Minireview

Cellular strategies for proteolytic targeting during migration and invasion

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Abstract Cell migration over or through the extracellular matrix (ECM) is an integral feature of both physiological and pathological processes. Regulation of the changing cell–ECM interactions involved can be effected by proteolysis and requires strict spatial and temporal targeting of proteinase activity. The versatile use of different proteinase systems, with a variety of localisation mechanisms and cleavage targets, is being revealed by a plethora of studies using in vitro models. This mini review reflects the status of our knowledge of strategies for the localisation of proteolytic activity effected during cell migration.

Key words: Serine proteinase; Metalloproteinase; Cell membrane; Extracellular matrix; Migration

1. Serine proteinases: old and new

Serine proteinases, and in particular those of the plasminogen activator/plasmin system, have been implicated in the migration and invasion of cells since the early 1970s when oncogenic transformation of cells was first shown to upregulate the expression of plasminogen activators and by the histological localisation of the plasminogen activators to actively invasive foci of experimental tumours (as described in the landmark review of Danø et al.) [1]. However the concept that the function of these proteinases might be dependent on membrane targeting (Fig. 1) did not emerge until the identification of uPAR, the specific high affinity receptor for the plasminogen activator uPA, in the late 1980s. This molecule has since generated a lot of interest as it appears that by targeting uPA to the plasma membrane, uPAR acts as a focal point for the assembly of multimolecular complexes that dynamically regulate plasmin generation and activity and modulate cell adhesion and signalling.

The binding of uPA, or its zymogen form pro-uPA, to uPAR on the plasma membrane greatly accelerates plasminogen activation [2]. This is not due to direct effects of uPAR on uPA catalytic activity as soluble uPAR does not enhance plasminogen activation [3], and recently it has been shown that uPAR-bound uPA mediates the assembly of catalytically favoured complexes with cell-associated plasminogen [4]. These interactions facilitate the process of reciprocal zymogen activation, i.e. the activation of plasminogen by uPA and the activation of pro-uPA by plasmin, and increase the catalytic efficiencies of both reactions primarily due to effects on their K_m. The efficiency of this system is such that, at least in vitro, it can circumvent the need for exogenous proteolytic activation and can be initiated by the low intrinsic catalytic activity present in pro-uPA [5]. The activity of this system has an absolute dependence on plasminogen binding, although this appears to be a relatively non-selective phenomenon as a range of molecules have been demonstrated to bind plasminogen at the cell surface with affinities in the low μM range. The common feature amongst these molecules, which include α-enolase, annexin II and cytokeratin 8 [6–8], is that they have C-terminal lysine residues. These residues are either present in the native protein or exposed by limited proteolysis, and are the preferred ligand for the kringle modules of plasminogen. The large capacity of cells to bind plasminogen suggests that this is part of the activation mechanism, but it is possible that a small sub-set of the plasminogen binding molecules is functionally favoured, e.g. by specific co-localisation with uPAR. This concept is supported by a number of lines of evidence, including kinetic modelling which demonstrates that simple stoichiometric complex formation can give catalytic efficiencies equivalent to those observed for the system assembled on the plasma membrane [5]. Although uPAR strictly targets plasmin generation to the plasma membrane, this plasmin dissociates from the cell surface within minutes giving the possibility that it does not act locally. However an alternative mechanism appears to be used to confine the activity of plasmin to the local environment, as dissociated plasmin is very rapidly inactivated by the abundant plasma inhibitor α_2-antiplasmin, whereas cell-associated plasmin is almost completely protected from inhibition [2]. Therefore plasmin activity is dynamically regulated at the cell surface, with α_2-antiplasmin suppressing the dissemination of plasmin activity and PAI-1 inhibiting its generation.

In spite of the abundance of observations both in vitro and in vivo [9] implicating uPAR in the regulation of plasmin generation, mice with ablation of the uPAR gene have no overt physiological phenotype [10]. This reflects both the redundancy that has become evident in matrix-degrading proteolytic systems and the very precisely controlled levels of proteolytic activity required for cell migration in pathological situations. An excellent example of this is the observation that although plasmin generation is implicated in the pericellular proteolysis necessary for angiogenesis in vivo which is consequently reduced in $Plg^{-/-}$ mice, it is paradoxically also de-

