NIH Public Access
Author Manuscript
Exp Eye Res. Author manuscript; available in PMC 2010 April 1.

Published in final edited form as:
Exp Eye Res. 2009 April ; 88(4): 676–682. doi:10.1016/j.exer.2008.11.023.

Extracellular Matrix Turnover and Outflow Resistance

Kate E. Keller, **Aga Mini**, **John M. Bradley**, **Mary J. Kelley**, and **Ted S. Acott**
Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, USA

Abstract

Normal homeostatic adjustment of elevated intraocular pressure (IOP) involves remodeling the extracellular matrix (ECM) of the trabecular meshwork (TM). This entails sensing elevated IOP, releasing numerous activated proteinases to degrade existing ECM and concurrent biosynthesis of replacement ECM components. To increase or decrease IOP, the quantity, physical properties and/or organization of new components should be somewhat different from those replaced in order to modify outflow resistance. ECM degradation and replacement biosynthesis in the outflow pathway must be tightly controlled and focused to retain the complex structural organization of the tissue. Recently identified podosome- or invadopodia-like structures (PILS) may aid in the focal degradation of ECM and organization of replacement components.

Keywords

Aqueous humor outflow resistance; extracellular matrix turnover; biosynthetic extracellular matrix replacement

Introduction

Increased resistance to aqueous humor flow through the trabecular meshwork (TM) results in elevated intraocular pressure (IOP), which is a primary risk factor for primary open-angle glaucoma (POAG)(Boland and Quigley, 2007). Normal homeostatic adjustment of outflow resistance appears to be triggered by cellular sensing of changes in stretch or distortion of the cribriform or juxtacanalicular region of the TM (Bradley et al., 2001; Acott and Kelley, 2008). When these signals are received, extracellular matrix (ECM) turnover is adjusted to shift the balance toward higher or lower resistance. This homeostatic adjustment appears to begin with selective proteinase secretion and activation, targeted ECM cleavage and fragment uptake, and biosynthesis of replacement ECM components (Acott and Kelley, 2008). Since mRNA levels for many ECM genes in the TM are relatively high (Vittal et al., 2005), ongoing ECM turnover must be a regular maintenance event, even when the resistance does not need to be modified (Bradley et al., 1998).

Various proteinases and their inhibitors are expressed in the TM in a variety of instances. These include matrix metalloproteinases (MMPs), membrane type (MT) MMPs, ADAMs (A Disintegrin-like And Metalloproteinase), ADAMTSs (ADAM with ThromboSpondin type 1

© 2008 Elsevier Ltd. All rights reserved.

Correspondence: E-mail: acott@ohsu.edu Casey Eye Institute / OHSU, 3375 SW Terwilliger, Portland, OR 97239-4197, Phone: 503-494-8455, Fax: 503-418-2399.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

motifs), plasminogen activators (PA), tissue inhibitors of metalloproteinases (TIMPs), PA inhibitors, and serine proteinase inhibitors (serpins) (Table 1 and Table 2)(Alexander et al., 1991;Borras, 2003;Fuchshofer et al., 2003;Lo et al., 2003;Vittal et al., 2005;Oh et al., 2006). The significance of MMPs in outflow resistance was shown when treatment of anterior segments in perfusion culture with MMPs was found to increase outflow, while specific inhibition of MMP activity decreased outflow facility (Bradley et al., 1998). Also, when pressure was increased in perfusion culture there was a concomitant increase in outflow facility, which stabilized over time. This homeostatic pressure response likely involves MMPs, since adjustment of outflow facility was concurrent with increased MMP activity and ECM turnover. The proteolytic degradation of ECM components probably affects structural organization and alters biological interactions, leading to a modified outflow resistance. However, despite many years of research, the ECM components that contribute to outflow resistance remain elusive (Acott and Kelley, 2008). Glycosaminoglycans (GAGs) are thought to be a major contributing factor since treatment with enzymes that specifically degrade one or more type of GAG, or with agents that modify GAG chain biosynthesis, increase outflow facility (Barany and Scotchbrook, 1954;Francois, 1975;Knepper et al., 1984;Sawaguchi et al., 1992;Sawaguchi et al., 1993;Hubbard et al., 1997;Johnson and Bahler, 1999;Keller et al., 2008). However, GAG-specific enzymatic changes in outflow of humans or higher primates remain controversial (Acott and Kelley, 2008).

In addition to their degradation activities, many of these proteinases participate in cell-cell and cell-matrix interactions, process latent proteins to active forms, convert structural ECM proteins to signaling molecules, change tissue architecture, and provide cues for cell proliferation and survival (Page-McCaw et al., 2007). Thus, degradation of structural components alone may not directly result in IOP adjustment, but that proteolytic alterations could cause secondary effects that modify outflow resistance. In order to facilitate these adjustments, replacement ECM is likely to differ from what was degraded. Biosynthesis of replacement molecules is therefore a crucial component for normal homeostatic adjustment of outflow resistance.

Matrix Metalloproteinases

MMPs are a group of 23 related proteinases that degrade ECM (Page-McCaw et al., 2007). All MMPs have a similar domain structure and in their simplest form are composed of a prodomain and a catalytic domain (Fig. 1)(Chakraborti et al., 2003; Ra and Parks, 2007). MMPs may also contain C-terminal hemopexin-like (PEX) domains, which function in substrate recognition or proteinase localization, that are separated from the N-terminal catalytic domain by a flexible hinge region. Some MMPs also have a transmembrane or a glycosylphosphatidylinositol anchor, which anchors them to the cell surface. MMPs are synthesized as zymogens, inactive proenzymes, where the prodomain confers latency to the active enzymes. A free thiol of a conserved cysteine residue in the prodomain electrostatically interacts with a Zn^{2+} ion that is histidine-ligated into the active site of the catalytic domain in the sequence HEXXHXXGXXH (Fig. 1). Extracellular posttranslational cleavage, usually by another MMP or by a furin proprotein convertase, disrupts the thiol-Zn^{2+} interaction and releases the biologically active proteinase, a process known as the cysteine switch (Chakraborti et al., 2003). Serine proteinases, such as plasmin and thrombin, can activate proMMPs, while interaction with αV integrin has been implicated for MMP2 (Brooks et al., 1996; Ra and Parks, 2007). However, for most MMPs, the actual physiologic activation mechanisms are uncertain.

Numerous MMPs have been detected in TM cells and tissue (Table 1) and MMP mRNA and protein levels were upregulated in response to mechanical stretching, elevated pressure and various cytokines or growth factors (Alexander et al., 1991;Samples et al., 1993;Alexander et al., 1998;Bradley et al., 1998;Bradley et al., 2000;Gonzalez et al., 2000;WuDunn, 2001;Fleenor

