Life Sciences 228 (2019) 30–34

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

What is the role of peptide fragments of collagen I and IV in health and disease?

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ARTICLE INFO

Keywords:
Collagen peptide fragments
ECM
Collagen type I
Type III & type IV
Ratio of collagen I:III
Matrikine
Matricryptin

ABSTRACT

Collagen is the most abundant protein in mammalian systems; it can be found in organs such as bones, the liver, kidney, heart, teeth, and skin. Collagen provides the necessary structural framework for tissues in which it is found. However, if there are any alterations in the delicate balance of collagen types in the extracellular matrix (ECM), then problems arise. For example, increasing collagen I:III ratio would provide additional rigidity to tissue structure, whereas decreasing this ratio would provide elasticity and flexibility to the tissue. The proper function of tissues is reliant on this scale not tipping too far in either direction. Major players in the process of ECM remodeling, both normal and adverse, are the fibroblast cells via the secretion of collagen precursors and matrix metalloproteinases, with the latter responsible for ECM degradation. The collagen peptides created by the proteolytic cleavage of these collagen fibrils, while once thought to have an absence of function, have been shown over recent years to potentiate and regulate a variety of cellular processes acting through integrin receptors. Many collagen peptides have been identified from many different collagen types and have been shown to regulate processes such as cell proliferation, migration, apoptosis, and reduce angiogenesis. The collagen peptides of interest are those generated from the primary collagen type of tissue interstitial matrix, collagen type I, and the basement membrane, collagen type IV. Thus, this review looks to highlight some examples of unorthodox functional roles of collagen and its peptides in regulating physiological health and disease.

1. Introduction

Collagen is the most abundant protein found in animals and is the key structural component in the connective tissues of cartilage, tendons, and ligaments, as well as in a multitude of organs such as blood vessels, bones, lung, heart, kidney, liver, teeth, and skin [1]. Within each tissue, the extracellular matrix (ECM) consists of two basic sections: 1) extracellular sheets of the basement membrane that serve to separate both the epithelium and endothelium from the mesenchyme and provide an anchoring point for the epithelium; 2) the complex intertwined network of proteoglycans, glycoproteins, collagens, and elastin of the interstitial matrix [2]. Collagen of the interstitial matrix includes fibrillar collagen types I-III, V, XI, XXIV, and XXVII, while collagen of the basement membrane includes types IV, XV, and XVIII [3–5]. However, each collagen type is not equally distributed throughout the ECM of tissues and organs in which it is found. Although many tissues may contain similar collagen types, the ratios of components in the matrices will differ to complement the unique function and structure of each organ. For example, collagen type I is typically localized to tissues such as tendons, bone, teeth, skin, lung, heart, and the vasculature, while collagen type II is localized to cartilage, and collagen type III forms fibers alongside collagen type I. Although, of the 28 different collagen types, collagen type I is the most abundant in the human body [1,3].

The numerous types of collagen arise from the distinct domains that constitute their individual α-chains, combined with the various combinations of trimeric α-chain associations. Mature collagen's three-dimensional structure of a right-handed super-helix is composed of three individual left-handed α-chains [6]. The primary sequence of each alpha chain typically follows the pattern of Gly-X-Y repeats, with X and Y typically representing proline and hydroxyproline, respectively. The abundance of glycine residues in each α-chain of collagen allows for the close association of the chains while the abundance of proline and hydroxyproline allow for their tight, left-handed twisting and site of association with other ECM components. This region of approximately 338 triplet repeats is referred to as the “collagenous domain” or the

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https://doi.org/10.1016/j.lfs.2019.04.042
Received 14 January 2019; Received in revised form 10 April 2019; Accepted 16 April 2019
Available online 17 April 2019
0024-3205/

"triple helix motif" [5]. Flanking the collagenous domain of the fibrillar α-chains on each side are the N-propeptide and C-propeptide domains on the N-terminus and C-terminus of the chain, respectively. Bioactive fragments of collagen peptides are commonly peptide sequences of the collagenous domain, or the N- and C-propeptide sequences.

