Role of Integrins in Regulating Proteases to Mediate Extracellular Matrix Remodeling

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Received: 13 January 2012 / Accepted: 1 March 2012 / Published online: 22 March 2012
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Abstract The extracellular matrix (ECM) is an extracellular scaffold composed of complex mixtures of proteins that plays a pivotal role in tumor progression. ECM remodeling is crucial for tumor migration and invasion during the process of metastasis. ECM can be remodeled by several processes including synthesis, contraction and proteolytic degradation. In order to cross through the ECM barriers, malignant cells produce a spectrum of extracellular proteinases including matrix metalloproteinases (MMPs), serine proteases (mainly the urokinase plasminogen activator (uPA) system) and cysteine proteases to degrade ECM components. As major adhesion molecules to support cell attachment to ECM, integrins play critical roles in tumor progression by enhancing tumor cell survival, migration and invasion. Previous studies have shown that integrins can regulate the expression and activity of these proteases through different pathways. This review summarizes the roles of MMPs and uPA system in ECM remodeling and discusses the regulatory functions of integrins on these proteases in invasive tumors.

Keywords ECM remodeling · Metastasis · Integrins · MMPs · uPA system

Abbreviations

ECM	Extracellular matrix
MMP	Matrix metalloproteinase
uPA	Urokinase plasminogen activator
CAM	Cell adhesion molecule
ILK	Integrin-linked kinase
FAK	Focal adhesion kinase
MT-MMP	Membrane-anchored type matrix metalloproteinase
TIMP	Tissue inhibitor of metalloproteinase
RECK	Reversion-inducing cysteine-rich protein with kazal motifs
SCC	Squamous cell carcinoma
HMW	High molecular weight
JNK	c-Jun N-terminal kinase
uPAR	uPA receptor
PAI	Plasminogen activator inhibitor
MPI	MMP inhibitor

Introduction

ECM, a key component of the microenvironment, plays a pivotal role in tumor pathogenesis and progression. It is a complex assembly of many proteins such as fibrous structural proteins and proteoglycans, forming an elaborate network within tissues [1, 2]. ECM is not only a simple static scaffold, but also can be modified through remodeling to create an environment for tumor metastasis [3].

Metastasis is the leading cause of cancer mortality, by which cancer cells leave from the primary tumor, disseminate and settle at distant sites to form secondary tumors. The

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metastatic cascade is very complicated and remains poorly understood. Generally, the process can be summarized as follows: 1) formation of new blood vessels for the growing tumor; 2) release of tumor cells from the primary site; 3) invasion and migration through the barriers of epithelial basement membrane and surrounding ECM; 4) invasion into the vasculature; 5) adhesion to endothelial cells and extravasation; 6) formation of metastatic tumors at the new sites [4–6].

ECM remodeling is important for many development processes and contributes to tumor metastasis [3, 7]. ECM can be remodeled by several processes including synthesis, contraction and proteolytic degradation [3]. As a barrier to progressing tumor cells, their surrounding ECM must be degraded to facilitate the metastasis of invasive tumor [8]. The ECM can be degraded directly by proteases including MMPs, serine proteases (mainly the uPA system) and cysteine proteases, or indirectly in response to signals transduced by ECM receptors [7]. In metastatic tumors, the protease activity and those signals are often dysregulated.

Cells sense and respond to the changes in ECM via integrins. Integrins are a family of heterodimeric transmembrane adhesion receptors comprising α and β subunits. In vertebrates, 18 α and 8 β subunits give rise to at least 24 different heterodimers recognizing distinct but often overlapping ligands (Fig. 1) [9–11]. As important adhesion molecules, integrins mediate cell-cell, cell-ECM, cell-pathogen interactions and bidirectional signaling across the plasma membrane and involve in various cell functions such as differentiation, migration and survival [11, 12]. Previous studies have demonstrated that integrins can promote metastasis by modulating the proteolytic enzymes [13, 14]. Thus, understanding the interplay between integrins and ECM remodeling proteases is one of the major challenges

in cancer research. In this review, we will summarize the role of integrins on regulating the function of proteases and discuss the mechanism.

