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Review

Leukocyte cell surface proteinases: Regulation of expression, functions, and mechanisms of surface localization

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Abstract

A number of proteinases are expressed on the surface of leukocytes including members of the serine, metallo-, and cysteine proteinase superfamilies. Some proteinases are anchored to the plasma membrane of leukocytes by a transmembrane domain or a glycosyl phosphatidyl inositol (GPI) anchor. Other proteinases bind with high affinity to classical receptors, or with lower affinity to integrins, proteoglycans, or other leukocyte surface molecules. Leukocyte surface levels of proteinases are regulated by: (1) cytokines, chemokines, bacterial products, and growth factors which stimulate synthesis and/or release of proteinase by cells; (2) the availability of surface binding sites for proteinases; and/or (3) internalization or shedding of surface-bound proteinases. The binding of proteinases to leukocyte surfaces serves many functions including: (1) concentrating the activity of proteinases to the immediate pericellular environment; (2) facilitating pro-enzyme activation; (3) increasing proteinase stability and retention in the extracellular space; (4) regulating leukocyte function by proteinases signaling through cell surface binding sites or other surface proteins; and (5) protecting proteinases from inhibition by extracellular proteinase inhibitors. There is strong evidence that membrane-associated proteinases on leukocytes play critical roles in wound healing, inflammation, extracellular matrix remodeling, fibrinolysis, and coagulation. This review will outline the biology of membrane-associated proteinases expressed by leukocytes and their roles in physiologic and pathologic processes.
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Keywords: Proteinase; Cell surface binding; Pericellular proteolysis; Metalloproteinase; Serine proteinase

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1. Introduction

Q1 Leukocytes and resident tissue cells produce a diverse array of proteinases that contribute to physiologic processes such as extracellular matrix (ECM) remodeling, wound healing, inflammation, coagulation, fibrinolysis, host defense against infection, and various pathologic processes. Until recently, there has been little information available about the mechanisms by which cells use and control their proteinases to degrade extracellular proteins in vivo. Proteinases must circumvent the effects of high-affinity, extracellular proteinase inhibitors in order to cleave extracellular proteins. Inflammatory cells bathed in fluids containing physiologic proteinase inhibitors are associated with pericellular proteolysis (Fig. 1). One mechanism that enables cells to cleave or degrade proteins in their immediate environment is the localization of proteinases on cell surfaces. In vertebrates, serine, metallo-, and cysteine proteinases are expressed on the surfaces of various cell types including leukocytes, fibroblasts, epithelial cells, endothelial cells, and tumor cells (Table 1). These enzymes include members of the serine proteinase superfamily such as the leukocyte serine proteinases, proteinases involved in fibrinolysis, the type II transmembrane serine protease (TTSP) family (Qiu, Owen, Gray, Bass, & Ellis, 2007; Szabo et al., 2003), and the kallikrein/kinin system [reviewed in Schmaier & McCrae, 2007]. Serine proteases involved in the coagulation cascades can also bind to endothelial, platelet, and leukocyte cell surfaces [reviewed in Bouchard & Tracy, 2001; Doshi & Marmur, 2002 and Table 1]. Metalloproteinases and lysosomal cysteine proteinase also function as cell membrane-associated enzymes (Cavallo-Medved & Sloane, 2003). Space limitations of the journal preclude comprehensive coverage of all proteinases known to be expressed on the surface of all types of cells. Because of my interest in leukocyte-proteinase-mediated tissue injury, I will focus this review on proteinases expressed on the surface of leukocytes that play important roles in leukocyte biology. I will review the biology of leukocyte surface-bound proteinases, the advantages that cell surface binding confers upon individual proteinases, and the roles of leukocyte membrane-associated proteinases in physiologic and pathologic processes.

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2. Serine proteinases

Serine proteinases were among the earliest proteinases shown to be expressed on the surface of leukocytes. In 1985, urokinase type plasminogen activator (uPA or urokinase) was shown to bind to a surface receptor on monocytes and U937 cells (Vassalli, Baccino, & Belin, 1985). In 1990, proteinase 3 was identified on the surface of polymorphonuclear neutrophils [PMNs (Csernok, Ludemann, Gross, & Bainton, 1990)], and in the mid 1990s, neutrophil elastase (NE) and cathepsin G (CG) were also localized on the surface of activated PMNs (Bangalore & Travis, 1994; Owen, Campbell, Sannes, Boukedes, & Campbell, 1995). More recently, a new family of membrane-associated serine proteinases was identified: type II transmembrane serine proteases. In 2006, a member of the TTSP family, matriptase, was identified on the monocyte surface (Kilpatrick et al., 2006).

2.1. Plasminogen activators

Plasminogen activators are serine proteinases which convert plasminogen (an abundant extracellular protein) to plasmin, another serine proteinase which plays critical roles in degrading fibrin in blood clots and the provisional matrix deposited at sites of tissue injury. There are two plasminogen activators which differ in the structure of their non-catalytic domains (Blasi & Carmeliet, 2002; Medcalf, 2007). Tissue-type plasminogen activator (tPA), and urokinase-type plasminogen activator (uPA or urokinase). Both enzymes function as both soluble and cell-associated proteinases, but active tPA is primarily a clot-associated protease. Urokinase is expressed by leukocytes. Tissue-type plasminogen activator is not expressed by leukocytes, but binds to CD11b/CD18 integrin on macrophages to promote macrophage adhesion to fibrin and macrophage migration in vitro (Cao et al., 2006).

2.1.1. Structure, expression, and regulation of urokinase

Urokinase is produced and released by cells as an inactive, single chain pro-enzyme (pro-urokinase). This inactive pro-enzyme is cleaved at a single locus by a wide range of serine proteinases including plasmin, kallikrein, factor XIIa, matriptase, tryptase epsilon, human T cell-associated proteinase-1, and hepsin which is a TTSP (Blasi et al., 2002; Brunner, Simon, & Kramer, 1990; Kilpatrick et al., 2006; Moran et al., 2006; Yasuda et al., 2005). Several non-serine proteinases such as cathepsin B, cathepsin L, matrix metalloproteinase-3 (MMP-3) and the bacterial metalloproteinases, thermolysin also activate pro-urokinase (Goretzki et al., 1992; Kobayashi et al., 1993a; Marcotte & Henkin, 1993; Orgel et al., 1998). Cleavage of pro-urokinase by these enzymes generates a disulfilde-linked, two-chain, active enzyme (Blasi et al., 2002; Kilpatrick et al., 2006). Urokinase has three functional domains: (1) an NH_2-terminal epidermal growth factor (EGF)-like domain which binds the enzyme to its cell surface receptor; (2) a kringle domain; and (3) a COOH-terminal catalytic domain with the His-Ser-Asp catalytic triad typical of the serine proteinase family. Pro-urokinase binds with high affinity ($K_D \sim 1$ nM) to a specific receptor (uPA receptor or uPAR) which is a GPI-anchored protein on leukocytes and many other cells (Blasi et al., 2002; Ragno, 2006; Yasuda et al., 2005). However, pro-urokinase also binds to CD11b/CD18 integrin on PMNs which accelerates plasminogen activation and fibrinolysis on the PMN surface (Pluskota, Soloviev, Bdeir, Cines, & Plow, 2004).

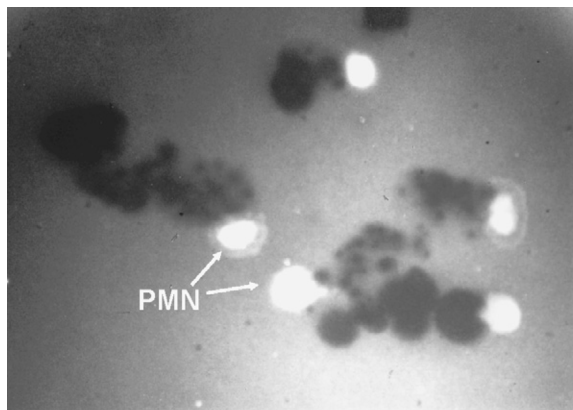

Fig. 1. PMN pericellular proteolysis. PMNs were incubated for 45 min at 37 °C on FITC-conjugated fibronectin which had been coated on tissue culture plates, and then opsonized. PMNs were bathed in 100% autologous serum which contains micromolar concentrations of TIMPs and serine proteinase inhibitors. Note that PMNs degrade fibronectin substrate as they migrate over it. However, fibronectin degradation is localized to the pericellular environment of the migrating PMNs by the inhibitors present in the bathing medium (arrows). Thus, physiologic proteinase inhibitors present in serum cannot block PMN pericellular proteolytic activity. When cells are bathed in inhibitor free buffers, the FITC-conjugated FN is completely degraded (not shown). One mechanism leading to this inhibitor-resistant pericellular proteolysis is expression of proteinases on the PMN surface in inhibitor-resistant forms which has been demonstrated for several serine and metalloproteinases families.