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

et al., 2003;Pang et al., 2003;Vittitow and Borras, 2004;Oh et al., 2006;Kelley et al., 2007). MMPs -2, -14, -15 and -16 are constitutively expressed at relatively high levels in the TM (Alexander et al., 1991;Bradley et al., 2001;Vittal et al., 2005). MMPs -1, -3, and -9 are normally expressed at low levels but are massively upregulated and activated in response to various stimulations. Agents that increase outflow facility in perfusion culture, or laser trabeculoplasty surgery and medications that lower IOP in POAG patients, also affect expression and/or activation of certain MMPs (Parshley et al., 1996;Johnson, 1997;Peterson et al., 1999;Shearer and Crosson, 2002;Fleenor et al., 2003;Pang et al., 2003;Oh et al., 2006;Sanka et al., 2007;Bahler et al., 2008). Addition of purified MMPs to human anterior segment perfusion cultures increased outflow facility, while inhibiting their endogenous activity by TIMP2 or synthetic MMP inhibitors reduced outflow facility (Bradley et al., 1998). This argues strongly that controlled ECM turnover is required for maintenance of outflow resistance and that MMP regulation seems to be a major component for adjusting outflow resistance. Immunofluorescence studies showed that MMP2 strongly stained normal human TM in the uveal, corneoscleral and juxtacanalicular regions and the inner wall of Schlemm's canal (Ronkko et al., 2007). In POAG TM, immunostaining intensity for MMPs -1 and -3 was greatly increased, while by Western blot, MMPs -2 and -9 were reduced compared to age-matched control eyes (Ronkko et al., 2007;Govindarajan et al., 2008). The increase in MMPs -1 and -3 levels suggests that POAG TM cells continually strive to correct outflow resistance, but instead the persistent action of these MMPs likely causes an overproduction of replacement ECM and/or cause cleavage of ECM components that are not usually accessible to degradation. TGFβ2, a cytokine whose levels are increased in POAG aqueous humor and decreases outflow facility in perfusion culture, increased expression, but not activation, of pro-MMP2 (Fuchshofer et al., 2003;Gottanka et al., 2004;Fleenor et al., 2006).

Compartmentalization of MMPs has been noted in many cell types and tissues, but especially in invadopodia and podosomes of invasive cells (Chen and Wang, 1999). The term compartmentalization refers to the location of the inactive enzyme in the pericellular matrix, and its site of activation (Ra and Parks, 2007). Due to the potency of these enzymes in degrading ECM, MMPs are targeted to specific locations where they become highly concentrated. This regulates activation of latent MMPs and targets their catalytic activity to certain substrates in the pericellular environment. For instance, MMP14 (MT1-MMP) cleaves pro-MMP2 and pro-MMP13 to their active forms on the cell surface, which triggers potent pericellular proteolytic activity (Itoh and Seiki, 2006). Recent identification of clusters of podosome- or invadopodia-like structures (PILS) in TM cells show that MMPs -2 and -14 are localized to regions of the cell that appear to function in both adhesion and matrix degradation (Fig. 2)(Linder, 2007; Aga et al., 2008). Focusing MMP14 at such structures could increase its local concentration to allow homodimerization of its PEX domains. This in turn would facilitate MMP2 activation and further augment targeted proteolytic activity at the cell surface. PILS have been found in TM tissue suggesting that these focal regions of regulated and targeted ECM turnover may be important in regulating outflow facility in response to elevated IOP (Aga et al., 2008).

Active MMPs degrade many different ECM molecules (Table 1)(Chakraborti et al., 2003), most of which are also expressed in the TM (Acott and Kelley, 2008). Rather than degrading all ECM, it is likely that only certain molecules or parts of molecules are degraded. This focal, targeted degradation is probably facilitated by PILS. For instance, collagen IV α3 is cleaved by MMP9 and collagen XVIII by other MMPs to release tumstatin or endostatin, respectively, but the structural triple-helical portion is not degraded (Page-McCaw et al., 2007). Both these collagen types are expressed in the TM (Hann et al., 2001;Ohlmann et al., 2005) and both statins bind integrins, which launch a signaling cascade that disrupts the actin cytoskeleton (Bix and Iozzo, 2005). Therefore, in the TM, proteolytically-released fragments could impact outflow resistance via cytoskeletal adjustments.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

ADAMs and ADAMTSs

Another class of zinc-dependent metalloproteinases is the adamalysins, which are categorized into two subfamilies known as the ADAMs and the ADAMTSs (Table 1). Both these proteinase groups are involved in ectodomain shedding, activation of cell surface receptors and growth factors and ECM protein cleavage (Apte, 2004;Huovila et al., 2005;Porter et al., 2005). The major difference between the two subfamilies is that ADAMs are mostly transmembrane proteins while ADAMTSs are secreted molecules that bind to the ECM.

There are currently 29 ADAM family members that cleave a wide range of substrates (Huovila et al., 2005). Similar to MMPs, ADAMs have a multi-domain structure and are synthesized as proenzymes that are activated by a cysteine switch (Fig. 1). A terminal aspartate residue in the sequence HEXXHXXGXXHD distinguishes the adamalysins from the MMPs. Lying C-terminal to the catalytic domain is the disintegrin domain, which contains an integrin-binding motif, a cysteine-rich region, an EGF-like domain, a transmembrane region and a C-terminal cytosolic tail. The tail contains multiple motifs which interact with other cytosolic proteins and can be phosphorylated on Ser/Thr and Tyr residues (Huovila et al., 2005).

There are 19 ADAMTSs and 3 ADAMTS-like enzymes. Like the ADAMs, ADAMTSs have a wide range of substrates including collagen, versican, and aggrecan (Porter et al., 2005). The domain structure of the ADAMTSs is similar to that of ADAMs and MMPs, but there are some differences that distinguish them (Fig. 1). There is some debate as to whether the prodomains confer latency to the ADAMTS enzyme, but the prodomains are removed by furin-cleavage in the secretory pathway or by MMP17 on the cell surface (Apte, 2004). The ancillary region is comprised of a disintegrin-like domain, a central thrombospondin-like (TS) domain, a cysteine-rich domain, a spacer domain, and a varying number (0–14) of C-terminal TS domains. The ancillary domain can be proteolytically cleaved, which either augments or inhibits activity of the ADAMTS enzyme (Gao et al., 2002).

Although ADAMs and ADAMTS are expressed in other eye tissues (Wride et al., 2006), little is known about the action of these proteinases in the TM. Our studies have shown that TNFα and/or IL-1α treatment of TM cells stimulate mRNA expression of ADAMs -9 and -10 and ADAMTSs -4, -5, -7 and -13 (Chen et al., 2005; Acott and Kelley, 2008). TGFβ2 treatment of glaucomatous TM cells increased ADAMTS5 mRNA expression (Fleenor et al., 2006). A neo-epitope of versican that is exposed following ADAMTS4 cleavage was found to localize to PILS (Fig. 2)(Aga et al., 2008) and in areas of the TM that experience high segmental flow, as assessed by fluorescent Qdot nanoparticle labeling of anterior segments (Bradley et al., 2008). Immunolocalization of ADAMTS4 showed that its expression was highly increased in the JCT region in human anterior segments that were subjected to elevated pressure (Keller et al., unpublished observations). Moreover, treatment of human and pig anterior segments in perfusion culture with ADAMTS4 increased outflow facility. Further studies are required to clarify the possible roles of ADAMs and ADAMTSs in outflow resistance.

