HHS Public Access

Author manuscript

Biochim Biophys Acta. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Biochim Biophys Acta. 2017 November ; 1864(11 Pt A): 1940–1951. doi:10.1016/j.bbamcr.2017.04.015.

Matrix metalloproteinase collagenolysis in health and disease

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Abstract

The proteolytic processing of collagen (collagenolysis) is critical in development and homeostasis, but also contributes to numerous pathologies. Mammalian interstitial collagenolytic enzymes include members of the matrix metalloproteinase (MMP) family and cathepsin K. While MMPs have long been recognized for their ability to catalyze the hydrolysis of collagen, the roles of individual MMPs in physiological and pathological collagenolysis are less defined. The use of knockout and mutant animal models, which reflect human diseases, has revealed distinct collagenolytic roles for MT1-MMP and MMP-13. A better understanding of temporal and spatial collagen processing, along with the knowledge of the specific MMP involved, will ultimately lead to more effective treatments for cancer, arthritis, cardiovascular conditions, and infectious diseases.

Keywords

Arthritis; Collagen; Matrix metalloproteinase; Metastasis; Skeletal defects; Wound healing

1. Introduction

The matrix metalloproteinases (MMPs) are a family of Zn^{2+}-dependent endopeptidases. MMPs were first identified as enzymes capable of catalyzing the hydrolysis of collagen [1]. MMP-mediated collagenolysis has long been implicated in the physiological remodeling of tissues and embryonic development as well as the progression of disease pathologies. Inhibition of MMP collagenolytic activity has been extensively pursued [2–4], but with little success in the clinic [5–7]. One of the limitations of previous inhibitor development was the lack of recognition that some MMPs have host beneficial functions that should not be modulated if possible [8–11]. Systems biology approaches have allowed for a more global view of MMP activities [12–18], and insights into the MMP collagenolytic mechanism [19–21] has revealed possibilities for selective inhibition of collagenolytic MMPs. The role of

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specific MMPs in collagenolysis, and the relationship between collagenolysis and disease, has been better defined through the use of knockout and mutant animal models.

2. Structural organization and assembly of interstitial collagens

Collagens are the most abundant proteins in the human body and the main components of the extracellular matrix (ECM). The collagen family is made up of at least 28 members [22–24]. Collagens are composed of three α chains of primarily repeating Gly-Xaa-Yaa triplets, which induce each α chain to adopt a left-handed polyPro II helix. Three chains then intertwine, staggered by one residue and coiled, to form a right-handed superhelix [25, 26]. Triple-helical structure provides collagens with exceptional mechanical strength, broad resistance to the proteolytic enzymes, and a distinct topology for protein-protein interactions [27].

Collagens have been classified according to their α chains. Homotrimeric collagens (i.e., types II and III) have three α chains of identical sequence. Heterotrimeric collagens have two α chains of identical sequence (designated α1) and one α chain of differing sequence (designated α2) (i.e., type I), or three α chains with different sequences (designated α1, α2, and α3) (i.e., type VI) [28]. Collagens are further classified into subfamilies, based on their quaternary structure. These subfamilies include fibrillar, fibril associated with interrupted triple-helices, short chain, basement membrane, multiplexins, and membrane associated with interrupted triple-helices [28]. The most common collagens (types I, II, III, V, and XI) have fibrillar structures [29].

Types I, II, and III collagen compose the interstitial collagen subfamily. Interstitial collagens are so named because of their proximity to cells in the extracellular space. Type I collagen, the most profuse and ubiquitous of the collagens, is found in the majority of connective and embryonic tissues [28, 30]. Type II collagen is found in cartilage and the vitreous humor [30]. Its expression also occurs during embryogenesis. Type III collagen is found in visceral and cardiovascular tissues [30], as well as in numerous tissues characterized by high type I collagen content. Type V collagen is found associated with type I collagen, while type XI collagen is associated with type II collagen [31, 32].

The triple-helical domains of types I, II, and III collagen span 1014–1023 residues. Each of these collagens also initially possess *N*- and *C*-terminal non-triple-helical regions (propeptides). Following synthesis, but before interstitial procollagen can be properly folded, a series of post-translational modifications must occur on the central $(\text{Gly-Xaa-Yaa})_n$ domain, including hydroxylation of most Pro and some Lys residues in the Yaa position (by prolyl 4-hydroxylase, prolyl 3-hydroxylase, and lysyl 5-hydroxylases) followed by glycosylation of selective 5-hydroxylysine residues [33–36]. Glycosylation also occurs on some Asn residues in the *C*-terminal propeptides. Disulfide bonds between the propeptides are rearranged by protein disulfide isomerase and isomerization of Pro and 4-hydroxy-L-proline (Hyp) from *cis* to *trans* takes place [37–39]. Assembly and correct folding of procollagen occurs within the endoplasmic reticulum [40]. Hsp47 stabilizes the folded triple-helix [41–43].

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The *C*-terminal propeptides mediate interaction between three α chains and hold these chains in place, nucleating triple-helical formation. Lateral association of triple-helices occurs in the Golgi [40]. The triple-helical molecules are then secreted from the cell and the *N*- and *C*-terminal propeptides that flank the central $(Gly\text{-}Xaa\text{-}Yaa)_n$ domain are removed. The resulting tropocollagen contains short *N*- and *C*-terminal telopeptides and the central triple-helical domain. A disintegrin and metalloproteinase with thrombospondin motifs 2 (ADAMTS-2) removes the *N*-terminal propeptide from types I, II, and III procollagens [44]. ADAMTS-3 processes the *N*-terminal propeptide from type II procollagen, while ADAMTS-14 processes the *N*-terminal propeptide from type I procollagen [44]. Procollagen C-proteinase-2/bone morphogenetic protein-1 cleaves the *C*-terminal propeptides from types I, II, and III procollagens [45, 46]. Meprins α and β also cleave procollagen III *N*- and *C*-propeptides, releasing the mature protein which then assembles into fibrils [47]. Cleavage by meprins is at the same site as procollagen C-proteinase-2. Oxidation of Lys residues by lysyl oxidases (LOXs) allows for the formation of intermolecular crosslinks, which stabilize higher order structures such as fibrils and fibers [48].

