complex containing Src kinase, the formin mDia1, actin, and Spire1, a protein which serves as the connection to Rab3A GTPase (Weaver 2008; Lagal et al. 2014). As an important component of the invadopodial machine, myosin 1e is located to the invadopodial core where it may act as a scaffold, linking the plasma membrane to the actin cytoskeleton (Oudekirk and Krendel 2014). In their interaction with the extracellular matrix, invadopodia are potently induced by dense fibrillar collagen via a kindlin2 serine phosphorylation signaling pathway (Artym et al. 2015). Furthermore, invadopodia are equipped with a complex set of regulatory and signaling proteins (Table 1). In particular, pathways leading to invadopodia

Table 1 Molecular composition of invadopodia

Cytoskeletal components
Actin
N-WASP
ARP2/3
Cortactin
Tensin
Gelsolin
Cofilin
Paxillin
Formin
VASP
Actopaxin
Adhesion-related proteins
Integrins
CD44
Vinculin
Signaling proteins
RhoGTPase/Cdc42
Wnt/beta-catenin signaling
ARF
GTPase-activating proteins
Focal adhesion kinase/FAK
Tyrosine kinases
Src kinases
Protein kinase Cmu
Abl interactor 1
EGFR
ASAP1/AMAP1
Dynamin 2
Tks5/Fish
Matrix-degrading enzymes and associated proteins
Metalloproteinases (mainly MMP-2, MMP-9, and MT1-MMP)
Tissue inhibitors of metalloproteinases/TIMPs
ADAMs
ADAMTS and ADAMTS-like proteins
Serine proteinase (seprase)
Dipeptidyl dipeptidase

formation are linked with a signaling cascade that also critically affects cell proliferation and differentiation, Wnt/beta-catenin signaling. Specifically, the Wnt5a-Ror2 axis is involved in enhanced formation of invadopodia (Endo et al. 2015). Biogenesis of invadopodia is strongly induced by Cdc42, while the adaptor protein is required for the degradative activity of invadosomes (Di Martino et al. 2014). A further

protein which markedly promotes formation of invadopodia is the cytoskeletal protein WAVE3, which induces cancer cell invasion and metastasis via induction of MMP-9 and other MMPs (Davuluri et al. 2014). Invadopodia biogenesis depends on diaphanous-related formins (Lizarraga et al. 2009). Paxillin, which plays a role in several steps of invadopodia biogenesis and function, is a focal adhesion-associated, phosphotyrosine-containing protein that possesses several domains for protein-protein interactions. These domains are the necessary docking site for several cytoskeletal proteins, including vinculin and actopaxin, tyrosine kinases and serine/threonine kinases, and GTPase-activating proteins and numerous adaptor proteins (Turner 2000; Schaller 2001; Pignatelli et al. 2012b). Paxillin is associated with the paxillin kinase linker/PKL, a protein regulating directed cell migration (Yu et al. 2009). At sites of ECM degradation, an invasion-related complex constructed of paxillin, cortactin, and protein kinase Cmu associated with invadopodia (Bowden et al. 1999). For the function of the actin-based network, the atypical GTP-binding protein dynamin is required, dynamin being a central modulator of cellular protrusive events (McNiven et al. 2004). In the protruding edge of invadopodia and similar structures, actin-associated proteins are accumulated. The interaction of these proteins is coordinated by a member of the F-BAR family of proteins, CIP4/Cdc42-interacting protein 4, in a Rac1/WAVE1-dependent manner (Saengsawang et al. 2013).

Induction and Regulation of Invadopodia in Cancer Cells

In cancer cells, numerous factors can elicit the biogenesis of invadopodia. A major role is played by a complex interaction of cancer cells with the extracellular matrix (ECM) located to tumor stroma. Invadopodia are strongly induced upon contact of tumor cells with distinct domains of the ECM (review: Hoshino et al. 2013a). This contact promotes the activity of several signaling pathways that induce actin cytoskeleton rearrangement, the recruiting of actin-associated proteins, and the generation of cell protrusions (Destaing et al. 2011; Linder et al. 2011). Similar to lamellipodia and related cell protrusions, formation of invadopodia depends on interactions between focal adhesions and the actin cytoskeleton. Via focal adhesions and integrin receptors, invadopodia interact with proteins in the extracellular matrix/ECM. Among ECM proteoglycans and proteins, hyaluronan interacting proteins RHAMM play a role in invadopodia induction (Gurksy et al. 2012). Generally, adhesion signaling has a central role in invadopodia formation, with the critical involvement of protein kinase C and Src kinases (Destaing et al. 2011). Src signaling to induced invadopodia is a regulated protein involved in cell migration and invasion, TM4SF5/transmembrane 4 L six family member 5 (Jung et al. 2013). Src kinase associates with diaphanous formin-1, actin, and Spire-1 in a complex that contributes to invadopodia biogenesis (Lagal et al. 2014). Invadopodia formation is stimulated by proteins that induce epithelial-mesenchymal transition/EMT, e.g., Twist1 (Eckert et al. 2011) and the focal adhesion protein Hic-5, a paxillin homologue (Pignatelli et al. 2012a), linking EMT with mechanisms that determine tissue invasion. Invadopodia are induced by Src-mediated phosphorylation of ASAP1 (Bharti et al. 2007) and by the activation of Cdc42, e.g., by the stromal cell-derived protein palladin (Goicoechea et al. 2014). Src kinases orchestrate several steps of invadopodia biogenesis in a distinct spatiotemporal pattern (Boateng and Huttenlocher 2012). The latter mechanism illustrates the close interaction between tumor cell and matrix for the induction of invadosomes. Invadopodia are induced by a key regulator of the F/G-actin switch mechanism, Abl interactor 1/Abi 1, which affects invadopodia formation in an Src-dependent manner (Sun et al. 2009). Formation of invadopodia depends on the activity of GTPases, e.g., RhoGTPases, which provide signals to the cytoskeleton through small G proteins of the Rho family (Spuul et al. 2014). Invadopodia contain the Arf GTPase-activating protein ASAP1, whereas ASAP3 is not expressed (Ha et al. 2008). The contact between cancer cells and ECM also