There is constant turnover of collagen throughout the human body, especially within the interstitial matrix of tissues. It has been known for over a decade now that myofibroblasts of cardiac connective tissue are local sources of peptides such as angiotensin and endothelin [7,8]. These same peptides are known to stimulate the accumulation of collagen types I and III in the cardiac interstitial matrix via fibroblast and myofibroblast cells, with endothelin-1 even reducing collagenase activity [9]. It was proposed in 1995 by *Weber* et al. that the connective tissue be thought of as metabolically active, capable of regulating peptide hormone composition that then regulates the structure and composition of the interstitial space [10]. Thus, if peptide hormones such as angiotensin peptides can be generated from the "entity" that is the connective tissue, independent of renin, then what other bioactive peptides may be generated? As it turns out, peptides from collagens I and IV of the ECM may contribute to biologically active responses in the surrounding cells. Bioactive fragments of the collagenous domain and of the non-collagenous C- and N-propeptides of collagen have been shown to coordinate processes such as angiogenesis, tissue repair, tumor growth, and tissue development (see abstract schematic figure) [6,11]. Thus, the constant turnover of collagen may play a role in sustaining the proper function of tissues in ways that have otherwise been overlooked.

2. Collagen degradation

Matrix metalloproteinases (MMP) are zinc-dependent proteases responsible for the degradation of extracellular matrix components. With 24 known enzymes in the human MMP family of proteins, the substrate array produced by the degradation of components is widespread [12]. So, it is no surprise that MMPs are involved in physiological roles such as embryonic development, organogenesis, morphogenesis, angiogenesis, wound healing, and tissue remodeling [13,14]. However, this also means MMPs can play significant roles in the development of pathological conditions such as cancer and chronic inflammation [12]. While every component of the ECM, constituents of both the interstitial matrix and basement membrane, can be degraded by MMPs, not every MMP has the same substrate [12]. For example, collagen types I is a substrate for degradation by MMPs -1, -8, -13 (commonly referred to as collagenases), and membrane-type matrix metalloproteinase-1 (MT1-MMP) [15]. These fragment products can then further be degraded by MMPs -2, and -9, commonly referred to as gelatinases [12,15]. While many bioactive peptides are a result from MMP proteolysis of ECM components (Table 1), these same peptides can just as easily be degraded before accumulating to a concentration necessary to elicit a biological response; as is the case with p-1158/59 in the heart interstitial matrix [16]. Regulation of MMP activity can occur at seven different levels: MMP gene transcription, mRNA translation into protein, secretion from cells, correct localization within cells or in the extracellular matrix, MMP activation from their inactive zymogen form, protease inhibition through the presence of tissue inhibitors of metalloproteinases (TIMPs), and degradation of MMPs [17]. A balanced ratio of MMP function to MMP inhibition is necessary for the proper physiological structure and function of the ECM. While it may be beneficial to increase the presence of the bioactive peptide fragments of collagen, shifting the delicate balance of EMC constituents may produce more harm than good if left unchecked. For example, a large increase in the proteolytic activity of MMPs can facilitate the development of volume-overloaded hearts through the diminution of key interstitial collagens (types I and III) [18].

3. Collagen fragments regulate biological activities

Over the past decade, the idea that collagen may play additional roles in tissue physiology greater than simply to provide structural support for the cells in which it is surrounded has increasingly gained recognition. The fragments generated from the degradation of proteins and various molecules of the ECM can be broadly classified as either "natural" matrikines or "cryptic" matrikines (matricryptins) [19]. While the definition of these classes has evolved over time, the definitions recognized in this review are as described by *Tran* et al.: matrikines are ligands, with "naturally" occurring domains within parent constituents of the ECM, that bind to cell surface receptors of the chemokine, cytokine, ion channel, or growth factor families of receptors. Matricryptins, on the other hand, are ligands, with "hidden" or functionally "inactive" domains within parent constituents of the ECM, that become exposed, or "active", once fragmented from their parent molecule [19]. The matrikines and matricryptins that will be discussed below will be those of collagen degradation relating to the primary collagen types of the interstitial matrix and basement membrane of many tissues (types I and IV). For an extensive review of the wide variety of matrikines and matricryptins produced from fragmented constituents of the ECM and their various effects on tissue structure and function, the review published by Ricard-Blum and Vallet [11] would be a beneficial resource.