Overview of Integrin Functions in Tumor Metastasis

Cells attach to the ECM via integrins [15]. Upon ligand binding, integrins transduce the extracellular cues from the ECM to intracellular cytoskeleton, a process called “outside-in signaling” [16]. Inversely, the binding of intracellular proteins such as talin and kindlin to the cytoplasmic tails of integrin triggers the conformational changes and activation of integrin, which is termed “inside-out signaling” [16]. The bidirectional signaling involves assembly and disassembly of numerous components that form around the cytoplasmic tail of integrins [17]. The adhesion complexes formed by integrin is known as “integrin adhesome”, which consists of at least 156 components interlinked by hundreds of interactions [18, 19]. Among the components of adhesome, talin, paxillin, filamin, integrin-linked kinase (ILK) and focal adhesion kinase (FAK) have prominent functions [16].

Extensive studies have revealed that alterations of integrin expression and function are frequently found in most human cancers [20–23]. In particular, integrins have been implicated in all steps of tumor metastasis [13, 24]. Angiogenesis, providing oxygen and nutrients to the rapidly proliferating tumor cells, has essential roles in tumor metastasis [25]. Several integrins are involved in angiogenesis, such as $\alpha V\beta 3$, $\alpha V\beta 5$ and $\alpha 5\beta 1$ [26, 27]. Antagonists of these integrins can block tumor induced angiogenesis in multiple animal models and have clinical benefits in humans with solid tumors [26, 27]. Abnormal migration is one crucial step during the metastasis of malignant tumor cells [28]. Integrins play critical roles in regulating protrusion and adhesion in migrating cells [29]. For example, the integrin downstream FAK signaling is necessary for directional cell movement [30]. FAK functions as an integrin-regulated scaffold to recruit Src to focal adhesion, targeting several pathways to promote cell migration [30]. Rho GTPases mediate modifications of the actin cytoskeleton required for cell migration and promote the assembly of integrin based matrix adhesion complexes to generate traction forces at the front and in the body of the migratory cells [31].

To metastasize to a distant organ, tumor cells must invade the surrounding ECM barriers, which need to be degraded and remodeled by multiple proteases. Integrins have been shown to regulate the expression and activity of those proteases especially MMPs and uPA system, which will be elaborated in the following sections.

MMPs

Characteristics of MMPs

Efficient tumor invasion and metastasis require degradation of the ECM at the invasion front. As the main proteases involved in remodeling ECM, MMPs play a pivotal role in remodeling tumor microenvironment [32, 33].

MMPs are a large family of zinc-dependent endopeptidases, which include 25 members in vertebrate categorized into eight structure classes by their architectural features [32–34]. In general, three domains are common to almost all MMPs, the pro-peptide for enzyme latency, the catalytic domain, and the hemopexin-like C-terminal domain [33]. MMPs can be divided into two groups, the membrane-anchored type (MT-MMPs) and the secreted type [35]. MMPs are synthesized as zymogens and activated by proteinase cleavage to remove the auto-inhibitory domain [33]. And their activity can be down-regulated by endogenous inhibitors like tissue inhibitors of metalloproteinases (TIMPs), α_2 -macroglobulin, and the membrane-bound inhibitor reversion-inducing cysteine-rich protein with kazal motifs (RECK) [36]. TIMPs are best-studied endogenous inhibitors of MMPs. In the ECM, TIMPs bind to the active site of the MMPs in a stoichiometric 1:1 molar ratio, thereby inhibiting the proteolytic activity of MMPs [37]. Four types of TIMPs (TIMP-1, -2, -3, and -4) are present in humans [37], and individual TIMPs differ in tissue-specific expression and ability to inhibit various MMPs [37].