3. Am I a collagenase? MMPs that catalyze interstitial collagen catabolism

Hydrolysis of interstitial collagens occurs by a limited number of proteases. The scientific literature contains numerous examples of proteases deemed “collagenolytic,” but this is often obscured by the lack of criteria by which an enzyme is classified to efficiently catalyze the hydrolysis of an intact triple-helix. A collagenolytic enzyme should be considered one that processes a triple-helix under conditions by which that triple-helix is intact. One standard test for triple-helical integrity is susceptibility to trypsin hydrolysis [49]. Some collagens (type III) have more “flexible” potential cleavage sites than others (type I), and thus are more susceptible to hydrolysis by a variety of proteases [50–52]. A collagenolytic enzyme should thus process the triple-helix efficiently, i.e. with a reasonable k_{cat}/K_M value for soluble collagen or specific activity for fibrillar collagen [53]. The fibrillar form of collagen is more resistant to general proteolysis [54], and MMP hydrolysis of fibrillar collagen has a higher activation energy than for soluble collagen [55]. Collagenolytic activities between enzymes can also be directly compared to determine relative efficiencies of proteolysis.

Interstitial collagens have long been recognized as being hydrolyzed by the “classic” collagenases, MMP-1, MMP-8, and MMP-13, into ¾ and ¼ length fragments (Table 1 and Fig. 1) [53, 56–62]. All three of these enzymes catalyze collagen hydrolysis efficiently (Table 2), but their relative activities towards interstitial collagens differ. MMP-1 has greater catalytic activity on type III collagen as a substrate. At 25 °C, the MMP-1 collagen preference is III > I ≫ II [63]. MMP-8 preferentially cleaves type I collagen over types II and III collagen at 25 °C [63]. MMP-13 cleaves type II collagen 5- and 6-times faster than types I and type III collagen, respectively, at 25 °C [53].

There is some ambiguity as to the collagenolytic activity of the gelatinase members of the MMP family, MMP-2 and MMP-9. MMP-2 has been reported to cleave types I, II, and III collagen [64–66], although other reports have brought into question how robust the type I collagenolytic activity of MMP-2 is [67, 68]. Recombinant MMP-9 (0.5 μg) was found to

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cleave type I collagen (27 μg) at 37 °C after 72 h [69]. MMP-9 also digested type III collagen at 25 °C following 98 h treatment [69]. For MMP-2 and MMP-9, the interstitial collagen cleavage site is the same as the classic collagenases (Table 1). For both MMP-2 and MMP-9, type III collagen is a preferred substrate compared with types I and II [65, 69]. Most likely, MMP-2 and MMP-9 do not contribute significantly to interstitial collagen turnover *in vivo*, but instead produce collagen fragments following the action of MMP-13 or MT1-MMP (see below).

The ability of MMP-9 to cleave the intact triple-helix of type V collagen has been reported [70–72]. Conditions were 438–876 nM MMP-9, 2 μg human type V collagen for 30 h at 30 °C [71], which resulted in near complete digestion of the collagen, or 22–43 nM MMP-9, 1 μg/μL human type V collagen for 18 h at 30 °C [72], which resulted in more moderate digestion of the collagen. Although the cleavage sites within type V collagen was identified by treatment at 30 °C for 16 h, the sites were slightly out of alignment within the $[\alpha 1(V)]_2\alpha 2(V)$ heterotrimeric triple-helix (Table 1) [70].

Transfection of two membrane type-MMPs (MT-MMPs), MT1-MMP/MMP-14 and MT2-MMP/MMP-15, allowed invasion-incompetent cells to penetrate type I collagen matrices [73]. MT1-MMP processes types I–III collagen at the same site as the classic collagenases (Table 1) [74]. MT1-MMP prefers type I collagen, as activity against type I collagen was estimated to be 4 times that of type II collagen and 6.5 times that of type III collagen [74].

Some studies indicated a requirement of MT1-MMP homodimerization through the hemopexin-like (HPX) domain for efficient collagenolysis [75, 76]. Alternatively, deletion of the HPX domain did not inhibit collagen invasion modulated by cell surface-bound MT1-MMP [77, 78]. In solution, MT1-MMP was not found as a dimer [21, 79] and the MT1-MMP HPX domain alone did not form a dimer [80]. The low level of collagenolytic activity observed with an MT1-MMP HPX domain mutant [81] may have been due to disruption of favorable MT1-MMP interaction with the cell surface rather than dimer disruption [79]. The conflicting results in prior studies may result from different MT1-MMP constructs being utilized. When MT1-MMP residues 336-535 were deleted (the resulting enzyme contained the CAT domain, the linker, and 18 residues from the HPX domain), collagenolysis was inhibited [76]. In this construct Cys318 is present; in the full-length MT1-MMP, Cys318 forms a disulfide bond with Cys507. When MT1-MMP residues 318-535 were deleted (the resulting enzyme contained the CAT domain and the linker), collagenolyis was still observed [77]. In this construct there are no unpaired Cys residues. Ultimately, recent studies have concluded that dimerization is not necessary for MT1-MMP catalyzed collagenolysis [21, 79], and that collagenolysis can occur without the HPX domain when the enzyme is cell-surface bound [77, 78].

MT3-MMP/MMP-16 was found to cleave type III collagen at the classic site (Table 1), and was more efficient at processing type III collagen than MT1-MMP (Table 2) [82]. Conversely, MT3-MMP did not cleave types I and II collagen within their triple-helical domains [82]. Transfection of MT3-MMP either did not allow or only weakly allowed invasion-incompetent cells to penetrate type I collagen matrices [73, 83]. Similar behavior was observed with MT3-MMP-expressing WM852 melanoma cells [84]. However, in

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complete contrast, Shi *et al.* found MT3-MMP to efficiently process types I and II collagen films [85]. The differences in observed MT3-MMP collagenolytic activities may originate from the constructs or cell types (MDCK cells [73, 83], WM852 melanoma [84], and Cos-7 cells [85]) used.

MT6-MMP/MMP-25 was initially reported to have little or no collagenolytic activity [86, 87], but subsequently was found to cleave types I and II collagen (albeit at 37 °C) [88] and a triple-helical peptide model of the classic collagenase cleavage site in interstitial collagen [89]. The MT6-MMP cleavage sites in the α1 and α2 chains of type I collagen did not align, and many sites were located in the non-triple-helical C-terminal telopeptide region [88]. This indicates that MT6-MMP is not aa truly collagenolytic protease.