Urokinase is expressed by PMNs, monocytes, macrophages, and many other types of cells (Table 1). However, the biology of urokinase differs in PMNs compared to other urokinase-expressing cell types. PMNs do not syn-

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Table 1
Q12 Mechanisms of cell surface binding of proteinases

Binding mechanism	Proteinases bound	Cell types	Proteolytic activities
Transmembrane domain	MT1-MMP	Epithelial cells	ECM degradation, tumor invasiveness
	MT2-MMP	Tumor cells	Pro-MMP-2 and -13 binding and activation, TNF-α activation, proteinase inhibitor degradation
	MT3-MMP	Fibroblasts	
	MT5-MMP	Macrophages	
	ADAMs	Epithelial cells	Shedding of membrane-associated cytokines, apoptosis ligands, growth factors and receptors for these molecules
		Endothelial cells	
		Fibroblasts	
		Smooth muscle cells	
		Inflammatory cells	
		Tumor cells	Pro-urokinase activation
	Type II serine proteases (matriptase)	Monocytes, B lymphocytes	
GPI anchor	uPAR and urokinase	PMN mononuclear phagocytes	Fibrinolysis
		Fibroblasts	Activation of latent growth factors and pro-MMPs
		Epithelial cells	
		Smooth muscle cells	
	MT4-MMP	CNS	ECM degradation
		Eosinophils	Pro-MMP-2 activation
	MT6-MMP	PMN	ECM degradation
Proteoglycans	Pro- and active MMP-2, -7, -9, and -13	Uterine epithelial cells	ECM degradation
			Host defense
	NE, CG, PR3	PMN, macrophages	Wound healing
			Inflammation
Integrins	β2: pro-MMP-9 and -8, NE, CG	PMN	Unknown
	α2β1: MMP-1	Keratinocytes	Cell migration
	αvβ3: MMP-2	Endothelial cells and melanoma cells	Tumor invasiveness and neovascularization
TIMP-2	Pro-MMP-2 and -13	Fibroblasts endothelium	ECM degradation
		Tumor cells	Tumor invasiveness
CD44	MMP-2 and -9	Tumor cells and keratinocytes	ECM degradation, activation of latent TGF-β
	MMP-7	Tumor cells and epithelial cells	Post partum uterine involution, and lactation through HB-EGF shedding
Tissue factor	Factor VII	Monocytes/macrophages	Activation of actor VII and other serine proteases involved in thrombosis
High-molecular-weight kininogen	Prekallirein	Endothelial cells	Factor XI activation leading to thrombosis
			Bradykinin generation
			Pro-urokinase activation
P11	Cathepsin B	Tumor cells	Tumor growth and metastasis
Unknown	Cathepsin B	Macrophages, CTLs	Elastin degradation, degradation of perforins

ECM, extracellular matrix; PMN, polymorphonuclear neutrophils; TNF-α, tumor necrosis factor-α; GPI, glycosyl phosphatidyl inositol; CNS, central nervous system; NE, neutrophil elastase; CG, cathepsin G; PR3, proteinase 3; TGF-β, transforming growth factor-β, HB-EGF, heparin binding epidermal growth factor; CTLs, cytotoxic T lymphocytes.

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thesize urokinase de novo. Preformed urokinase is stored in the specific granules of PMNs along with uPAR. Unstimulated PMNs express minimal cell surface uPAR or urokinase, but both proteins translocate rapidly from the specific granules to the PMN surface when PMNs are activated to degranulate by phorbol esters, chemoattractants, and cytokines (Heiple & Ossowski, 1986; Plesner et al., 1994). In monocytes, macrophages, and other cells, urokinase expression is regulated at the transcriptional level by pro-inflammatory mediators and growth factors (Medcalf, 2007). During the chemotactic response, receptor-bound uPA becomes rapidly polarized to the leading edge of these phagocytes where it regulates cell adherence and migration (Blasi et al., 2002; Mondino & Blasi, 2004). The main inhibitor of urokinase in plasma is plasminogen activator inhibitor-1 (PAI-1), a member of the serine proteinase inhibitor (serpin) family which is secreted by many cell types including endothelial cells. Other less efficient inhibitors of urokinase include PAI-2, and protease nexin I (Blasi et al., 2002; Mondino et al., 2004). These inhibitors inhibit urokinase by forming irreversible covalent complexes with the enzyme.

The binding of pro-urokinase to its surface receptor not only promotes urokinase and plasmin activation on the cell surface (Blasi et al., 2002), but also protects both enzymes from inhibition, and regulates urokinase surface levels by inducing urokinase–uPAR endocytosis. Urokinase bound to uPAR has a 40% reduction in its association rate constant for PAI-1 and PAI-2 when compared to soluble urokinase (Ellis, Wun, Behrendt, Ronne, & Dano, 1990). Urokinase-mediated cleavage of cell membrane-bound plasminogen generates membrane-bound plasmin which is also resistant to inhibition by α_2-plasmin inhibitor which is an effective inhibitor of soluble plasmin (Ellis et al., 1990). Although binding of PAI-1 to surface-bound urokinase is reduced, when this happens, it is followed by endocytosis of the proteinase–inhibitor complex by clathrin-coated pits and members of the low-density lipoprotein receptor family. The enzyme–inhibitor complex dissociates from uPAR, and the inhibitor–enzyme complex is degraded in the lysosomes, but uPAR is recycled back to the cell surface to bind additional urokinase (Blasi et al., 2002; Mondino et al., 2004). However, cleavage and shedding of uPAR is currently regarded as a major regulatory process for this receptor (Blasi et al., 2002).

2.1.2. In vitro activities of urokinase and plasmin

Urokinase and tPA both have critical roles in fibrinolysis by generating active plasmin (Blasi et al., 2002; Carmeliet et al., 1994). The urokinase–uPAR system was initially thought to simply concentrate plasmin-mediated fibrinolysis at cell surfaces during tissue injury. However, plasmin has numerous other functions including cleaving proteins other than fibrin and activating cells. For example, plasmin cleaves and activates latent growth factors (Taipale, Koli, & Keski-Oja, 1992) and latent pro-MMPs (Parks, Wilson, & Lopez-Boado, 2004). Thus, plasmin may inhibit fibrotic responses to injury by clearing the provisional fibrin matrix at sites of injury and by activating pro-MMPs, or promote tissue fibrosis by activating latent transforming growth factor-β (TGF-β) which stimulates (myo)fibroblasts to deposit collagen in tissues. Plasmin also binds with low affinity (likely via its lysine binding sites) to plasma membrane sites of leukocytes, platelets, and endothelial cells and activates these cells by an active site-dependent manner (Syrovets & Simmet, 2004). This leads to homotypic aggregation of PMNs, platelet degranulation, release of arachidonic acid from endothelial cells, release of pro-inflammatory mediators from monocytes, and induction of monocyte chemotaxis (Syrovets et al., 2004). Plasmin activates platelets by cleaving and activating platelet protease activated receptor-4 [PAR-4 (Quinton, Kim, Derian, Jin, & Kunapuli, 2004)], but has no effect on platelet PAR-1. However, plasmin activates PAR-1 on the surface of macrophages, which increases macrophage MMP-12 production (Churg et al., 2007; Raza, Nehring, Shapiro, & Cornelius, 2000). Thus by generating plasmin, urokinase stimulates not only fibrinolysis, but also regulates ECM turnover and inflammation in tissues.

Urokinase also stimulates intracellular signaling to promote adhesion and migration of leukocytes and other cells by binding to uPAR even though this receptor lacks a cytoplasmic domain. After binding urokinase, uPAR signals by binding to other transmembrane proteins (including integrins and G protein coupled receptors) or to ECM proteins to promote cell adhesion, migration, apoptosis, and cell proliferation [reviewed in Blasi, 2001; Blasi et al., 2002; Crippa, 2007; Mondino et al., 2004; Ragno, 2006]. For example, uPAR stimulates chemotaxis of leukocytes after urokinase binds to uPAR which unmasks a chemotactic epitope in uPAR. The uncovering of this normally cryptic epitope in intact uPAR is caused by endoproteolytic removal of the amino-terminal domain of uPAR by active proteinases including those resulting from the biologic activity of uPAR [such as uPA, plasmin, and several active MMPs (Blasi et al., 2002)]. This signal is transduced by uPAR binding to a G protein-coupled fMLP receptor (Blasi, 2001; Resnati et al., 2002). The urokinase receptor also binds with high affinity to α3β1 and α5β1 integrins, and with lower affinity to β2 and β3 integrins, to promote adhesion and spreading of leukocytes and tumor cells

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on ECM proteins (Blasi et al., 2002; Sidenius & Blasi, 2003; Wei et al., 1996). Urokinase–uPAR binding also regulates cell survival and apoptosis. For example, urokinase activates and releases various growth factors which promote cell survival and proliferation (Hildenbrand et al., 2008). Urokinase–uPAR intracellular signaling also modulates the cell proliferation/apoptosis ratio by regulating cell–matrix interactions and the expression of anti-apoptotic proteins of the Bcl family which protect cells from apoptosis (Alfano, Laccarino, & Stoppelli, 2006; Hildenbrand et al., 2008).

2.1.3. *In vivo studies of urokinase and plasmin*

Studies of humans and mice with altered expression of components of the plasminogen system confirm critical roles for this system not only in fibrinolysis, but also in wound healing, inflammation, angiogenesis, and fibrotic responses to tissue injury. This system also plays critical roles in promoting tumor cell growth and metastasis [reviewed in Aguirre-Ghiso, 2007; Blasi et al., 2002; Laufs, Schumacher, & Allgayer, 2006; Montuori, Visconte, Rossi, & Ragno, 2005; Pillay, Dass, & Choong, 2007].

2.1.3.1. Fibrinolysis. Human subjects with severe homozygous type I plasminogen deficiency develop ligneous conjunctivitis, a rare and unusual form of chronic pseudomembranous conjunctivitis, and also develop additional pseudo-membranous lesions of other mucous membranes (Mingers, Heimburger, Zeitler, Kreth, & Schuster, 1997). These lesions are caused by massive fibrin depositions within the extravascular space of mucous membranes due to the lack of clearance of these depositions by plasmin. Mice genetically deficient in plasminogen (plasminogen$^{-/-}$ mice) also develop ligneous conjunctivitis (Drew et al., 1998). Plasminogen$^{-/-}$ mice are also predisposed to developing spontaneous severe thrombosis in multiple organ systems due to impaired fibrinolysis, and also suffer retarded growth, reduced fertility, and decreased survival (Bugge, Flick, Daugherty, & Degen, 1995; Ploplis et al., 1995). Mice singly deficient in tPA, urokinase, or uPAR are healthy and have normal life span in the unchallenged state, but tPA$^{-/-}$ mice have impaired clot lysis, and urokinase$^{-/-}$ mice have occasional hepatic fibrin deposits (Bugge, Flick, et al., 1996; Carmeliet et al., 1994). However, mice with combined deficiency of tPA and uPA suffer extensive spontaneous fibrin deposition and have impaired growth, reduced fertility, and decreased survival similar to that occurring in plasminogen$^{-/-}$ mice (Carmeliet et al., 1994). Mice deficient in urokinase, tPA and plasminogen die from generalized thrombosis and inflammation (Carmeliet et al., 1994). The inflammation in these mice is secondary to thrombosis and extravascular fibrin deposition (Bugge, Kombrinck, et al., 1996; Drew et al., 1998). These data indicate that in mice there is no significant alternative fibrinolytic pathway to tPA and urokinase.