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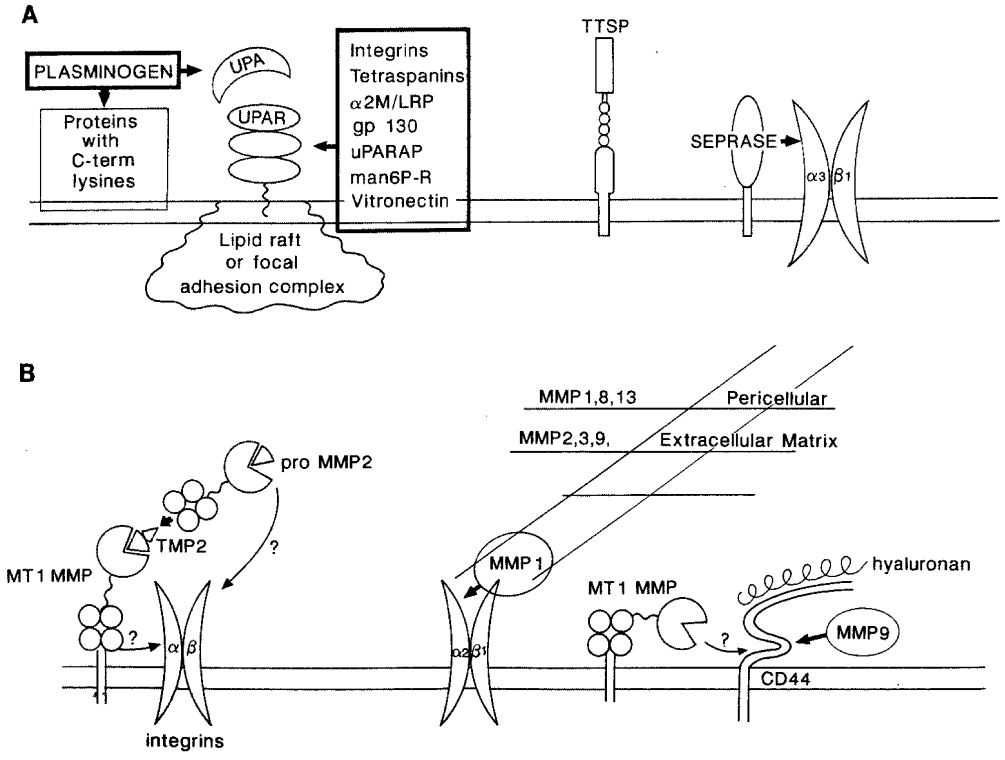

Fig. 1. Strategies for the targeting of serine and metalloproteinases to the cell surface. A: Serine proteinases: the GPI-anchored protein uPAR binds uPA with high affinity and specificity, but various other proteins have been shown to associate, or collaborate closely, with either uPAR or the uPA/uPAR complex. These include vitronectin, integrins ($\alpha_V\beta_3$, $\beta_1\beta_2$, e.g. in focal adhesion complexes) and other transmembrane receptors and adaptors including the α_2-macroglobulin receptor (α_2M-R), also known as LRP, gp130 (potentially leading to intracellular signal transduction), tetraspanins, uPARAP (or endo180), and intracellularly, the mannose-6-phosphate receptor (Man6P-R). Cells with cholesterol-rich lipid rafts and caveolae can concentrate the GPI-anchored uPAR alongside numerous signalling pathways [67] which can regulate cell migration. Plasminogen is also cell-associated, notably by binding to cell surface proteins with C-terminal lysine residues, and this is necessary for its efficient activation. The family of TTSPs directly target proteolytic activity to the cell surface and tentative roles in cell migration have been proposed for some of these activities. Seprase, a transmembrane serine peptidase, has been localised to the invading front ('invadopodia') of tumour cells along with $\alpha_3\beta_1$-integrin, and a role in cell migration has been proposed. B: Metalloproteinases: the membrane-associated MT1-MMP has a proteolytic function in its own right and mediates the activation of the soluble pro-MMP-2 through the formation of a complex with TIMP-2 which then acts as a pro-MMP-2 'receptor'. Clustering of MT1-MMP at the cell surface, possibly in association with integrins ($\alpha_V\beta_3$, $\alpha_2\beta_1$, $\alpha_3\beta_1$) or CD44, may promote the efficiency of this activation cascade. Forms of MMP-2 may also bind to $\alpha_V\beta_3$-integrin and to ECM components such as collagen and heparan sulphate proteoglycans. Other soluble MMPs bind to collagen, including the specific collagenases MMP-1, -8 and -13, as well as non-collagenolytic MMPs, MMP-3 and -9. Recently MMP-1 was found to bind to the I domain of the α_2 chain of the integrin $\alpha_2\beta_1$. An association between CD44 and MMP-9 at the cell surface has also been described.

creased in PAI-$1^{-/-}$ mice [11]. Therefore, both reduced and increased proteolytic activities are non-permissive for cell migration in this in vivo model.

