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Matrix Biology special issue on "Fibroblasts: The arbiters of tissue remodeling" Mini-review: "Extracellular matrix-derived peptides in tissue remodeling and fibrosis"

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Summary

Alterations in the composition of the extracellular matrix (ECM) critically regulate the cellular responses in tissue repair, remodeling, and fibrosis. After injury, proteolytic degradation of ECM generates bioactive ECM fragments, named matricryptins, exposing cryptic sites with actions distinct from the parent molecule. Matricryptins contribute to the regulation of inflammatory, reparative, and fibrogenic cascades through effects on several different cell types both in acute and chronic settings. Fibroblasts play a major role in matricryptin generation not only as the main cellular source of ECM proteins, but also as producers of matrix-degrading proteases. Moreover, several matricryptins exert fibrogenic or reparative actions by modulating fibroblast phenotype and function. This review manuscript focuses on the mechanisms of matricyptin generation in injured and remodeling tissues with an emphasis on fibroblast-matricryptin interactions.

Keywords

Matricryptins; fibroblasts; extracellular matrix; peptides; remodeling; fibrosis

Introduction

The extracellular matrix (ECM) is the non-cellular component present in all tissues and organs. ECM is a highly dynamic 3-dimensional network that acts not only as physical scaffolding for cells but also provides mechanical support and initiates vital biochemical and biomechanical cues required for tissue homeostasis.[1] The ECM is composed mainly of water, proteins and polysaccharides; however, each tissue type has an ECM with a unique

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None.

composition and topology that is generated during tissue development. Independent of tissue type, the ECM is composed of a combination of proteoglycans (such as decorin, aggrecan, and versican), hyaluronan, collagens (fibrillar, network-forming, fibril-associated, and membrane-associated), elastin and elastin-associated proteins (such as fibrillins, fibulins, and EMILIN-1), fibronectin, laminins, and variable amounts of matricellular proteins (such as SPARC/secreted protein acidic and rich in cysteine, osteopontin, periostin, tenascin-C, and thrombospondins) that typically increase following injury.[2] Although all cell types (i.e. epithelial, fibroblasts, immune cells, endothelial cells) synthesize and secrete matrix macromolecules, in most soft connective tissues the bulk of ECM is transcribed and secreted by fibroblasts. Importantly, fibroblasts not only secrete ECM but also control the overall ECM structural organization through their synthetic and mechanical machinery. Thus, fibroblasts are major effectors of tissue mechanical properties.[3] In addition, fibroblasts maintain ECM and participate in ECM turnover by secretion of proteases, most notably members of the matrix metalloproteinase (MMP) family, that degrade the various molecular components.[4] In fact, the ECM is continually being remodeled, either enzymatically or non-enzymatically, under physiologic conditions and most dramatically in pathological settings. After tissue injury, the ECM is dynamically remodeled throughout all phases of wound healing – inflammation, proliferation, and maturation.[5] Alterations in ECM composition play critical roles in the regulation of the cellular responses that mediate tissue healing. In the inflammatory phase of tissue repair, clearance of dead cells and damaged tissue is accomplished by degradation of ECM proteins. This process generates bioactive ECM fragments, named matricryptins, that interact with cell surface receptors, modulating inflammatory, fibrogenic, angiogenic, and reparative cascades.[6]

The term matricryptin was coined in 2000 by Davis and colleagues to describe proteolytically released ECM fragments that contain exposed matricryptic sites.[7] These sites contain a cryptic domain normally not exposed in the intact molecule that renders biological activity. Several years later, Ricard-Blum and colleagues extended the definition of matricryptins to include the ectodomains of membrane collagens and membrane proteoglycans, which are released in the ECM by sheddases, and fragments of ECM-associated enzymes such as lysyl oxidase and MMPs.[8, 9] Matricryptins have biological activities on their own, distinct from the parent molecule, and have been reported to regulate various physiological and pathological processes such as tissue repair, fibrosis, angiogenesis, cancer, and neurodegenerative diseases. Within the literature, the term matrikine is occasionally used interchangeably with matricryptin.[10–12] However, historically these terms describe distinct peptide origin and functions. In 1999, Maquart et al. defined matrikines as ‘ECM-derived peptides able to regulate cell activity’.[13] The term matrikine was independently used by Swindle and colleagues to describe low-affinity ligands for growth factor receptors.[14] Matrikines were defined by these authors as signaling elements that exist as subcomponents of ECM proteins and bind to cell surface receptors that belong to the cytokine, chemokine, ion channel, or growth factor receptor families.[8] Even though distinction between the terms matrikine and matricryptin is sometimes blurred; matricryptin is restricted to describing biologically active ECM fragments that contain exposed functional matricryptic sites that are not normally exposed in the full-length molecules.

