Published in final edited form as:

Semin Cell Dev Biol. 2008 February ; 19(1): 24–33. doi:10.1016/j.semcdb.2007.06.008.

Membrane Type 1-Matrix Metalloproteinase: Substrate Diversity in Pericellular Proteolysis

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Keywords

membrane type-1 matrix metalloproteinase; pericellular proteolysis; extracellular matrix

I. Introduction

a. Pericellular Proteolysis

Enzymes in the matrix metalloproteinase (MMP) family have been linked to key events in developmental biology since the first discovery of collagenolytic activity in amphibians undergoing metamorphosis by Gross and Lapiere in 1962¹. A plethora of subsequent biochemical, cellular and *in vivo* analyses have established that pericellular proteolysis contributes to numerous aspects of ontogeny, including ovulation, fertilization, implantation, cellular migration, tissue remodeling and repair. Stringent control of proteolysis is essential for maintenance of tissue integrity and homeostasis, and multiple mechanisms have evolved for both systemic and highly localized control of proteolytic activity^{2,3}. An effective mechanism for post-translational control of substrate processing is to anchor proteinases to the cell surface via a transmembrane domain, glycosyl-phosphatidyl inositol (GPI) anchor, or surface-localized proteinase receptor. Surface anchoring thereby provides spatial restrictions on substrate targeting and may afford protection from circulating proteinase inhibitors⁴. This review will utilize membrane type 1 (MT1)-MMP as an example to highlight substrate diversity in pericellular proteolysis. This captivating proteinase was originally discovered based on its ability to catalyze cell surface-associated processing of a soluble substrate, proMMP-2^{5,6}. In recent years, however, a wealth of additional protein and polypeptide MT1-MMP substrates have been described, providing abundant examples to illustrate the diverse functional consequences of pericellular proteolytic processing of matrix, soluble, and cell surface-associated substrates.

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³M.V.B. is supported in part by a grant from the Illinois Department of Public Health. The contents of this article are solely the responsibility of the authors and do not necessarily reflect the official views of the Illinois Department of Public Health. Financial support was also provided by the 2006 Ovarian Cancer Research Foundation Program of Excellence award (M.V.B.) and the Katten Muchin Rosenman Travel Scholarship Award from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (M.V.B.). The authors also gratefully acknowledge financial support from National Cancer Institute Research Grant RO1 CA86984 (M.S.S.).

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b. MT1-MMP Structure

MT1-MMP is comprised of seven domains, including a pre/propeptide (M¹ – R¹¹¹), a catalytic domain (Y¹¹² – G²⁸⁵) containing the Zn⁺⁺-binding consensus region, a hinge or linker region (E²⁸⁶ – I³¹⁸), hemopexin domain (C³¹⁹ – C⁵⁰⁸), stalk region (P⁵⁰⁹ – S⁵³⁸), transmembrane domain (A⁵³⁹ – F⁵⁶²), and a cytoplasmic tail (R⁵⁶³ – V⁵⁸²)^{6–10} [Fig. 1]. The enzyme is expressed as a zymogen (proMT1-MMP) containing a furin recognition motif (R¹⁰⁸–R¹¹¹) between the pro- and catalytic domains and is processed by proprotein convertases such as furin in the secretory pathway^{11, 12}. MT1-MMP is thereby presented to the cell surface in active form and recent data suggest that zymogen activation may actually be a pre-requisite for plasma membrane trafficking of the proteinase^{13, 14}. In addition to the catalytically competent 55–60 kDa active species, proteolytic processing generates a membrane anchored form [Fig. 1] lacking the catalytic domain^{15–19}. This 44–45 kDa hemopexin domain-containing species may play a role in regulating activity of the mature enzyme^{20–23}.