The CAT domain of MMP-12 processes types I and III collagens at 33 °C, where hydrolysis occurs at the classic cleavage site and at numerous other sequences [90]. The classic collagenase cleavage site seemed to be the most sensitive to MMP-12 (Table 1). However, we found that MMP-12 could not cleave type I collagen efficiently under conditions comparable to other collagenases (Fig. 2). The observed hydrolysis reported previously was most likely due to the combination of high concentration of enzyme and substrate (10 μg/mL of enzyme with 1 mg/mL substrate), temperature (33 °C), and time (24 h). In similar fashion, although the MMP-12 catalytic domain has been reported to cleave the triple-helix of type V collagen [91], we found that it could not cleave type V collagen efficiently (Fig. 3). The prior study used 0.2 μg of enzyme and 10 μg of type V collagen at room temperature for 16 h.

MMP-3 binds to type I collagen, but does not cleave the native triple-helix [92, 93]. However, the MMP-3 catalytic (CAT) domain can cleave collagen when the triple-helix is destabilized by catalytically inactive MMP-1 [94]. Thus, MMP-3 is entirely competent to cleave type I collagen, but does not. Based on the MMP collagenolysis mechanism, the linker needs to be able to properly orient the CAT and HPX domains [19–21]. Large domain movements based on the flexible linker have been observed for MMP-1, MMP-9, and MMP-12 [20, 95–98]. Gly_{272} is critical for the collagenolytic activity of MMP-1, with its role proposed to be the linker-bending motion that allows the HPX domain to present collagen to the CAT domain [99, 100]. MMP-1 and MMP-8 linkers are considerably shorter than the MMP-3 linker, while MT1-MMP linker is very long (33 residues), with significant and heterogeneous *O*-glycosylation [101]. Thus, linker length *per se* is not the ultimate criteria for efficient collagenolysis. A chimeric MMP-8 whose linker region (16 residues) was replaced with the corresponding MMP-3 sequence (25 residues) lost activity towards collagen [102]. In similar fashion, MMP-1/MMP-3 chimeras possessing the MMP-3 linker are not active towards collagen [93, 103]. The linker appears critical for proper alignment of the CAT and HPX domains during collagenolysis. Ultimately, there may be negative regulation of collagenolytic activity due to (mis)alignment of the CAT and HPX domains in the case of MMP-3 and other non-collagenolytic MMPs.

The intact triple-helix of interstitial collagen is cleaved efficiently by the cysteine protease cathepsin K under acidic conditions (optimum pH 5.0) [104–106]. Five distinct sites of

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cathepsin K hydrolysis of type I collagen have been identified, as well as one in type II collagen (Table 1 and Fig. 1) [105, 107].

To determine "am I a collagenase?", the most prudent approach is to compare an enzyme to a known collagenase (such as MMP-1) and a non-collagenolytic protease (such as trypsin) using gel-based analysis of collagen degradation (as shown in Figs. 2 and 3). One can readily monitor the disappearance of the intact collagen chains over time to evaluate kinetic parameters. Active enzyme concentrations should be comparable on a molar basis, and an appropriate temperature used whereby there is no collagenolysis by the non-collagenolytic protease. For cell surface-bound enzymes, comparisons to MT1-MMP-producing or -transfected cells can be performed for invasion of collagen matrices or processing of collagen films. *In lieu* of titrating the amount of active enzyme on the cell surface (which can be quite difficult), total protein concentration of the enzyme and MT1-MMP should be comparable.

4. The role of collagen catabolism in normal physiology

The proteolysis of collagen is integral for numerous physiological functions including morphogenesis, tissue remodeling, and wound healing. Determining which MMPs participate in collagenolysis is difficult, based on the fact that MMPs have multiple activities beyond collagenolysis. For example, MT1-MMP participates in collagenolysis, shedding of cell surface biomolecules, hydrolysis of serum proteins, cytokines, fibrillar amyloid β-protein, fibronectin, Notch1, and the laminin-5 γ2 chain, and activation of proMMP-2 and the pro-αv integrin subunit [108–125]. MT1-MMP is also active *intracellularly*, processing centrosomal breast cancer type 2 susceptibility gene (BRCA2) and pericentrin, where the latter event leads to chromosomal instability [126, 127]. In addition, collagen hydrolysis by MMPs has other effects, such as directly disrupting the fibronectin binding site [128] and revealing cryptic binding sites within collagen chains [129–132]. Bulk collagenolysis may be performed by several MMPs in a redundant and compensatory fashion [78]. However, the ultimate products of collagenolysis and their effects on cellular behaviors differ based on the specific MMP [132]. Precise roles for collagen catabolism have been ascertained from MMP knockout mice or mutant collagen mice.

There are several pathways that have been considered for mammalian collagen catabolism [62]. One pathway involves initial extracellular MMP hydrolysis of collagen fibrils, followed by the large collagen fragments undergoing urokinase plasminogen activator receptor-associated protein (uPARAP)/Endo180-mediated (on mesenchymal cells) and mannose receptor-mediated (on macrophages) endocytosis, lysosomal delivery, and cathepsin catalyzed degradation [133–136]. The initial collagen proteolysis has been ascribed to MT1-MMP [133, 137].

Knockout studies showed that MT1-MMP has a variety of roles in skeletal development, as aberrant cranial bone formation was observed at birth in MT1-MMP knockout mice, and over time osteopenia increased and bone mass decreased [138]. These effects were attributed to a lack of interstitial collagenolytic activity of MT1-MMP [138, 139], as the knockout mice exhibited increasing fibrosis in tendons, ligaments, synovial capsules, musculotendinal

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junctions, and septal/fascial structures and persistence of parietal cartilage [138]. The skeletal defects may also have contributions from the lack of other proteolytic activities of MT1-MMP, or indirect effects of decreased collagenolysis, such as the lack of regulation of fibronectin binding to collagen (see above). A mutation in the signal peptide (Thr17Arg) results in decreased production of active MT1-MMP in Winchester Syndrome [140]. The mutation is hypothesized to affect MT1-MMP transport to the cell membrane [140]. Winchester Syndrome is characterized by osteolysis, or “vanishing bone” syndrome, whose skeletal phenotype parallels that observed in the MT1-MMP knockout mouse [140].

MT3-MMP also contributes to skeletal development [85]. MT1-MMP/MT3-MMP double deficiency mice have severe craniofacial dysmorphism and shortening of cortical bone beyond that observed in MT1-MMP knockout mice. These contributions of MT3-MMP are proposed to be a result of the collagenolytic activity of the enzyme (see above) [85].