Fibroblasts have a major role in matricryptin generation by serving as the main cellular source of ECM and by secreting a wide range of proteases that cleave the matrix and expose the cryptic sites. In injured tissues, fibroblasts not only serve as regulators of ECM remodeling but also represent major targets of matrix fragments. Matricryptins modulate fibroblast function either directly (by transducing signals in fibroblasts) or indirectly (through actions on immune and vascular cells that may modulate fibroblast activation). Thus, matricryptin-mediated actions are implicated in tissue remodeling and fibrosis. This review manuscript discusses the mechanisms of matricryptin generation in injured and remodeling tissues and their cellular actions that may play an important role in regulation of fibroblast phenotype, contributing to reparative and fibrotic responses.

Matricryptin generation during tissue repair

Tissue repair is a complex biological process that entails replacing damaged tissue to restore tissue integrity.[15] The reparative response involves interactions between several different cell types (including platelets, leukocytes, fibroblasts, endothelial cells (ECs), epithelial cells, and organ-specific resident parenchymal cells) and components of the ECM.[16, 17] Since all ECM components are subject to degradation and modification during tissue remodeling, matricryptins are generated throughout all phases of tissue healing and actively participate in regulation of inflammatory, fibrogenic and angiogenic responses by binding to cell surface receptors.

In all tissues, inflammation can be initiated and propagated by ECM disruption. Most types of tissue injury result in rapid activation of proteases, leading to generation and release of matricryptins. Several mechanisms have been reported to regulate the exposure of matricryptic sites within the ECM molecules; those include enzymatic proteolysis, protein multimerization, adsorption, cell-mediated mechanical forces, and denaturation.[7, 18] In addition, reactive oxygen species can also expose cryptic sites as reported for epitopes associated with the autoimmune Goodpasture syndrome.[19] Nonetheless, the primary mechanism of matricryptin generation is by enzymatic cleavage. Two main families of enzymes are responsible for ECM degradation and remodeling [20]: the MMPs and the members of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family. To a lesser extent, serine proteinases such as plasmin and cathepsin G, which are active at neutral pH, can also degrade ECM components extracellularly.[20–22] By proteolytic cleavage, numerous matricryptins are generated with a wide range of sizes and with molecular weight ranging from 269 Da to 85 kDa. To date, the smallest matricryptins reported are made of 3 amino acids (e.g. PGP tripeptide from collagen I, GHK tripeptide from collagen Iα2)[23–25] and the longest is composed of 705 amino acids (endorepellin, a perlecan-derived matricryptin)[26]. A matricryptin may be proteolytically generated by 3 ways: 1) cleavage by a single enzyme; 2) by action of several enzymes acting independently to generate several forms (different sizes) of a matricryptin (e.g. 20, 28, and 30 kDa endostatin-related fragments);[27] or 3) sequentially via a multistep processing.[9] Table 1 lists matricryptins generated in injured tissues by ECM source and decryptive enzyme(s).

The enzymes responsible for decrypting the ECM to generate matricryptins are mainly produced by leukocytes; however, both fibroblasts and ECs can also secrete these enzymes.