2.1.3.2. Wound healing. Studies of urokinase$^{-/-}$ mice also demonstrate that urokinase-mediated activation of plasmin plays an important role in healing skin wounds in mice by clearing fibrin (Bugge, Flick, et al., 1996; Romer et al., 1996). Urokinase also plays a critical role in the repair of the ischemic myocardium in mice by promoting the migration of fibroblasts into the injured myocardium, activating TGF-β, and promoting angiogenesis by inducing migration of vascular smooth muscle cells and endothelial cells into the injured myocardium (Heymans et al., 1999). In these wound healing models, urokinase does not signal through uPAR since uPAR$^{-/-}$ mice have minimal abnormalities in these model systems (Carmeliet et al., 1997; Levi et al., 2001). Likely, urokinase binds to ECM proteins in the pericellular environment in lieu of uPAR during wound healing.

2.1.3.3. Leukocyte migration. The role of uPAR in regulating leukocyte migration in vivo is controversial. Some studies of uPAR$^{-/-}$ mice have found no role for uPAR in regulating leukocyte recruitment into various organs (Cao et al., 2006; Dewerchin et al., 1996), whereas other studies report that uPAR promotes PMN and lymphocyte recruitment into inflamed peritoneum and into the lung in murine models of lung inflammation and infection, possibly by uPAR signaling through β2 integrins, leading to decreased clearance of pathogens and impaired host survival (Gyetko et al., 2000, 2001; May et al., 1998; Rijneveld et al., 2002).

2.1.3.4. Fibrosis. Plasminogen activators and their inhibitors regulate lung fibrotic responses to injury. Transgenic mice over-expressing PAI-1 have increased lung fibrosis compared to control mice in the bleomycin-mediated lung fibrosis (Eitzman et al., 1996), whereas PAI-1$^{-/-}$ mice and transgenic mice over-expressing urokinase in the lung in an inducible manner are protected in this model (Eitzman et al., 1996; Sisson et al., 2002). Likely, urokinase protects against lung fibrotic responses to injury by generating plasmin which digests fibrin in the provisional matrix generated during bleomycin-mediated lung injury, and activates pro-MMPs leading to increased removal of collagen and other ECM proteins deposited in the lung.

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2.2. Neutrophil elastase, cathepsin G and proteinase 3 (PR3)

2.2.1. Structure, expression, and regulation

NE, CG and PR3 are serine proteinases comprised of a single chain glycoprotein with ∼200 amino acid residues (Pham, 2006). All three enzymes are all highly cationic with CG being the most and PR3 the least cationic. These proteinases are predominantly expressed by PMNs, but are not synthesized de novo by mature blood PMNs. Instead, they are synthesized at the promyelocyte stage of PMN development in the bone marrow and stored at millimolar concentrations as active enzymes in PMN azurophil granules (Borregaard & Cowland, 1997). A subpopulation of monocytes with a PMN-like pro-inflammatory phenotype (P monocytes) also stores preformed NE, CG and PR3 in their primary granules (Kargi, Campbell, & Kuhn, 1990; Owen, Campbell, Boukedes, Stockley, & Campbell, 1994). Macrophages do express serine proteinases under physiologic conditions but can be induced to synthesize NE under some pathologic conditions (Dollery et al., 2003).

The major inhibitors of NE, CG, and PR3 are serpins which comprise about 10% of all plasma proteins, and include α_1-proteinase inhibitor (α_1-PI) and α_1-antichymotrypsin (α_1-Ach), which are synthesized and secreted by hepatocytes. The universal inhibitor, α_2-macroglobulin (α_2-M), also inhibits these enzymes (Carrell, 1986). Other inhibitors of these enzymes are secretory leukocyte proteinase inhibitor (SLPI) and elafin which are produced by epithelial cells and found in a variety of glandular secretions such as the upper and lower respiratory tract and synovial fluid (Kramps, Rudolphus, Stolk, Willems, & Dijkman, 1991; Sallenave, Silva, Marsden, & Ryle, 1993).

2.2.2. Membrane binding of serine proteinases

Under some circumstances, NE, CG, and PR3 are freely released from the azurophilic granules of PMNs and the primary granules of P monocytes when cells are activated to degranulate. In contrast to other proteinase-containing granules and vesicles in PMNs which translocate to and fuse with the plasma membrane when PMNs are activated, the azurophilic granules translocate to the PMN plasma membrane but do not fuse with it (Borregaard et al., 1997). Serine proteinases are released from PMNs into the extracellular space in large amounts in vitro only when the cells are exposed to pharmacologic agonists that potently induce degranulation such as cytochalasin B, phorbol esters, and calcium ionophores. Activation of PMNs with physiologically relevant stimuli such as cytokines, chemokines, and bacterial products induces more modest free release of these enzymes [less than 2% of the cellular content in vitro (Campbell, Campbell, & Owen, 2000; Owen, Campbell, Boukedes, & Campbell, 1995, 1997)]. However, significant free release of serine proteinases from PMNs may occur in vivo during extensive or frustrated phagocytosis (Liszt, Schnittker-Schulze, Stuhlsatz, & Greiling, 1991) or in diseases in which macrophage clearance of apoptotic PMNs is either impaired or inadequate due to excessive influx of PMNs into tissues. This occurs in the airways of COPD patients during acute infective disease exacerbations or in the airways and lungs of patients with cystic fibrosis (Matthay & Zimmerman, 2005; Naylor et al., 2007; Vandivier et al., 2002). In these diseases, PMNs undergo necrosis and PMN proteinases are discharged into the extracellular space where they contribute to tissue destruction.

All three serine proteinases are also expressed on the surface of PMNs and membrane-bound NE, CG, and PR3 are likely to be the most important forms of the enzymes during physiologic and pathologic processes. Unstimulated PMNs express minimal amounts of membrane-bound NE and CG. Activation of PMNs with cytokines, bacterial products, chemoattractants, and fMLP, a synthetic bacterial-like peptide induces up to 20-fold increases in PMN surface expression of NE, CG, and PR3 [Campbell et al., 2000; Owen, Campbell, Boukedes, et al., 1995; Owen et al., 1997; Owen, Campbell, Sannes, et al., 1995 and Fig. 2]. Under these conditions, 6-fold more NE and CG binds to the PMN plasma membrane than is freely released by cells.

There are several notable differences between PR3 versus NE and CG which may explain, in part, why among these enzymes only PR3 has been implicated in the pathogenesis of Wegener's granulomatosis (vide infra). First, the subcellular localization of PR3 differs from that of NE and CG. NE and CG are only stored in the azurophil granules of PMNs, but PR3 is also present in the membrane of secretory vesicles which translocate to the plasma membrane much more readily than the azurophil granules (Witko-Sarsat, Cramer, et al., 1999). Second, PR3 moves also to the plasma membrane during apoptosis in the absence of degranulation (Kantari et al., 2007). Third, in contrast to NE and CG significant PR3 is expressed on the surface of unstimulated PMNs (Witko-Sarsat, Lesavre, et al., 1999).

2.2.3. Biologic roles of membrane-bound serine proteinases

Soluble NE, CG, and PR3 have diverse activities including bacterial killing, and cleaving diverse proteins including ECM proteins, inflammatory media-

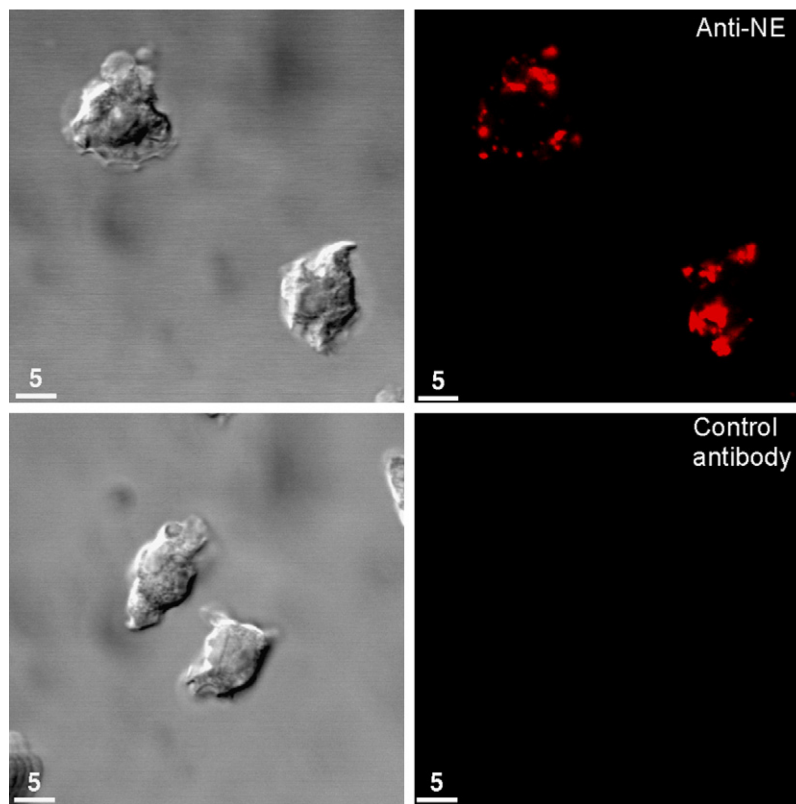

Fig. 2. Neutrophil elastase is expressed on the surface of activated PMNs. Human PMNs were activated for 30 min at 37 °C with 10^{-7} M fMLP and then fixed and immunostained with rabbit anti-NE (top panel) or non-immune rabbit IgG (bottom panel) followed by a secondary antibody conjugated to a red fluorophore. Cells were examined using Normaski objective (left panel) and confocal miscroscopy (right panel). Note the intense staining for NE on the surface of activated PMNs. Most NE (and CG) bind to HSPG and CSPG on the PMN surface by an active site-independent manner (Campbell et al., 2007). However, a small proportion of NE and CG bind via their active sites to CD11b/CD18 integrins on PMNs to regulate Q11 PMN adhesion to extracellular matrix proteins (Cai et al., 1996).