How then do migrating cells utilise the activity of this system in the absence of a direct linkage of the glycophospholipid (GPI)-anchored uPAR to the cytoskeleton? The polarisation of uPAR to the leading edge of migrating cells was first observed in monocytes [12] and has since been demonstrated in a variety of cell types. In stationary cells uPAR is found both in focal adhesions and lipid rafts including caveolae. The presence of uPAR in the latter has been reported to lead to an increase in uPAR-mediated proteolysis in some [13], but not all, cell types [14]. The presence of uPAR in focal adhesions and its polarisation in migrating cells is thought to be dependent on interactions with other proteins and a number of potential mechanisms for this have emerged involving direct binding of uPA/uPAR to the adhesion protein vitronectin and interactions with integrins. uPAR can support the adhesion of leukocytes to vitronectin in an integrin-independent manner [15] and over-expression studies in fibroblasts have recently shown that uPAR binding to vitronectin leads to a reorganisation of the actin cytoskeleton and increases cell motility through activation of a Rac-dependent signalling pathway [16]. A variety of experiments have indirectly implied interactions between uPAR and integrins of different classes and co-immunoprecipitation studies have demonstrated interactions with the β_2-integrin Mac-1 (CD11b/CD18) [17]. The difficulty in demonstrating these interactions directly may be that they are transitory, at least in motile cells, as it has been shown by FRET techniques that uPAR interactions with β_2-integrins oscillate in migrating neutrophils [18]. Computer modelling studies have suggested that a direct transport mechanism is involved in the translocation of uPAR to lamellipodia during polarisation of these cells (i.e. it is not a diffusional process) [19], and this process may also be mediated by integrins. Both β_1- and β_3-integrins have been shown to bind soluble uPAR and suggested to be a mechanism for in *trans* uPAR–integrin interactions [20].

An important question that has yet to be fully addressed is whether these various interactions regulate cell adhesion, as has been proposed by a number of groups, or regulate proteolysis by directing uPAR-dependent proteolytic activity to

the relevant area of the cell surface and/or by dynamically affecting the activity of the system. There is some support for the latter, as vitronectin-dependent relocalisation of uPAR to focal adhesions has been reported to reduce cell surface uPA activity [21] and it has been observed that certain members of the tetraspan family of integrin-interacting proteins can influence the uPA/uPAR interaction (Ellis, Bass and Berditchevski, unpublished observations). The effective function of uPAR-mediated proteolysis in cell migration also appears to be regulated by the low density lipoprotein (LDL) receptor-related protein LRP [22], which acts to clear uPAR-bound uPA–PAI-1 complexes from the cell surface leading to a recycling of unoccupied uPAR [23], presumably leading to further cycles of activation and inhibition. The C-type lectin endo180 (uPAR-associated protein (uPARAP)) has recently been shown to specifically associate with the uPA/uPAR complex [24].

The binding of a secreted proteinase to a plasma membrane receptor or binding site as a mechanism targeting proteolytic activity allows the possibility of paracrine interactions. In the uPAR system such interactions have been shown to be of importance in a number of human cancers where cancer cells and stromal cells collaborate in proteolysis [25]. However direct targeting of proteolytic activity to the plasma membrane also occurs in the serine proteinase sub-family known as the type II transmembrane serine proteinases (TTSPs). These proteinases have recently been reviewed [26], so we will focus here on those that may be involved in cell migration and invasion as they were either initially identified as tumour-associated genes or have been found to be upregulated in tumours. These include TMPRSS-2, TMPRSS-4 and matriptase (also known as MT-SP1, TADG-15 or epithin). These proteinases are predicted to have a trypsin-like specificity, although biochemical analysis has only been carried out with matriptase, which has been shown to both directly degrade extracellular matrix (ECM) [27] and to activate pro-uPA [28,29]. The latter observation raises the possibility that matriptase could be an initiator of a proteolytic cascade leading to plasmin generation. However it is not yet known whether this activation can take place in the cellular context with transmembrane matriptase and uPAR-bound pro-uPA, as these studies were performed in solution with the isolated proteinase domain of matriptase. Interestingly the modules present N-terminally of the protease domain in these proteins are rarely found in other mosaic serine proteinases and include LDL receptor class A, scavenger receptor cysteine-rich and CUB domains. In many other proteins these domains are associated with protein–protein interactions and ligand binding, giving the possibility that they are involved in substrate recognition by these proteinases and/or used to target them to specific regions of the plasma membrane. The elucidation of the biological roles of these proteinases is likely to be an area of intense research over the coming years, with identification of their substrates and the functions of their ancillary domains being key issues.