Tissue Inhibitors of the MMPs

In order to regulate these potent proteinases, MMP activity needs to be tightly controlled. TM cells can downregulate MMP mRNA or protein levels, change the activation state of these enzymes or release inhibitors that inactivate the enzymes. There are four TIMPs all of which are expressed in human TM cells (Table 2). Factors known to upregulate MMP expression also affect TIMP mRNA expression and therefore a delicate balance likely exists *in vivo* between MMP activation and inhibition by TIMPs (Samples et al., 1993;Pang et al., 2003;Oh et al., 2006). TIMP2 not only acts as an inhibitor of MMP activity, but it is also involved in activation of pro-MMP2 (Wang et al., 2000). The C-terminal domain of TIMP2 simultaneously binds to the C-terminus of pro-MMP2 and the N-terminus of activated MMP14 (Fig. 3). This trimeric

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

complex recruits an adjacent MMP14 molecule, which is responsible for the resultant cleavage of pro-MMP2. The relative concentration and binding of TIMP2 influences whether MMP14 will participate in cleavage of MMP2 and whether it will cleave other substrates (Kudo et al., 2007). In perfused anterior segment organ culture, increased pressure resulted in more activated MMP2 (Bradley et al., 2001). In cell culture, mechanical stretch, which is presumable mimicking pressure increases, increased MMPs -2 and 14 while decreasing TIMP2 levels (Bradley et al., 2001). This reduction in TIMP2 appears to bring it to the correct level to facilitate activation of MMP2 without completely blocking the process. TIMP1 inhibits ADAM10 but not ADAM17, whereas TIMP3 inhibits both enzymes (Rapti et al., 2008). TIMP3 inhibits ADAMTSs -4 and -5 activity (Kashiwagi et al., 2001).

Other Proteinases and inhibitors

Many other proteinases are expressed in the TM and may function directly or indirectly to modulate outflow resistance (Table 1). Tissue plasminogen activator (tPA), a serine proteinase that converts plasminogen to plasmin, is expressed in the TM (Park et al., 1987;Shuman et al., 1988;Chen et al., 2005) and by Schlemm's canal endothelial cells (Stamer et al., 1998). Since plasmin can activate proMMPs, the action of tPA may be a secondary effect rather than direct ECM proteolysis. tPA activity was reduced in response to dexamethasone, a corticosteroid that can induce glaucoma and decrease outflow facility in human anterior perfusion culture (Snyder et al., 1993;Clark et al., 1995). Urokinase-type PA (uPA) distribution overlaps with that of tPA and may also be involved in ECM turnover (Tripathi et al., 1990;Chen et al., 2005;Vittal et al., 2005).

Serpins are a class of serine proteinase inhibitors (Table 2) (Gettins, 2002). There are 16 members of this family including antithrombin, α1-proteinase inhibitor (PAI-1), and antitrypsin and they function in a wide range of physiological processes. Serpin expression is modulated by various stimulations in TM cells (Zhao et al., 2004;Chen et al., 2005;Rozsa et al., 2006;Fan et al., 2008). SerpinA3 (α1-chymotrypsin) was upregulated, while serpinB2 (PAI-2) was downregulated by corticosteroid treatment of human TM cells (Lo et al., 2003;Rozsa et al., 2006;Fan et al., 2008). SerpinE1 (PAI-1) was upregulated 6.8-fold by TGFβ2 treatment of glaucomatous TM cells and by TGFβ1 in HTM cells (Zhao et al., 2004;Fleenor et al., 2006). Furthermore, TGFβ2-induced expression and secretion of PAI-1 reduced MMP2 activity (Fuchshofer et al., 2003). Thus, modulation of serpin expression in response to various factors may affect MMP activity. Aqueous humor contains significant amounts of serpinC1 (antithrombin III), serpinA1 (α-1-antitrypsin), α-2-macroglobulin, and tPA (Tripathi et al., 1988;Ando et al., 1993;Rao et al., 2000). Interestingly, α-2-macroglobulin is an endogenous inhibitor of ADAMTSs -4 and-5 (Tortorella et al., 2004). Increased concentrations of these inhibitors in aqueous humor may alter MMP activity in active flow areas.

Regulation of proteinases by GAGs and other ECM molecules

MMPs and other proteinases in the TM may bind GAGs, which could limit diffusion of the active enzyme in tissue (Page-McCaw et al., 2007). GAGs are long sugar chains that are usually attached to a core protein. Since GAGs are thought to be a significant source of outflow resistance, GAG binding may directly affect expression and/or activation of MMPs. The types of GAGs are chondroitin/dermatan sulfate (CS/DS), heparin/heparan sulfate (HS), keratan sulfate (KS) and hyaluronan (HA). Chondroitin-4-sulfate (C-4-S) concomitantly binds MMP2 and MMP16 to facilitate the conversion of latent pro-MMP2 to its active form (Iida et al., 2007). It is feasible that MMP2 located in PILS could, in part, be activated by a similar mechanism. MMP2 can also bind tightly to HS chains of syndecan-2, which suppresses its activation (Munesue et al., 2007). Hyaluronan, applied exogenously to corneal explants in

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

organ culture, resulted in increased expression and activation of MMPs -2 and -9 (Isnard et al., 2001), while treatment of cartilage chondrocytes with low molecular weight HA fragments increased MMP3 mRNA expression (Ohno et al., 2005). Together, these studies suggest that GAG chains, or GAG chain fragments, may facilitate expression and activation of pro-MMPs and therefore play a role in targeted degradation of pericellular matrix. TM GAG content varies with age and POAG disease progression (Gong et al., 1992; Knepper et al., 1996; Knepper et al., 1996), so minor changes may profoundly affect proteinase activity and/or inhibition and potentially disrupt normal ECM turnover during homeostatic adjustment of IOP.

CD44, the major hyaluronan receptor, also plays an important role in MMP regulation. CD44 can attenuate the secretion and activation of MMP2 (Takahashi et al., 1999). CD44 is also a receptor for active MMP9 in keratinocytes and this interaction subsequently activates latent TGFβ (Yu and Stamenkovic, 1999). MMP14 can bind directly to CD44 via its PEX domains, which results in shedding of a soluble 70kDa extracellular fragment (sCD44) (Kajita et al., 2001; Mori et al., 2002). sCD44 concentrations were higher in aqueous humor of POAG patients than in age-matched control samples (Knepper et al., 2002; Nolan et al., 2007). Thus, CD44 not only regulates MMP activity, but is itself a substrate for MMP cleavage.

Other proteinases and inhibitors also bind GAGs and ECM molecules, e.g. ADAM12 binds to syndecan-4 and ADAM-9 binds $\alpha_6\alpha_1$ and $\alpha_v\alpha_5$ integrins (Huovila et al., 2005). Integrin-ADAM association facilitates cell-cell interactions and sequesters the enzyme in an inactive state at the cell surface (Bridges and Bowditch, 2005). There is no evidence to suggest that the disintegrin domains of ADAMTSs also bind integrins (Porter et al., 2005). ADAMTSs binds sulfated GAGs in the ECM or on the cell surface, or to HS and CS chains of syndecan-1 (Apte, 2004; Gao et al., 2004). The spacer region of ADAMTS4 binds the C-terminal region of fibronectin, which may inhibit its enzymatic activity (Fig. 1)(Hashimoto et al., 2004). MMP inhibitors also bind GAGs. The N-terminal region of TIMP3 interacts with HS and possibly CS GAG chains (Yu et al., 2000). Serpin activity is also profoundly affected by the presence of GAGs, such as HS and DS, which accelerate interaction with their target proteinases (Pike et al., 2005).