II. Processing of Extracellular Matrix Substrates

a. MT1-MMP as an interstitial collagenase

Shortly after discovery of the enzyme, early biochemical studies using active MT1-MMP retaining the hemopexin domain demonstrated the ability of MT1-MMP to process interstitial collagens I, II, and III *in vitro*, producing the ¾ and ¼ fragments characteristic of mammalian collagenases^{24, 25}. Generation of mice deficient in MT1-MMP expression provided strong genetic evidence to support the *in vitro* data, demonstrating a key role for MT1-MMP as an interstitial collagenase during development. MT1-MMP^{-/-} mice exhibited severe connective tissue abnormalities including dwarfism, osteopenia, soft tissue fibrosis, arthritis and skeletal dysplasia resulting from the inability to process interstitial collagen during development^{26, 27}. Lack of MT1-MMP activity also resulted in aberrant cranial morphogenesis and suture formation, due to the persistence of cartilage primordia in intramembranous ossification²⁶. Defective vascularization was also observed, both in the cartilage of growth plates and in a corneal angiogenesis assay, suggesting a role for MT1-MMP in initiating angiogenesis²⁷. Furthermore, skin fibroblasts isolated from MT1-MMP^{-/-} mice were deficient in collagenolytic activity, leading to a defect in stromal remodeling²⁶.

Further evidence attributing the ability of migrating cells to traverse type I collagen-rich tissue barriers to MT1-MMP-catalyzed pericellular collagenolytic activity was provided from cell culture studies. Transfection of MDCK cells with a variety of MMPs, followed by growth factor stimulation and analysis of invasion and tubulogenesis in 3-dimensional collagen gels, showed that membrane anchoring was required to properly position type I collagenase activity on the cell surface for effective pericellular collagenolysis²⁸. Surface MT1-MMP activity also potentiated invasion of 3-dimensional collagen gels by carcinoma cells *in vitro* and of collagen-rich bone matrix *in vivo* [Fig. 2 and 2, 23, 29–33]. In addition to modulating motility by matrix clearance, MT1-MMP-catalyzed pericellular collagenolysis conferred a growth advantage to cells in 3-dimensional collagen environments by enabling cells to remove matrix barriers that constrain cell shape and prohibit cytoskeletal alternation and associated proliferative responses³⁴. Modulation of pericellular collagen rigidity by MT1-MMP-mediated proteolysis also controls adipogenesis³⁵ and osteocytogenesis³⁶, providing evidence for a key role of MT1-MMP-catalyzed collagen cleavage in normal development as well as neoplasia. Evidence for reciprocal regulation of MT1-MMP by collagen has been generated in numerous model systems that show type I collagen induces MT1-MMP expression and surface activity via integrin signaling and/or cytoskeletal alterations^{15, 37–42}, further supporting the importance of MT1-MMP in collagen homeostasis [Fig. 3].

b. MT1-MMP Processing of Adhesive Glycoproteins and Proteoglycans

In addition to degradation of interstitial collagens, MT1-MMP has also been implicated in the cleavage of a variety of adhesive glycoproteins including fibronectin^{24, 25, 42}, laminin^{24, 43, 44}, vitronectin²⁴, tenascin, nidogen²⁵, fibrin and fibrinogen^{45–49}. Laminin processing has been the most extensively studied, following an initial report that MT1-MMP promoted processing of the rat laminin-5 γ 2 subunit, resulting in enhanced migration of a variety of cell types⁴³. Similarly, cleavage of the laminin-5 β 3 subunit has also been attributed to MT1-MMP, corresponding to increased motility of prostate carcinoma cells on the modified substratum⁵⁰. Other laminin isoforms including laminin-10, prevalent in the prostate basement membrane and laminin-2/4 found in muscle basement membrane can also be processed by MT1-MMP, regulating invasion and myoblast differentiation, respectively^{51, 52}.

Endothelial cell MT1-MMP also participates in pericellular fibronolysis as well as regulation of angiogenesis by MT1-MMP-catalyzed collagen cleavage,⁴⁸. Using tissues from plasminogen and/or plasminogen activator-deficient mice, invasion of fibrin barriers and neovessel formation occurred in an MT1-MMP-dependent manner, suggesting an alternative fibrinolytic pathway. Biochemical studies supported this observation and showed MT1-MMP solubilization of cross-linked fibrin clots⁴⁶. MT1-MMP can also impair clotting by cleavage of fibrinogen as well as via inactivation of Factor XII^{47, 53}, providing additional evidence for a plasmin-independent impact of MT1-MMP on the fibrinolytic system.