involves a complex mode of pH sensing. Several pH regulators such as V-ATPases and Na(+)/H(+) exchangers are expressed in invadosomes, and these sensors/regulators control the acid microenvironment to provide a milieu for appropriate activation of MMPs and other degradases (Brisson et al. 2012).

A second major pathway that induces invadopodia in cancer cells is epithelial-mesenchymal transition (EMT). Formation of invadopodia is stimulated by EMT taking place upon contact of tumor cells with the extracellular matrix. Apart from its central role in EMT induction, the transcription factor Twist1 is capable to induce invadopodia formation, probably via its transcriptional target, PDGFRalpha (Eckert et al. 2011). Also the EMT-inducing factor TGF-beta induces invadopodia formation via ectopic expression of the focal adhesion protein, Hic-5 (Pignatelli et al. 2012a). In the setting of EMT, podosome-like structures occurring in noninvasive carcinoma cells switch to actin comet-embedded invadopodia containing MMP-1. In the course of this transition, the podosomes become smaller and achieve the shape of numerous invadopodia, structures in which talin is replaced by tensin. Therefore, EMT can induce the production of the potent degrading engine required for cancer invasion (Takkunen et al. 2010). Invadopodia are also induced by a factor involved in the regulation of EMT, CD147/basigin (Grass et al. 2012).

Invadopodia maintenance and function are regulated by integrins, Src tyrosine kinase signaling, cortactin, AMAP/ASAP1, the adaptor protein Tks5/Fish, receptor tyrosine kinases, Rho family GTPases, ARF6, and dynamin 2. Beta1 integrins are required for the formation of competent invadopodia, whereby beta1 integrin interacts with the tyrosine kinase Arg and stimulates Arg-dependent phosphorylation of cortactin (Beaty et al. 2013). Beta1A integrin is a master regulator of podosome and invadopodia organization and function (review: Destaing et al. 2010). ASAP1 is an Arf GTPase-activating protein/GAP containing a BAR domain and is a substrate for Src kinase.

Tissue and Matrix Destruction (Histolysis) as a Major Mechanism of Cancer Invasion

Introduction

Both invadopodia and lamellipodia engage in contacts with the underlying extracellular matrix (ECM) and are then stimulated to secrete matrix metalloproteinases (MMPs; see below; Coussens and Werb 1996; Stamenkovic 2000; Linder 2007; Linder et al. 2011; van Horssen et al. 2013). The contact between invadopodia and ECM is a complex process that involves signals from matrix rigidity and myosin II-FAK/Cas pathways (Alexander et al. 2008). Typical MMPs produced by invadopodia are MMP-2 and MMP-9 and in part of neoplasms also MT1-MMP (Watanabe et al. 2013). Expression and secretion of these enzymes causes pericellular proteolysis in cancer (Sevenich and Joyce 2014). Invadopodia express latent MMP-2 and membrane type 1 MPP at the cell surface, where they are activated (Chen and Wang 1999). ECM degradation by invadopodia is regulated by the action of the phosphoinositide-binding protein, ZF21, a protein that promotes cancer cell migration and invasion (Hoshino et al. 2013b). The function of invadopodia also requires several types of ADAMs, which interact with integrins in invadopodia and cooperate with certain invadopodial adaptor proteins, such as Tks5/Fish. Physiological type I collagen can induce a special type of invadosomes, the linear invadosomes. Linear invadosomes, cortactin- and N-WASP-containing protrusions that can degrade matrix, result through replacement of podosomes or invadopodia upon contact with type I collagen present in collagen-rich ECMs (Juin et al. 2012).