Therefore, ECM components can be degraded and remodeled throughout all the phases of wound healing, predominantly during the inflammatory and proliferative phases and to a lower extent during wound maturation. Each stage of repair may be associated with a distinct profile of matricryptin generation, dependent on the predominant proteases, the composition of the ECM, and the level of proteolytic activation of the cell types involved. During the proliferation phase, fibroblasts are the main proliferative cell and display a secretory phenotype to produce high amounts of ECM, particularly collagens, to form a new scar. The formation of the new collagenous scar is a dynamic process with constant remodeling that continues through the maturation phase. In some types of injury, uncontrolled fibroblast activation may lead to prolonged release of matricryptins, causing adverse matrix remodeling and progressive fibrosis.

ECM-derived peptides and tissue remodeling

Following tissue injury, protease-generated matricryptins act as damage-associated molecular patterns (DAMPs) by binding to pattern recognition receptors, such as toll-like receptors (TLRs) in innate immune cells.[28, 29]. Matricryptic ECM-derived fragments can also bind to integrins, growth factor receptors, CD44, purinergic receptors, and other cell-surface proteins, of both resident and infiltrating cells, through which they exert their actions.[30–34]

a. Specific cellular actions of matricryptins

A wide range of ECM proteins, including structural fibrillar proteins, non-fibrillar proteins, matricellular macromolecules, and proteoglycans, can serve as a source of matricryptins, generating fragments that modulate phenotype and function of inflammatory cells, vascular cells, and fibroblasts (Figure 1). While ECM degradation during the inflammatory phase generates matricryptins capable of interacting with leukocytes, as the healing response evolves matricryptins also interact with fibroblasts and ECs.

Collagen type I, as one of the most abundant structural ECM proteins, is cleaved early by MMPs in injured tissues, generating several matricryptins that participate in the inflammatory response. The peptide DGGRYY (collagen Iα1, amino acids 1211 to 1216) binds to the lymphocyte function-associated antigen (LFA)-1 integrin to activate neutrophils and the tripeptide GHK (derived from both collagen Iα2 and the matricellular protein SPARC) is chemotactic for monocytes, macrophages, and mast cells.[24, 25]. Also collagen-derived, the tripeptide PGP was observed in cystic fibrosis patients at levels well above the control group.[23] In that study, the formation of the peptide PGP was reduced by inhibitors specific for MMP-8 and −9, suggesting that both these MMPs are responsible for its generation. In addition, the same study showed that PGP acts as a chemoattractant for neutrophils by binding to CXC chemokine receptors 1 and 2.[23]. The effects of collagen I-derived matricryptins are not limited to actions on immune cells. GHK and the collagen Iα1 C-1158/59 matricryptin have been reported to exert angiogenic properties, thus participating in scar vascularization.[30, 35] In myocardial infarction (MI), C-1158/59 generated both through MMP-2 and MMP-9 actions, has been shown to directly bind to fibroblasts to robustly induce cell migration, while reducing collagen secretion.[30]

Elastin, a polymer of tropoelastin, is characterized by domains rich in lysine and alanine and hydrophobic domains rich in glycine, valine, and proline.[36, 37] Elastolytic enzymes, including aspartic proteases, cysteine proteases, serine proteases, and metalloproteinases, are activated following injury and can generate bioactive fragments with pro-inflammatory properties.[38] Elastin-derived peptides, such as kappa-elastin,[39] have been reported to be chemotactic to monocytes.[39–42] Cleavage of the C-terminus of tropoelastin generates the matricryptin VGVAPG, a fragment with chemotactic properties for both monocytes and fibroblasts.[43–45]. Elastin-derived matricryptins have also been suggested to play an autoregulatory role. The elastin peptide VPGVG reduces elastin transcription and translation, while promoting proliferation of smooth muscle cells.[46] These matricryptin-mediated effects, i.e. simultaneous increase in cell proliferation and reduction of elastin expression, may serve as an important regulatory mechanism by which elastin synthesis is controlled in physiological and pathological conditions. Elastin-derived matricryptins have also been reported to participate in matrix remodeling by affecting protease expression. Elastin matricryptins bind to the elastin binding protein found on the surface of dermal fibroblasts, to promote fibroblast proliferation[47] and induce expression of collagenase-1 via the activation of extracellular signal-regulated kinase (ERK)1/2 in a Ras-independent manner.[48]