Replacement ECM

An integral component of any normal ongoing or homeostatic resistance adjustment involving ECM turnover is the biosynthetic replacement of degraded components (Acott and Kelley, 2008). Modifications in outflow resistance will likely include changes in levels or organization of ECM components. TM cells alter mRNA expression of many ECM genes in response to mechanical stretching, exposure to exogenous soluble factors and synthetic agents or by treatment with IOP-lowering drugs and laser trabeculoplasty (Lo et al., 2003; Zhao et al., 2004; Vittal et al., 2005; Fleenor et al., 2006; Rozsa et al., 2006; Fan et al., 2008). ECM gene mRNA levels also vary between non-glaucomatous and glaucomatous eyes (Diskin et al., 2006; Liton et al., 2006). PILS could potentially coordinate the biosynthetic replacement and organization of ECM components in degraded areas. Some of the ECM molecules that are synthesized are different from their predecessors and can have extra exons included, or excluded, which may contain additional ECM or cell binding sites (Vittal et al., 2005; Zhao and Russell, 2005; Keller et al., 2007). Continued exposure of TM cells to elevated IOP, or from many years of normal homeostatic adjustment, could conceivably cause an excess of cell-cell, cell-protein and/or protein-protein interactions that would contribute to the observed increased rigidity of the TM in POAG or with age (Gabelt and Kaufman, 2005; Schlunck et al., 2008). In addition, stiffness could be exacerbated by an increase in ECM cross-linking. For instance, POAG TM cells have increased protein levels and activity of the enzyme tissue transglutaminase (Tovar-Vidales et al., 2008). Increased stiffness may hinder detection of mechanical stretch/distortion signals by cells in the JCT region. Consequently, the normal

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

signals that are required to initiate ECM turnover may not be received and the typical mechanisms to adjust outflow resistance would not be activated. Alternatively, such ECM cross-linking could change susceptibility of ECM substrates to proteinase cleavage and turnover.

Acknowledgments

Support was provided by NIH EY003279, EY008247, EY010572, the Glaucoma Research Foundation (to KEK), and by an unrestricted grant to Casey Eye Institute from Research to Prevent Blindness, New York, NY.

References

Acott TS, Kelley MJ. Extracellular matrix in the trabecular meshwork. Exp Eye Res 2008;86:543–561. [PubMed: 18313051]

Aga M, Bradley JM, et al. Specialized podosome- or invadopodia-like structures (PILS) for focal trabecular meshwork extracellular matrix turnover. Invest Ophthalmol Vis Sci. 2008In Press

Alexander JP, Samples JR, et al. Growth factor and cytokine modulation of trabecular meshwork matrix metalloproteinase and TIMP expression. Curr Eye Res 1998;17:276–285. [PubMed: 9543636]

Alexander JP, Samples JR, et al. Expression of matrix metalloproteinases and inhibitor by human trabecular meshwork. Invest Ophthalmol Vis Sci 1991;32:172–180. [PubMed: 1846130]

Ando H, Twining SS, et al. MMPs and proteinase inhibitors in the human aqueous humor. Invest Ophthalmol Vis Sci 1993;34:3541–3548. [PubMed: 7505006]

Apte SS. A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family. Int J Biochem Cell Biol 2004;36:981–985. [PubMed: 15094112]

Bahler CK, Howell KG, et al. Prostaglandins increase trabecular meshwork outflow facility in cultured human anterior segments. Am J Ophthalmol 2008;145:114–119. [PubMed: 17988642]

Barany EH, Scotchbrook S. Influence of testicular hyaluronidase on the resistance to flow through the angle of the anterior chamber. Acta Physiol Scand 1954;30:240–248. [PubMed: 13158098]

Bix G, Iozzo RV. Matrix revolutions: "tails" of basement-membrane components with angiostatic functions. Trends Cell Biol 2005;15:52–60. [PubMed: 15653078]

Boland MV, Quigley HA. Risk factors and open-angle glaucoma: classification and application. J Glaucoma 2007;16:406–418. [PubMed: 17571004]

Borras T. Gene expression in the trabecular meshwork and the influence of intraocular pressure. Prog Retin Eye Res 2003;22:435–463. [PubMed: 12742391]

Bradley JM, Anderssohn AM, et al. Mediation of laser trabeculoplasty-induced matrix metalloproteinase expression by IL-1beta and TNFalpha. Invest Ophthalmol Vis Sci 2000;41:422–430. [PubMed: 10670472]

Bradley JM, Keller KE, et al. Quantum dot analyses of segmental flow patterns in the trabecular meshwork. Invest Ophthalmol Vis Sci 2008;49E-abstract 1635

Bradley JM, Kelley MJ, et al. Effects of mechanical stretching on trabecular matrix metalloproteinases. Invest Ophthalmol Vis Sci 2001;42:1505–1513. [PubMed: 11381054]

Bradley JM, Vranka J, et al. Effect of matrix metalloproteinases activity on outflow in perfused human organ culture. Invest Ophthalmol Vis Sci 1998;39:2649–2658. [PubMed: 9856774]

Bridges LC, Bowditch RD. ADAM-Integrin Interactions: potential integrin regulated ectodomain shedding activity. Curr Pharm Des 2005;11:837–847. [PubMed: 15777238]

Brooks PC, Stromblad S, et al. Localization of matrix metalloproteinase MMP-2 to the surface of invasive cells by interaction with integrin alpha v beta 3. Cell 1996;85:683–693. [PubMed: 8646777]

Chakraborti S, Mandal M, et al. Regulation of matrix metalloproteinases: an overview. Mol Cell Biochem 2003;253:269–285. [PubMed: 14619979]

Chen WT, Wang JY. Specialized surface protrusions of invasive cells, invadopodia and lamellipodia, have differential MT1-MMP, MMP-2, and TIMP-2 localization. Ann N Y Acad Sci 1999;878:361–371. [PubMed: 10415741]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Chen Y, Kelley MJ, et al. DNA microarray analysis of gene expression in trabecular meshwork cells in response to TNFα and IL-1α. Invest Ophthalmol Vis Sci 2005;46E-abstract 1349

Clark AF, Wilson K, et al. Dexamethasone-induced ocular hypertension in perfusion-cultured human eyes. Invest Ophthalmol Vis Sci 1995;36:478–489. [PubMed: 7843916]

Diskin S, Kumar J, et al. Detection of differentially expressed glycogenes in trabecular meshwork of eyes with primary open-angle glaucoma. Invest Ophthalmol Vis Sci 2006;47:1491–1499. [PubMed: 16565384]

Fan BJ, Wang DY. Gene expression profiles of human trabecular meshwork cells induced by triamcinolone and dexamethasone. Invest Ophthalmol Vis Sci 2008;49:1886–1897. [PubMed: 18436822]

Fleenor DL, Pang IH, et al. Involvement of AP-1 in interleukin-1alpha-stimulated MMP-3 expression in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2003;44:3494–3501. [PubMed: 12882799]

Fleenor DL, Shepard AR, et al. TGFbeta2-induced changes in human trabecular meshwork: implications for intraocular pressure. Invest Ophthalmol Vis Sci 2006;47:226–234. [PubMed: 16384967]

Francois J. The importance of the mucopolysaccharides in intraocular pressure regulation. Invest Ophthalmol 1975;14:173–176. [PubMed: 123231]

Fuchshofer R, Welge-Lussen U, et al. The effect of TGF-beta2 on human trabecular meshwork extracellular proteolytic system. Exp Eye Res 2003;77:757–765. [PubMed: 14609564]

Gabelt BT, Kaufman PL. Changes in aqueous humor dynamics with age and glaucoma. Prog Retin Eye Res 2005;24:612–637. [PubMed: 15919228]

Gao G, Plaas A, et al. ADAMTS4 (aggrecanase-1) activation on the cell surface involves C-terminal cleavage by glycosylphosphatidyl inositol-anchored membrane type 4-matrix metalloproteinase and binding of the activated proteinase to chondroitin sulfate and heparan sulfate on syndecan-1. J Biol Chem 2004;279:10042–10051. [PubMed: 14701864]