Knockout studies indicated that MMP-13 functions in skeletal growth plate development (the transition from cartilage to bone) [141]. More specifically, in the knockout mice growth plates had a lengthened hypertrophic chondrocyte zone and trabecular bone was increased over time [141]. The lack of MMP-13 to process cartilage type II collagen was key to these effects [139, 141]. A mutation in the propeptide of MMP-13 (Phe56Ser) results in the Missouri variant of spondyloepimetaphyseal dysplasia (SEMD), a human disorder [142]. The mutant MMP-13 is degraded intracellularly [142]. SEMD is characterized by abnormalities in development and growth of endochondral skeletal components [141, 142]. An Arg792Gly mutation in type II collagen results in SEMD congenita [143]. This mutation has been suggested to negatively effect the MMP HPX domain interaction with the P_{17}’ subsite of collagen [144] and hence decrease collagen turnover. Alternatively, it has also been proposed that the mutation results in increased binding of type II collagen to fibronectin and poor ECM assembly [145].

MT1-MMP knockout mice have arrested tendon development around the time of birth [146]. The knockout mouse tendons had collagen fibrils of ~50 nm diameter that were retained by fibripositors (actin-dependent invaginations of the plasma membrane). It was determined that collagenolysis by MT1-MMP was not essential for tendon development, but MT1-MMP processing of fibronectin was, resulting in the release of fibrils from fibripositors [146].

Substitution of Pro for Gln_{774} and Ala_{777} in the *Col1a-1* gene results in the production of type I collagen resistant to MMP-1, MMP-8, and MT1-MMP processing [147–149]. Introduction of this MMP resistant type I collagen in mice did not affect development to young adulthood [150]. MMP-13 cleaved the *N*-terminal telopeptide region of the resistant type I collagen [151, 152]. The relatively mild effects of the mutant collagen on development to young adulthood may be due to release of triple-helices from fibrils by aminotelopeptidase activity [150], denaturation of the isolated triple-helices at body temperature [153], and general proteolysis of isolated chains. However, after 3–6 months of age, mice displayed thickened skin with dermal fibrosis [150]. Additionally, postpartum involution of the uterus was impaired in female mice bearing the mutant collagen [150]. The uteri were filled with nodules consisting of primarily type I collagen fibers [150]. Thus, it was proposed that cleavage in the *N*-terminal telopeptide region contributed to remodeling

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of type I collagen during development to young adulthood, but cleavage within the triple-helix was needed for remodeling during adulthood [151]. This may be due to collagen cross-linking over time.

Skeletal remodeling was altered in the collagen mutant mice, with increased calvarial periosteal and tibial/femoral endosteal bone deposition observed at 3–12 months of age [154]. Osteocyte/osteoblast apoptosis occurred in the collagen mutant mice starting at 2 weeks of age [154]. It has been proposed that MMP-derived collagen cleavage products are anti-apoptotic [131, 141, 155]. This may be the reason that parathyroid hormone induction of osteoclastic bone resorption is greatly reduced in the collagen mutant mice [156]. Failure to degrade type I collagen impaired hepatic stellate cell apoptosis and may prevent the effective restoration of hepatocyte mass in liver fibrosis [157]. Wound healing, reepithelization, and contraction were delayed in the first 2 weeks after injury in type I collagen mutant mice [158]. The number of contractile myofibroblasts in the wound was decreased, and thus differentiation of fibroblasts to myofibroblasts was impaired [158]. The signal to produce α smooth muscle actin to generate tensile force to contract the tissue was not received [158]. It is possible that apoptosis, as described above, may be the reason why wound healing is impaired [158]. In addition, MMP-1 processing of type I collagen has been shown to promote keratinocyte migration during reepithelialization [159, 160].

For the mutant collagen studies, the precise MMP involved was not identified. As described above, specific roles for MT1-MMP and MMP-13 collagenolysis have been identified. MT1-MMP also contributes to postnatal vascular development and skin homeostasis by cleaving type I collagen [139, 161]. MT1-MMP does not appear to be the critical collagenase for wound repair [161].

Cathepsin K deficiency resulted in pycnodysostosis, a bone-sclerosing dysplasia [162]. Undigested collagen fibrils are observed in osteoblasts and fibroblasts during pycnodysostosis [163, 164]. Patients treated with the cathepsin K inhibitor balicatib exhibited skin hardening, which was correlated to thickened collagen bundles and a hypocellular and hypovascular dermis [165].

5. The role of collagen catabolism in disease

The proteolysis of collagen has been recognized as a contributing factor to multiple pathologies, including tumor cell spreading (metastasis), arthritis, glomerulonephritis, periodontal disease, tissue ulcerations, cardiovascular disease, and neurodegenerative diseases [166–171].

It has long been demonstrated that tumor extracts can possess collagenolytic activity [61, 171, 172]. MT1-MMP is the dominant pericellular collagenase operative *in vivo* enabling cells to migrate through connective tissue matrices where collagens exist as insoluble fibers [121, 173–175]. MT1-MMP appears to play a significant role in tumor metastasis [173, 176, 177]. Interestingly, even though MT1-MMP is an interstitial collagenase, in similar fashion to several secreted MMPs (MMP-1, MMP-8, and MMP-13), the activity of MT1-MMP, but not of secreted collagenases, is critical for transmigration of tumor cells, endothelial cells,

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and fibroblasts through collagen matrices [73, 78, 178–183]. Tumor cell invasion through type I collagen is dependent upon MT1-MMP activity [182]. Collagen degradation by MT1-MMP results in cryptic Arg-Gly-Asp sites being revealed and binding to the αvβ3 integrin. Integrin ligation then activates ERK through c-Src, which in turn causes tumor cell proliferation [184]. MT1-MMP collagenolysis has been correlated to metastasis *in vivo* [176]. Additional roles for collagenolysis in tumor progression have been described [185], including participation of MMP-1 collagenolytic activity in metastasis [186].

Homotrimeric type I collagen is produced by a variety of tumor cells but not cancer-associated fibroblasts [187]. Homotrimeric type I collagen is highly resistant to collagenolytic MMPs [188], and wild type fibroblasts degraded heterotrimeric type I collagen matrices but not homotrimeric type I collagen matrices [187]. Homotrimeric type I collagen enhances tumor cell proliferation and migration compared with heterotrimeric type I collagen. It has been suggested that tumor cells might use MMP-resistant homotrimeric type I collagen fibers as “roadways” for invasion [187].