Matrix Metalloproteinases (MMPs): Types and Classification

Matrix metalloproteinases (MMPs) are enzymes that are implicated in remodeling of the extracellular matrix (EMC), including the basement membranes (Deryugina and Quigley 2006; Friedl and Wolf 2009; Shiomi et al. 2010). MMPs are

Table 2 Types of metalloproteases (MMPs) and their substrates

Type of MMP	Substrate(s)
Membrane-bound MMPs	
MT1-MMP (MMP-14)	Collagens I–III, gelatins, aggrecan, laminin
MT2-MMP (MMP-15)	Nidogen, tenascin, aggrecan, perlecan, laminin
MT3-MMP (MMP-16)	Collagen III, gelatins, fibronectin
MT4-MMP (MMP-17)	Gelatins, fibrinogen
MT5-MMP (MMP-24)	Proteoglycans
MT6-MMP (MMP-25)	Collagen IV, gelatins, laminin, fibronectin
MMP-23	Gelatin
GPI-linked MMP	
Secreted MMPs	
MMP-1 (interstitial collagenase)	Collagens I–III, VII, and X, gelatins, proteoglycans
MMP-2 (gelatinase A)	Gelatins, collagens, laminin, fibronectin
MMP-3 (stromelysin-1)	Gelatins, laminin, fibronectin, proteoglycans
MMP-7 (matrilysin-1)	Proteoglycans, gelatins, elastin, tenascin, entactin
MMP-8 (neutrophil collagenase)	Collagens I–III, gelatins, aggrecan
MMP-9 (gelatinase B)	Gelatins, collagens III–V, aggrecan, elastin
MMP-10 (stromelysin-2)	Aggrecan, laminin, fibronectin, collagens III–V
MMP-11 (stromelysin-3)	Fibronectin, laminin, aggrecan, gelatins
MMP-12 (metalloelastase)	Elastin, aggrecan, fibronectin, collagen IV
MMP-13 (collagenase-3)	Collagens I–IV, IX, X, and XIV, aggrecan, tenascin
MMP-19 (RASI-1)	Collagen IV, gelatin, fibronectin, tenascin
MMP-20 (enamelysin)	Amelogenin, aggrecan, gelatin
MMP-21	?
MMP-26 (matrilysin-2)	Gelatin, collagen IV, fibronectin, vitronectin
MMP-27	?
MMP-28 (epilysin)	?

classified as two main types of proteases, i.e., those that are anchored to the cell surface membrane and a second group that is secreted into the extracellular space (Table 2).

General Roles and Regulation of MMPs in Liver Cancer

Generally, MMPs play pleiotropic roles in cancer, exceeding aspects of mere "degradomics" but also including effects on cell adhesion, growth signaling, and other pathways (Kleiner and Stetler-Stevenson 1999; Overall and Dean 2006). The activity of MMPs is regulated and controlled at several levels, such as enzyme activation or inhibition at the cell surface, complex formation, and compartmentalization in various subcellular compartments. Within normal and cancer cells, MMPs can be localized at the cell surface, in the cytosol, and in organelles and the nucleus. The role of intracellular MMPs has not yet been clarified in detail (review: Mannello and Medda 2012). Downregulation of the Notch signaling pathway impairs HCC cell migration (Zhou et al. 2013b) and inhibits HCC cell invasion by inactivating MMP-2 and MMP-9 expression via the extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling pathways (Zhou et al. 2012), while high levels of Notch1 augment MMP-2 and MMP-9 and promote a highly invasive HCC phenotype. Conversely, sonic hedgehog, a ligand of hedgehog, is frequently expressed in HCC cells and decreases the expression of MMP-9 via the ERK pathway (Lu et al. 2012). High Notch1 expression in HCCs was correlated with tumor size, tumor grade, venous invasion, and the metastatic state (Zhou et al. 2013a). In its inhibitory action on migration and invasion, Notch1 operates by regulating CD44v6, E-cadherin, MMPs, and uPA via the COX-2 and ERK1/2 pathways (Zhou et al. 2013). Downregulation of Notch1 inhibits HCC cell invasion by inactivating the COX2/Snail/E-cadherin pathway involved in EMT (Zhou et al. 2013c). Secretion of multiple MMPs is promoted by HGF via the transcription factor Ets-1 which activates MMP transcription (Ozaki et al. 2003). Secretion of MMPs by stromal cells is stimulated by CD147 (EMMPRIN; basigin), a cell surface glycoprotein that belongs to the immunoglobulin superfamily and is strongly expressed on the surface of many tumor cell types. Basigin exists in several isoforms with differential functions. Basigin stimulates the

secretion of VEGF and hyaluronan, promoting angiogenesis and anchorage-independent growth (Nabeshima et al. 2006). These effects are abolished by depletion of CD147, mainly downregulating MMP-11 and VEGF (Jia et al. 2007). CD147 exerts its pro-metastatic effects also in HCCs (Xu et al. 2007; Zhang et al. 2007c; Jia et al. 2008). In HCC cells, downregulation of CD147 inhibits gelatinase production, interferes with tumor cell adhesion to type IV collagen, and alters cytoskeletal structure (Qian et al. 2008). One basigin isoform, basigin-3, inhibited proliferation of HCC cells and MMP induction (Liao et al. 2011). CD147 interacts with integrin alpha6beta1, stimulating invasion and MMP secretion in HCC cells (Dai et al. 2009). A further protein with which CD147 interacts is annexin, a Ca(2+)- and phospholipid-binding protein subject to phosphorylation by tyrosine kinases and protein kinase C. This interaction promotes migration and MMP-mediated invasion of HCC cells. The pro-invasive and pro-metastatic effect of basigin/CD147 is counteracted by the basigin isoform, basigin-3, in HCC (Liao et al. 2011).