Gao G, Westling J, et al. Activation of the proteolytic activity of ADAMTS4 (aggrecanase-1) by C-terminal truncation. J Biol Chem 2002;277:11034–11041. [PubMed: 11796708]

Gettins PG. Serpin structure, mechanism, and function. Chem Rev 2002;102:4751–4804. [PubMed: 12475206]

Gong H, Freddo TF, et al. Age-related changes of sulfated proteoglycans in the normal human trabecular meshwork. Exp Eye Res 1992;55:691–709. [PubMed: 1478279]

Gonzalez P, Epstein DL. Genes upregulated in the human trabecular meshwork in response to elevated intraocular pressure. Invest Ophthalmol Vis Sci 2000;41:352–361. [PubMed: 10670462]

Gottanka J, Chan D, et al. Effects of TGF-beta2 in perfused human eyes. Invest Ophthalmol Vis Sci 2004;45:153–158. [PubMed: 14691167]

Govindarajan B, Salomon RG, et al. Role of oxidatively modified extracellular matrix proteins and matrix metalloproteinases in glaucomatous trabecular meshwork. invest Ophthalmol Vis Sci 2008;49E-abstract 1645

Hann CR, Springett MJ, et al. Ultrastructural localization of collagen IV, fibronectin, and laminin in the trabecular meshwork of normal and glaucomatous eyes. Ophthalmic Res 2001;33:314–324. [PubMed: 11721183]

Hashimoto G, Shimoda M, et al. ADAMTS4 (aggrecanase-1) interaction with the C-terminal domain of fibronectin inhibits proteolysis of aggrecan. J Biol Chem 2004;279:32483–32491. [PubMed: 15161923]

Hubbard WC, Johnson M, et al. Intraocular pressure and outflow facility are unchanged following acute and chronic intracameral chondroitinase ABC and hyaluronidase in monkeys. Exp Eye Res 1997;65:177–190. [PubMed: 9268586]

Huovila AP, Turner AJ, et al. Shedding light on ADAM metalloproteinases. Trends Biochem Sci 2005;30:413–422. [PubMed: 15949939]

Iida J, Wilhelmson KL, et al. Cell surface chondroitin sulfate glycosaminoglycan in melanoma: role in the activation of pro-MMP-2 (progelatinase A). Biochem J 2007;403:553–563. [PubMed: 17217338]

Isnard N, Legeais JM, et al. Effect of hyaluronan on MMP expression and activation. Cell Biol Int 2001;25:735–739. [PubMed: 11482897]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Itoh Y, Seiki M. MT1-MMP: a potent modifier of pericellular microenvironment. J Cell Physiol 2006;206:1–8. [PubMed: 15920734]

Johnson DH. The effect of cytochalasin D on outflow facility and the trabecular meshwork of the human eye in perfusion organ culture. Invest Ophthalmol Vis Sci 1997;38:2790–2799. [PubMed: 9418732]

Johnson DH, Bahler CH. Heparitinase increases outflow facility in the human eye. Invest Ophthalmol Vis Sci 1999;40:S504.

Kajita M, Itoh Y, et al. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. J Cell Biol 2001;153:893–904. [PubMed: 11381077]

Kashiwagi M, Tortorella M, et al. TIMP-3 is a potent inhibitor of aggrecanase 1 (ADAM-TS4) and aggrecanase 2 (ADAM-TS5). J Biol Chem 2001;276:12501–12504. [PubMed: 11278243]

Keller KE, Bradley JM, et al. Effects of modifiers of glycosaminoglycan biosynthesis on outflow facility in perfusion culture. Invest Ophthalmol Vis Sci 2008;49:2495–2505. [PubMed: 18515587]

Keller KE, Kelley MJ, et al. Extracellular matrix gene alternative splicing by trabecular meshwork cells in response to mechanical stretching. Invest Ophthalmol Vis Sci 2007;48:1164–1172. [PubMed: 17325160]

Kelley MJ, Rose AY, et al. Synergism of TNF and IL-1 in the Induction of Matrix Metalloproteinase-3 in Trabecular Meshwork. Invest Ophthalmol Vis Sci 2007;48:2634–2643. [PubMed: 17525194]

Knepper PA, Farbman AI, et al. Exogenous hyaluronidases and degradation of hyaluronic acid in the rabbit eye. Invest Ophthalmol Vis Sci 1984;25:286–293. [PubMed: 6698747]

Knepper PA, Goossens W, et al. Glycosaminoglycans of the human trabecular meshwork in primary open-angle glaucoma. Invest Ophthalmol Vis Sci 1996;37:1360–1367. [PubMed: 8641839]

Knepper PA, Goossens W, et al. Glycosaminoglycan stratification of the juxtacanalicular tissue in normal and primary open-angle glaucoma. Invest Ophthalmol Vis Sci 1996;37:2414–2425. [PubMed: 8933758]

Knepper PA, Mayanil CS, et al. Aqueous humor in primary open-angle glaucoma contains an increased level of CD44S. Invest Ophthalmol Vis Sci 2002;43:133–139. [PubMed: 11773023]

Kudo T, Takino T, et al. Substrate choice of membrane-type 1 matrix metalloproteinase is dictated by tissue inhibitor of metalloproteinase-2 levels. Cancer Sci 2007;98:563–568. [PubMed: 17425593]

Linder S. The matrix corroded: podosomes and invadopodia in extracellular matrix degradation. Trends Cell Biol 2007;17:107–117. [PubMed: 17275303]

Liton PB, Luna C, et al. Genome-wide expression profile of human trabecular meshwork cultured cells, nonglaucomatous and primary open angle glaucoma tissue. Mol Vis 2006;12:774–790. [PubMed: 16862071]

Lo WR, Rowlette LL, et al. Tissue differential microarray analysis of dexamethasone induction reveals potential mechanisms of steroid glaucoma. Invest Ophthalmol Vis Sci 2003;44:473–485. [PubMed: 12556371]

Mori H, Tomari T, et al. CD44 directs membrane-type 1 matrix metalloproteinase to lamellipodia by associating with its hemopexin-like domain. EMBO J 2002;21:3949–3959. [PubMed: 12145196]

Munesue S, Yoshitomi Y, et al. A novel function of syndecan-2, suppression of matrix metalloproteinase-2 activation, which causes suppression of metastasis. J Biol Chem 2007;282:28164–28174. [PubMed: 17623663]

Nolan MJ, Giovingo MC, et al. Aqueous humor sCD44 concentration and visual field loss in primary open-angle glaucoma. J Glaucoma 2007;16:419–429. [PubMed: 17700283]

Oh DJ, Martin JL, et al. Effect of latanoprost on the expression of matrix metalloproteinases and their tissue inhibitors in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2006;47:3887–3895. [PubMed: 16936101]

Ohlmann AV, Ohlmann A, et al. Localization of collagen XVIII and endostatin in the human eye. Curr Eye Res 2005;30:27–34. [PubMed: 15875362]

Ohno S, Ohno-Nakahara M, et al. Induction of MMP-3 by hyaluronan oligosaccharides in temporomandibular joint chondrocytes. J Dent Res 2005;84:1005–1009. [PubMed: 16246931]

Page-McCaw A, Ewald AJ, et al. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol 2007;8:221–233. [PubMed: 17318226]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Pang IH, Fleenor DL, et al. Aqueous outflow-enhancing effect of tert-butylhydroquinone: involvement of AP-1 activation and MMP-3 expression. Invest Ophthalmol Vis Sci 2003;44:3502–3510. [PubMed: 12882800]