Matrix stiffness has been implicated in tumor progression, with collagen considered a significant contributor to changes in the cellular mechanical microenvironment [189, 190]. Increased orientation of interstitial and fibrillar collagens, and increased stiffness, is seen in the invasive front of human breast cancer [190]. Transforming growth factor β (TGF-β) enhances collagen deposition in breast and pancreatic cancers [190, 191], and TGF-β can be activated by MMP-2, MMP-9, and MT1-MMP [192–195]. Increased matrix tension due to LOX crosslinking of collagen induces integrin signaling [196]. In turn, inhibition of LOX activity impedes breast tumor progression [196]. Mechanotransduction and oncogenic signaling pathways may be synergistic in promoting tumorigenicity [189], and there is mechanical heterogeneity within tumors [190]. While intact collagen is required for signaling and matrix stiffness, MMP degradation of collagen facilitates tumorigenesis [189]. LOX and MMPs most likely collaborate to create a dynamic collagen-based microenvironment [189].

Osteoarthritis (OA), the most common form of arthritis, is characterized by the destruction of articular cartilage. The main constituents of articular or joint cartilage are type II collagen and various proteoglycans, such as aggrecan, chondroitin sulfate, and hyaluronan [197]. Tensile strength of articular cartilage is due to the triple-helical structure of type II collagen [198]. In native joint cartilage, type II collagen fibrils are protected from cleavage by tight association with molecles of aggrecan [199]. In arthritic cartilage, aggrecan is hydrolyzed by ADAMTS-1, ADAMTS-4, and ADAMTS-5, collectively known as aggrecanases [200]. Aggrecanolysis removes aggrecan molecules from type II collagen fibrils, which makes collagenolysis possible.

MMP-13 has been shown to be the main collagenase responsible for degradation of articular cartilage during OA [201, 202]. Under normal circumstances, MMP-13 is constitutively produced in human chondrocytes, but is rapidly endocytosed and degraded [203, 204]. MMP-13 is specifically expressed in the cartilage of human OA patients and is not present in normal cartilage. MMP-13 synovial fluid levels correlate to human OA severity [205]. Furthermore, transgenic animal models indicate that overexpression of MMP-13 induces

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joint abnormalities characteristic of human OA [206]. More specifically, mice expressing an inducible transgene of spontaneously active MMP-13 had increased cartilage collagen cleavage and OA progression [202]. Studies with semi-selective and selective MMP-13 inhibitors demonstrated that MMP-13 inhibition renders protection to human and bovine cartilage cultures as well as providing chondroprotective effects *in vivo* [206, 207]. Cathepsin K has also been implicated in fibroblast-mediated degradation of type II collagen in cartilage [208].

Osteoporosis (OP) is a chronic skeletal disease that is predicted to affect nearly 61 million women over the age of 50 in the United States by the year 2020 [209]. The skeletal density is dependent on constant bone remodeling events, which are regulated by the balance of osteoblast bone building and osteoclast resorptive actions. Bone is primarily comprised of type I collagen which is mineralized via the deposition of apatite during its synthesis by osteoblasts. Estrogen deficiency increases osteoclast formation by increasing the levels of available pro-osteoclastogenic cytokines [210, 211]. Osteoblastic cells have been shown to secrete multiple MMPs, including MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, and MT1-MMP, while MMP-9 is mainly expressed by osteoclasts [212]. These MMPs have been shown to be capable of degradation of the osteoid that covers the bone trabeculae and to initiate or activate bone remodeling in mice, rats, and humans [213, 214]. MMP-13 is mainly associated with mineralized bone matrix, is thought to be essential for osteoclastogenesis, and plays an important role in degradation of type I collagen in bone matrix in concert with cathepsin K and MMP-9 [212]. One of the mechanisms of estrogen deficiency-induced bone loss is ascribed to the abnormal expression of multiple MMPs in osteoblastic cells, as estrogen inhibits bone resorption and reduces bone turnover rate by down-regulating the expression of MMP-13 in osteoblastic cells [214].

The selection of MMP-13, as opposed to other proteases, as a target in OA and OP is well justified. For example, cartilage degradation is reversible in the presence of aggrecanase activity, but not once type II collagen degradation has proceeded [215]. Inhibition of cathepsin K, which has been pursued for OP, may indiscriminately prevent normal collagen turnover outside of the skeletal system [216].

During pathological vessel remodeling, neointimal lesions and subsequent occlusive events found in atherosclerosis and postangioplasty restenosis result from MT1-MMP activity [217]. Vascular smooth muscle cells use MT1-MMP to degrade and infiltrate three-dimensional collagenous barriers including the arterial wall (which is rich in type I collagen) [217]. Amongst several causes, atherosclerotic plaque vulnerability (rupture) has been postulated to result from processing of interstitial collagens in the fibrous cap of the plaque [218]. It is presently not clear which collagenase (MMP-1, MMP-8, and/or MMP-13) contributes to plaque instability [218].

Increased collagen synthesis over catabolism can result in myocardial fibrosis, leading to ventricular hypertrophy and diastolic dysfunction [219]. In contrast, increased collagen catabolism over synthesis can lead to ventricular dilatation and systolic dysfunction [219]. MT1-MMP myocardial levels are increased post-myocardial infarction (MI) and coincident with adverse left ventricular remodeling [220, 221]. MT1-MMP is the dominant collagenase

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within myocardial tissues [221]. Following MI, MT1-MMP$^{+/-}$ mice have a survival advantage over MT1-MMP$^{+/+}$ mice, while post-MI survival is reduced when MT1-MMP is overexpressed [220]. Survival has been correlated to decreased collagenolytic potential of cardiac fibroblasts (preservation of myocardial type I collagen network) [221]. Liberation of collagen fragments and subsequent processing by MMP-9 can help or hinder left ventricle remodeling post-MI, depending upon the timing and extent of MMP-9 action [222, 223].

Pulmonary fibrosis occurs following repeated bouts of lung injury, as observed in cystic fibrosis, usual interstitial pneumonitis (UIP)/idiopathic pulmonary fibrosis (IPF), and acute respiratory distress syndrome (ARDS). Pulmonary fibrosis corresponds to excess collagen production compared with degradation. [224]. Fibrosis may be the result of a change in collagen composition, resulting in decreased degradation, or an increase in the production of protease inhibitors. A greater proportion of type I collagen compared with type III collagen is observed in lung fibrotic tissue compared to normal lung tissue. Fibrotic tissue also has increased amounts of collagen binding biomolecules, such as fibronectin and proteoglycans, increased proportion of hydroxylated Lys residues within the collagen, and an increase in collagen crosslinking via lysyl oxidase. An increased tissue inhibitor of metalloproteinase (TIMP) to MMP ratio and decreased collagenolysis in the lung is found in human UIP/IPF patients. Knockout studies have implicated MT1-MMP and cathepsin K as key collagenases in fibrosis [224].