Expression of the Diverse Metalloproteinases in Liver Cancer

Several members of the large MMP family are expressed or overexpressed in HCCs and cholangiocarcinomas and affect the development of a metastatic phenotype (Yamamoto et al. 1999; Bodey et al. 2000; Giannelli et al. 2002; McKenna et al. 2002; Ishii et al. 2003; Ozaki et al. 2003; Matsunaga et al. 2004; Okamoto et al. 2005; Gao et al. 2006; Altadill et al. 2009). Generally, expression of MMPs in cancer cells is augmented by EMT. The EMT factor, Twist1, activates MMPs and by this induces tumor cell invasion (Zhao et al. 2011). Snail, an inducer of EMT, accelerates cancer invasion by an EMT-associated up-regulation of MMPs (Miyoshi et al. 2004, 2005). Expression of MMPs increases as a function of increasing stage (Gao et al. 2006). Secretion of MMPs by stromal myofibroblasts is suppressed by TGF-beta1, while the hormone relaxin binding

to its cognate receptor, relaxin family peptide receptor 1, upregulates MMPs (Chow et al. 2012).

MMP-1

MMP-1 is involved in both tumor cell invasion and the generation of metastases, also in HCCs (Ogasawara et al. 2005). MMP-1 proteolytically activates protease-activated receptor-1 (PAR-1). In HCCs, the MMP-1/PAR-1 signaling axis is strongly activated and associated with tumor invasion and progression (Liao et al. 2011, 2012). Increased expression of MMP-1 and MMP-2 in HCCs is correlated with tumor differentiation (Ogata et al. 1999). However, other studies arrived at different results. For example, high levels of MMP-1 transcripts were detected in well-differentiated cancer cells of early HCCs, but not in moderately to poorly differentiated HCCs, suggesting an MMP-1-mediated role in early invasive processes, such as destruction of portal tracts (Okazaki et al. 1997).

MMP-2

Expression of MMP-2 is involved in HCC invasion, and its activity is influenced by several genetic variants that modulate the enzyme's effects in the invasive pathway (Wu et al. 2008). Expression of MMP-2 in HCCs is associated with dedifferentiation in HCC (Ogata et al. 1999) and was correlated with intra- and extrahepatic metastases (Liu et al. 2003). Expression of MMP-2 predicted lymph node metastasis in HCCs (Xiang et al. 2011). The secretion of MMP-2 is stimulated by the transcription factor, Snail, which is expressed in HCC cells and mediates EMT. On the other hand, downregulation of Snail in HCC cells is associated with increased expression of the adhesion molecule, E-cadherin, and downregulation of MMP-2 (Chen et al. 2012a). MMP-2 is also upregulated by osteopontin (Chen et al. 2011a,b), through the SDF-1/CXC4 axis (Zhang et al. 2011), via Notch signaling (Zhou et al. 2012), by secreted clusterin (Chen et al. 2012a), Rock2 (Huang et al. 2014), and by sonic hedgehog signaling through focal

adhesion kinase/AKT signaling (Chen et al. 2013a). Osteopontin itself is downregulated by microRNA-181a (Bhattacharyya et al. 2010). The activity of MMP-2 in HCC is strongly controlled by TIMP-2 (Musso et al. 1997; Giannelli et al. 2002). MMP-2 expression is downregulated by microRNA-29b, a microRNA that suppresses angiogenesis, invasion, and metastasis (Fang et al. 2011). As with other MMPs, MMP-2 is regulated by tissue inhibitor of metalloproteinase-2/TIMP-2. Strong expression of TIMP-2 in hilar cholangiocarcinomas is associated with inhibition of cancer invasion and metastasis (Xiao et al. 2004). MMP-2 is also expressed in subsets of gallbladder carcinoma (Karadag et al. 2008).

MMP-3

Expression of MMP-3 is associated with the prognosis of HCV-related HCCs (Okamoto et al. 2010). In HGF-induced invasion of HCC cells, MMP-3 is involved, in that HGF stimulates the secretion of pro-MMP-3 (Monvoisin et al. 2002). Upregulation of MMP-3 in hepatoma cells is associated with a downstream mediation of autocrine motility factor (Yu et al. 2004). MMP-3 is also induced by HBV X protein, which is a known promoter of cell migration (Yu et al. 2005). The pro-metastatic activity of MMP-3 depends on its genetic polymorphism, in that the MMP-3 5A allele was the most prominent MMP-3 enzyme to promote invasion (Okamoto et al. 2010). Expression of MMP-3 in HCC cells is reduced by microRNA-30a-3p (Wang et al. 2014).