The core protein of the heparin sulfate proteoglycan syndecan-1 is also an MT1-MMP substrate, as HT1080 cells (that express endogenous MT1-MMP) spontaneously shed exogenously transfected syndecan-1⁵⁴. A syndecan-1 mutant resistant to MT1-MMP cleavage reduced both syndecan-1 shedding and cell migration, supporting a role for MT1-MMP in these processes. MT1-MMP-catalyzed cleavage of aggrecan and perlecan has also been reported²⁵. The small leucine-rich proteoglycan lumican can function as a tumor suppressor via induction of p21/Waf-1 expression and reduction of colony formation in soft agar. These activities are abolished by MT1-MMP, while, conversely, broad spectrum MMP inhibitors such as BB-94 lead to lumican accumulation and high p21 levels⁵⁵.

III. Cleavage of Soluble Proteins by MT1-MMP

a. Intracellular Substrates

Although MT1-MMP is trafficked to the cell surface and processes predominantly extracellular substrates, summarized above, recent studies have identified an intracellular recycling pathway involving the tubulin cytoskeleton, resulting in accumulation of MT1-MMP in the centrosomal compartment^{56, 57}. Processing of the centrosomal protein pericentrin can be catalyzed by MT1-MMP, leading to mitotic spindle aberrations. Ectopic expression of MT1-MMP in normal mammary epithelium led to enhanced extracellular invasive activity, pericentrin cleavage, and tumor growth in a xenograft model⁵⁸, suggesting that MT1-MMP may function in malignant transformation as well as metastasis.

b. Latent Enzymes and Growth Factors

An MT1-MMP-like activity was initially reported as a “plasma membrane-dependent” activator of proMMP-2, catalyzing zymogen activation at the cell surface⁵⁹. Cloning of a cDNA encoding an MMP containing a transmembrane domain and ectopic expression of the construct supported this observation, showing enhanced proMMP-2 zymogen activation⁶. Purification of a pro-MMP-2 activating activity from plasma membranes showed identity to the newly cloned MT1-MMP and identified a trimeric activation complex comprised of MT1-MMP, proMMP-2 and TIMP-2 [Fig. 1]⁶⁰. Since these early reports, numerous investigators have evaluated the biochemistry of trimeric complex formation and the functional

consequences of proMMP-2 activation⁸. In addition to proMMP-2, both proMMP-13⁶¹ and proMMP-8⁶² are MT1-MMP substrates, indicating involvement of this enzyme in multiple zymogen activation pathways. Because active MMP-2, -8, and -13 have been reported to participate in interstitial collagen degradation^{22, 63–65}, MT1-MMP may modulate collagen turnover through direct cleavage as well as through zymogen activation. Processing of latent growth factors such as transforming growth factor beta (TGF-beta) has also been reported in epithelial cells, neuronal cells⁶⁶ and osteoblasts⁶⁷. These data suggest that MT1-MMP may indirectly impact cellular functions by altering the pericellular concentration of active growth factors that regulate matrix deposition.

c. Other Secreted Substrates

Secreted mannose-binding lectin (MBL) plays an essential role in innate immunity by recognizing microorganisms and mediating their destruction by complement activation of phagocytosis⁶⁸. Several point mutations of the *MBL* gene predispose patients to infections and diseases. It was shown that mutants of MBL were susceptible to MT1-MMP-catalyzed cleavage at Gly³⁹-Leu⁴⁰ → Asn⁸⁰-Met⁸¹ sites, homologous to those cleaved in denatured human MBL, suggesting that MT1-MMP may be involved in altering the host response through clearing MBL⁶⁹.

Chemokines belong to a large family of structurally related chemoattractant cytokines that modulate leukocyte migration and other host responses during inflammatory processes⁷⁰. Chemokine substrates of MT1-MMP include stromal cell-derived factor (SDF-1)⁷¹ and monocyte chemoattractant protein (MCP)-3⁷². Both substrates were cleaved at position 4–5, releasing a small N-terminal tetrapeptide. SDF-1 cleavage resulted in loss of receptor binding to CXCR-4, functionally manifested as a loss of CD34(+) hematopoietic stem cell chemoattractant activity⁷¹. MMP-cleaved MCP-3 retained CC chemokine receptor binding activity, but was unable to stimulate a chemoattractant response following receptor engagement⁷². These data provide a functional link between MT1-MMP activity and modulation of inflammatory and immune responses.

