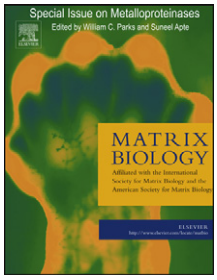
Review



Matrix metalloproteinase interactions with collagen and elastin

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http://dx.doi.org/10.1016/j.matbio.2015.01.005
Edited by W.C. Parks and S. Apte

Abstract

Most abundant in the extracellular matrix are collagens, joined by elastin that confers elastic recoil to the lung, aorta, and skin. These fibrils are highly resistant to proteolysis but can succumb to a minority of the matrix metalloproteinases (MMPs). Considerable inroads to understanding how such MMPs move to the susceptible sites in collagen and then unwind the triple helix of collagen monomers have been gained. The essential role in unwinding of the hemopexin-like domain of interstitial collagenases or the collagen binding domain of gelatinases is highlighted. Elastolysis is also facilitated by the collagen binding domain in the cases of MMP-2 and MMP-9, and remote exosites of the catalytic domain in the case of MMP-12.
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Introduction

Collagens and elastin comprise highly abundant fibrils that are each repetitive in sequence, enriched in polyproline II conformation, cross-linked, insoluble when assembled, and resistant to most proteolytic enzymes. The “monomer” unit of type I collagen comprises two extended α1 chains and one α2 chain twisted together into a triple helix. The detailed structural features of collagen, the many types of collagen, and the supramolecular assembly of the fibrils have been reviewed [1]. Elastin provides the extraordinary, enduring elasticity of the aorta and lung and is integrated with other proteins from the extracellular matrix in elastic fibrils [2–5]. The tropoelastin monomer is boot-shaped and contains the elasticity in the elongated N-terminal coil region [5,6]. The foot-like C-terminal end can bind cells and was proposed to grasp the next monomer in a head-to-tail manner in the extended polymer [5]. Proteolytic fragments of elastin are highly chemotactic and stimulating of inflammation, proliferation, and angiogenesis [7].

Collagenolysis and elastolysis by matrix metalloproteinases (MMPs) occur in development, wound healing, and major inflammatory diseases [7,8]. The MMPs proposed to be elastolytic have been MMP-2, MMP-7, MMP-9, MMP-12, and MT1-MMP, but with MMP-3 and MMP-10 in doubt [4]. Experiments using highly elastolytic human monocyte-derived macrophages (MDMs) asserted MMP-7 to be the principal elastolytic MMP under the very elastolytic conditions when activated by a urokinase-type plasminogen activator pathway [9]. Parallel experiments using the MDMs suggested the unlikelihood of direct elastolysis by MMP-9, and rather that MMP-12 deposited on elastin fibrils is the MMP required for digesting elastin in the absence of plasminogen. The authors proposed that MMP-12 might influence elastolysis indirectly by digesting chemokines and other extracellular proteins [9]. (Chemokines and numerous non-matrix proteins have been identified as physiological substrates of MMP-12 [10–12]). Degradation of interstitial collagen fibrils, e.g., types I and III, to generate the classic 3/4 and 1/4 fragments is catalyzed by MMP-1, MMP-8, MMP-13, MT1-MMP, MT3-MMP, and presumably MT2-MMP [8]. MMP-2 digests *solubilized* monomers of collagens I, II, and III [13–15]. MMP-9 digests solubilized collagen I and III monomers [16]. Mechanistic insights into MMP binding and hydrolysis of fibrillar collagens and elastin are surveyed below. The specific questions considered regard how do MMPs (i) move across collagens to sites for attack, (ii) interact with and

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distort the sites of cleavage in collagen, and (iii) employ multiple sites of interaction to engage elastin?

MMP movements to susceptible sites in collagen

The question of how do MMPs move to their sites of cleavage in collagen has been answered with great insight by biophysical approaches, though some methods do not recognize arrival at the site of cleavage. MMP-2 and MMP-9 randomly diffuse laterally on intact collagen fibrils [17]. Atomic force microscopy visualized MMP-9 diffusion along the MMP-8-generated 3/4 and 1/4 fragments of collagen II, especially the preferred 3/4 fragments, resulting in MMP-9 accumulation at their termini [18]. The MMP-9 first unwound the termini into an expanded, gelatin-like state prior to proteolysis. Bound to collagen this way, MMP-9 itself became more compact with its domains drawing close. The helicase activity of MMP-9 at the termini distinguishes it from MMP-1, 8 and 13 that unwind and cleave collagen internally at the 3/4–1/4 site [18]. Collagen fibrils first cleaved by MMP-1, 8, or 13 may subsequently experience MMP-2 and MMP-9 diffusing across them and then unwinding and digesting the fibrils further [17–19].