MMP-7

Similar to other MMPs, MMP-7 has recently been demonstrated to act in the invasion cascade, also in metastatic HCCs (Gao et al. 2006). In particular, MMP-7 expression is a prognostic factor in cholangiocarcinoma, whereby cholangiocarcinoma cells show strong immunoreactivity for this enzyme (Miwa et al. 2002). Expression of MMP-7 is associated with poor

prognosis in patients with intrahepatic cholangiocarcinoma (Hirashita et al. 2012) and is an unfavorable postoperative prognostic factor in perihilar, hilar, and extrahepatic cholangiocarcinomas (Itatsu et al. 2008), and serum MMP-7 seems to be a valuable diagnostic marker in discrimination of cholangiocarcinomas from reactive biliary pathologies (Leelawat et al. 2009). One non-synonymous variant of MMP-7 was found to confer risk of liver cirrhosis in patients with HCC (Hung et al. 2009). MMP-7 engages in a signaling pathway together with beta-catenin. Upregulation of MMP-7 expression by beta-catenin is promoted by DKK1, which is overexpressed in HCCs (Chen et al. 2013b). Similar to sclerostin, DKK1 (Dickkopf-related protein 1) is an antagonist of the Wnt/beta-catenin signaling cascade. DKK1 promotes invasion and metastasis in HCCs, associated with increased RhoA and JNK levels (Tao et al. 2013). In cholangiocarcinomas, DKK1 is related to lymphatic metastasis and an aggressive course (Shi et al. 2013). This phenomenon may be caused by the induction of an invasive phenotype by DKK1. MMP-7 expression is downregulated in HCCs by the tumor suppressor, fibulin-5 (Tu et al. 2014).

MMP-9

MMP-9 has an important role in HCC invasion (Arii et al. 1996; Sun et al. 2005; Nart et al. 2010; Tao et al. 2010; Yeh et al. 2010; Thieringer et al. 2012) and is also involved in invasion of hilar cholangiocarcinoma (Li et al. 2005). Upregulation of MMP-9 is found in a majority of HCCs and is subject to MMP-9 gene polymorphism (El-Samanoudy et al. 2014). Overexpression of MMP-9 mRNA may be associated with the progression of small HCCs with a diameter of <=2 cm (Sakamoto et al. 2000). MMP-9 expression is a significant predictor of recurrence after liver transplantation in HCC patients (Zhang et al. 2006). The MMP family members, MMP-2 and MMP-9, are critical for the invasive potential of numerous malignancies, including HCC. Overexpression of MMP-9 in HCCs is correlated with growth and invasion in

small tumors already (Sakamoto et al. 2000) and is associated with macrovessel invasion in larger tumors (Nart et al. 2010). High expression of MMP-9 was associated with both time to recurrence and overall survival, while high expression of MMP-2 was only correlated with time to recurrence (Chen et al. 2012b). MMP-9 cleaves osteopontin to produce a fragment that is essential for osteopontin-induced invasion of HCC cells (Takafuji et al. 2007). MMP-9 is also expressed in tumor-associated macrophages (TAMs) located at the invasive front of murine HCC (Roderfeld et al. 2010). MMP-9 cooperates with focal adhesion kinase (FAK), whereby this mechanism that is active in HCC cell migration is stimulated by activated hepatic stellate cells (Han et al. 2014). In addition to its role as mediators of histolysis, MMPs may cause other biologic effects, e.g., angiogenesis in cancers (Bergers et al. 2000). In mice, hepatocyte-specific expression of MMP-9 promoted liver tumor development (Thieringer et al. 2012).

The induction and localization of MMP-9 are regulated by several factors. MMP-9 signaling in HCC is promoted by activated hepatic stellate cells (Han et al. 2014), which occur in tumor stroma. MMP-9 activity for mediating invasion is regulated by the calcium-binding protein S100A4 (Zhang et al. 2013) and is strongly regulated by protein kinase C-dependent NF-kappaB activation in HCC cells (Hah and Lee 2003). Trafficking of MMP-9 in invadopodia is regulated by Rab GTPases, specifically Rab40b (Jacob et al. 2013). Induction of MMP-9 expression in HCC is stimulated by interleukin 23 through NF-kappaB induction (Li et al. 2012). Expression of MMP-9 is promoted by the PRL (phosphatase of regenerating liver) phosphatase, a group of distinct protein tyrosine phosphatases. Activation of MMPs is mediated by Twist-induced EMT, whereby specifically MMP-2 and MMP-9 are secreted (Zhao et al. 2011). The activity of MMP-9 and MMP-2 is attenuated by the protein, RECK (reversion-inducing cysteine-rich protein with Kazal motifs), an important regulated metalloproteinase. Downregulating of RECK in cholangiocarcinomas is associated with enhanced MMP-2/MMP-9 activity and a metastatic phenotype (Namwat et al. 2011). HBV viral X protein induces MMP-9 gene expression via activation of ERK and PI-3K/AKT pathway activation (Chung et al. 2004), whereas hepatitis C virus NS3 protein enhances cancer cell invasion by activating MMP-9 activity (Lu et al. 2015). MicroRNA-133a inhibits HCC cell migration and invasion by targeting MMP-9 (Chen et al. 2015). The expression of MMP-9 is inhibited by microRNA-491, which also blocks EMT in HCC (Zhou et al. 2013d). MMP-9 is upregulated in other hepatic and biliary tract cancers, including cholangiocarcinoma. In cholangiocarcinomas, MMP-9 expression is enhanced by downregulation of microRNA-138 (Wang et al. 2013b). MMP-9 expression is enhanced in gallbladder carcinoma (Karadag et al. 2008).