Collagen type IV is a major constituent of the basement membrane in all tissues and is composed of six homologous subunits that form 3 separate α-chains: α1α2α1, α3α4α5, and α5α5α6.[49] Collagen type IV has the potential to generate a vast array of bioac` tive peptides during tissue remodeling. So far 6 collagen IV-derived matricryptins have been reported to interact predominantly with fibroblasts and ECs and are known for their anti-tumor functions.[50–53] These peptides are fragments of non-collagenous domains from the α1 (arresten, 26 kDa polypeptide), α2 (canstatin, 24 kDa polypeptide), α3 (tumstatin, 28 kDa polypeptide), α4 (tetrastatin, 20 amino acids), α5 (pentastatin, 2455 Da), and α6 collagen type IV chains (hexastatin, 25 kDa polypeptide).[54, 55] Arresten is an endogenous inhibitor of angiogenesis and functions via integrin (Itg) α1β1.[56, 57] *In vitro* studies show that by binding to Itgα1β1, arresten inhibits angiogenesis by blocking EC proliferation, migration, and tube formation.[58, 59] Canstatin and hexastatin have also been shown to inhibit angiogenesis in tumors by binding to ECs via Itgαvβ1, Itgαvβ3, and Itgαvβ5, possibly by inactivating Akt (protein kinase B) and focal adhesion kinase (FAK) downstream signaling.[60–64] Similarly, tetrastatin also prevents tumor growth possibly via Itgαvβ3 and downstream inhibition of the FAK/PI_3K/Akt pathway.[65, 66] Both canstatin and tumstatin have been shown to target fibroblasts. Specifically, canstatin, which is generated through proteolytic actions of the membrane type (MT) MMPs MT1-MMP and MT2-MMP,[67] has been suggested to modulate fibroblast migration and proliferation, exerting organ-specific actions. In cardiac fibroblasts, canstatin induces fibroblast migration via ERK-mediated actions and subsequent secretion of MMP-2.[68] In contrast, in lung fibroblasts canstatin inhibited migration.[69] Canstatin has also been reported to stimulate myofibroblast proliferation via Akt activation.[70] Moreover, in isolated lung fibroblasts, transforming growth factor (TGF) β-induced fibroblast to myofibroblast conversion was associated with canstatin release.[69] Whether canstatin contributes to myofibroblast phenoconversion, or simply accompanies the overexpression of myofibroblast markers

remains unknown. Tumstatin, generated by MMP-9 cleavage, is mostly known for its anti-angiogenic properties,[71] but also promotes proliferation and migration of cardiac fibroblasts via phosphorylation (Ser473) of Akt.[72]

The peptides generated from MMP9-mediated cleavage of **collagen type XVIII,** termed endostatins, bind to vascular endothelial growth factor (VEGF) receptors (VEGFR-1, −2, and −3) and inhibit angiogenesis.[73] Additionally, the endostatin peptide 4 (E4, 26 monomers long) selectively phosphorylates VEGFR-3 in fibroblasts, activating downstream ERK/mitogen-activated protein kinases (MAPK) signaling.[74]

Fibronectin (Fn) is a ubiquitous glycoprotein synthesized by many cell types. Fn plays key roles in fibroblast migration through interactions involving both its cell-binding and heparin-binding domains.[75] Fibronectin-derived matricryptins have been suggested to regulate phenotype and function of fibroblasts and ECs in healing wounds. The Fn matricryptin anastellin (amino acids 630–704) promotes Fn fibrillogenesis, has anti-angiogenic activity by inhibiting the Ras/ERK pathway, and also binds to platelet-derived growth factor (PDGF)-BB, a major mitogen and survival factor for fibroblasts.[76–79] The peptide PHSRN, derived from plasma Fn, has been proposed to have a major role in acquisition of a migratory phenotype in wound fibroblasts [80], through effects that may involve Itgα5β1.[80, 81]