Pang IH, Hellberg PE, et al. Expression of matrix metalloproteinases and their inhibitors in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2003;44:3485–3493. [PubMed: 12882798]

Park JK, Tripathi RC, et al. Tissue plasminogen activator in the trabecular endothelium. Invest Ophthalmol Vis Sci 1987;28:1341–1345. [PubMed: 3112034]

Parshley DE, Bradley JM, et al. Laser trabeculoplasty induces stromelysin expression by trabecular juxtacanalicular cells. Invest Ophthalmol Vis Sci 1996;37:795–804. [PubMed: 8603864]

Peterson JA, Tian B, et al. Latrunculin-A increases outflow facility in the monkey. Invest Ophthalmol Vis Sci 1999;40:931–941. [PubMed: 10102290]

Pike RN, Buckle AM, et al. Control of the coagulation system by serpins. Getting by with a little help from glycosaminoglycans. FEBS J 2005;272:4842–4851. [PubMed: 16176258]

Porter S, Clark IM, et al. The ADAMTS metalloproteinases. Biochem J 2005;386:15–27. [PubMed: 15554875]

Ra HJ, Parks WC. Control of matrix metalloproteinase catalytic activity. Matrix Biol 2007;26:587–596. [PubMed: 17669641]

Rao PV, Allingham RR, et al. Antithrombin III, a serpin family protease inhibitor, is a major heparin binding protein in porcine aqueous humor. Biochem Biophys Res Commun 2000;272:1–5. [PubMed: 10872794]

Rapti M, Atkinson SJ, et al. The isolated N-terminal domains of TIMP-1 and TIMP-3 are insufficient for ADAM10 inhibition. Biochem J 2008;411:433–439. [PubMed: 18215140]

Ronkko S, Rekonen P, et al. Matrix metalloproteinases and their inhibitors in the chamber angle of normal eyes and patients with primary open-angle glaucoma and exfoliation glaucoma. Graefes Arch Clin Exp Ophthalmol 2007;245:697–704. [PubMed: 17028863]

Rozsa FW, Reed DM, et al. Gene expression profile of human trabecular meshwork cells in response to long-term dexamethasone exposure. Mol Vis 2006;12:125–141. [PubMed: 16541013]

Samples JR, Alexander JP, et al. Regulation of the levels of human trabecular matrix metalloproteinases and inhibitor by interleukin-1 and dexamethasone. Invest Ophthalmol Vis Sci 1993;34:3386–3395. [PubMed: 8225873]

Sanka K, Maddala R, et al. Influence of actin cytoskeletal integrity on matrix metalloproteinase-2 activation in cultured human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2007;48:2105–2114. [PubMed: 17460268]

Sawaguchi S, Lam TT, et al. Effects of Glycosaminoglycan-Degrading Enzymes on Bovine Trabecular Meshwork in Organ Culture. J Glaucoma 1993;2:80–86.

Sawaguchi S, Yue BY, et al. Effects of intracameral injection of chondroitinase ABC in vivo. Arch Ophthalmol 1992;110:110–117. [PubMed: 1731702]

Schlunck G, Han H, et al. Substrate rigidity modulates cell matrix interactions and protein expression in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2008;49:262–269. [PubMed: 18172101]

Shearer TW, Crosson CE. Adenosine A1 receptor modulation of MMP-2 secretion by trabecular meshwork cells. Invest Ophthalmol Vis Sci 2002;43:3016–3020. [PubMed: 12202524]

Shuman MA, Polansky JR, et al. Tissue plasminogen activator in cultured human trabecular meshwork cells. Predominance of enzyme over plasminogen activator inhibitor. Invest Ophthalmol Vis Sci 1988;29:401–405. [PubMed: 3125123]

Snyder RW, Stamer WD, et al. Corticosteroid treatment and trabecular meshwork proteases in cell and organ culture supernatants. Exp Eye Res 1993;57:461–468. [PubMed: 8282032]

Stamer WD, Roberts BC, et al. Isolation, culture, and characterization of endothelial cells from Schlemm's canal. Invest Ophthalmol Vis Sci 1998;39:1804–1812. [PubMed: 9727403]

Takahashi K, Eto H, et al. Involvement of CD44 in matrix metalloproteinase-2 regulation in human melanoma cells. Int J Cancer 1999;80:387–395. [PubMed: 9935179]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Tortorella MD, Arner EC, et al. Alpha2-macroglobulin is a novel substrate for ADAMTS-4 and ADAMTS-5 and represents an endogenous inhibitor of these enzymes. J Biol Chem 2004;279:17554–17561. [PubMed: 14715656]

Tovar-Vidales T, Roque R, et al. Tissue transglutaminase expression and activity in normal and glaucomatous human trabecular meshwork cells and tissues. Invest Ophthalmol Vis Sci 2008;49:622–628. [PubMed: 18235007]

Tripathi RC, Park JK, et al. Tissue plasminogen activator in human aqueous humor and its possible therapeutic significance. Am J Ophthalmol 1988;106:719–722. [PubMed: 3143267]

Tripathi RC, Tripathi BJ, et al. Localization of urokinase-type plasminogen activator in human eyes: an immunocytochemical study. Exp Eye Res 1990;51:545–552. [PubMed: 2123459]

Vittal V, Rose A, et al. Changes in gene expression by trabecular meshwork cells in response to mechanical stretching. Invest Ophthalmol Vis Sci 2005;46:2857–2868. [PubMed: 16043860]

Vittitow J, Borras T. Genes expressed in the human trabecular meshwork during pressure-induced homeostatic response. J Cell Physiol 2004;201:126–137. [PubMed: 15281095]

Wang Z, Juttermann R, et al. TIMP-2 is required for efficient activation of proMMP-2 in vivo. J Biol Chem 2000;275:26411–26415. [PubMed: 10827175]

Wride MA, Geatrell J, et al. Proteases in eye development and disease. Birth Defects Res C Embryo Today 2006;78:90–105. [PubMed: 16622853]

WuDunn D. The effect of mechanical strain on matrix metalloproteinase production by bovine trabecular meshwork cells. Curr Eye Res 2001;22:394–397. [PubMed: 11600941]

Yu Q, Stamenkovic I. Localization of matrix metalloproteinase 9 to the cell surface provides a mechanism for CD44-mediated tumor invasion. Genes Dev 1999;13:35–48. [PubMed: 9887098]

Yu WH, Yu S, et al. TIMP-3 binds to sulfated glycosaminoglycans of the extracellular matrix. J Biol Chem 2000;275:31226–31232. [PubMed: 10900194]

Zhao X, Ramsey KE, et al. Gene and protein expression changes in human trabecular meshwork cells treated with transforming growth factor-beta. Invest Ophthalmol Vis Sci 2004;45:4023–4034. [PubMed: 15505052]

Zhao X, Russell P. Versican splice variants in human trabecular meshwork and ciliary muscle. Mol Vis 2005;11:603–608. [PubMed: 16110303]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