MMP-10

Strong immunoreactivity for MMP-10 was found in HCCs, especially in the extracellular matrix adjacent to blood vessels (Bodey et al. 2000). MMP-10 can be activated by C-terminal-truncated HBV X protein, a process stimulating HCC invasion (Sze et al. 2013).

MMP-11

MMP-11 is strongly expressed in both tumor cells and stromal cells surrounding cancer. There is evidence that MMP-11 is a tumor lymphatic metastasis-associated MMP (Jia et al. 2007). MMP-11 is downregulated by CD147 (basigin), affecting the lymphatic metastasis pattern of HCC in a mouse model (Jia et al. 2007). Expression and secretion of MMP-11, together with VEGF, is inhibited in HCCs by ectopic expression of microRNA-125a (Bi et al. 2012).

MMP-12

Overexpression of MMP-12 was found in 58 % of human HCCs, and its expression was significantly correlated with an invasive phenotype (in particular venous invasion) and poor prognosis in HCC (Ng et al. 2011).

MMP-14

Membrane type 1 MPP (MT1-MMP, MMP-14) promotes invasiveness in HCC cell lines (Murakami et al. 1999), is overexpressed in highly invasive HCCs (Harada et al. 1998), and induces metastases in HCC, but MMP-14 gene polymorphisms also contribute to HCC susceptibility (Chen et al. 2011c). Increased MMP-14 mRNA expression by tumor cells in HCCs may have prognostic significance (Määtä et al. 2000). An aggressive phenotype is observed in HCCs that show atypical localization of MT1-MMP in the tumor cell nuclei (Ip et al. 2007). By its enzymatic activity, it not only degrades extracellular matrix but it also induces a signaling pathway stimulating cell adhesion and proliferation (Ip et al. 2005). MT1-MMP confers a proteolytic activity to invadopodia (see above), particularly upon tumor cell contact with ECM. This activity is regulated by the v-SNARE TI-VAMP/VAMP7 (Steffen et al. 2008). The cell surface level and endocytosis of MMP-14 are also regulated by the planar cell polarity-associated protein, VANGL2, a protein that also induced invadopodium formation (Williams et al. 2012). In tumor cells, endocytosis of MT1-MPP by clathrin- and caveolae-dependent pathways is counteracted by mechanisms stabilizing the enzyme at the cell surface (Poincloux et al. 2009). MT1-MPP is targeted by microRNA-150-5p which inhibits HCC migration and invasion. In metastasizing liver cancers, expression of this MiR is reduced (Li et al. 2014). MT1-MMP can be upregulated by HBV X protein (Ou et al. 2007). Similar to MT1-MMP, also MT3-MMP expression was associated with an invasive phenotype in HCCs (Arai et al. 2007).

Tissue Inhibitors of Metalloproteinases (TIMPs) in Liver Cancer

Tissue inhibitors of metalloproteinases (TIMPs; four members, TIMP-1, TIMP-2, TIMP-3, and TIMP-4) are important regulator proteins that interfere with the activity of certain MMPs. TIMP-1 inhibits MMP-9, while TIMP-2 inhibits MMP-2. Both TIMPs were detected in HCC tumor cells, stromal cells, and endothelial cells, whereby expression signals were stronger for TIMP-1 than for TIMP-2 (Joo et al. 2000; Matsumoto et al. 2004), which is of special interest in the light of the MMP expression patterns in HCCs. In one study, TIMP was preferentially expressed in the capsule of HCCs (Fukuda et al. 1991). Metastatic HCCs showed lower levels of TIMPs (Gao et al. 2006), and HCC tissue expression levels of TIMP-2 were higher in patients without metastases (Giannelli et al. 2002). However, TIMP-1 can create a premetastatic niche in the murine liver through stromal cell-derived factor 1/CXCR4-dependent neutrophil recruitment (Seubert et al. 2015). Expression of TIMPs is heterogeneous and varies considerably among HCC nodules, but there was no clear correlation between the TIMP expression levels, differentiation grade, and invasion, although TIMP expression was also detectable in HCC metastases (Nakatsukasa et al. 1996). In cholangiocarcinoma, expression of TIMP-1 was strong and was associated with the extent of invasion (Nakatsukasa et al. 1996). In cultured cells, expression of TIMP-1 was negatively regulated by the EMT effector, Twist1 (Okamura et al. 2009). In addition to TIMP-1 and TIMP-2, TIMP-3 is involved in the regulation of cancer invasion. Transfection of TIMP-3 in HCC cell lines suppresses invasive capacity (Zhang et al. 2007b). In HBV-associated HCC, TIMP3 can be epigenetically silenced (Lai and Lo 2005).