Fibulin-1 is normally incorporated in fibronectin-containing matrix fibers and is known to play roles in cell adhesion and migration.[82] *In vitro* studies have demonstrated that the fibulin-1 peptide 1 (FBLN1C1), amino acids 567 to 586, enhances pulmonary fibroblast attachment, proliferation, viability, and mitochondrial activity.[83]

The **laminin** family consists of at least 15 large trimeric basement membrane proteins and each is made of α, β, and γ chains.[84] Laminin-1 (α1β1γ1) is one of the best characterized laminins and plays central roles in tumor metastasis, cell spreading and attachment, and angiogenesis.[85, 86] Several synthetic peptides derived from all 3 chains have been shown to have adhesive properties, mainly through the heparin-binding domains;[87, 88]. The profile and potential role of laminin-derived matricryptins in tissue repair and remodeling is not known.

The matricellular protein **tenascin-C**, an important protein in fibrosis and tissue remodeling, harbors a cryptic functional site composed of the amino acid sequence YTITIRGV. Upon decryption by MMP-2,[89] the 22-mer tenascin-C peptide, termed TNIIIA2, activates stromal fibroblasts via Itgβ1.[90, 91]

Under physiologic conditions, **hyaluronic acid** (HA, also known as hyaluronan) exists mainly as a high molecular weight polysaccharide; however, upon injury hyaluronidases hydrolyze the linkage between N-acetyl-glucosamine and glucuronic acid residues to generate low molecular weight fragments.[92, 93] In acute lung injury models and in tumors, HA peptides have been reported to initiate inflammatory responses by activating TLR2- and TLR4-mediated MyD88-dependent signaling.[94, 95] HA oligosaccharides can also target fibroblasts and may modulate their reparative potential and inflammatory activity. In a model of cutaneous wound healing low molecular weight HA (LMWHA) prepared by

γ-irradiation, improved fibroblast survival, promoting repair.[96] In contrast, in synovial fibroblasts 4-mer hyaluronan oligosaccharides stimulated inflammatory activation through TGFβ-activated kinase 1 (TAK1) and p38 MAPK pathways.[97]

The large heparan sulfate proteoglycan **perlecan**, expressed on cell surfaces and within basement membranes, is a well-defined pro-angiogenic molecule in its intact form. However, when processed by cathepsin L during matrix remodeling,[98] the C-terminal 85 kDa fragment of perlecan, endorepellin, has the opposite effect of its parent molecule.[99] Like other anti-angiogenic matricryptins, endorepellin acts through integrin binding. In ECs, endorepellin modulates Itgα2β1-dependent intracellular pathways, reversibly disrupting actin cytoskeleton and focal adhesions of ECs, in a Ca^{2+}-dependent and heparan sulfate-independent manner; thus, inhibiting cell migration.[100, 101] Some of the effects of endorepellin may be mediated through interactions with other matricryptins, such as endostatin.[26] In addition to its effects on vascular cells, endorepellin has also been suggested to modulate fibroblast phenotype. One of the 3 LG domains of endorepellin, LG3, exerts anti-apoptotic effects on fibroblasts.[102] Pathologically, LG3 functions may be important in the pathogenesis of fibrosis by promoting fibroblast survival.

b. Generation and role of matricryptins in fibrotic conditions

Considering their rapid and continuous generation in fibrotic tissues, and their potent effects on phenotype and function of immune cells, vascular cells and fibroblasts, matricryptins may play an important role in the pathogenesis and progression of fibrosis. Moreover, matricryptins may be useful biomarkers, reflecting matrix-degrading activity in many fibrotic conditions.[103]

Extensive associative evidence implicates matricryptins derived from collagens I and V and fibulin-1 in diseases associated with pulmonary fibrosis. Idiopathic interstitial pneumonias, such as usual interstitial pneumonia (UIP) and organizing pneumonia (OP), exhibit early fibrotic lesions that contain small aggregates of myofibroblasts, fibroblasts, and ECM.[104] These early fibrotic lesions are thought to be the initial manifestations of lung fibrogenesis. Urushiyama and colleagues found release of the collagen type IV-derived matricryptin canstatin in the early fibrotic lesions of patients with UIP but not in patients with OP.[69] Canstatin expression in these lesions was predominantly localized in α-smooth muscle actin-expressing myofibroblast-like cells. Although *in vitro* canstatin has been shown to modulate migration and proliferation of lung fibroblasts,[69] the *in vivo* significance of these findings remains unclear.