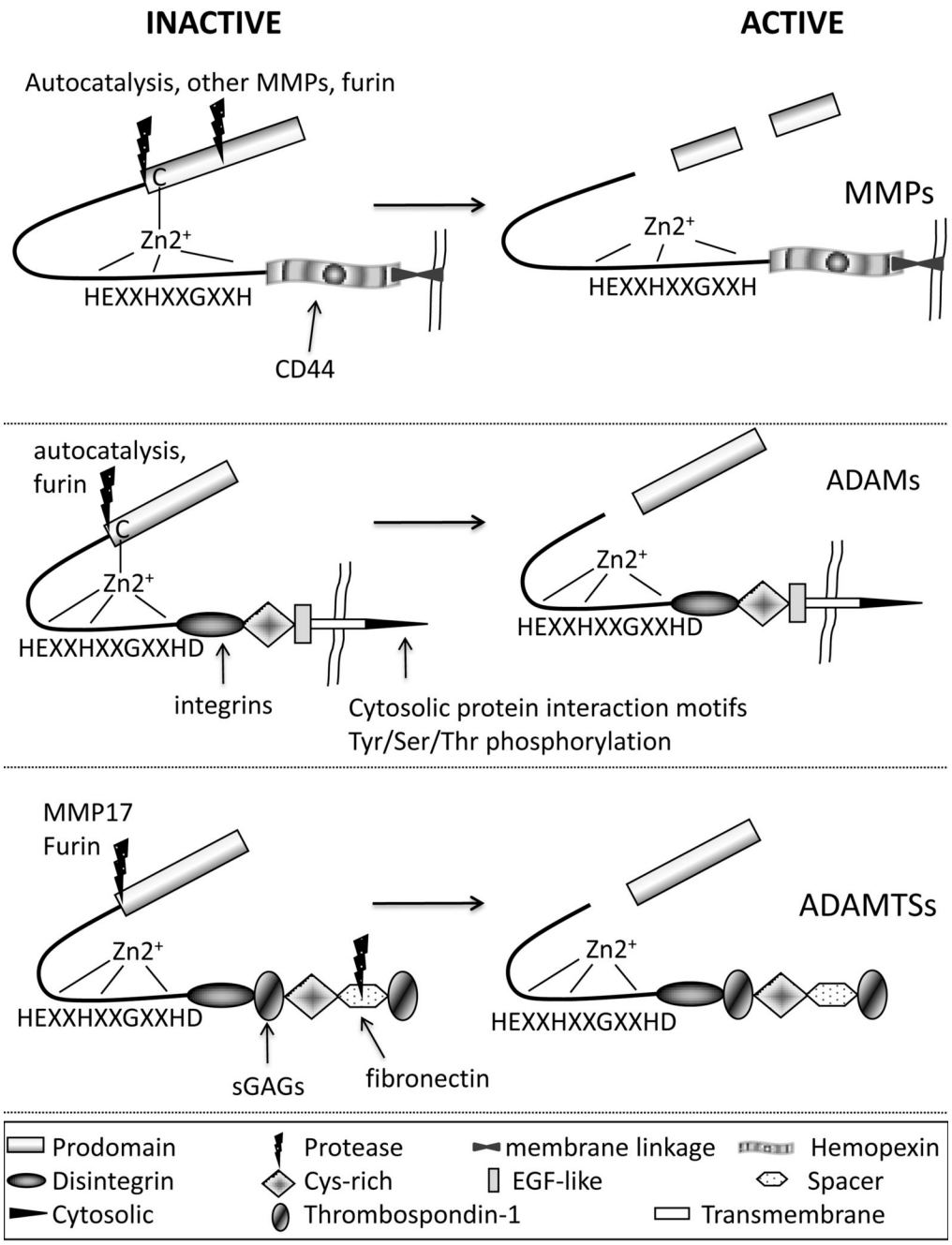

Figure 1.

Schematic showing the multi-domain structure of MMPs, ADAMs and ADAMTSs. Zinc is histidine-ligated into the catalytic site and cleavage of the prodomain disrupts the thiol-zinc bond and activates the enzyme, a mechanism known as the cysteine-switch. The hemopexin domains of MMPs function in substrate recognition, targeting or localization and can homodimerize to augment proteolytic activity. ADAMs can interact with various integrins via the disintegrin domain and with a number of intracellular binding motifs through its cytosolic tail. ADAMTSs can interact with sulfated GAGs and fibronectin and can be proteolytically cleaved in the spacer region. The number of C-terminal thrombospondin domains varies from 0–14 between family members.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

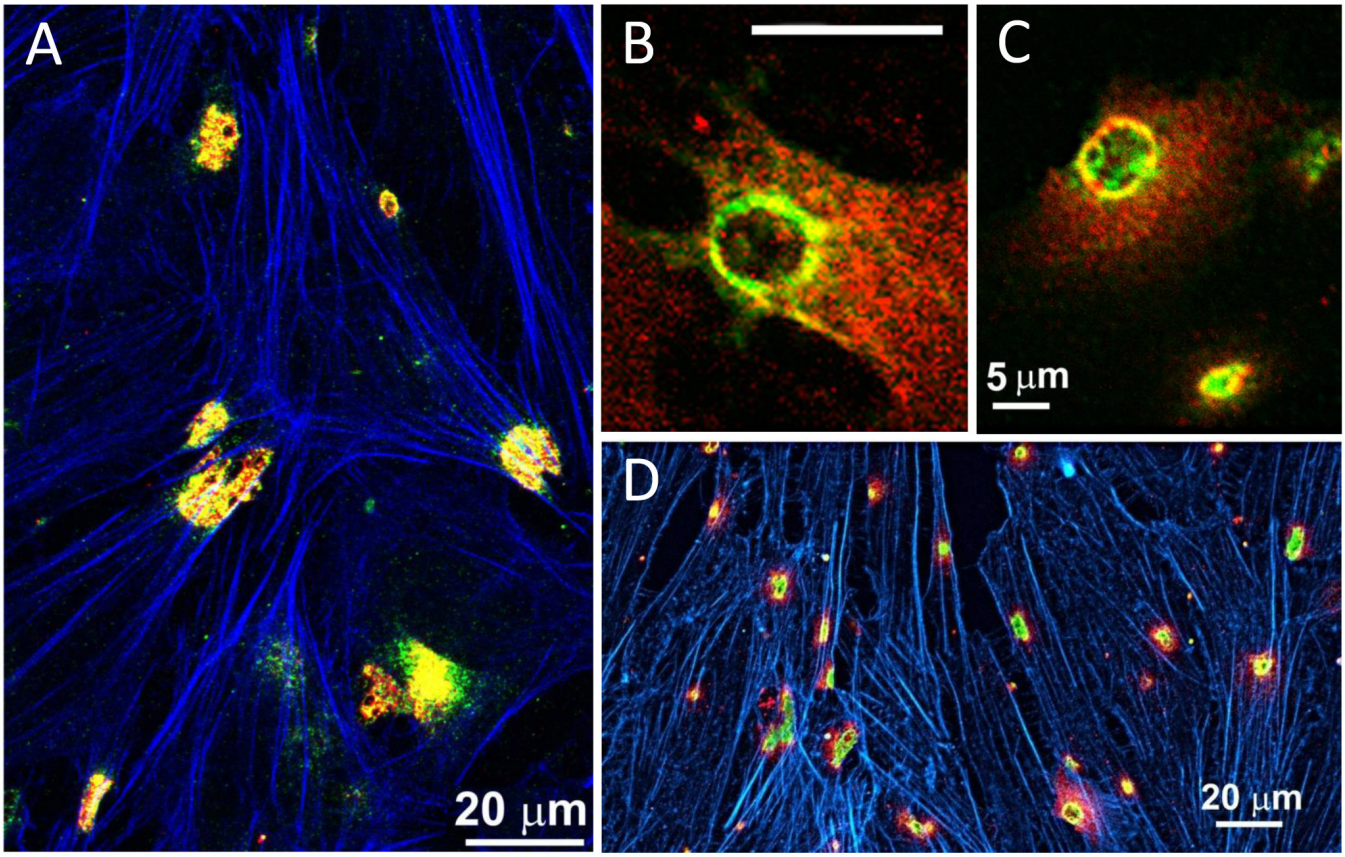

Figure 2.