There are protease inhibitors different from TIMPs. The serine protease inhibitor, clade B, member 1/SERPINB1, is a member of the SERPINB family involved in suppression of migration and invasion in various cancers. SERPINB1 expression in HCCs is correlated with tumor invasion and an aggressive course (Cui et al. 2014).

Metzincin Superfamily Members: ADAMs

A disintegrin and metalloproteinases (ADAMs) or MDCs (metalloprotease-like, disintegrin-like, cysteine-rich proteins) are membrane-bound

metzincins and the adamalysin subfamily. Twenty-two members of ADAM family are known (reviews: Porter et al. 2005; Edwards et al. 2008). ADAMs possess a domain structure similar to that of MMPs, but in contrast to the latter, ADAMs display a cysteine-rich domain, an epidermal growth factor-like repeat domain, and the disintegrin domain, but lack the hemopexin-like domain of MMPs (review: Klein and Bischoff 2011). The main functional activity of ADAM metalloproteases is ectodomain shedding of various receptors, growth factors, Notch, cytokines, and other signaling substances involved in cellular homeostasis ("ADAM sheddases"). For example, ADAM17 is critically involved in post-shedding activation of pro-TNF-alpha and is therefore also termed tumor necrosis factor-alpha convertase or TACE. For several cell membrane signaling proteins, cleave by ADAM sheddases prepares what is called regulated intramembrane proteolysis or RIP, resulting in intracellular domains that can be translocated to the nucleus for the regulation of gene transcription (Edwards et al. 2008).

Various malignant neoplasms express several species of ADAMs, particularly ADAM8, ADAM9, ADAM10, ADAM12, ADAM15, ADAM17, ADAM19, and ADAM28 (review: Mochizuki and Okada 2007; Duffy et al. 2009). In cancer invasion and spread, the critical function of ADAMs is the metalloproteinase activity of these enzymes (Rocks et al. 2008). Similar to MMPs, the metalloprotease domain is shielded by a pro-domain that involves the cysteine switch mechanism. For activation of the protease, this protecting shield is removed in the trans-Golgi network by the action of proprotein convertases, such as furin (Klein and Bischoff 2011). ADAM8 is overexpressed in HCCs in comparison with normal liver. Expression levels were positively correlated with tumor size, grade, recurrence, and metastasis (Zhang et al. 2013). Downregulation of ADAM10 expression inhibits invasiveness and metastasis of human HCC cells, associated with increased E-cadherin protein levels and a related change in cell migration (Yue et al. 2013). ADAM12 mediates the shedding of the epidermal growth factor receptor (EGFR) ligand, heparin-binding EGF-like growth factor/HB-EGF, in a Notch-dependent manner. Released EB-EGF induces the formation of invadopodia under hypoxic conditions (Diaz et al. 2013). ADAM17 is involved in the cleavage of the ectodomain of numerous transmembrane proteins. ADAM17 is overexpressed in HCC under hypoxic conditions and enhances the phosphorylation of the EGFR (Wang et al. 2013a). ADAM17 is targeted by microRNA-145 which suppresses invasion of HCC cells (Yang et al. 2014). In HCCs, ADAM17 is also regulated by microRNA-122, a tumor suppressor microRNA (Tsai et al. 2009). ADAM28 is implicated in tumor growth and progression in several human cancers (Mochizuki and Okada 2009). It operates through cleavage of the proapoptotic von Willebrand factor. Tumor cells with low expression levels of ADAM28 display a higher rate of apoptosis (Mochizuki et al. 2012).

ADAMTS and ADAMTS-Like Proteins

ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs) are a family of extracellular proteases that is distinguished from ADAM metalloproteases by the presence of multiple copies of thrombospondin 1-like repeats. ADAMTS bind to and process various components of ECM proteins and proteoglycans, including heparin; procollagens I, II, and II; aggrecan; brevican; versican; decorin; fibronectin; and von Willebrand factor. ADAMTS are involved in the regulation of critically important processes such as morphogenesis, angiogenesis, and carcinogenesis. For example, of the at least 20 members in this family, ADAMTS2 is a procollagen N-proteinase; ADAMTS4 and ADAMTS5 are aggrecanases active in the hydrolysis of cartilage aggrecan (review: Tang 2001). Overexpression of ADAMTS1 results in shedding of semaphorin 3C from the ECM, a step that stimulates cell migration (Esselens et al. 2010). The seven ADAMTS-like proteins are proteins that lack proteolytic activity but possess ADAMTS ancillary domains. The proteins have important regulatory roles in the ECM (review: Apte 2009).