MMPs have broad substrate specificities for a variety of ECM components, such as collagen, laminin and fibronectin [38]. Besides, they can also target cell surface molecules and other non-matrix proteins [38]. Thus, MMPs serve as the key molecular messengers between tumor and stroma. In addition to degrade physical ECM barriers, MMPs can interact with cell surface receptors such as integrins to affect multiple signaling pathways that modulate the biology of cells in both physiological and pathological processes [39]. For example, leukocyte migration is known to be dependent on MMPs and β_2 integrin interaction, and the combined participation of MMPs and integrins is also required for tumor metastasis [39, 40]. Moreover, MMPs mediate a wide range of biological effects that contribute to tumor cell invasion and metastasis [33]. MMPs can affect growth signals by proteolytically activating TGF- β to selectively promote stroma-mediated tumor invasion and metastasis [41, 42]. They can also interfere with the induction of apoptosis in malignant cells by cleavage of the ligands/receptors that transduce pro-apoptotic signals [33, 43].

The activity of MMPs can be regulated at different levels including gene expression, localization, switch from zymogen to active form, and inactivation by specific inhibitors

[33]. Notably, integrins play prominent roles in all of these regulation levels.

Up-Regulation of MMPs Expression by Integrins

The expression level of MMPs is always elevated in the circumstance of tumor [33]. MMP gene expression is regulated by numerous stimulatory and suppressive factors that influence multiple signaling pathways [38]. Integrin is one of the most important regulatory factors. Upon binding to ECM, integrins can activate MMP synthesis and then up-regulate the expression of MMPs. Some α_V [44–48] and β_1 [49–52] integrins have been shown to promote the expression of several MMPs. For example, integrin $\alpha_V\beta_6$ has been shown to promote the expression of MMPs in various cancers [44–47]. In oral squamous cell carcinoma (SCC), increased $\alpha_V\beta_6$ leads to the activation of MMP-3 and promote oral SCC cell proliferation and metastasis in vivo [44]. Upon bound to fibronectin, $\alpha_V\beta_6$ complexes with Fyn and leads to its activation. Subsequently, the activated Fyn recruits and activates FAK, which is necessary to activate Shc and couple $\alpha_V\beta_6$ signaling to the Raf-ERK/MAPK pathway, thus transcriptionally activates MMP-3 gene [44]. Besides, the high expression of $\alpha_V\beta_6$ integrin in ovarian cancer cells correlates with increased expression and secretion of pro-MMP-2, pro-MMP-9 and high molecular weight (HMW)-uPA for ECM degradation [45]. Another α_V integrin, $\alpha_V\beta_3$, is found to up-regulate MMP-2 expression in invasive breast cancer cell once the integrin binds RGD peptide [48]. Two collagen receptors, integrin $\alpha_1\beta_1$ and $\alpha_2\beta_1$, have been reported to induce MMP-13 expression in a p38 MAPK dependent manner in human skin fibroblasts cultured in three dimensional collagen [49]. While in v-Src transformed fibroblast, the expression of MMP-2 and MMP-9 are up-regulated through the β_1 integrin-FAK-JNK (c-Jun N-terminal kinase) signaling pathway [50]. As a cell adhesion receptor for laminin 5, integrin $\alpha_3\beta_1$ has been shown to be required for MMP-9 secretion and potentiate TGF- β mediated induction of MMP-9 in immortalized keratinocytes [51, 52].

Regulation of MMPs Localization by Integrins

The physical location of MMPs dictates their biological functions and is fundamental to the physiological roles of these enzymes in tumor progression. The compartmentalization of MMPs to cell surface can be achieved by the expression of MT-MMPs which directly anchor to cell membrane [53–55] or binding to cell surface docking receptors such as integrins [40, 56, 57], CD147 [58] and CD44 [41, 59]. In the process of tumor invasion, degradation of ECM occurs at specific sites where invasive cells make contact with ECM through specialized cell membrane