482 tors, and cell surface receptors, and activating various 483 types of cells (Owen & Campbell, 1999; Pham, 2006). 484 Membrane-bound NE, CG and PR3 on PMNs have 485 similar catalytic activity and efficiency as the soluble 486 forms of the proteinases since membrane-bound NE 487 and PR3 degrade ECM components (Campbell et 488 al., 2000; Owen, Campbell, Sannes, et al., 1995), 489 membrane-bound NE and CG activate coagulation pro-490 teins on monocyte surfaces (Allen & Tracy, 1995) and 491 membrane-bound CG potently converts the biologically 492 inactive peptide angiotensin I to angiotensin II (Owen 493 & Campbell, 1998) which increases vascular smooth 494 muscle tone and permeability, and stimulates mononu-495 clear cell chemotaxis. Membrane-bound NE and CG 496 are also potent inducers of goblet cell degranulation 497 (Takeyama et al., 1998). However, membrane-bound 498 NE, CG and PR3 have been shown to be resistant to 499 inhibition by physiologic inhibitors including α_1-PI and 500 α_1-Ach, and membrane-bound CG activates angioten-501 sin I even when cells are bathed in undiluted serum 502 which contains high concentrations of physiologic inhi-503 bitors of CG (Bangalore & Travis, 1994; Campbell et 504 al., 2000; Owen, Campbell, Sannes, et al., 1995; Owen 505 et al., 1998). Q7 Recently, surface-bound NE on PMNs 506 was shown to be inhibited by α_1-PI in bronchoalveo-507 lar lavage (BAL) samples from patients with pneumonia 508 and acute lung injury, but PMN surface-bound CG and 509 PR3 were substantially resistant to inhibition by α_1-510 PI (Korkmaz, Attucci, Jourdan, Juliano, & Gauthier, 511 2005). It is not clear why differences in susceptibility of 512 membrane-bound NE to inhibition by α_1-PI have been 513 reported. One possibility is that in the study of Korkmaz 514 et al., much lower concentrations of membrane-bound 515 NE were assayed for their susceptibility to inhibition 516 than in the earlier published studies. It is possible that 517 when low concentrations of membrane-bound NE are 518 tested in vitro, α_1-PI binds with much higher affinity to 519 membrane-bound NE than to membrane-bound CG or 520 PR3. Under these conditions, α_1-PI–membrane-bound 521 NE interactions are sufficient to produce substantial

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inhibition of membrane-bound NE. However, during inflammatory reactions in vivo, high concentrations of membrane-bound NE on activated PMNs are likely to be present in tissues which may not be efficiently inhibited by α_1-PI present in extracellular fluids leading to NE-mediated tissue injury.

2.2.4. Surface receptors for serine proteinases on PMNs

The first receptor reported for serine proteinases on PMNs was CD11b/CD18 integrin. NE binds via its active site to this integrin which leads to detachment of PMNs from fibrinogen-coated surfaces (Cai & Wright, 1996). However, CD11b/CD18 integrins bind only a small fraction of the total number of NE molecules expressed on the surface of activated PMNs. More recently, we showed that NE and CG bind by an active site-independent but charge-dependent manner to high-capacity, low-affinity binding sites (~10^7 sites per cell and $K_D \sim 10^{-7}$ M) which are the negatively charged sulfate groups in heparan sulfate- and chondroitin sulfate-containing proteoglycans (HSPG and CSPG) in PMN plasma membranes (Campbell & Owen, 2007). Likely, most of the NE and CG molecules expressed on the PMN surface bind by their positively charged external residues to HSPG and CSPG which form a reservoir which sequesters the large amounts of these enzymes released during PMN degranulation. A small proportion of serine proteinases bound to HSPG and CSPG may bind subsequently to CD11b/CD18 integrins to regulate PMN adhesion. Macrophages also express high-capacity, low-affinity binding sites for NE and CG, which are also likely to be HSPG and CSPG (Campbell, 1982). NE and CG released by PMNs bind to these macrophage binding sites and are subsequently internalized by macrophages (Campbell, White, Senior, Rodriguez, & Kuhn, 1979). CG also binds to and activates a high affinity fMLP receptor on PMNs and monocytes which stimulates migration of these cells (Chertov et al., 1997; Sun et al., 2004). The binding sites for PR3 on PMNs are less clear, but PR3 competes with NE and CG for HSPG and CSPG bindings sites on PMNs (Campbell et al., 2007). PR3 also binds to lipid components in PMN membranes (Goldmann, Niles, & Arnaout, 1999) including the phospholipid, scramblase-1 (Kantari et al., 2007). CD177 (also called NB1), a GPI-anchored glycoprotein on PMNs may also serve as a receptor for PR3 (Bauer et al., 2007; von Vietinghoff et al., 2007). Thus, although NE and PR3 are homologs, there are differences in the mechanisms by which they bind to the surface of PMNs which suggests that they may play different roles in regulating acute inflammatory processes.

2.2.5. Biologic roles of membrane-bound NE, CG, and PR3

Based upon their catalytic activities membrane-bound NE, CG, and PR3 are well equipped to contribute to PMN pericellular proteolysis. While there is little evidence to support a role for PMN proteinases in degrading ECM proteins during PMN migration through tissues (Hirche, Atkinson, Bahr, & Belaaouaj, 2004; MacIvor et al., 1999), membrane-bound serine proteinases on PMNs may clear tissue debris and regulate the biologic activities of inflammatory mediators during wound healing and inflammatory responses to injury (Abbott et al., 1998; Pham, 2006). Membrane-bound serine proteinases on PMNs may also contribute directly to lung ECM destruction in COPD and inflammatory arthritis (Adkison, Raptis, Kelley, & Pham, 2002; Shapiro et al., 2003) and mucus hyper-secretion in COPD (Takeyama et al., 1998).

2.2.6. Wegener's granulomatosis

Membrane-bound PR3 plays a critical role in the pathogenesis of Wegener's granulomatosis which is a systemic, autoimmune vasculitis affecting the kidneys and the upper respiratory tract. Circulating anti-neutrophil cytoplasmic autoantibodies (cANCA) are detected in ~95% of patients with active Wegener's granulomatosis (Gross, Csernok, & Flesch, 1993). These autoantibodies are directed against PR3 and play a direct role in vascular injury in this disease (Bosch et al., 1993; Gross, Trabandt, & Csernok, 1998). Circulating PMNs and monocytes from patients with Wegener's granulomatosis express PR3 on their surface and cANCA bind via their $F(ab)_2$ component to membrane-bound PR3 (Csernok et al., 1990; Csernok, Schmitt, Ernst, Bainton, & Gross, 1993). Ligation of $Fc\gamma$ receptors on leukocytes by the Fc component of cANCA is a potent stimulus for leukocyte degranulation and activation of the respiratory burst (Kettritz, Jennette, & Falk, 1997; Ralston, Marsh, Lowe, & Wewers, 1997). Proteinases and oxidants released by PMNs activated in this way cause the vascular inflammation and injury characteristic of this syndrome.

Individuals differ in percentage of circulating PMNs that constitutively express membrane-bound PR3. This percentage is genetically determined and is now considered as a risk factor for Wegener's granulomastosis and other inflammatory diseases. For example, individuals that have a large subset of neutrophils expressing membrane PR3 at baseline are at increased risk for developing vasculitis and rheumatoid arthritis (Schreiber, Busjahn, Luft, & Kettritz, 2003; Schreiber et al., 2005; van Rossum, Limburg, & Kallenberg, 2003; Witko-Sarsat,

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Lesavre, et al., 1999). The differences in subcellular localization and mobilization of PR3 to the PMN surface compared to that of NE and CG (vide supra) may explain, in part, why PR3 rather than NE or CG plays a critical role in the pathogenesis of Wegener's granulomastosis.

2.3. Type II transmembrane serine proteinases

TTSPs are a large family of serine proteinases anchored to the surface of diverse cell types by a transmembrane domain [reviewed in Szabo et al., 2003]. All members have a short hydrophobic signal anchor located at their amino terminus and an extracellular serine proteinase domain at their carboxy terminus. These domains are separated by a stem region that may contain different additional protein domains. Hespin was the first identified TTSP in 1998, and at least 17 mammalian TTSP have been identified in humans. Evidence is emerging that these enzymes play important roles in embryonic development and in tumor growth and metastasis (List, Bugge, & Szabo, 2006; Szabo et al., 2003). One member of this family, matriptase is expressed by leukocytes.

2.4. Membrane-type serine protease-1 (MT1-SP or matriptase)

2.4.1. Expression and localization

This enzyme was first described in 1993 and was found to be expressed predominantly by normal and malignant epithelial cells (Oberst et al., 2001). More recently, matriptase has been shown to be expressed by monocytes, B lymphocytes, and endothelial cells (Kilpatrick et al., 2006; Qiu et al., 2007; Seitz et al., 2007). Matriptase is an 80–90 kDa protein which is synthesized as an inactive single chain zymogen. Matriptase activation is a complex process involving its non-catalytic domains and its main inhibitor, Kunitz-type inhibitor hepatocytes growth factor activator inhibitor (List et al., 2005). The zymogen is cleaved within its activation motif in the serine proteinase domain generating a two-chain enzyme from the single chain zymogen.

2.4.2. Biologic functions

In epithelial cells, matriptase plays a critical role in epithelial differentiation, in part, by processing profilaggrin (List et al., 2006). Other substrates reported for matriptase are pro-urokinase, hepatocytes growth factor, and PAR-2 (Lee, Dickson, & Lin, 2000; Takeuchi et al., 2000). Matriptase is expressed at high levels on the surface of freshly isolated monocytes and B lymphocytes (Kilpatrick et al., 2006). Activation of these cells in vitro leads rapidly to loss of expression of matriptase from their surfaces. Surface-bound matriptase is co-localized with uPAR on the surface of monocytic cell lines where it potently activates pro-urokinase bound to uPAR, albeit 100-fold less efficiently than plasmin. Thus, monocyte-derived matriptase may contribute to the generation of plasmin on the surface of monocytes. Matriptase is also upregulated on the surface of monocytes adherent to endothelial cells in atherosclerotic lesions, and monocyte-derived matriptase may stimulate inflammation in these lesions by activating endothelial PAR-2 and increasing endothelial production of pro-inflammatory mediators (Seitz et al., 2007). However, it is not clear whether matriptase expressed by B lymphocytes function plays any role in physiologic or pathologic processes.