The collagen I-derived matricryptin PGP has been also implicated in lung fibrosis. PGP levels were reported to directly correlate with disease severity in patients with a wide range of lung conditions, including chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiolitis obliterans syndrome, and acute respiratory distress syndrome.[23, 105–107] Prolonged generation of PGP in experimental models of pulmonary injury may perpetuate neutrophilic inflammation,[108] ultimately inducing fibrotic changes. PGP generates a positive feedback inflammatory signal, triggering neutrophil influx through binding to the chemokine receptors CXCR1 and CXCR2. PGP-mediated neutrophil activation drives the

release of MMP-9 from the neutrophil tertiary granules, which in turn leads to further cleavage of collagen, promotion of fibrosis, and release of additional PGP and subsequent neutrophil influx.[109, 110] While PGP is normally cleared by further enzymatic degradation, it can become stable by chemical acetylation on its N-terminus (Ac-PGP), which functions to enhance its chemotactic potential.[111] Accordingly, there has been increased emphasis on processes that both define the bioavailability of and promote the degradation of the acetylated form of PGP. Recently, O'Reilly and colleagues demonstrated Ac-PGP is degraded through action of the enzyme angiotensin-converting enzyme (ACE) and suggested the ACE pathway is aberrant in COPD, enabling accumulation of Ac-PGP. [111]

Fibulin-1 levels are elevated in the serum and lung tissue from patients with a variety of lung diseases, including idiopathic pulmonary fibrosis (IPF).[112, 113] The fibulin-1-derived matricryptin FBLN1C1 has been suggested to play an important role in the pathogenesis of pulmonary fibrosis. In a mouse model of bleomycin-induced lung fibrosis, genetic FBLN1C depletion protected animals from developing airway and lung remodeling and fibrosis by attenuation of the TGFβ signaling pathway and myofibroblast generation.[114] FBLN1C binds to latent TGFβ–binding protein 1 (LTBP1) to induce TGFβ activation and mediates downstream Smad3 phosphorylation, promoting myofibroblast conversion and collagen deposition. The clinical significance of the animal model findings are supported by evidence showing FBLN1C and LTBP1 colocalization in lung tissues from patients with IPF.[114, 115] Moreover, in fibroblasts harvested from both normal subjects and patients with lung disease (IPF or COPD), FBLN1C1 was found to stimulate fibroblast proliferation, attachment, survival, and ECM deposition.[83]

Other matricryptin-mediated actions inhibit lung fibrosis and may have therapeutic implications. The endostatin-derived peptide E4 attenuated pulmonary and cutaneous fibrosis in a bleomycin model and prevented TGFβ-induced dermal fibrosis both *in vivo* in a mouse model and *ex vivo* in human skin.[116] The antifibrotic actions of endostatin may involve modulation of PDGFR/ERK and RhoA/ROCK signaling pathways.[117, 118]. Matricryptins have also been implicated in cardiac fibrosis. PGP generation in pressure-overloaded hearts was accentuated upon disruption of the matrix-preserving properties of cardiac fibroblasts; additionally, PGP has been suggested to enhance inflammation and promote dysfunction.[115] On the other hand, the collagen I-derived matricryptin C-1158/59 reduced fibrosis in a rodent model of permanent occlusion MI.[30] Consistent with its anti-fibrotic effects in other organs, endostatin was found to inhibit fibrosis in the infarcted heart. In a rat model of MI, endostatin inhibition through administration of a neutralizing antibody worsened interstitial fibrosis, increased mortality, and accentuated cardiac hypertrophy, indicating that endostatin may have protective roles against cardiac remodeling and heart failure after MI.[119]