protrusions called invadopodia [60]. Invadopodial protrusions are enriched in integrins, MMPs, tyrosine kinase signaling machinery, actin, and actin-associated proteins [60]. Membrane type 1 metalloprotease (MT1-MMP, MMP14) is one key invadopodial protease that co-localizes with integrin $\alpha V\beta 3$ [61]. The high local concentration of active MT1-MMP on cell membrane has been shown to promote tumor metastasis [62]. Localization to cell membrane through the interaction with integrins has been demonstrated for multiple MMPs, including binding of MMP-2 to $\alpha V\beta 3$ [40], and MMP-9 to $\alpha V\beta 6$ or $\alpha 3\beta 1$ [56, 57]. Specifically, MMP-2 is recruited to cell surface via binding to $\alpha V\beta 3$ through its C-terminus hemopexin domain, which results in the ECM degradation to promote invasion of tumor cells [40]. Another study on colon cancer metastasis to liver has shown that the MMP-9 expression is elevated and co-localized with integrin $\alpha V\beta 6$ at the invading edge of the tumor [56]. As a matter of fact, the activity of MMPs is dependent on integrin expression and its ligand-binding ability since treatment of a malignant breast cancer cell line MDA-MB-231 with a function-blocking anti- $\alpha 3$ antibody results in a marked reduction in MMP-9 activity, leading to inhibited migration and invasion [57].

MMPs Activation Requires Integrin

MMPs are first synthesized as inactive zymogens called pro-MMPs [32, 33]. Conversion of the zymogen into an active protease is a key step in regulating MMP activity [32, 33]. MMP-2 is often constitutively expressed and is activated at cell surface through a unique multistep pathway [63]. First, TIMP-2 binds MT1-MMP at its amino terminus and pro-MMP-2 at its carboxyl terminus. Next, the bound pro-MMP-2 is cleaved by an adjacent TIMP-2-free MT1-MMP to the intermediate form, and another already activated MMP-2 is required to remove a residual portion of the MMP-2 pro-peptide which leads to conversion of pro-MMP2 to a fully active enzyme [63, 64]. Besides, there is another alternative TIMP-2-independent pathway for MMP-2 activation [65]. Studies on melanomas, gliomas, lung and breast cancer cells indicate that this multi-protein MMP activating complex also includes integrin $\alpha V\beta 3$, an receptor for RGD-containing components of ECM, such as vitronectin, fibronectin and thrombospondin [63, 66–69]. MT1-MMP and integrin $\alpha V\beta 3$ may jointly enforce efficient docking, activation, and maturation of MMP-2, and then strongly facilitate tumor cell migration [63, 69]. Integrin $\alpha V\beta 3$ is found up-regulated in glioblastomas and melanomas [70, 71]. Evidence showed that $\alpha V\beta 3$ can promote tumor invasion and metastasis through recruiting and activating MMP-2 and plasmin [72], whereas disruption of MMP-2- $\alpha V\beta 3$ binding inhibits angiogenesis and tumor growth [73]. The active MMP-2 can cleave type IV collagen

and lead to the exposure of a cryptic site for $\alpha V\beta 3$ binding. As a result, the increased MMP2- $\alpha V\beta 3$ binding will facilitate angiogenesis and tumor growth [74].

Inhibition of MMPs Activity

The balanced MMPs activity is required to prevent excessive ECM degradation. The proteolytic activity of MMPs is down-regulated primarily by TIMPs [37]. Experimental evidences have shown that the inhibition of MMPs by TIMPs may reduce or even abolish tumor metastasis [75, 76]. However, the relationship between MMPs and TIMPs in tumor development is elusive since TIMPs is sometimes up-regulated with the over-expression of individual MMPs [77, 78]. In the serum of patients with lung carcinomas, both MMP-9 and TIMP-1 have been found elevated [78]. In addition to TIMPs, a naturally occurring form of the C-terminus hemopexin domain from MMP-2 can be detected in association with $\alpha V\beta 3$ expression in tumors [79]. This hemopexin domain can compete with MMP-2 to bind integrin $\alpha V\beta 3$, serving as a natural inhibitor of MMP-2 activity to prevent excessive angiogenesis [79].

uPA System

Introduction of uPA System

The uPA system represents a family of serine proteases that are involved in the degradation of ECM, which plays important roles in a variety of biologic processes, including fibrinolysis [80], inflammation [81], ECM remodeling during tumor invasion, angiogenesis, and metastasis [82–84].