3.1. Collagen type I fragments

Bioactive fragments of collagen type I include peptides such as proline-glycine-proline (PGP), α1 C-1158/59, and the C-propeptide fragment (Table 1). In 2008, *Gaggar* et al. studied the role of the proline-glycine-proline matrikine during chronic neutrophil inflammation, using cystic fibrosis (CF) as a model [20]. In this study, the authors demonstrated that sputum of CF patients is capable of generating PGP well above (148 ng/mL compared to 1.3 ng/mL, CF vs control) the value found in the sputum of the control group [20]. It was also found that inhibitors specific for MMPs -8 and -9 reduce PGP levels in CF sputum and that PGP acts as a chemoattractant for neutrophils by binding to the cell's CXC chemokine receptors 1 and 2 (receptors responding to the cytokines of the "CXC" family) [20]. While PGP has not yet been studied in the context of its role in cardiac ECM turnover, it would be interesting to see if MMP-9 plays a role with neutrophils in chronic ECM turnover through the production of PGP.

A recent study in 2015 discovered a new MMP-2 and MMP-9 cleavage site 37 amino acids upstream of the c-terminus telopeptide between amino acids 1158 & 1159 of collagen I α1 [16]. Through the use of a 15 amino acid peptide from the cleavage site (amino acids 1159-1173), these same authors demonstrated enhanced wound healing in mouse hearts up to seven days post-myocardial infarction (MI) and suggested c-1158/59 may play a role in stimulating cell migration processes and enhancing fibroblast wound healing [16].

Additionally, the C-propeptide fragment of collagen type I has been shown to be a chemoattractant for endothelial cells. This introduces the potential of this peptide fragment playing a role in vascularization of tissues that express this collagen type [21].

3.2. Collagen type IV fragments

Type IV collagen is a major constituent of the basement membrane that is widespread throughout tissues (only the α1α2α1 trimer of type IV collagen) and self-associates to provide a three-dimensional framework for the structural support of vascular tissue [3,4]. The six homologous α-chains of type IV collagen include an N-terminal 7S domain, a Gly-X-Y collagenous domain, and a C-terminal non-collagenous domain. Three separate α-chain trimers exist for type IV collagen: α1α2α1, α3α4α5, and α5α5α6 [3].

Due to the three separate α-chain trimers that exist for collagen type

IV, formed from α1-α6, collagen type IV degradation can potentially give rise to a vast array of matricryptins and matrikines. However, to date there are only to six known bioactive peptides generated from collagen type IV [3,11]. These peptides are fragments of non-collagenous domains from the α1 (arresten), α2 (canstatin), α3 (tumstatin), α4 (tetrastatin), α5 (pentastatin), and α6 chains (hexastatin). An overview of these collagen fragments and their bioactive influences can be seen in Table 1.

Arresten, the matricryptin of the α1 chain, has been shown to be an inhibitor of angiogenesis in squamous cell carcinoma, binding with α1β1 integrin in endothelial cells [11,22]. This same study noted that carcinoma cells showing overexpression of arresten changed to an endothelial phenotype, suggesting inhibition of migrating carcinoma cells by inducing mesenchymal to endothelial (MET) transition [22]. In another study, arresten content in myocardial tissue was shown to be significantly increased in pigs after mild hypothermic ischemia-reperfusion injury [23]. Additionally, arresten seems to produce anti-angiogenic effects through inhibiting the in vitro and in vivo proteolytic activity of MMP-2 [24].