Conclusions and future directions

The role of the ECM is not limited to structural support of tissues and organs. In injured and remodeling tissues, proteolytic degradation of the matrix generates bioactive fragments with a critical role in regulation of inflammatory, reparative, angiogenic, and fibrogenic

responses. A growing body of descriptive evidence suggests that tissue injury is associated with release of a broad range of matricryptins. *In vitro,* many of these bioactive fragments exhibit potent effects on immune cells, vascular cells, and fibroblasts. Considering their actions on all cells involved in fibrogenesis, matricryptins may be implicated in the pathogenesis of fibrotic conditions. Unfortunately, our understanding of the *in vivo* role of matricryptins in tissue fibrosis remains limited. Systematic proteomic analysis of the profile of matricryptins in fibrotic diseases is lacking. Moreover, robust *in vivo* studies establishing the role of specific bioactive ECM fragments and dissecting their cellular targets remain particularly challenging. The potent antifibrotic effects of certain matricryptins, such as endostatin, highlight that understanding the role of matricryptins in fibrotic conditions may also have therapeutic implications. Unfortunately, clinical evidence supporting the role of matricryptins in progression of fibrotic diseases is limited to associative data. In patients with diabetic renal disease, circulating levels of endostatin were associated with fibrosis and predicted adverse outcome.[120] Moreover, in a small population of patients with acute respiratory distress syndrome, high levels of PGP were associated with worse pulmonary function and worse prognosis.[121] This emerging evidence supports the clinical significance of matricryptins and their potential involvement in human inflammatory and fibrotic diseases.

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Abbreviations:

ACE	angiotensin-converting enzyme
ADAMTS	a disintegrin and metalloproteinase with thrombospondin motifs
Akt	protein kinase B
COPD	chronic obstructive pulmonary disease
EC	endothelial cell
ECM	extracellular matrix
ERK	extracellular signal-regulated kinase
FAK	focal adhesion kinase
Fn	fibronectin
HA	hyaluronic acid
IPF	idiopathic pulmonary fibrosis
ITG	integrin
LTBP1	latent transforming growth factor β–binding protein 1

MAPK	mitogen-activated protein kinases
MI	myocardial infarction
MMP	matrix metalloproteinases
MT-MMP	membrane-type matrix metalloproteinases
OP	organizing pneumonia
PDGF	platelet derived growth factor
PDGFR	platelet derived growth factor receptor
RhoA	ras homolog gene family, member A
ROCK	Rho-associated protein kinase
SPARC	secreted protein acidic and rich in cysteine
TGFβ	transforming growth factor β
TLR	Toll-like receptor
UIP	usual interstitial pneumonia
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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Highlights

- Fibroblasts are essential cells for ECM homeostasis
- ECM proteolytic cleavage generates biologically active peptides named matricryptins
- Matricryptins modulate fibroblast functions
- Matricryptins may be involved in the pathogenesis of fibrotic conditions