The uPA system includes uPA, glycolipid-anchored uPA receptor (uPAR), and plasminogen activator inhibitor 1 and 2 (PAI-1 and PAI-2) [85, 87]. Binding of uPA zymogen (pro-uPA) to uPAR leads to uPA activation [85–87]. In the other hand, uPA activity is rapidly neutralized by its specific inhibitors, PAI-1 and PAI-2 [85–87]. Activated uPA initiates a proteolytic cascade that results in the conversion of a zymogen called plasminogen to protease plasmin, which can degrade a range of ECM components and activate other proteases such as MMPs [88, 89]. These proteolytic cascades degrade ECM to allow cells cross through the ECM barriers, and in addition, release various growth and differentiation factors, which contribute to the migratory and invasive phenotype characteristic of malignant tumor cells [90].

Recent findings suggest that uPA system is frequently involved at multiple steps in tumor progression, particularly in remodeling ECM, modulating cell adhesion and enhancing cell proliferation and migration [84, 87]. Consistent with its role in tumor progression, several groups have shown

that over-expression of uPA or uPAR is a feature of malignancy and is correlated with tumor progression and metastasis [84, 85, 91, 92]. The uPA system has been suggested as a promising candidate for targeted cancer therapy [93].

Integrins are essential uPAR signaling co-receptors and a second uPAR ligand [86]. The uPA system is intimately connected to integrins in following aspects: 1) integrins regulate the expression of uPA system; 2) integrins regulate the localization of uPA system; 3) integrins promote the signaling mediated by uPA system and vice versa. The following sections will give a general review on the above aspects.

Regulation of uPA System Expression by Integrins

Evidence for physical and functional association between integrins and uPAR is also provided by observations that integrin-dependent signaling events regulate the expression of the components of uPA system [94]. Binding of an RGD-bearing ligand to integrin $\alpha V\beta 3$ in metastatic murine mammary cancer cells transcriptionally up-regulates uPA expression through ILK-dependent AP-1 activation [95]. In another case, ligand-induced clustering of integrin $\alpha 3\beta 1$ promotes uPAR- $\alpha 3\beta 1$ interaction and enhances uPA expression in a Src-ERK-dependent pathway [96]. uPAR expression can also be up-regulated by integrins. It is reported that the ligation of either $\beta 1$ or $\beta 2$ integrins with T cell receptors results in robust up-regulation of uPAR expression in primary T lymphocytes [97].

Regulation of uPA/uPAR Localization by Integrins

To assure the spatial control over ECM degradation, uPAR is localized to the leading edge of migrating cells which focuses uPA activity in the direction of cell movement [98]. The mechanism that governs the spatial localization of uPAR on the cell surface appears to depend on the association of uPAR with uPA, integrins and the ECM protein vitronectin [83, 87]. Similar to MMPs, uPAR is often found clustered with integrins within invadopodia [99]. Evidence has shown that uPAR localizes to integrin-containing adhesion complexes, and interacts with integrins [86]. Up to now, uPAR has been found to physically and functionally associated with several $\beta 1$ [96, 100], $\beta 2$ [101, 102], and αV [103, 104] integrins, which can recruit uPA/uPAR to the cell surface [87, 105]. A good example is that uPA and uPAR are associated with integrin $\alpha V\beta 3$, which recruits them to the leading edge of migrating tumor cells for ECM degradation [106].