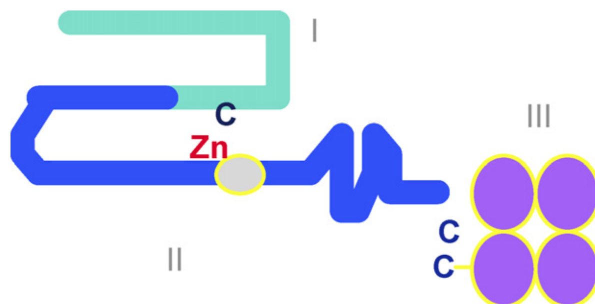

Fig. 3. Domain structure of MMPs. MMPs share common features including a pro-enzyme domain (I), a catalytic domain with the active site zinc bound to the HEXXHXXGXXH consensus sequence (II), and a C-terminal domain (III) which may regulate MMPs binding to their substrates and to tissue inhibitors of metalloproteinases. The catalytic zinc (Zn) atom interacts with a conserved cysteine (C) in domain I to maintain the pro-enzyme in an inactive conformation. The gelatinases have an additional domain similar to the fibronectin type II domain, which interrupts the catalytic domain. MMP-9 also has a region with homology to type V collagen (not shown).

3. Metalloproteinases

Members of the matrix metalloproteinase and ADAM subfamilies of metalloproteinases are expressed on the surface of leukocytes.

3.1. Matrix metalloproteinases (MMPs)

3.1.1. Structure, expression, and activation of MMPs

This class of more than 20 proteinases in humans depend on Zn^{2+} ions for their activity (Parks et al., 2004; Puente, Sanchez, Overall, & Lopez-Otin, 2003). MMPs are 40–50% identical at the amino acid level and have common structural domains (Fig. 3). The domains include: (1) a pro-enzyme domain that

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maintains the enzyme in its latent form; (2) the catalytic domain containing the zinc binding consensus sequence HEXXHXXGXXH which binds the zinc molecule essential for catalysis; and (3) a carboxy-terminal hemopexin domain which binds MMPs to their substrates, cell membranes, and tissue inhibitors of MMPs (TIMPs). The gelatinases (MMP-2 and -9) have additional domains (Fig. 3). The six membrane-type MMPs (MT-MMP) also have either a membrane-spanning domain or a GPI membrane anchor.

MMPs are synthesized and secreted from cells as latent pro-enzymes (pro-MMPs). Activation of pro-MMPs can be achieved in vitro by various proteinases and reactive oxygen species which disrupt the interaction between the active site zinc atom in the catalytic domain and a conserved cysteine within the pro-enzyme domain (Murphy et al., 1999). Exposure of the zinc results in auto-cleavage of the pro-domain yielding the mature active enzyme. The mechanism of extracellular activation of pro-MMPs in vivo has not been determined, but reactive oxygen species inactivate rather than activate MMPs in the lung in vivo (Fu, Kassim, Parks, & Heinecke, 2003).

3.1.2. Regulation of MMPs

In most cells including leukocytes, the MMP genes are tightly regulated at the transcriptional level and their expression is induced during tissue remodeling, wound healing, inflammation and other processes by a variety of growth factors, cytokines, chemokines, bacterial products, and surfactant proteins (Busiek, Baraji, Nehring, Parks, & Welgus, 1995; Campbell, Cury, Lazarus, & Welgus, 1987; Cury, Campbell, Lazarus, Albin, & Welgus, 1988; Trask et al., 2001; Wahl & Corcoran, 1993). In mononuclear phagocytes, MMPs are synthesized and then rapidly secreted by cells rather than stored. PMN-derived MMP-8 and -9 are notable exceptions to this rule, since they are stored in PMN secondary and tertiary granules, respectively, and rapidly released from these granules when PMNs are activated with degranulating agonists (Chatham, Heck, & Blackburn, 1992; Dewald, Bretz, & Baggiolini, 1982).

3.1.3. Inhibitors of MMPs

The activity of MMPs is controlled by the four members of the tissue inhibitors of metalloproteinase family and by α_2-macroglobulin (Murphy et al., 2003). In addition, a transmembrane inhibitor, RECK, which inhibits MMP-2 and -9 and MT1-MMP, has recently been shown to be essential for restricting MMP activity during embryonic development (Oh et al., 2001).

3.1.4. Activities of MMPs

MMPs can degrade all of the components of the ECM in vitro. Based on this, MMPs can be divided into groups (Shapiro, 1998) including: (1) the interstitial collagenases (MMP-1 [human only], -8, -13) which cleave native triple helical interstitial collagens; (2) the gelatinases (MMP-2 and -9) which degrade gelatins (denatured collagens), elastin and basement membrane proteins; (3) the stromelysins (MMP-3, -10, and -11) which have a broad spectrum of activity against ECM proteins; (4) the elastolytic MMP-7 and -12 which also have a broad spectrum of susceptible ECM substrates including basement membrane components; and (5) the MT-MMP (see below).

The main function of MMPs in vivo was initially thought to be in ECM remodeling. Some studies support a role for MMPs in ECM degradation in vivo. For example, MMP-12 degrades lung elastin in cigarette smoke-exposed mice leading to pulmonary emphysema (Hautamaki, Kobayashi, Senior, & Shapiro, 1997). The lung elastin fragments generated by MMP-12 are chemotactic for blood monocytes and thereby amplify chronic lung inflammation and ECM destruction in the lungs of smoke-exposed mice (Houghton et al., 2006). Many MMPs are expressed by tumor cells, and tumor cell MMP-mediated ECM degradation plays a critical role in promoting tumor growth and metastasis in vivo [reviewed in Stamenkovic, 2000]. However, there is increasing evidence that MMPs play important roles in regulating inflammation, host defense, and angiogenesis by cleaving diverse molecules such as cytokines, chemokines, clotting factors, regulators of angiogenesis, defensins, to either increase or decrease their biologic activities. For example, MMP-7 sheds KC from syndecans on the surface of lung epithelial cells thereby promoting PMN influx into the lung during bleomycin-mediated ALI in mice (Li, Park, Wilson, & Parks, 2002), MMP-8 activates a PMN chemokine in murine skin inflammatory reactions (Balbin et al., 2003), and MMP-12 sheds and activates pro-TNF-α from macrophage surfaces in murine lung acutely exposed to cigarette smoke thereby increasing neutrophilic lung inflammation (Churg et al., 2003). Several MMPs inactivate pro-inflammatory mediators to dampen inflammation in tissues (McQuibban et al., 2002). MMP-7 cleaves and activates defensins to promote host defense in the murine gut (Wilson et al., 1999). MMP-12 cleaves plasminogen to generate angiostatin which inhibits angiogenesis and tumor growth (Balbin et al., 2003; Cornelius et al., 1998). Some MMPs activate PARs leading to activation of leukocytes, platelets, and tumor cells (Chung et al., 2004; Goerge et al., 2006; Pei, 2005).

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3.1.5. Membrane binding of MMPs lacking transmembrane domains or GPI anchors

MMP-1, -2, -7, -8, -9, and -13 lack a transmembrane domain and have been thought to function exclusively as soluble proteinases after their secretion from cells. However, these MMPs have recently been shown to bind to various molecules on the surfaces of leukocytes (vide infra) and other cells types (summarized in Table 1). Examples of MMPs that bind to cells other than leukocytes are active MMP-1 which binds to α2β1 integrin on keratinocytes during wound healing (Dumin et al., 2001), and active MMP-2 which binds to αvβ3 integrin on the surface of melanoma cells and angiogenic blood vessels and participates in pericellular proteolysis (Brooks et al., 1996). Pro- and active forms of MMP-2, -7, -9 and -13 are bound to HSPGs in the plasma membrane of rat uterine epithelial cells [Table 1; Yu & Woessner, 2000] where they may maintain the patency of the glandular lumen, promote host defense against bacteria by activating defensins, and activate or degrade cell surface proteins that regulate epithelial cell function. MMP-7 binds to CD44 on the surface of tumor cell lines, postpartum uterine and lactating mammary gland epithelia, and uterine smooth muscle cells where it forms a complex with and activates the HB-EGF precursor. The active HB-EGF thus generated, engages and activates its receptor, ErbB4, promoting epithelial cell survival (Yu, Woessner, McNeish, & Stamenkovic, 2002). CD44 is a docking molecule for active MMP-2 and -9 and on the surface of breast tumor cells, melanoma cells, and normal keratinocytes (Yu & Stamenkovic, 1999, 2000). MMP-9 bound to CD44 on tumor surfaces degrades collagen IV in the pericellular environment and promotes tumor cell invasion (Yu et al., 1999). MMP-2 and -9 bound to CD44 may also promote tissue remodeling by tumor cells by cleaving and activating latent TGF-β (Yu et al., 2000).

3.1.6. Binding of MMPs to leukocyte integrins

PMN-derived MMP-8 and -9 are rapidly secreted by degranulating PMNs. Until recently, they have been thought to function exclusively as soluble enzymes. However, PMNs also express MMP-8 and -9 on their surface. Unstimulated cells have minimal cell-associated MMP-8 or -9, but activation of PMNs with cytokines, chemokines, and bacterial products leads rapidly to 10-fold increases in surface expression of these MMP due to translocation of the MMP-containing granules the PMN surface (Owen, Hu, Barrick, & Shapiro, 2003; Owen, Hu, Lopez-Otin, & Shapiro, 2004). Latent and active forms of these MMPs have been detected on the PMN surface, and active forms of membrane-bound MMP-8 and -9 on PMNs degrade ECM proteins as efficiently as the soluble forms of the proteinases (Owen et al., 2003, 2004). However, membrane-bound MMPs are resistant to inhibition by TIMPs. The pro-forms of these MMPs bind, at least in part, to a β2 integrin, CD11b/CD18 (Mac-1) on the PMN surface (Stefanidakis, Ruohtula, Borregaard, Gahmberg, & Koivunen, 2004). The pro-MMPs bind via negatively charged residues in their catalytic domain to the I domain of the CD11b chain on PMNs (Stefanidakis, Bjorklund, Ihanus, Gahmberg, & Koivunen, 2003). However, the mechanism by which MMP-8 and -9 are activated and subsequently retained on the PMN surface is not clear.

3.1.7. Biologic roles of membrane-bound MMP-8 and -9 on PMNs

Membrane-bound MMP-8 and -9 play no direct role in PMN migration through tissues since PMNs from MMP-8$^{-/-}$ and -9$^{-/-}$ mice are able to migrate in vitro and into inflamed tissues in vivo (Betsuyaku, Shipley, Liu, & Senior, 1999; Owen et al., 2004). Surface-bound MMP-8 and -9 on activated PMNs may locally degrade the ECM, and remove tissue debris during wound healing or contribute to resolution of inflammatory responses since they cleave pro-inflammatory mediators in vitro, and MMP-8$^{-/-}$ mice have increased neutrophilic pulmonary inflammation in murine models of asthma and acute lung injury (Gueders et al., 2005; Owen et al., 2004).