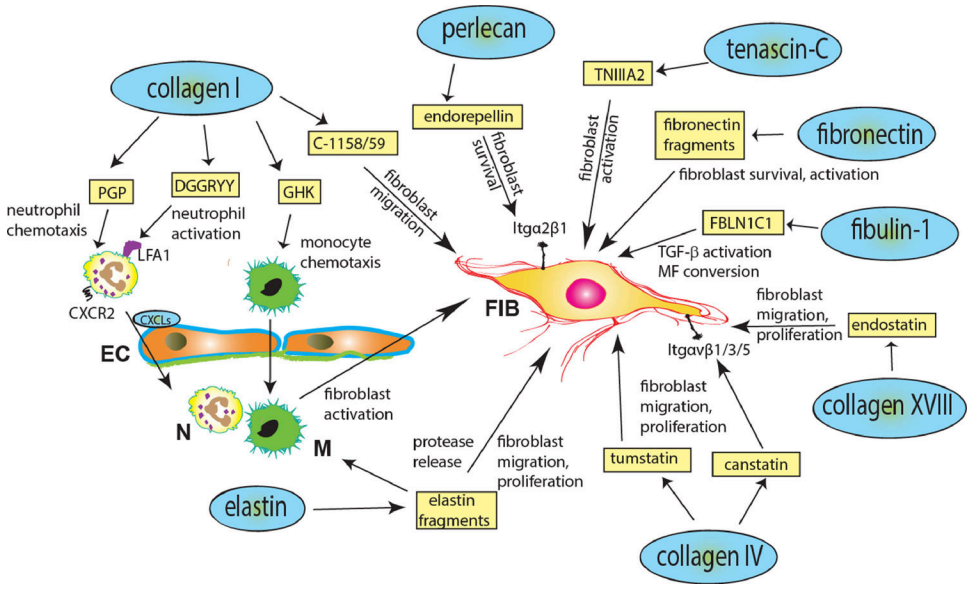

Figure 1.

Effects of matricryptins in tissue fibrosis. Following tissue injury, proteolytic degradation of ECM proteins generates a wide range of matricryptins that may participate in the pathogenesis of fibrosis, either directly, through actions on steady state fibroblasts (FIB), that can become activated and differentiate into a myofibroblast (MF), or indirectly by recruiting or activating inflammatory cells (N, neutrophil; M, monocyte) and endothelial cells (EC).

Table 1 -

List of matricryptins and reported functions.

ECM component	Matricryptin	Decryptive enzyme	Known functions	References
Collagen Iα1	C-1158/59 *	MMP-2, MMP-9	anti-fibrotic, pro-angiogenic	[30]
	DGGRYY	unknown	neutrophil activator	[24, 25]
Collagen I	PGP *	MMP-8, MMP-9, prolyl endopeptidase (serine protease)	chemotactic for neutrophils fibrosis	[23, 105–111,115]
Collagen Iα2, SPARC	GHK	unknown	chemotactic for monocytes, macrophages, and mast cells; pro-angiogenic	[25, 35]
Collagen IV	arresten (IVα1)	MT1-MMP, MT2-MMP	anti-angiogenic	[56–59]
	canstatin (IVα2) *	MT1-MMP, MT2-MMP	promotes MMP-2 expression, fibroblast migration, inhibit myofibroblast contraction, fibrosis	[60–64, 67–70]
	tumstatin (IVα3)	MMP-9	anti-angiogenic, fibroblast proliferation & migration	[71, 72]
	tetrastatin (IVα4)	MT1-MMP (expected)	anti-tumor	[65, 66]
	pentastatin (IVα5)	MT1-MMP (expected)	anti-tumor	[54, 55]
	hexastatin (IVα6)	MT1-MMP (expected)	inhibits EC migration and survival	[60, 64]
Collagen XVIII	endostatin *	MMP-9	anti-angiogenic, anti-fibrotic	[73, 74, 116–119]
Elastin	VGVAPG	MMP-1, MMP-2, MMP-8, MMP-9, MMP-12	chemotactic for monocytes and fibroblasts	[43–45]
	kappa-elastin peptides	aspartic proteases, cysteine proteases, serine proteases, and MMPs	chemotactic for monocytes, promote collagenase-1 expression, induce fibroblast proliferation	[39–42]
Fibronectin	anastellin	cathepsin D and mechanical decryption	fibrillogenesis, anti-angiogenic, and binds to PDGF-BB	[76–79]
	PHSRN	neutrophil elastase	fibroblast migration	[80, 81]
Fibulin-1	fibulin-1 peptide 1 *	unknown	fibroblast attachment, proliferation, and mitochondrial activity, fibrosis	[83, 114, 115]
Hyaluronic acid	LMWHA/oHA	Hyaluronidase 1 and −2	fibroblast migration and pro-inflammatory effects	[92–97]
Perlecan	endorepellin	cathepsin L	anti-angiogenic, fibroblast survival	[26, 99–102]
Tenascin-C	YTITIRGV	MMP-2	activates stromal fibroblasts, promotes invasion and metastasis in colon cancer cells	[89–91]

* represents matricryptins reported to have roles in fibrosis.