Canstatin, as stated previously, is formed from the non-collagenous fragment of the α2 chain and has been shown to play a role in epithelial cell proliferation during submandibular gland morphogenesis. Important to note is MT2 of the MT-MMPs is responsible for the production of canstatin peptides which then signal through α3β1 integrin signaling [11,25]. *Rebustini* et al. demonstrated that recombinant canstatin matricryptins (NC1 of α2 chain of collagen IV) were able to rescue epithelial cell morphogenesis and proliferation in submandibular glands that had been treated with MT2-siRNA [25]. Canstatin has also been suggested to enhance fibroblast cell migration via the pathway of stimulating the Rho/Rho-associated protein kinase (Rho/ROCK) pathway, increasing MMP-2 secretion from fibroblasts, which mediates extracellular signal-regulated kinase (ERK) phosphorylation that subsequently induces fibroblast migration [22]. Tumstatin is a matricryptin derived from the NC1 domain of α3 chain in collagen type IV and signals through the α3β1, α6β1, αvβ3, αvβ5 integrins and is produced through MMP-9 proteolysis [11]. T3, a bioactive peptide of tumstatin was shown by *Yasuda* et al. to enhance rat cardiac fibroblast proliferation and migration by binding to αvβ3 and αvβ5 integrin receptors [27]. On the other hand, other studies have demonstrated antiangiogenic regulation associated with tumor growth via the αvβ3 integrin [28,29]. Additionally, tumstatin has been observed to also inhibit angiogenesis through perturbation of VEGF activity in endothelial cells [30].

Tetrastatin is a matricryptin of the α4 chain and has been shown to exert anti-tumor effects through association with the αvβ3 integrin receptor and inhibition of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway [31]. Another study reported inhibitory in vitro migration and proliferation effects of tetrastatin on human melanoma cells coupled with tumor-specific targeting of the peptide, as there was no effect observed on dermal fibroblast proliferation and migration [32].

Pentastatin-1, -2, and -3 are peptide fragments derived from the NC1 domain of the α5 chain of collagen type IV [33] and has been shown to bind to β_1 and β_3 integrins [34,35]. Of these peptides, pentastatin-1 has been implicated in multiple studies to play a role in antiangiogenic effects. For example, concentrations $\geq 40\,\mu g/mL$ showed significant decreases in cell viability (in vitro) of the MD-MBA-231 triple negative breast cancer cell line [36]. Additionally, another study by many of the same researchers showed pentastatin-1 reduced the rate of tumor growth in vivo in a small lung cancer xenograft model [35].

The table above depicts an overview of the various collagen peptide fragments generated from their parent proteins (substrate) and their subsequent biological influences (MMP: matrix metalloproteinase; MET: mesenchymal-endothelial transition; Tissue Distribution: Examples of tissue samples, in vivo or in vitro, in which studies have shown the respective peptide's biological influences).

Similar to canstatin and tumstatin, the NC1 domain of the α6 chain of collagen IV, hexastatin, has been shown to play a role in inhibiting angiogenesis and cell growth in association to tumors [37]. More specifically, a study in 2013 reported that hexastatin was able to inhibit the elastin-dependent migration of mouse choroidal endothelial cells [38]. Whether the NC1 domain of α6 plays a role in the progression or attenuation of pathogenic fibrosis remains to be elucidated.

3.3. Time-sensitive signaling

The time during which the signals induced by collagen peptides are presented will have a great impact on whether the response will be beneficial or detrimental to the tissue in which they reside. Key time frames when observing the function of these peptides would be at time intervals post-MI and during regular cardiac function. Another temporal aspect to consider would be in the time length of exposure to the matricryptins. While some matricryptins may be beneficial immediately post-injury, such as those that promote fibroblast migration [16,26,27], prolonged signaling may reverse the initial beneficial effect and exacerbate the injury. For example, cleavage of α1 chain of collagen I by MMPs -2 and -9 produces endogenous C-1158/59 fragments which has been shown to promote fibroblast migration [16]. Yet MMP-9 at high enough concentrations also degrades the c-1158/59 peptide, inhibiting its potential beneficial effects early on in the wound [16]. However, continuous delivery of p-1158/59 over seven days resulted in earlier and improved scar formation, increased fibroblast migration, attenuation of fibrosis, and preserved left ventricular wall geometry and

Table 1
Bioactive peptides generated from collagen and their biological influences.