IV. Cleavage of Cell Surface Substrates

a. Autolysis

Expression of active MT1-MMP results in autolytic degradation and generation of a catalytically inactive species on the cell surface [Fig. 1]^{15, 73–75}. Autolysis is the result of cleavage at G²⁸⁴-G²⁸⁵ in the linker region of MT1-MMP, followed by an additional cleavage at A²⁵⁵-I²⁵⁶ near the conserved methionine turn, rendering the resulting autolysis product catalytically inactive^{19, 73}. Although lacking the catalytic domain, the 44 kDa transmembrane hemopexin domain-containing autolysis product is retained on the cell surface¹⁵ and inhibits collagenolytic activity, cellular invasion of collagen gels, and tumor formation⁷⁶.

b. Adhesion Molecules

Both limited proteolytic processing and ectodomain shedding catalyzed by MT1-MMP have been reported for a variety of membrane-anchored adhesion molecules [Fig. 4]. Integrins are a family of transmembrane receptors for extracellular matrix ligands and are involved in cell adhesion and recognition in a variety of processes including embryogenesis, hemostasis, tissue repair, immune response, cellular motility, and metastatic dissemination of tumor cells^{77–80}. MT1-MMP has been demonstrated to exhibit integrin convertase activity and participate in an alternative processing of the pro- α v integrin subunit, generating a disulfide-bonded heavy chain and light chains⁸¹. This cleavage facilitated $\alpha_v\beta_3$ -dependent adhesion, contributing to migration of MCF-7 breast cancer cells on vitronectin⁸². Other integrin precursors, including pro- α 5, were also cleaved by MT1-MMP while pro- α 2 was resistant to MT1-MMP processing

⁸³. In the absence of MT1-MMP, expression of $\alpha v\beta 3$ resulted in diminished $\alpha 2\beta 1$ -mediated collagen binding; however addition of MT1-MMP to these cells restored collagen binding. Based on these results, the authors proposed the interesting conclusion that MT1-MMP-catalyzed $\alpha v\beta 3$ processing regulates integrin cross-talk ⁸³.

Cadherins associate with catenin family proteins and these complexes support cell-cell interactions, cell polarity and cytoskeletal organization ⁸⁴. Soluble E-cadherin ectodomain has been detected serum, urine and ascites fluids of cancer patients and is frequently associated with development of metastases and poor outcome ^{85–90} and several metalloproteinases have been identified as cadherin sheddases ^{91–94}. In a kidney ischemia model, increased MT1-MMP expression correlated with processing of both E- and N-cadherin ⁹⁵. Culturing cells on fibronectin surfaces abrogated the ischemia-induced MT1-MMP expression and cadherin ectodomain shedding. Neutralizing antibodies and shRNA directed against MT1-MMP were used to demonstrate a key role for MT1-MMP in cadherin shedding, thereby implicating MT1-MMP in ischemia-induced acute renal failure.

Other adhesion receptors such as CD44, a hyaluronan receptor, are also processed by MT1-MMP, generating shed ectodomain fragments of various sizes. For example in MIA PaCa-2 pancreatic cancer cells, MT1-MMP catalyzed shedding of a 70 kDa CD44 ectodomain fragment, resulting in enhanced motility, while a mutant CD44 lacking the MT1-MMP cleavage site was not processed and did not enhance migration ⁹⁶. Furthermore, transfection of the cleavage-resistant mutant CD44H inhibited motility, suggesting coordinate control of migration by CD44 and MT1-MMP. CD44 ectodomain shedding by MT1-MMP was stimulated by lactate in trabecular meshwork cells, providing a model system in which to evaluate the effects of CD44 shedding in glaucoma ⁹⁷. An alternative shedding pattern was observed in A375 melanoma cells. In this report, expression of MT1-MMP promoted ADAM-dependent shedding of a 65–70 kDa CD44 ectodomain, while MT1-MMP itself was implicated in release of a smaller 37–40 kDa ectodomain fragment ⁹⁸. The functional significance of differential CD44 processing and the role of the distinct fragments in cell motility remain under investigation.

c. Other Receptor/Ligand Substrates of MT1-MMP

The low density lipoprotein receptor-related protein (LRP) is a member of a family of cell surface associated endocytic receptors and is essential for the clearance of multiple proteinase ligands by internalization ^{99, 100}, including secreted MMPs. *In vitro* analyses showed proteolytic processing of the high molecular weight alpha subunit of LRP by recombinant MT1-MMP catalytic domain and a concomitant decrease in cell surface LRP levels in cells co-expressing LRP and MT1-MMP ¹⁰¹. These data suggest that MT1-MMP-catalyzed LRP cleavage may function ultimately in the regulation of proteinase clearance.