Another transmembrane proteinase potentially involved in migration and invasion is seprase, which although a serine proteinase is completely distinct from the trypsin-like proteinases discussed here, it has an α/β-hydrolase fold and is related to dipeptidyl peptidase-IV (CD26). Seprase has gelatinolytic activity and has been shown to localise to invadapodia where it associates with the $\alpha_3\beta_1$-integrin in a collagen-dependent manner [30], Fig. 1.

2. Metalloproteinases move in on the act

The matrix metalloproteinases (MMPs) have been implicated in cell migration and invasion in both model systems and in vivo by the observation that inhibitors of metalloproteinases frequently, although not always, abrogate such events. Since many MMPs are secreted as soluble proteins the question arises as to how their function might be spatially regulated. Synthesis and secretion of soluble MMPs by cells at specific locations may occur, e.g. the front of migrating epithelial sheets, as seen for MMP-1 and MMP-10 in keratinocytes [31], MMP-9 in bronchial epithelial cells [32] and MMP-2 in mammary epithelial cells [33], and the activation of secreted proforms of the MMPs by the plasmin cascade may to some extent confine function to a relatively specified pericellular environment [34]. MMP-2 and -9 have domains related to the type II repeats in fibronectin which bind both collagens and gelatin, allowing efficient ECM sequestration. Many of the collagenases (MMP-1, -8, -13) and stromelysin-1 (MMP-3) have C-terminal hemopexin-like domains that bind to collagen. MMP-9 has been found in association with the heparan sulphate-containing $CD44_{v3,\,8-10}$ splice variant displayed on the membrane of invadopodial structures of a breast cancer cell line, Fig. 1. This form of CD44 is known to be preferentially expressed on the surface of metastatic tumour cells and to promote cell migration. Hyaluronan-mediated clustering of CD44 appeared to be a feature of the co-localisation of CD44 and MMP-9 [35,36]. A precise role for the heparan sulphate proteoglycan has not been shown, but the concept of sequestration of some proteinases on the charged glycosaminoglycan chains seems reasonable. It has also been shown that pro-MMP-9 binds relatively tightly to the α_2 chain of type IV collagen [37] and can form a heterodimer with the chondroitin sulphate proteoglycan core protein [38]. This is interesting in the light of a study of pulmonary epithelial cell migration in a monolayer 'wound' model, where MMP-9 and type IV collagen secretion may be seen in cells with an active migratory phenotype. Their localisation coincides with those of vinculin and actin, i.e. at substratum contacts [32]. In this study the role of integrins was not specifically addressed, but in view of the known association of integrins with the uPA/uPAR system (see above), the question of interactions between integrins and their associated signalling assemblies and MMPs is an important one. In keratinocyte migration it is thought that there is a close association between MMP-1 and the α_2-integrin subunit. MMP-1 was shown to bind to the A domain of the α_2-integrin in a cation-dependent manner. MMP-1 and type I collagen appear to bind at different sites, however, as a mutated I domain which no longer binds type I collagen can still bind to MMP-1. Hence MMP-1 may be tightly focused to the leading edge of the migrating keratinocyte [39]. An interaction between MMP-2 and the integrin $\alpha_V\beta_3$ was originally described in endothelial cells and thought to be important for the promotion of angiogenesis [40]. This interaction is turning out to be more complex than at first study and is discussed below in the light of new data.

The discovery of the membrane-type (MT)-MMPs that are genuinely associated with the plasma membrane, including the membrane spanning forms MT1-, 2-, 3- and 5-MMP (MMPs 14, 15, 16 and 24) and the GPI-anchored forms MT4- and MT6-MMP (MMPs 17 and 25), has elicited a hugely exciting new area of research activity in relation to the mechanism for