Inducible deletion of MT1-MMP in stromal fibroblasts was used to examine the role of this enzyme in skin fibrosis [161]. Deletion of MT1-MMP resulted in increased type I collagen accumulation in skin due to a lack of collagen degradation, and a subsequent continuous increase in skin thickness and stiffness. Fibrosis was entirely due to the lack of collagen turnover, as collagen fibril diameters did not increase [161].

MT1-MMP also contributes to tissue damage and mortality in infectious diseases. Tuberculosis, once the leading cause of death in the U.S., remains a global threat due to limited treatment options, high percentage of infection transmission, and increasing *Mycobacterium tuberculosis* resistance [225]. The interaction between the *Mycobacterium tuberculosis* bacteria and the host immune response (macrophage infection) evokes inflammation and breakdown of the pulmonary ECM leading to formation of granulomas, the hallmark of the disease [226]. Granulomas, formed by aggregates of lung epithelial and immune cells, were once thought to curtail the spread of the disease by encasing *Mycobacterium tuberculosis*. However, recently it has been shown that infected macrophages shuttle between granulomas and the lung surface in order to recruit uninfected macrophages. Upon arrival in the granulomas, newly attracted macrophages become infected by the bacteria and further propagate the infection [225].

MT1-MMP expression is upregulated in *Mycobacterium tuberculosis*-infected macrophages [227]. MT1-MMP is significantly upregulated in patients with pulmonary tuberculosis, expressed throughout granulomas, upregulated by monocyte-monocyte networks, and is functionally active [226]. This upregulation was correlated to local tissue degradation (including collagen destruction) and leukocyte recruitment to the granuloma, contributing to the disease pathology [226].

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The lung epithelial barriers, supported by the ECM scaffold and functioning as the first line of defense against pathogens, are severely damaged during viral infections.[228, 229] Uncontrolled immune-mediated ECM-remodeling events act as a double-edged sword, allowing multiple immune cells to infiltrate the infection focus while causing devastating collateral damage that promotes acute respiratory failure. Global genomics analysis of lung tissue derived from an H1N1 influenza mouse model detected extremely elevated ECM remodeling collagenase genes (mostly MT1-MMP) without a corresponding increase in tissue inhibitor of metalloproteinase-2 [230]. Follow-up experiments, including fluorescence-correlated electron microscopy of intact tissues [231], global mass spectrometry, immune staining, and tissue zymography, revealed dramatic morphologic and compositional ECM changes in influenza-infected lungs, including depletion of fibrillar collagens [230]. The majority of the MT1-MMP-expressing cells during the infection were immune cells of myeloid origin. Remarkably, mice receiving Tamiflu exhibited a devastating ECM phenotype, despite having extremely low viral titers [230]. Mice treated with an anti-MT1-MMP Fab fragment [232] showed tissue recovery, both at the level of morphology and composition (including improved collagen component abundance), and therapeutic effects [230]. The two mouse models used were influenza A infection and influenza A co-infected with *Streptococcus pneumoniae* [230]. Treatment with anti-MT1-MMP Fab fragment significantly increased the ability of virally infected mice to fight off secondary *Streptococcus pneumoniae* bacterial infection over control. This was demonstrated by the finding that 50% of the mice receiving the anti-MT1-MMP Fab fragment survived the double-infection, whereas 100% of the mock treated mice died. Mice that did not receive the inhibitor exhibited bacteremia and dissemination of *Streptococcus pneumoniae* bacteria into the spleen and liver, whereas the infection of treated mice remained confined within the lungs, with no systemic bacterial dissemination [230]. The results suggested that the ECM damage is caused by infiltrating immune cells contributing to the lethal outcome from influenza infection. Immune cell invasion and respiratory failure depended on tissue damage, presumably by MT1-MMP. Blocking MT1-MMP dysregulated collagenolytic activity *in vivo* and prompted a therapeutic effect in both primary and co-infected disease stages/models.

Mutations of type I collagen genes have been identified in osteogenesis imperfecta (OI) [22, 28, 32, 39, 233, 234]. OI dominant-negative mutations can occur in either gene that encode the α chains of type I collagen and are typically missense mutations that change the Gly codons in the triple-helical motifs. Gly substitutions result in different effects on helix stability, depending on their location and the newly substituted amino acid. Mutations near the MMP cleavage site, particularly in the α1(I) chain, often result in severe forms of the disease [235]. This may be due to rendering the cleavage site susceptible to proteases that are normally inhibited by triple-helical structure. We have found that decreasing the thermal stability of the MMP cleavage site renders it more susceptible to MMP-2 and MMP-9 hydrolysis [236].

MMP processing of type I collagen can ultimately result in the production of numerous, distinct fragments (see prior discussion). One fragment resulting from collagenolysis, CO1-764/C1M (Gly-Ser-Pro-Gly-Lys-Asp-Gly-Val-Arg-Gly_{586}; numbering based on the α1(I) chain triple-helical region), is generated by the action of MMP-13, MMP-2, and/or

MMP-9 [237]. It is presumed that a collagenase first cleaves type I collagen at the 775–776 bond (see Table 1), followed by MMP-13, MMP-2, and/or MMP-9 action at the 586–587 bond of the denatured α1(I) chain. CO1-764/C1M was proposed as a biomaker for liver fibrosis [237]. Serum levels of C1M were found to be predictive of increased mortality in women up to 9 years prior to death, while no correlation was observed for a cathpesin K generated type I collagen fragment (CTX-1) and mortality [238]. The most prevalent primary causes of death in the study were cancer and cardiovascular disease [238]. Increased C1M levels in the serum has been associated with chronic inflammation [238], and recent studies have focused on the interrelationships between chronic inflammation and numerous diseases, including cancer and vascular diseases, as well as the role of MMPs in inflammation [11, 194, 239].

The peptide Pro-Gly-Pro is generated by the initial processing of type I or II collagen by neutrophil MMP-8, followed by the proteolytic action of MMP-9 and prolyl endopeptidase [240, 241]. Pro-Gly-Pro is a neutrophil chemoattractant and induces production of superoxide [242]. Pro-Gly-Pro has been implicated in neutrophilic inflammation in lung diseases such as cystic fibrosis and chronic obstructive pulmonary disease (COPD) [240, 242].