Receptor activator of NF- κ B ligand (RANKL) is a transmembrane glycoprotein that is an important regulator of osteoclast maturation and function ¹⁰². Proteolytic processing by tumor necrosis factor- α convertase (TACE, ADAM-17) generates soluble RANKL that, similar to cell-associated RANKL, supports osteoclast differentiation, as both cell-bound and soluble RANKL bind the RANK receptor on osteoclasts ¹⁰³. A recent report demonstrated shedding of RANKL by both ADAM-10 and MT1-MMP, generating two distinct products ¹⁰⁴. Downregulation of MT1-MMP expression in osteoblasts resulted in enhanced membrane-associated RANKL and promoted osteoclastogenesis. Similarly, osteoblasts from MT1-MMP deficient mice produced reduced levels of soluble RANKL and also displayed enhanced osteoclastogenesis *in vivo*. These data support a model wherein MT1-MMP-mediated RANKL shedding contributes to downregulation of osteoclastogenesis.

Semaphorin 4D is a membrane bound ligand for the plexin-B1 receptor and participates in axonal guidance in the developing nervous system as well as blood vessel development¹⁰⁵. The membrane-bound ligand is highly expressed in multiple solid tumors including head and neck squamous cell carcinoma¹⁰⁶, suggesting a regulatory role in tumor angiogenesis. It was recently demonstrated that MT1-MMP-catalyzed proteolytic processing of semaphorin 4D from the tumor cell surface is necessary for stimulation of endothelial cells¹⁰⁶, providing a novel mechanistic link between MT1-MMP activity and tumor angiogenesis.

d. Other Cell Surface Substrates

Cell surface tissue transglutaminase mediates the interaction of integrins with fibronectin via direct associations with β_1 and β_3 integrins and binding to fibronectin, and ultimately promotes integrin-dependent adhesion and spreading of cells¹⁰⁷. It has been demonstrated that MT1-MMP can proteolytically degrade the cell surface transglutaminase into three fragments of approximately 53, 41, and 32 kDa, resulting in decreased adhesion to and migration on fibronectin in glioma and fibrosarcoma cells¹⁰⁸. In contrast, motility on collagen surfaces was enhanced by MT1-MMP cleavage of transglutaminase, suggesting a role for MT1-MMP in regulating matrix-driven motility.

The transmembrane heparan sulfate proteoglycan syndecan-1 is an integral membrane protein that participates in cell proliferation, cell migration and cell-matrix interactions as an extracellular matrix protein receptor. Cleavage of syndecan-1 by MT1-MMP stimulated cell migration in human embryonic kidney HEK293 cells⁵⁴. Proteolytic release of the transmembrane mucin MUC-1 in human uterine epithelial cells is absent in MT1-MMP-deficient fibroblasts and, together with co-localization of the proteinase with MUC-1, support a role for MT1-MMP as a MUC-1 sheddase¹⁰⁹. Cleavage of the membrane-anchored proteoglycan betaglycan, that binds transforming growth factor-beta and regulates its cellular availability, is also catalyzed by MT1-MMP¹¹⁰. Interestingly, both MUC-1 and betaglycan shedding are stimulated by the tyrosine phosphatase inhibitor pervanadate, highlighting a potential role for tyrosine phosphorylation in MT1-MMP regulation^{110, 111}.

Extracellular matrix metalloproteinase inducer (EMMPRIN) is a membrane associated Ig-domain-containing inducer of MMP activity in surrounding cells^{112, 113}. Phorbol ester stimulation of HT1080 and A431 cells resulted in shedding of a 22 kDa EMMPRIN fragment¹¹⁴. The cleavage site was identified in the linker region between the two Ig domains and shedding was blocked by siRNA directed against MT1-MMP. While this cleavage released the functional N-terminal domain of EMMPRIN from the cell surface, the shed 22 kDa fragment retained MMP-inducing activity, suggesting a potential mechanism for dysregulated MMP expression.