The diffusion of MMP-1 and MT1-MMP along collagen is biased into a single direction, requiring the proteolytic activity which “burns bridges” to prevent regress [17,20]. The probability of fibril-bound MMP-1 digesting the collagen (~5% when MMP-1 is active) is largely sufficient to model the diffusion. Inhibition of the collagenolytic activity of MMP-1 or MT1-MMP converts the diffusion on the collagen fibril to mostly bidirectional and random [17,20].

In intact collagen fibrils, MMP-1 cannot reach the vulnerable sites in the collagen monomer, apparently because they are covered by the C-terminal telopeptide [21]. This could account for around 90% of MMP-1 on collagen fibrils being hindered. The paused states are either (i) shorter in duration and non-periodic or (ii) longer-lasting (near 1.1 s) and periodically at 1.3 and 1.5 μm intervals along the fibril [22]. After long pauses, wild-type MMP-1 moved faster and farther than did inactivated MMP-1. The active MMP-1 was propelled in the C-terminal direction along the fibril by the burnt bridges effect [22]. Only 5% of the longer pauses of MMP-1 on the periodic hotspots appear to be productively associated with an average of 13 to 15 irreversible steps of escape, attributed to a rapid succession of proteolysis spaced 67 nm apart [22]. Removal of the collagen C-terminus was proposed to be necessary to expose the scissile bond en route to digestion of the outer layer of monomers in the collagen fibril [21]. The large size of the thermal activation energy for collagenolysis [23] probably includes disruption of the steric obstacle of the collagen C-terminus impeding collagenolysis [22]. Removal of the structural barriers to collagen digestion may be integral to the kinetically hindered, intermittent, and directional behaviors [22].

Association of collagen fibrils with cell surfaces and MMPs was hypothesized to allow cells to move on collagen [20], e.g. keratinocyte migration on collagen [24]. Also fulfilling this hypothesis are the collagenolytic activities of (i) MMP-8 supporting neutrophil migration [25] and (ii) MT1-MMP in developing the full force of cells migrating through 3D collagen-based tissue models [17]. Since all of the components of the MMP-2/TIMP-2/MT1-MMP complexes of cell surfaces diffuse readily on collagen fibrils, their complexes were proposed to support cell movement on collagen, together with integrins and the cytoskeleton [17]. The extended shape and mobility between domains of these MMPs was likened to DNA-binding proteins and restriction enzymes diffusing on DNA [17]. The extreme flexibility between the MMP-9 catalytic and HPX domains was proposed to aid interactions between substrates and cells on the move [26], possibly through inchworm-like extension and retraction between domains [27].

Vulnerability of cleavage sites in fibrillar collagens

Reasons have been sought for collagenolytic MMPs cleaving specifically the 3/4–1/4 locus in interstitial collagen monomers, despite the many non-specific sites of MMP binding imaged [18,28]. The sequences recognized by MMP-1, MMP-8, MMP-13, and MT1-MMP span about 30 residues from P_{13} through P_{17}' positions in the sequences tested [29–33]. The N-terminal side of each cleavage site has tightly wound triple helix rich in the imino acids Pro and Hyp. The C-terminal side of the scissile bond has more loosely wound triple helix that is relatively poor in the imino acids [29]. While pepsin-treated collagen fibrils thermally melt at 42 °C [34], collagen monomers are less stable and melt around body temperature [35]. Less thermally stable segments are found at many positions across the long triple helix [34,36–38] and are attributable to imino-poor sequences [29,37]. Among these destabilized loci, MMP cleavage of the 3/4–1/4 locus could be attributed to burial within the fibril and the proteolytic removal of the C-terminus to expose the 3/4–1/4 site [21], plus MMP preferences that restrict the choices in the collagen sequence [31,39].

The triple helix of monomers of collagens I and III was simulated to undergo localized separation of

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