6. Summary

The role of specific MMPs in collagenolysis has been better defined through the use of animal models and the correlation of animal studies with human diseases. The processing of collagen by MT1-MMP is now associated with metastasis and progression of tuberculosis and influenza to the lungs. In turn, MMP-13-mediated collagenolysis contributes significantly to osteoarthritis as well as normal bone development, while collagen turnover by MMP-1 is a contributor to wound healing. As we improve our understanding of temporal and spatial collagen processing, along with the knowledge of the specific MMP involved, we will ultimately be able to design more effective treatments for cancer, arthritis, cardiovascular conditions, and infectious diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the National Institutes of Health (CA98799, AR063795, MH078948, and NHLBI contract 268201000036C), the Multiple Sclerosis National Research Institute, the Robert A. Welch Foundation, and the Lustgarten Foundation for support of our laboratory's research on MMPs. We thank Dr. Anna Knapinska for creating Fig. 1.

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Highlights

- Collagenolysis is critical in numerous developmental processes.
- MT1-MMP, MT3-MMP, and MMP-13 contribute to bone development.
- MT1-MMP-mediated collagenolysis facilitates numerous pathologies.
- Collagenolysis generates bioactive peptides.

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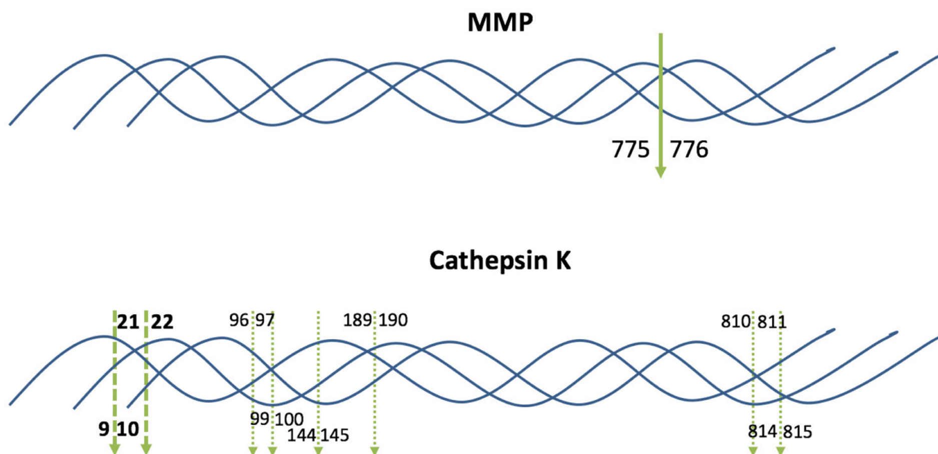

Fig. 1.

Schematic representation of MMP and cathepsin K cleavage sites in type I collagen. The bold, solid green arrow indicates the known MMP cleavage site (bond 775–776) aligned in all three chains in the triple-helix. The bold, dashed green arrows indicate the cathepsin K cleavage sites where all three chains in the triple-helix align (bonds 9–10 and 21–22; see Table 1). The dashed green arrows indicate the cathepsin K cleavage sites in individual collagen chains that do not align within the triple-helix (see Table 1). For cleavage by cathepsin K within individual chains, sites in the α1(I) chain are noted above the triple-helix, while cleavage sites in the α2(I) chain are noted below the triple-helix.

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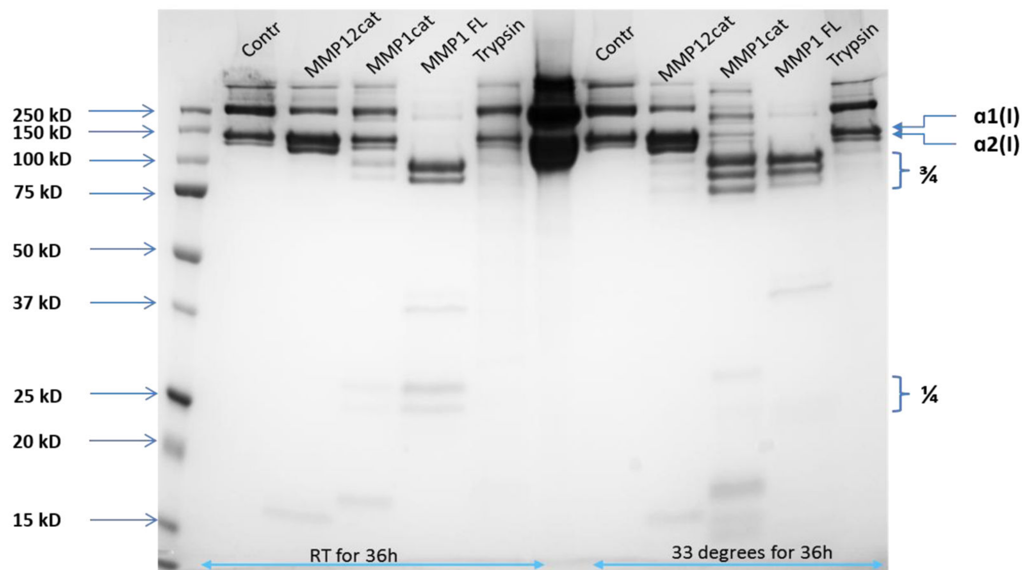

Fig. 2.

Cleavage of type I collagen by MMP-1 CAT domain, full-length MMP-1, MMP-12 CAT domain, and trypsin. Type I collagen (10 μg) was treated with 200 ng of enzyme in 50 mM Tris•HCl, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$, 0.05% Brij35, 1 μM $ZnCl_2$ for 36 h at either room temperature or 33 °C. Full-length MMP-1 (MMP1 FL) cleaved type I collagen at room temperature, resulting in the characteristic ¾ and ¼ fragments, while MMP-1 CAT domain (MMP1cat) showed a low level of hydrolysis and MMP-12 CAT domain (MMP12cat) did not cleave the collagen. At 33 °C, increased hydrolysis by MMP-1 CAT domain and a low level of hydrolysis by MMP-12 CAT domain was observed. Trypsin showed minimal collagen hydrolysis at either temperature. "Contr" is type I collagen alone.