Integrins Are uPAR Signaling Co-Receptors

In addition to regulating proteolysis, uPAR also serves as a signaling receptor to promote cell proliferation, survival, migration, and invasion [86]. Due to lacking transmembrane and intracellular domains, uPAR requires transmembrane

co-receptors for signaling. Considerable evidences suggest that integrins are essential uPAR signaling co-receptors, and several integrins have been shown to work with uPAR [96, 101, 107–112]. $\alpha M\beta 2$ is the first integrin found to interact with uPAR, which cooperates with uPAR to mediate leukocytes adhesion and recruitment during inflammatory responses in an uPA-independent signaling pathway [101, 107]. Recent studies suggest that uPAR signals through $\alpha V\beta 3$ play important roles in cell migration and invasion. The uPAR- $\alpha V\beta 3$ interaction can activate the Rho family GTPase, which stimulate actin polymerization and membrane protrusion, and promote cell migration and invasion [108, 109]. uPAR can also interact with integrin $\alpha 3\beta 1$ and $\alpha 5\beta 1$. These uPAR- $\beta 1$ integrin interactions stimulate FAK-Src and lead to downstream activation of Ras-MAPK pathway, which promotes tumor cell proliferation and tumor invasion [96, 110, 111]. Either the disruption of uPAR- $\alpha 5\beta 1$ interaction or down-regulation of uPAR can induce tumor growth arrest (dormancy) in vivo [112].

Conclusions and Perspectives

Degradation of ECM at the invasion front of tumor cells is critical for efficient tumor invasion and metastasis. Proteases such as MMPs and uPA system play pivotal roles in remodeling tumor microenvironment. Components from both MMPs

Fig. 2 The regulatory functions of integrins on MMPs and uPA system. MMPs: integrins can activate MMPs synthesis at the transcriptional level, compartmentalize them to cell surface for the spatial ECM degradation, and promote the activation of pro-MMPs. uPA system: integrins can enhance the expression of uPA/uPAR and govern the spatial localization of uPA/uPAR to the leading edge of migrating cells. Besides, integrins cooperate with uPAR to transduce multiple signals that contribute to tumor-related events including cell migration, invasion and proliferation

and uPA system are found up-regulated or over-activated in various cancers, seen as a feature of malignancy and are correlated with tumor progression and metastasis. Integrins represent a major family of receptors that mediate cell adhesion to ECM, and also play critical roles in tumor progression by enhancing tumor cell invasion, metastasis, and survival. Integrins serve as the key regulators of MMPs and uPA system (Fig. 2). For MMPs, integrins can activate MMP synthesis at the transcriptional level, compartmentalize them to cell surface for the spatial ECM degradation, and promote the activation of pro-MMPs. For uPA system, integrins can enhance the expression of uPA/uPAR and govern the spatial localization of uPA/uPAR to the leading edge of migrating cells. Besides, as the co-receptor of uPAR signaling, integrin cooperates with uPAR to transduce multiple signals that contribute to tumor-related events. However, there are still a number of questions remain elusive. Is the integrin binding required by the maturation of all latent MMPs? Can MMPs transduce signals into cells via their binding to integrins? Do integrin affinity and avidity affect its interaction with MMPs and uPAR? It will be interesting to address these questions in the future.

Over the past years, a lot of efforts have been made to design MMP inhibitors (MPIs), and synthetic MPIs were rapidly developed and applied in human clinical trials. However, the results of these clinical trials have been disappointing [113]. Based on the findings that integrins can promote functions of MMPs, more effective cancer therapeutics could be achieved by interfering with MMPs association with integrins. In the other hand, it is reported that individual components of the uPA system are distinctly expressed in tumor tissues compared with normal tissues, thus they present multiple opportunities for therapeutic targets. The anti-uPAR therapeutic agents are yet to enter clinical trials, which might be advantageous in cancer therapy [86, 114]. Besides, there would be attractive targets for new drugs to block tumor progression or metastasis considering the interactions between uPAR and integrins.

Acknowledgements This work was supported by grants from the National Basic Research Program of China (2010CB529703), National Natural Science Foundation of China (31190061, 30700119, 30970604), Science and Technology Commission of Shanghai Municipality (11JC1414200) and the Shanghai Pujiang Program (08PJ1410600).

Disclosures There are no financial disclosures or conflicts of interests regarding the preparation of this manuscript.

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