Other Proteases Involved in Cancer Invasion and Progression

In invadopodia, few other proteolytic enzymes are expressed, including serine proteinase/seprase, aspartate proteases, threonine proteases, dipeptidyl dipeptidase, and cysteine cathepsins (Jevnikar et al. 2012; Rakashanda et al. 2012). A group of calcium-dependent cysteine proteases is the calpains, enzymes involved in several homeostatic mechanisms. Among the various calpain members, m- and m-calpain are involved in regulating cell migration and invasion. In comparison with normal hepatocytes, these two calpains are elevated in HCC cells and regulate HCC cell migration and invasion (Chen et al. 2013c).

Several types of enzymes active on matrix proteins are produced and secreted by leukocytes infiltrating the tumor stroma. Macrophages express a distinct metalloelastase, a member of the MMP family. Expression of metalloelastase by tumor-associated macrophages in HCC is correlated with angiostatin generation and survival, in that tumors having no metalloelastase expression and hence a reduced angiostatin showed poorer survival (Gorrin Rivas et al. 1998). Human neutrophils produce an elastase that can degrade TIMP-1, a process accelerated by heparin (Nunes et al. 2011).

HCCs can express and secrete various ectopeptidases, including neprilysin (CD10), aminopeptidase N (CD13), and angiotensin-I-converting enzyme (CD143), whereby this expression differs considerably between normal liver and HCCs. In HCCs, neprilysin immunoreactivity is found on canalicular domains, a feature with diagnostic significance (Borscheri et al. 2001). In comparison with normal parenchyma, CD10 is low in HCCs, while CD13 and CD143 were mildly increased. CD13 may be involved in the regulation of cell polarity, whereas CD143 may influence angiogenesis (Rocken et al. 2004).

Thrombin can induce cell migration in HCCs. HCCs express several proteinase-activated receptors (PAR), mainly the thrombin receptors PAR(1), PAR(3), and PAR(4). PAR form a novel G-protein-coupled receptor subfamily. Stimulation of HCC cells in vitro with thrombin increased migration across a collagen barrier (Kaufmann et al. 2007). The urokinase system involves three key components, urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), and plasminogen activator inhibitor type 1 (PAI-1). This system is activated in several tumor types and potently affects tumor invasion and metastasis. Urokinase-type plasminogen activator (uPA) is a key protein in the plasminogen activation system and is critically involved in proteolytic steps in tumor invasion. In human HCCs, uPA and c-met overexpression are coordinated in a complex fashion. Following its binding to its c-met receptor, HGF can upregulate uPA in a dose-dependent manner and by this mechanism augments HCC invasion (Lee et al. 2008). High levels of uPA in HCCs were correlated with macrovessel invasion and metastasis, and in tumors expressing uPA, uPAR, and PAI-1, a more prominent invasion phenotype was observed (Zheng et al. 2000). Overexpression of microRNA-23b in HCC cells leads to uPA and c-met downregulation and to decreased migration (Salvi et al. 2009). Plasmin- and trypsin-mediated activation of MMPs is inhibited by TFPI-2 (tissue factor pathway inhibitor), an extracellular matrix-associated Kunitz-type serine proteinase inhibitor. TFPI-2 inhibits the invasion of HCC cells (Xu et al. 2011).

Non-protease Proteins Involved in ECM Degradation

In the setting of the invasion process, heparan sulfate chains of heparan sulfate proteoglycans located in the ECM are cleaved by the endoglycosidase heparanase. Heparanase is upregulated in HCCs with an invasive-metastatic phenotype (El-Assal et al. 2001; Xiao et al. 2003; Edovitsky et al. 2004; Zhang et al. 2007a). In these neoplasms, heparanase also promotes angiogenesis (Ilan et al. 2006). HCCs also synthesize heparin-degrading sulfatases, sulfatase 1 (SULF1) and sulfatase 2 (SULF2). These two enzymes

desulfatize heparan sulfate proteoglycans localized to cell surface and ECM. SULF1 and SULF2 are differentially expressed in HCCs, in that SULF1 is downregulated in up to a third of HCCs, while SULF2 is upregulated in up to 60 % of primary HCCs, and SULF2 activates MAP kinase and AKT pathways, promoting HCC growth and invasion (Lai et al. 2008).

In the invasion process, several nonstructural proteins of the extracellular matrix play a significant role. These proteins are called matricellular proteins and belong to various protein families. Well-known members include CCN family member cysteine-rich angiogenic inducer 61 (Cyr61/CCN1), CCN6, osteopontin, secreted protein acidic and rich in cysteine (SPARC), angiopoietin-like protein 4 (ANGPTL4), and thrombospondin-1 and thrombospondin-2 (review: Chong et al. 2012).

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