3.2. Integral membrane MMPs (MT-MMPs)

3.2.1. Structure, activation, expression, and regulation

There are six members of this subfamily of metalloproteinases (Table 1). They share 30–50% sequence homology, the multi-domain structure typical of MMPs, and are expressed on cell surfaces by either a transmembrane domain spanning hydrophobic region or a GPI anchor (Itoh et al., 1999; Kang et al., 2001). Like MMPs, MT-MMPs are synthesized as inactive pro-enzymes, but unlike most MMPs, MT-MMPs are activated by furin-mediated cleavage on the pro-domain within the trans-Golgi network before they are transported to cell surfaces (Imai et al., 1996; Pei, 1999; Sato, Kinoshita, Takino, Nakayama, & Seiki, 1996).

The MT-MMP family is expressed by different cell types (Lehti, Lohi, Valtanen, & Keski-Oja, 1998) including leukocytes (Table 1). MT1-MMP is produced by macrophages, monocytes, and dendritic cells (Stawowy et al., 2005; Yang et al., 2006), MT4-MMP is expressed by eosinophils (Gauthier et al., 2003) and MT6-MMP is expressed only by PMNs (Kang et al., 2001). In

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most cells including mononuclear phagocytes, MT-MMP expression is generally upregulated at the steady state mRNA level by various cytokines and growth factors (Lohi, Lehti, Westermarck, Kahari, & Keski-Oja, 1996; Migita et al., 1996; Origuchi et al., 2000), or when cell adhere to ECM proteins (Ailenberg & Silverman, 1996). However, PMNs store MT6-MMP as a preformed proteinase within their gelatinase and secretory vesicles from where the enzyme translocates to the cell surface when PMNs are activated with degranulating agonists (Kang et al., 2001).

3.2.2. Inhibition

MT-MMPs vary in their susceptibility to inhibition by TIMPs. For example, TIMP-2, -3, and -4 inhibit MT1-MMP and MT2-MMP but TIMP-1 does not (Butler, Will, Atkinson, & Murphy, 1997; D'Ortho et al., 1998; Hernandez-Barrantes, Shimura, Soloway, Sang, & Fridman, 2001). MT3-MMP is inhibited by TIMP-2 and -3 (Zhao et al., 2004). MT4-MMP is inhibited efficiently by TIMP-1 (Kolkenbrock, Essers, Ulbrich, & Will, 1999) and MT6-MMP is inhibited by TIMP-1 and -2 (Alon et al., 1994). TIMP-3 is sequestered at cell surfaces by binding to proteoglycans, and this may explain, in part, its greater activity against MT-MMP compared to other TIMPs which function as soluble inhibitors (Murphy et al., 2003). MT-MMP expression can also be controlled by ectodomain shedding MT3-MMP (Zhao et al., 2004).

3.2.3. Biologic roles

MT-MMPs contribute to ECM remodeling and regulate inflammation, angiogenesis, cell migration, and tumor invasiveness and metastasis. MT1-MMP, MT2-MMP, and MT3-MMP play critical roles in degrading interstitial collagens and denatured collagens. MT1-MMP deficiency in mice causes craniofacial dysmorphism, arthritis, osteopenia, dwarfism, and fibrosis of soft tissues due to loss of MT1-MMP-mediated collagenase activity which is essential for modeling of skeletal and extra-skeletal connective tissues (Holmbeck et al., 1999). By degrading interstitial collagen and other ECM proteins, MT1-MMP, MT2-MMP, and MT3-MMP independently confer tumor cells with the ability to degrade the basement membrane scaffolding which promotes transmigration of tumor cells during metastasis (Hotary, Allen, Punturieri, Yana, & Weiss, 2000). MT-MMPs also degrade basement membrane components and cartilage proteoglycans (D'Ortho et al., 1998, 1997; Kang et al., 2001; Ohuchi et al., 1997) and degrade ECM proteins indirectly by activating pro-MMPs on cell surfaces (vide infra). MT-MMP may also regulate inflammation by cleaving and activating pro-tumor necrosis factor-α (TNF-α), and by degrading proteinase inhibitors (D'Ortho et al., 1997; English et al., 2000; Kang et al., 2001; Maquoi et al., 2000).

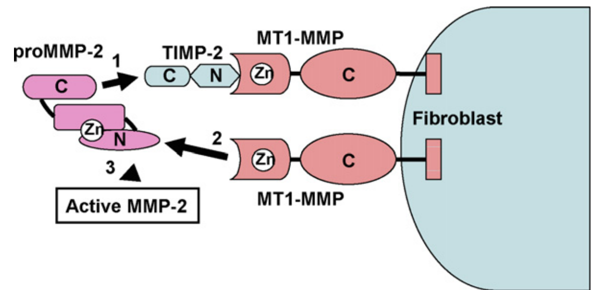

Fig. 4. MT1-MMP activates pro-MMP-2 on cell surfaces. Pro-MMP-2 and TIMP-2 form a ternary complex with MT1-MMP (or other MT-MMP family members) on the surface of fibroblasts, tumor cells, macrophages, and other cell types. TIMP-2 binds via its NH_2-terminal inhibitory domain to MT-1-MMP. The COOH-terminal domain of pro-MMP-2 binds to the COOH-terminal domain of TIMP-2. Pro-MMP-2 is activated by adjacent free MT1-MMP which cleaves the NH_2-terminal pro-domain of MMP-2, generating active MMP-2 anchored to the cell surface. Homotypic interactions between two adjacent MT1-MMP molecules facilitate pro-MMP-2 activation.

3.2.4. Activation of pro-MMPs on cell surfaces

MT-MMPs play critical roles in activating MMPs on cell surfaces to amplify pericellular proteolytic events. This was first reported for MT1-MMP activating pro-MMP-2 on tumor cells, fibroblasts, and endothelial cells (Butler et al., 1997; Cao, Rehemtulla, Bahou, & Zucker, 1996; Cao, Sato, Takino, & Seiki, 1995; Sato et al., 1996; Strongin et al., 1995). However, all members of the MT-MMP subfamily have now been shown to activate pro-MMP-2 on cell surfaces (Butler et al., 1997; Nie & Pei, 2003; Wang, Johnson, Ye, & Dyer, 1999; Wang, Yi, Lei, & Pei, 1999; Zhao et al., 2004), including MT1-MMP on the surface of macrophages (Stawowy et al., 2005). Activation of pro-MMP-2 involves the formation of a ternary complex of pro-MMP-2, TIMP-2 and MT1-MMP on cell surfaces (Fig. 4). The activation of pro-MMP-2 is a two step procedure in which pro-MMP-2 binds via its COOH-terminal domain to the COOH-terminal domain of TIMP-2 which itself binds via its NH_2-terminal inhibitory domain to the active site of MT1-MMP. Adjacent TIMP-free MT1-MMP then cleaves the cell-associated pro-MMP-2 generating an intermediate form. This initial cleavage destabilizes the MMP-2 pro-domain leading to auto-proteolytic cleavage in an MMP-2-dependent manner. It is also noteworthy that active MMP-2 also activates pro-MMP-13, thus MT-MMP activation of pro-MMP-2 can also lead to MMP-13 activation on cell surfaces. Many tumors express high levels of pro-MMP-2 and MT-MMP, and activation of

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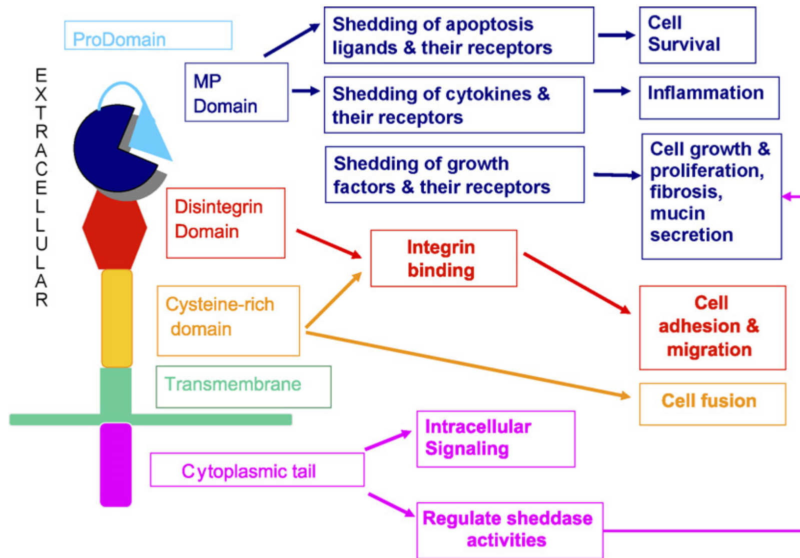

Fig. 5. Structure and function of the ADAMs family members. ADAMs have a multi-domain structure including a pro-domain which maintains the metalloproteinase domain in a latent form by a cysteine residue in the pro-domain coordinating with the active site zinc atom in the metalloproteinase domain. Many ADAMs are activated by furin-mediated cleavage of the pro-domain in the trans-Golgi network. All ADAMs have a metalloproteinase (MP) domain, but only 50% have the active site zinc atom and are predicted to be catalytically active. ADAMs with an active MP domain can shed cytokines, growth factors, apoptosis ligands and receptors for these molecules to regulate many cellular processes. The disintegrin domain binds to integrins to increase or decrease cell adhesion and migration. The cysteine-rich region may contain an epithelial growth factor (EGF)-like domain which plays roles in cell adhesion and cell–cell fusion. The transmembrane domain anchors ADAMs to cell membranes. The COOH-terminal cytoplasmic tail can regulate the sheddase activities of ADAMs and bind intracellular proteins and may play roles in intracellular signaling.

982 pro-MMP-2 on the tumor surface permits invadopodia to
983 locally degrade the ECM permitting tumor cell invasion
984 and metastasis (Chen, 1996).