focused proteolysis of the ECM, including in relation to cell movement. All these enzymes are efficient ECM-degrading proteinases in their own right. Studies on tubulogenesis of endothelial and MDCK cells have implicated the activity of MT1-MMP, but the mechanism of its action is not known [41–43]. Hotary et al. [44] have shown that MT1-MMP transfection of MDCK cells promotes tubulogenesis in collagen gels, but MT2-MMP and MT3-MMP differed. They proposed that distinct MT-MMPs promote invasive or morphogenic responses according to the cell type and the matrix interactions [45,46]. The involvement of MT1-MMP in osteoclast migration and its association with lamellipodia and invadopodia of these cells has been described. Interestingly, in non-migrating osteoclasts MT1-MMP was evenly distributed in dot-like structures at the cell membrane which co-localised with actin [47]. MT1-MMP was found in the lamellipodia of migratory mammary epithelial cells in an in vitro outgrowth assay, as well as at their basal surface in contact with the substrate [48]. Recently it was shown that MT1-MMP can co-localise with and act as a CD44 processing activity, promoting tumour cell migration [49], Fig. 1. MT1-MMP appears to require its transmembrane domain and cytoplasmic tail to localise to the invadopodia of tumour cells [50]. It has been pointed out that the MT1-MMP cytoplasmic tail contains potential T/S/Y phosphorylation sites that could be involved in the recruitment of intracellular proteins that drive the specific localisation of MT1-MMP [51]. The cytoplasmic tail of MT1-MMP has been shown to bind the Golgi protein p59 (GRASP55) as does transforming growth factor α [52], but the role of this association appears to be in intracellular trafficking of MT1-MMP. MT2-MMP appears to traffic in a very different fashion than MT1-MMP, and is largely confined to the Golgi when over-expressed in CHO cells [53]. MT3- and MT5-MMP have not been studied in detail but have many potential trafficking motifs in common with MT1-MMP. The potential localisation and role of the GPI-anchored MT4- and MT6-MMPs have not yet been fully investigated. By analogy with GPI-anchored uPAR, it may be that focusing of their activity into large molecular complexes occurs by the binding of adaptor proteins and integrins.

The membrane spanning MT-MMPs, notably MT1-MMP, have achieved most notoriety as the activators of MMP-2. The mechanism of activation has been well studied for MT1-MMP and involves the sequestration of MMP-2 on a 'receptor' involving MT1-MMP/TIMP-2 complexes at the cell surface, followed by propeptide cleavage, Fig. 1. The removal of the propeptide occurs by sequential proteolysis by MT1-MMP followed by MMP-2. This process appears to be regulated by the clustering of MT1-MMP/TIMP-2, and hence MMP-2, to allow an efficient catalytic cascade to be invoked. Interestingly, when MMP-2 activation is at its most efficient, MT1-MMP is destroyed, apparently by self-cleavage in the C-terminal region of the catalytic domain, yielding 40–43 kDa forms still bound into the membrane [54–56]. Further evaluation of this process has invoked the involvement of $\alpha_V\beta_3$ in certain cell types. The integrin is thought to promote more efficient activation of MMP-2 by MT1-MMP by transient binding of the cleaved propeptide intermediate and active MMP-2. Co-expression of MT1-MMP and $\alpha_V\beta_3$ in MCF7 carcinoma cells specifically enhances in *trans* autocatalytic maturation of MMP-2. Clustering of MT1-MMP and $\alpha_V\beta_3$ at discrete regions of the cell surface could be observed by immunolocalisation and was proposed to be an important mechanism for the clustering of MMP-2 at the invasive front of cells utilising $\alpha_V\beta_3$ as part of the migratory process. The work of Puyraimond [57] has shown co-localisation of MMP-2/MT1-MMP/TIMP-2/$\alpha_V\beta_3$ in caveolae. Since MMP-2 is known to interact with $\alpha_V\beta_3$ through its hemopexin-like domain, the mechanism for specific binding of the MMP-2 at certain stages of propeptide processing requires further study. However, the general concept of MT1-MMP/integrin associations is an attractive one. In other cell types the aggregation of β_1-integrins has been suggested as a key event in MMP-2 activation by MT1-MMP [51,56,58] and co-localisation of MT1-MMP and β_1 integrins has been observed [59]. MT1-MMP and MMP-2 have collagenolytic properties and their concentration at the cell surface would represent a powerful and highly localised means of regulating cell–collagen interactions [60]. The phenotype of the mouse with an ablation of the gene for MT1-MMP includes features which suggest a major role in collagen turnover in joint tissues [61] and in angiogenesis [62].

Other membrane-associated metalloproteinases, notably the ADAMs (a disintegrin and a metalloproteinase) family, and the astacins have been described in recent years [63–65]. They have been ascribed roles in the proteolysis of a number of cell surface proteins and ECM components but no direct role in cell migration has been established. They appear to be partially regulated by trafficking in the cell but little has been documented as yet. Soluble versions of the ADAMs, the ADAM-TS, have thrombospondin-1-like repeats which bind to heparan sulphate proteoglycans and could also potentially be focused at specific cell surface locations [66].

3. Conclusions

The number of both soluble and membrane-bound proteinases that can be focused by the cell to act at specific sites continues to be documented, and an astonishing array of cellular tactics to effect the spatial localisation of proteolytic activity is emerging. It is likely that the association of proteinases with other cellular or pericellular components will modify their function, not only by the concentration of their activity but by the subtle modification of substrate binding or specificity and also of the interaction with inhibitors and other effectors.

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