Podosome-like structures formed by porcine TM cells in culture. (A) Immuno-colocalization of MMP2 (green) and MMP14 (red) to PILS. Blue = F-actin phalloidin staining. (B) Colocalization of a typical PILS component, cortactin (green), and MMP2 (red) to a podosome rosette structure. Bar = 10 μm. (C) Colocalization of cortactin (green) and a neo-epitope of versican that is created by ADAMTS4 proteolysis (red). (D) Lower magnification image showing colocalization of cortactin (green) and the ADAMTS4-generated neo-epitope of versican (red) to PILS. Blue = F-actin phalloidin staining.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

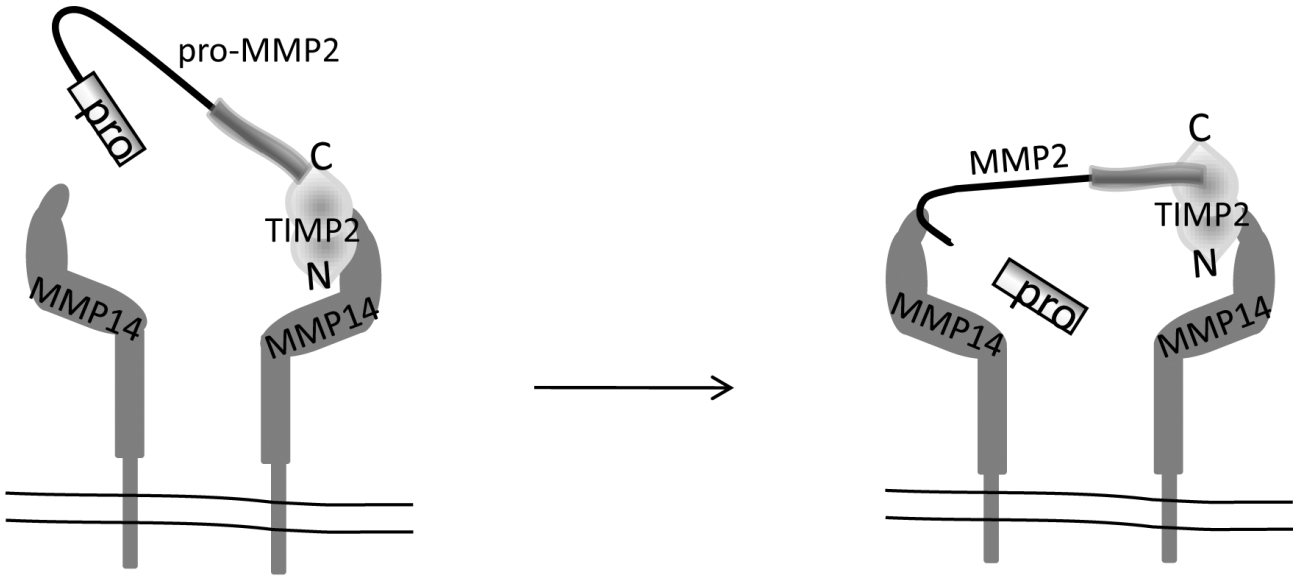

Figure 3.

Role of TIMP2 in the activation of pro-MMP2. The N-terminus of TIMP2 binds to one molecule of MMP14 at the cell surface. Concomitantly, the C-terminus of TIMP2 binds to the C-terminus of pro-MMP2. This trimeric complex then recruits another molecule of MMP14, which cleaves the propeptide to activate MMP2. This schematic depicts the simplest mechanism of pro-MMP2 activation, but other molecules are likely to be involved, e.g. CD44, integrins, etc.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Outflow pathway ECM turnover proteinases.

Proteinase	Common name	Selected Substrates
MMP-1	Collagenase-1	Collagens I, II, III, VII, VIII & X, gelatin, aggrecan, versican, tenascin, MMP-2, -9, pro-TNFα, IL-β1, α1-PI.
MMP-2	Gelatinase-A	Collagens I, IV, V, VII, X, XI & XIV, gelatin, elastin, fibronectin, aggrecan, decorin, laminin 1 & 5, HA'ase-treated versican, galectin-3, MMP-1, -9, -13, α1-PI.
MMP-3	Stromelysin-1	Collagens III, IV, V & IX, gelatin, decorin, laminin, versican, α1-PI, MMP2/9 complex, tenascin, perlecan, fibronectin, MMP-1,-7,-8,-9,-13, antithrombin III.
MMP-9	Gelatinase-B	Collagens IV, V, VII, X & XIV, gelatin, elastin, galectin-3, HA'ase-treated versican, fibronectin, IL-β1, α1-PI.
MMP-10	Stromelysin-2	Collagens III, IV & V, gelatin, elastin, MMP-1, -8.
MMP-11	Stromelysin-3	Casein, laminin, fibronectin, gelatin, collagen IV, α1-PI.
MMP-12	Metalloelastase	Collagen IV, elastin, gelatin, casein, laminin, fibronectin, vitronectin, entactin, α1-PI, fibrinogen, fibrin.
MMP-13	Collagenase-3	Collagens I, II, III, IV, IX, X & XIV, gelatin, aggrecan, perlecan, tenascin C, fibronectin, osteonectin, MMP9.
MMP-14	MT1-MMP	Collagens I, II, III, elastin, fibronectin, gelatin, laminin, vitronectin, tenascin C, entactin, MMP-2,-13, α1-PI.
MMP-15	MT2-MMP	Tenascin, fibronectin, laminin, perlecan, MMP-2
MMP-16	MT3-MMP	Collagen III, gelatin, casein, fibronectin, MMP-2.
MMP-17	MT4-MMP	N.D.
MMP-19	RASI	Gelatin.
MMP-24	MT5-MMP	N.D.
ADAM-9	Meltrin gamma	Ectodomain shedding, collagen XVII, pro-TNFα, heparin binding EGF-like growth factor, TNF receptor II.
ADAM-10	MADM	Ectodomain shedding, collagen XVII, pro-TNFα, IL-6 receptor, CD44, notch, delta, jagged, eprhin-A2.
ADAM-12	Meltrin alpha	Ectodomain shedding, heparin-binding EGF-like growth factor.
ADAMTS-1	Aggrecanase-3	Aggrecan, versican V1.
ADAMTS-4	Aggrecanase-1	Aggrecan, brevican, versican V1, fibromodulin, decorin.
ADAMTS-5	Aggrecanase-2	Aggrecan, brevican, decorin, biglycan.
Tissue PA	tPA	Plasminogen activation
Urokinase PA	uPA	Plasminogen activation

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Outflow pathway ECM turnover inhibitors.

Inhibitor	Other name	Inhibition target
TIMPs 1–4		MMPs and some ADAMTSs
α2-macroglobulin		General proteinases, ADAMTSs-4 & -5
SerpinC1	Antithrombin III	Thrombin
SerpinE1	PAI-1, α1-proteinase inhibitor	Plasminogen activator
SerpinB2	PAI-2	Plasminogen activator
SerpinA3	α1-chymotrypsin	Serine/threonine proteinase
SerpinD1	Heparin cofactor II	Serine/threonine proteinase
SerpinE2	Protease nexin 1	Serine/threonine proteinase
SerpinI1	neuroserpin	Serine/threonine proteinase