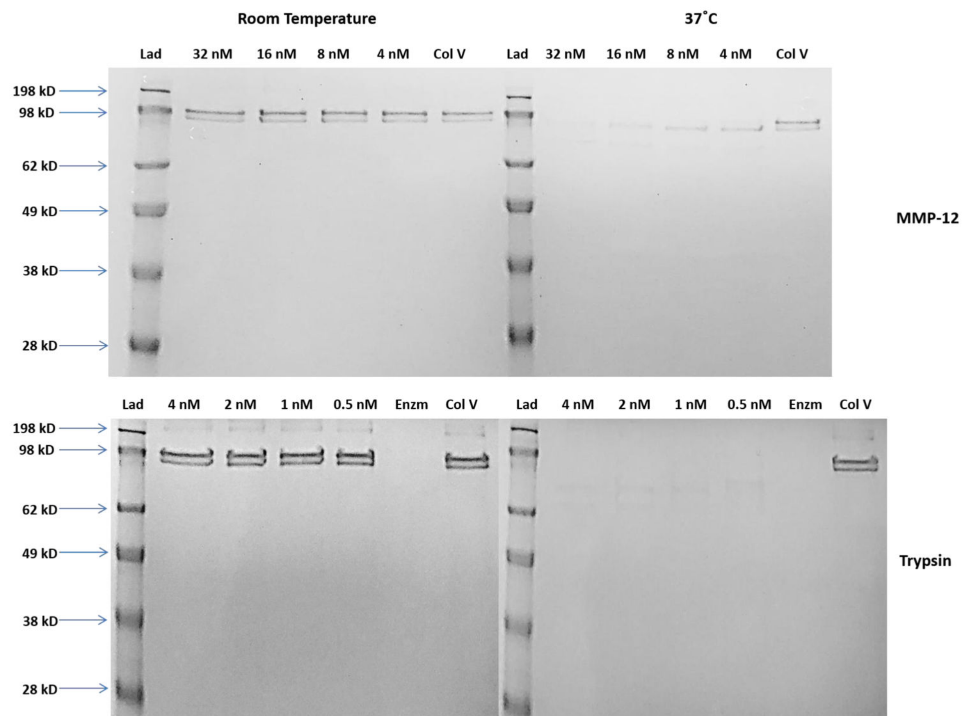

Fig. 3.

Cleavage of type V collagen by MMP-12 CAT domain (top) and trypsin (bottom). Type V collagen (333 nM) was treated with 4–32 nM of MMP-12 or 0.5–4 nM of trypsin in 50 mM Tris•HCl, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$, 0.05% Brij35, 1 μM $ZnCl_2$ overnight at either room temperature (gels on the left) or 37 °C (gels on the right). MMP12 CAT domain or trypsin catalyzed the hydrolysis of type V collagen at 37 °C, but not at room temperature. “Lad” is the molecular weight ladder, “Col V” is type V collagen alone, and “Enzm” is trypsin alone.

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Table 1

Representative MMP and cathepsin K cleavage sites within collagen triple-helical domains.

Enzyme	Collagen Chain (collagen type)	Sequence[a]
MMP-1, -2, -8, -9, -12, -13, MT1-MMP	α1(I)	Pro-Gln-Gly_{775}~Ile_{776}-Ala-Gly
MMP-1, -2, -8, -9, -12, -13, MT1-MMP	α2(I)	Pro-Gln-Gly_{775}~Leu_{776}-Leu-Gly
MMP-1, -8, -13, MT1-MMP	α1(II)	Pro-Gln-Gly_{775}~Leu_{776}-Ala-Gly
MMP-1, -8, -9, -12, -13, MT1-MMP, MT3-MMP	α1(III)	Pro-Leu-Gly_{775}~Ile_{776}-Ala-Gly
MMP-9	α1(V)	Pro-Pro-Gly_{439}~Val_{440}-Val-Gly
MMP-9	α2(V)	Pro-Pro-Gly_{445}~Leu_{446}-Arg-Gly
Cathepsin K	α1(I)	Gly-Pro-Arg_{9}~Gly_{10}-Leu-Pro
Cathepsin K	α1(I)	Gly-Pro-Gln_{21}~Gly_{22}-Phe-Gln
Cathepsin K	α1(I)	Gly-Leu-Asp_{96}~Gly_{97}-Ala-Lys
Cathepsin K	α1(I)	Gly-Pro-Gln_{189}~Gly_{190}-Val-Arg
Cathepsin K	α1(I)	Gly-Pro-Ser_{810}~Gly_{811}-Ala-Ser
Cathepsin K	α2(I)	Gly-Pro-Arg_{9}~Gly_{10}-Pro-Pro
Cathepsin K	α2(I)	Gly-Pro-Gln_{21}~Gly_{22}-Phe-Gln
Cathepsin K	α2(I)	Gly-Leu-Lys_{99}~Gly_{100}-Pro-Gln
Cathepsin K	α2(I)	Gly-Ala-Arg_{144}~Gly_{145}-Ser-Asp
Cathepsin K	α2(I)	Pro-Pro-Gly_{814}~Ala_{815}-Arg-Gly
Cathepsin K	α1(II)	Lys-Pro-Gly_{61}~Lys_{62}-Ser-Gly

[a]Numbering begins at the *N*-terminus of the triple-helical region of each collagen.

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Table 2

Kinetic parameters for human collagen hydrolysis by MMPs.

Collagen type	Enzyme	k_{cat}/K_M ($sec^{-1}M^{-1}$)	K_M (μM)	k_{cat} (sec^{-1})	Assay T (°C)	Reference
I	MMP-1	14,600	0.82	0.012	30	[56]
I	MMP-1	18,750	0.80	0.015	30	[56]
I	MMP-1	525,000	0.9	0.472	37	[243]
I[a]	MMP-1	742,000	0.31	0.23	27	[244]
I[b]	MMP-1	4,740	1.3	0.00617	27	[74]
I[c]	MMP-1	4,610	1.0	0.00461	25	[64]
I[c]	MMP-2	529	8.5	0.00450	25	[64]
I	MMP-8	2,540	0.7	0.00178	25	[63]
I[a]	MMP-8	2,260,000	0.21	0.470	37	[245]
I[b]	MT1-MMP	680	2.9	0.00197	27	[74]
II	MMP-1	132	2.1	0.00028	25	[246]
II	MMP-8	593	1.1	0.00065	25	[63]
III	MMP-1	112,000	1.4	0.157	25	[50]
III	MMP-1	118,000	1.3	0.153	25	[50]
III[d]	MMP-1	93,000	15	1.4	25	[247]
III[e]	MMP-1	59,000	1.3	0.08	25	[52]
III	MMP-8	131	1.8	0.00024	25	[63]
III[d]	MMP-13	22,600	14	0.32	25	[247]
III	MT1-MMP	366	0.95	0.00035	27	[82]
III	MT3-MMP	1,926	0.45	0.00087	27	[82]

[a] Bovine type I collagen.

[b] Guinea pig type I collagen.

[c] Rat type I collagen.

[d] Human type III collagen sequence inserted into bacterial collagen.

[e] Recombinant type III collagen expressed in *P. pastoris*.