985 3.3. ADAMs

986 ADAMs are a family of at least 35 members of
987 type I transmembrane proteins so called because they
988 have a disintegrin and a metalloproteinase domain (Seals
989 & Courtneidge, 2003). They belong to the adamalysin
990 subfamily of metalloproteinases along with ADAM-TS
991 enzymes. ADAM-TS proteinases are structurally simi-
992 lar to ADAMs, but differ from ADAMs in that they
993 function as soluble proteinases and have one or more
994 thrombospondin domains (Primakoff & Myles, 2000;
995 Stone, Kroeger, & Sang, 1999). The first ADAMs iden-
996 tified in the early 1990s were the two subunits of the
997 heterodimeric sperm protein, fertilin (ADAM-1 and -2),
998 which induce sperm–oocyte fusion by binding to $\alpha6\beta1$
999 integrin on oocytes (Myles, Kimmel, Blobel, White, &
1000 Primakoff, 1994; Wolfsberg et al., 1993). Interest in the
1001 ADAM family in the biomedical community soared in
1002 1997 when metalloproteinase inhibitors were shown to
1003 prevent LPS-induced death by blocking TNF-α release
1004 from the surface of macrophages in experimental ani-
1005 mals (Black et al., 1997). Characterization and cloning
1006 of the enzyme responsible for this activity led to the dis-
1007 covery of ADAM-17. Since then, other ADAMs have
1008 been shown to participate in diverse physiologic and
1009 pathologic processes.

1010 3.3.1. Structure, expression, and regulation

1011 Like the MMPs, ADAMs have a multi-domain struc-
1012 ture (Fig. 5) including: (1) a pro-domain which maintains
1013 the metalloproteinase domain in a latent form; (2)
1014 a metalloproteinase catalytic domain; (3) a disinte-
1015 grin domain which binds integrins; (4) a cysteine-rich
1016 region which may contain an epithelial growth factor
1017 (EGF)-like domain; (5) a transmembrane domain which
1018 anchors ADAMs to cell membranes; and (6) a carboxy-
1019 terminal cytoplasmic tail (Primakoff et al., 2000; Seals & Q10
1020 Courtneidge, 2003; Yamamoto et al., 1999). Although all
1021 ADAMs have a metalloproteinase domain, only ~50%
1022 carry the active sites Zn^{2+} atom and are predicted to
1023 be catalytically active. ADAMs are synthesized as latent
1024 enzymes and latency is maintained by an interaction bet-
1025 ween a conserved cysteine residue in the pro-domain and
1026 the active site zinc. Many of the ADAMs contain consen-
1027 sus sequences (RXXR) for furin and other pro-protein
1028 convertases and are activated by furin-mediated clea-

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vage in the trans-Golgi before ADAMs are transported to cell surfaces (Loechel, Overgaard, Oxvig, Albrechtsen, & Wewer, 1999; Lum, Reid, & Blobel, 1998; Roghani et al., 1999; Yamamoto et al., 1999).

The expression of ADAMs varies widely in mammalian tissues. ADAMs known to be expressed by leukocytes include ADAM-8, -10, -15, -17, and -28 (Armstrong, Godinho, Uppington, Whittington, & Millar, 2006; Bridges et al., 2002; Gomez-Gaviro et al., 2007; Li, Brazzell, Herrera, & Walcheck, 2006; Lum et al., 1998). ADAM expression is generally regulated at the transcriptional level by various mediators. For example, ADAM-10 and -17, are up-regulated in many cell types in vitro by various agonists including phorbol esters, cytokines, chemokines, and growth factors (Bandyopadhyay et al., 2006; Bzowska, Jura, Lassak, Black, & Bereta, 2004; Walcheck et al., 2006) which generally regulate ADAM expression at the steady state mRNA level (Bzowska et al., 2004; Fujita et al., 2006). However, ADAM-8 is stored as a preformed proteinase in PMN specific and gelatinase granules and translocates rapidly to the surface when PMNs are activated with phorbol esters (Gomez-Gaviro et al., 2007).

3.3.2. Inhibitors

The activity of the metalloproteinase domain can be regulated by TIMPs, but ADAMs vary widely in their susceptibility to inhibition by TIMPs. For example, ADAM-17 is inhibited by TIMP-3, but not by TIMP-1 or -2 (Amour et al., 1999, 1998). ADAM-10 is inhibited by TIMP-1 and -3, but not by TIMP-2 and -4 (Amour et al., 2000). ADAM -8 and -9 are not inhibited by TIMP-1, -2 or -3 (Amour et al., 2002).

3.3.3. Biologic activities

The major functions of ADAMs are linked to their domain structure and include role for: (1) the metalloproteinase domain in shedding cell surface proteins; (2) the disintegrin domain in regulating cell adhesion and migration; (3) the cysteine-rich and disintegrin domains in promoting cell fusion; and (4) the cytoplasmic tail in intracellular signaling events.

3.3.3.1. Sheddase activities. ADAMs have been reported to cleave only a limited number of ECM proteins (Millichip, Dallas, Wu, Dale, & McKie, 1998) and likely play little role in ECM turnover. The critical function of the metalloproteinase domain is the shedding of a wide variety of transmembrane proteins from cell surfaces by juxtamembrane cleavage. The best known example is that of ADAM-17 (TNF-α convertase or TACE). TNF-α is expressed as an inactive 26 kDa protein on the surface of macrophages, PMNs, and other cells. Pro-TNF-α is cleaved by juxtacrine ADAM-17 on the cell surface releasing soluble, active 17 kDa TNF-α (Black et al., 1997). Together, ADAMs cleave a wide variety of membrane-associated proteins, but they lack unique consensus sequences and there is considerable overlap in substrates. Membrane-bound proteins cleaved by ADAMs include: (1) other cytokines and their receptors such as TRANCE, fractalkine, CXCL-16, CD40 ligand, TNF receptors, and IL-6 receptor (Althoff, Reddy, Voltz, Rose-John, & Mullberg, 2000; Amour et al., 2000; Garton et al., 2001; Gough et al., 2004; Lum et al., 1999); (2) epidermal growth factor (EGR) ligands and receptors such as TGF-α, EGF, HB-EGF, amphiregulin, betacellulin, amphicellulin, and Erb4/HER (Rio, Buxbaum, Peschon, & Corfas, 2000; Sahin et al., 2004); (3) adhesion molecules such as VCAM-1, L-selectin, N-cadherin, and CD44 (Garton et al., 2003; Reiss et al., 2005; Vachon et al., 2002; Walcheck, Alexander, St Hill, & Matala, 2003); (4) other receptors such as CD23, Notch, and ErbB4/HER (Brou et al., 2000; Fourie, Coles, Moreno, & Karlsson, 2003; Hartmann et al., 2002). As a result of these sheddase activities, ADAMs play roles in development and in regulating inflammation, cell adhesion, cell growth, proliferation, and survival.

The activity of ADAM sheddases can be regulated by non-transcriptional mechanisms. For example, G-protein coupled receptor agonists increase ADAM-17-mediated shedding of EGFR ligands by activating EGFR/MAP/ERK pathway (Schafer, Gschwind, & Ullrich, 2004). The cytoplasmic tail of ADAM-17 is phosphorylated by various intracellular kinases including Ras/Raf/MEK kinase leading to activation of ADAM-17 sheddase activities (Fan, Turck, & Derynck, 2003). Phorbol esters also regulate the activity of ADAM-17, but this does not involve the cytoplasmic tail of ADAM-17 since phorbol ester also activates an ADAM-17 mutant lacking the cytoplasmic tail (Doedens, Mahimkar, & Black, 2003). Cigarette smoke increases ADAM-17 shedding of EGFR ligands to regulate airway mucin production but the mechanism involved is unknown (Basbaum, Li, Gensch, Gallup, & Lemjabbar, 2002; Lemjabbar et al., 2003).

3.3.3.2. Disintegrin domain in regulating cell adhesion and migration. This domain enables ADAMs to regulate cell adhesion and migration. This domain is structurally similar to the snake venom disintegrins which have an RGD-binding motif which binds integrin αIIbβ3 to impair platelet aggregation leading to

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severe hemorrhage. However, mammalian ADAMs lack RGD sequences with the notable exception of human ADAM-15. ADAM-15 has an RGD-binding site through which it binds to αvβ3 and α5β1 integrins (Nath et al., 1999). However, ADAM-15 also contains Rx_6DEVF sequences which mediate RGD-independent binding of many ADAMs to various integrins. By binding and regulating integrin activity ADAMs can either promote or inhibit cell adhesion, migration, and cell fusion. In addition to ADAM-1 and -2 binding to various integrins to promote sperm–oocyte fusion (Evans, 2001), ADAM-15 promotes cell–cell adhesion of fibroblasts to inhibit wound healing (Herren et al., 2001) and inhibits RGD-dependent αvβ3 adhesion and migration of ovarian tumor cells (Beck et al., 2005). Endothelial ADAM-15 binds to activated αIIbβ3 integrin on platelets to promote platelet adhesion and aggregation and thrombus formation (Langer, May, Bultmann, & Gawaz, 2005). ADAM-9 promotes fibroblast adhesion and motility by its disintegrin domain binding to α6β1 integrin (Nath et al., 2000). However, the roles of ADAMs in regulating leukocyte adhesion and migration have not been studied.

3.3.3.3. Cysteine-rich domain in regulating cell fusion and cell adhesion. This domain has been less well studied than the other ADAM domains, but has been implicated in cell fusion and adhesion. The cysteine rich domain of some ADAMs contains a sequence of amino acids resembling viral fusion peptides, and this domain plays roles in ADAM-12-mediated myoblast fusion and in ADAM-1- and ADAM-2-mediated sperm–oocyte fusion (Blobel et al., 1992; Brzoska, Bello, Darribere, & Moraczewski, 2006; Yagami-Hiromasa et al., 1995). The cysteine-rich domain of ADAM-2 also regulates cell adhesion by binding to the sulfate groups in the HSPG, syndecan-4, to promote cell adhesion which requires interactions between the cysteine-rich domain and activated β1 integrins (Iba et al., 2000). The disintegrin-cysteine rich domain of ADAM-9 binds to β1 integrins to promote keratinocyte adhesion and migration (Zigrino et al., 2007). However, the roles of this domain in leukocyte function have not been elucidated.