V. Conclusion

In the relatively short time since its discovery, it has become well established that the transmembrane proteinase MT1-MMP is involved in the breakdown of extracellular matrix in normal physiological processes, such as tissue remodeling, embryonic development, and reproduction, as well as in disease processes, including arthritis and cancer metastasis. More recently, novel research tools and approaches have identified new substrates and molecular pathways as targets of MT1-MMP proteolysis, highlighting a broader range of substrates than originally anticipated. Many details of MT1-MMP biochemistry and cell biology remain under investigation including key regulatory issues such as transcriptional control, enzyme trafficking, inhibition, and substrate targeting. The diversity of matrix, soluble and cell surface MT1-MMP targets summarized above provide abundant evidence that acquisition of MT1-MMP activity can dramatically alter the pericellular proteome, thereby regulating widely disparate cellular and organismal processes.

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Fig. 1. Domain structure of MT1-MMP

(a) Mature membrane-anchored MT1-MMP is comprised of a catalytic domain (Y112-G²⁸⁵) containing the Zn⁺⁺-binding consensus sequence, a hinge region (E²⁸⁶-I³¹⁸), hemopexin-like domain (C³¹⁹-C⁵⁰⁸), a membrane-adjacent stalk region (P⁵⁰⁹-S⁵³⁸), a transmembrane domain (A⁵³⁹-F⁵⁶²) and a cytoplasmic tail (R⁵⁶³-V⁵⁸²). (b) MT1-MMP undergoes autolytic processing at G²⁸⁴-G²⁸⁵ to generate a membrane-anchored species lacking the catalytic domain but retaining a surface-localized hemopexin domain that regulates activity of the mature enzyme. (c) MT1-MMP-catalyzed activation of proMMP-2 involves two molecules of MT1-MMP, likely functioning as a dimeric unit. One member of the complex forms a trimeric activation complex comprised of MT1-MMP, TIMP-2 and proMMP-2. The proMMP-2 in the trimeric complex is properly positioned for efficient activation by TIMP-2-free MT1-MMP, generating active MMP-2.

Fig. 2. Collagenolytic activity of MT1-MMP

(**A**, **B**) OvCa433 cells, with low endogenous MT1-MMP expression were transfected with either (**A**) a catalytically inactive (E240A mutant) or (**B**) wild type MT1-MMP and subcultured onto type I collagen gels containing quenched fluorescent type I collagen (DQ-collagen, Invitrogen). This collagen substrate is heavily conjugated with multiple fluorescein labels, leading to quenched fluorescence in the intact substrate. Upon hydrolysis to single dye labeled products, quenching is relieved yielding green fluorescent products indicative of collagenase activity. Note the pericellular collagenolysis in cells expressing wild type active MT1-MMP (**B**). (**C**) Invasion of type I collagen gels. OvCa433 cells transfected with wild type or catalytically inactive mutant (E240A) MT1-MMP or vector controls were seeded onto Transwell filters coated with a type I collagen gel and allowed to invade for 24 hr. Non-invading

cells were removed from the upper chamber with a cotton swab prior to staining and enumeration of cells adherent to the underside of the filter using an ocular micrometer. Data from triplicate experiments are presented with S.D. value shown (* $p < .005$). (Figures courtesy of Yueying Liu.)

Fig. 3. Reciprocal regulation of MT1-MMP expression by collagen

Migrating cells encountering a three-dimensional collagen matrix engage collagen via integrin-mediated attachments. Clustering of integrins resulting from interaction with 3-dimensional collagen induces phosphorylation of Src kinases, resulting in induction of the transcription factor Egr-1 and transcriptional activation of the MT1-MMP promoter. The active proteinase is trafficked to the cell surface where it participates in pericellular collagenolysis.

Fig. 4. MT1-MMP processing of cell surface substrates

MT1-MMP catalyzes limited proteolytic processing and/or ectodomain shedding of a variety of membrane-anchored molecules including cadherins, integrins, proteoglycans (PG) and PG receptors as well as other surface substrates including LRP, RANKL, semaphoring 4D etc. These cleavages have been shown to regulate diverse cellular processes as summarized above.