3.3.3.4. The cytoplasmic domain. This domain can regulate the sheddase activities of ADAMs or regulate intracellular signaling by binding to intracellular proteins or by being phosphorylated by intracellular kinases. For example, phosphorylation of the cytoplasmic tail of ADAM-17 by Ras/Raf/MEK kinase increases ADAM-17-mediated sheddase activities (Fan et al., 2003). The cytoplasmic domains of several ADAMs including ADAM-9, -12, and -15 have Src homology 3 (SH3)-binding motifs which binds Src kinases and other intracellular proteins (Howard, Nelson, Maciewicz, & Blobel, 1999; Nelson, Schlondorff, & Blobel, 1999). The cytoplasmic tails of ADAM-17 and -9 bind mitotic arrest deficient 2 (MAD2) and MAD2-β, respectively (Nelson et al., 1999). However, it is not clear whether the cytoplasmic tails of ADAM15 tranduce intracellular signaling events by binding intracellular proteins in leukocytes or other cells.

3.3.4. Biologic activities of ADAMs

Studies of mice or murine cells genetically deficient in ADAMs have confirmed roles for ADAMs in diverse physiologic processes (Table 2) including critical roles in morphogenesis for ADAM-10, -19 and -17. ADAM-10 is critical in early neural development by proteolytically activating Notch, which by binding to its receptors, promotes formation of different neural cell types in a spatially and temporally regulated manner (Hartmann et al., 2002). ADAM-17 deficient embryos have abnormal epithelial differentiation and growth in developing heart and lung which is likely due to defective EFGR ligand shedding (Peschon et al., 1998).

ADAM expression is also dysregulated in various organ systems during pathologic processes. Ischemia up-regulates ADAM-17 expression in rat forebrain (Hurtado et al., 2001). ADAM-15 and -17 expression are enhanced on macrophages and fibroblasts in rheumatoid synovium (Bohm, Aigner, Blobel, Kalden, & Burkhardt, 2001; Ohta et al., 2001), and ADAM-8 is upregulated in neurons, astrocytes, and microglia in neurodegenerative processes in the murine brain (Schlomann, Rathke-Hartlieb, Yamamoto, Jockusch, & Bartsch, 2000). ADAM-33 has been identified as the first asthma gene in Caucasians (Van Eerdewegh et al., 2002). ADAM-8 expression is upregulated in the airway structural cells and inflammatory infiltrates in human asthma subjects (Foley et al., 2007). However, the mechanisms by which ADAM-33 and -8 contribute to asthma pathogenesis are not clear (Shapiro & Owen, 2002). Several ADAMs are upregulated in tumors and hematologic malignancies including ADAM-10, -12, and -15 (Kenny & Bissell, 2007; Kveiborg et al., 2005; Liu et al., 2006; Ortiz, Karkkainen, & Huovila, 2004; Wu, Croucher, & McKie, 1997). Several ADAM deficient mice have no abnormalities in the unchallenged state (Table 2), but it is likely that future studies of these mice in murine models of disease will uncover critical roles for these in pathologic processes in various organs.

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Table 2
Q13 Phenotypes of mice genetically deficient in ADAMs

Genotype	Phenotype
ADAM8$^{-/-}$	Viable and fertile with no phenotype in the unchallenged state (Kelly et al., 2005)
ADAM9$^{-/-}$	Viable and fertile with no phenotype in the unchallenged state (Weskamp et al., 2002)
ADAM10$^{-/-}$	Embryonic lethal (E9.5). Defects in the heart and central nervous system development and vasculogenesis (Hartmann et al., 2002)
ADAM12$^{-/-}$	30% embryonic lethal. Surviving mice have normal fertility. Minor brown fat and neck muscle hypertrophy (Kurisaki et al., 2003)
ADAM15$^{-/-}$	Viable, fertile with and no phenotype in the unchallenged state. Reduced neovascularization in a murine model of retinopathy of prematurity (Horiuchi et al., 2003)
ADAM17$^{-/-}$	Perinatal lethal. Epithelial dysplasia similar to that in TGF-α deficient mice with defective heart and lung development, and defective EGFR ligand shedding (Peschon et al., 1998; Shi et al., 2003; Zhao et al., 2001)
ADAM19$^{-/-}$	80% post-natal lethality 1–3 days after birth with defective heart development (Zhou et al., 2004)

TGF-α, transforming growth factor-α; EGFR, epidermal growth factor receptor.

4. Cysteine proteinases

Cysteine proteinases have a two-domain globular structure, a similar size (about 23–27 kDa), and an active-site cysteine which is critical for catalytic activity (Turk, Turk, & Turk, 1997). There are four cysteine proteinases present in human lysosomal granules: cathepsins B, H, L, and S which are members of the papain superfamily of cysteine proteinases. They are synthesized as pro-enzymes which are processed by limited proteolysis to the active forms in lysosomes. The main naturally occurring inhibitors of cysteine proteinases in tissues are the cystatin superfamily. The kininogens and α_2-macroglobulin are the major inhibitors of cysteine proteinases in plasma (Henskens, Veerman, & Nieuw Amerongen, 1996).

The main role of lysosomal cysteine proteinases in to degrade intracellular proteins under the acidic conditions (pH 5–6.5) of the lysosomes (Henskens et al., 1996). However, these enzymes have also been implicated in extracellular proteolytic events at or near the surfaces of leukocytes, leukocyte-derived cells, and tumor cells. For example, osteoclasts do not store cysteine proteinases in large quantities within their lysosome. Rather, the enzymes are targeted to the osteoclast surface/bone interface where strong adhesive attachments and proton secretion by osteoclasts creates an environment that favors the resorption of bone matrix proteins in the pericellular environment (Baron, Neff, Louvard, & Courtoy, 1985; Blair, Teitelbaum, Ghiselli, & Gluck, 1989).

Cysteine proteinases including cathepsins S, L, and B are also involved in the degradation of insoluble extracellular elastin by lung macrophages at neutral pH in vitro (Chapman, Munger, & Shi, 1994; Mason, Johnson, Barrett, & Chapman, 1986; Shi, Munger, Meara, Rich, & Chapman, 1992). Among these lysosomal cysteine proteinases, only cathepsin B has been confirmed to be expressed on cell surfaces.

4.1. Cathepsin B

This lysosomal cysteine proteinase was first localized on the surface of alveolar macrophages in 1984 (Chapman & Stone, 1984). About 50% of the alveolar macrophage's content of cathepsin B was reported to be expressed on the cell surface where it contributes to extracellular elastin degradation. However, the binding site(s) for cathepsin B on macrophages have not yet been identified.

More recently, cathepsin B has been shown to be expressed on the surface of various tumor cells (Calkins, Sameni, Koblinski, Sloane, & Moin, 1998; Cavallo-Medved et al., 2003; Cavallo-Medved, Mai, Dosescu, Sameni, & Sloane, 2005). The light chain of annexin II tetramer, p11, has been reported to be the receptor for this enzyme on some tumor cells (Mai, Waisman, & Sloane, 2000). Surface-bound cathepsin B on tumor cells is active and can degrade extracellular proteins including type IV collagen and activates pro-urokinase, pro-MMPs, and activate growth factors (Guo, Mathieu, Linebaugh, Sloane, & Reiners, 2002; Kobayashi et al., 1993b; Sameni, Moin, & Sloane, 2000). Thus, surface cathepsin B on tumor cells may play roles in tumor growth and invasiveness (Podgorski & Sloane, 2003).

Catalytically active cathepsin B has also been reported on the surface of cytotoxic T cells (CTLs). Unstimulated CTLs express very low levels of surface cathepsin B but when they are activated to degranulate, surface cathepsin B levels rapidly increase (Balaji, Schaschke, Machleidt, Catalfamo, & Henkart, 2002). The binding sites for cathepsin B on CTLs have not been identified. Surface bound cathepsin B on CTLs

prevents lymphocyte cell death by cleaving and inactivating perforin molecules released along with cathepsin B during CTL degranulation, thereby preventing perforin molecules which diffuse back to the CTL surface from injuring CTLs (Balaji et al., 2002).

5. Conclusions

An increasing number of biologically important neutral and acidic proteinases have been shown to be expressed on the surface of leukocytes, and become associated with leukocyte plasma membranes by diverse mechanisms. Surface localization of proteinases likely focuses and restricts proteolysis to the leukocyte pericellular environment thereby keeping proteinase activity under close regulatory control by regulating cell surface levels of proteinases by the availability of binding sites and by internalization or shedding of proteinases from the cell surface. Localization of proteinases on leukocyte surfaces confers many advantages to proteinases including rendering them resistant to inhibition by physiologic processes, promoting and amplifying activation of pro-enzymes, and increasing the stability and half-life of proteinases in the extracellular space. Cell surface binding of proteinases also enables them to participate in intracellular signaling in leukocytes via the cytoplasmic tails or transmembrane proteinases, or by binding of proteinases to their receptors or adjacent cell surface proteins such as integrins. Leukocyte cell-surface proteinases make critical contributions to extracellular proteolysis, and cell adhesion and migration during physiologic and pathologic processes. Future studies likely will uncover additional roles for leukocyte cell-associated proteinases in disease processes.

The binding of proteinases to leukocytes has important therapeutic implications. Surface-bound serine and metallo-proteinases on PMNs and other cell types are likely to be the major bioactive forms of the proteinases in vivo. In addition, many membrane-associated proteinases are resistant to inhibition by physiologic inhibitors indicating that augmentation of physiologic inhibitors may not have therapeutic efficacy in diseases characterized by excessive proteolysis. However, low-molecular-weight synthetic inhibitors are very effective against membrane-bound forms of serine proteinases and MMPs on PMNs (Owen, Campbell, Sannes, et al., 1995; Owen et al., 2003, 2004, 1998), and against members of the ADAMs family (Amour et al., 2002; Martin, Eynstone, Davies, Williams, & Steadman, 2002) suggesting that they may have therapeutic potential in diseases characterized by excessive activity of membrane-bound proteinases. The binding sites for proteinases on leukocytes also represent novel therapeutic targets. In this respect it is noteworthy that delivering heparin or other sulfated compounds to animals dislodges MMPs from HSPG on cell surfaces, and attenuates excessive tissue destruction associated with inflammation and reduces tumor metastasis, and angiogenesis (Anees, 1996; Rogachefsky, Dean, Howell, & Altman, 1993). More knowledge about the mechanisms by which cell surface proteinases bind to and are regulated on leukocyte surfaces may facilitate the development of new treatment strategies to control the deleterious activities of these enzymes in inflammatory diseases.

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