Substrate	MMP enzyme	Tissue distribution	Bioactive peptide	Biological influence	References
Collagen type I	MMP-8 MMP-9	Lung endothelium	PGP	Inflammation; neutrophil chemoattractant	[20]
	MMP-2	Heart	C-1158/59	Improved wound healing; cell migration	[16]
	MMP-9	Bone	C-propeptide	Tissue vascularization; endothelial chemoattractant	[21]
Collagen type IV	MMP-2 MMP-9	Epithelial and endothelial tissues	Arresten	Inhibition of angiogenesis; MET transition of cells	[22–24]
	MMP-2	Heart, epithelial tissue of submandibular gland	Canstatin	Epithelial cell proliferation; fibroblast migration	[25,26]
	MMP-9	Heart, endothelium of vasculature	Tumstatin	Antiangiogenic effects; fibroblast proliferation and migration	[27–30]
	MMP-2 MMP-9	Dermal tissue	Tetrastatin	Anti-tumor migration effects	[31,32]
	MMP-2 MMP-9	Breast and lung tissue	Pentastatin-1	Antiangiogenic effects	[33–36]
	MMP-2 MMP-9	Eye, endothelium of vasculature	Hexastatin	Antiangiogenic and antimigratory effects	[37,38]

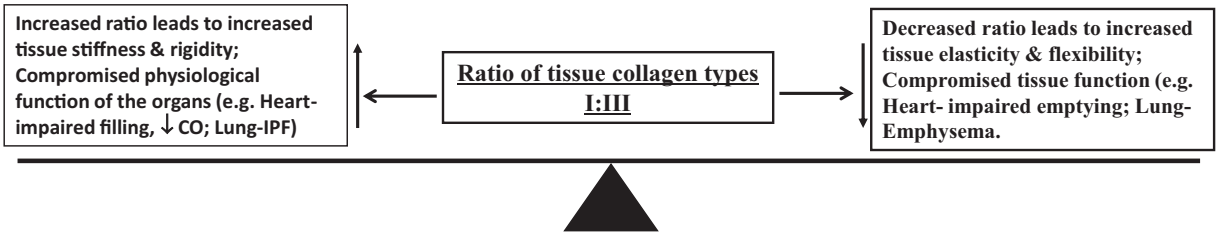

Fig. 1. Schematic depicting the delicate balance of the collagen I:III ratio in tissues. Both either increase in ratio or decrease in ratio of types I:III collagen have adverse effects on the organ function, particularly on the normal functions of heart and lung. (CO: cardiac output; IPF: Idiopathic pulmonary fibrosis; Upward arrow: increased ratio; Downward arrow: decreased ratio).

thickness [16]. This shows time dependence of the exposure to the matricryptin C-1158/59 of collagen type I α1.

4. Discussion and conclusion

Collagen is a necessary component for proper tissue structure and function. For example, the tensile strength and elasticity of the cardiac connective tissue provide resistance to excessive chamber filling as well as absorption and release of energy to aid in proper cardiac muscle contraction [39]. However, each collagen type is not created equal. Each collagen type contains a different combination of three α-chains, forming either a heterotrimeric or homotrimeric triple helix [4,5]. With variance in domains of each collagen α-chain, degradation through MMPs of different collagen types will result in a variety of fragmented products, with each product potentially eliciting a unique cellular response.

A peptide fragment of collagen type I, p-1158/59, has been found to attenuate fibrosis and enlargement of the left ventricular wall of the heart in mice [16]. This shows the therapeutic potential not only in the exogenous application of peptide fragments, but also in the potential for targeting the MMPs involved in the degradation of collagen to produce endogenous forms of these peptides [14]. For example, although MMP-9 was shown to produce c-1158/59 fragments, it also degrades that same fragment. Only until roughly seven days post-MI would the c-1158/59 peptide achieve its signaling potential, when concentrations of MMP-9 significantly decline [16]. Additionally, other collagen peptides such as arresten, canstatin, tumstatin, tetrastatin, and NC1-α6 have been shown to have potential signaling roles in processes such as mesenchymal-endothelial transition (MET) [22], inhibition of certain MMPs [24], endothelial cell proliferation [11,25], fibroblast proliferation and migration [26,27], and angiogenesis [33].

While there has not been much literature describing the potential activities of peptides produced from collagen III fragments, studies have suggested that the collagen I/III ratio is crucial to the functional integrity of various tissues [40,41]. Either through increasing the ratio, from the increase in collagen I content, or through decreasing the ratio, from the degradation of collagen type I or the synthesis of collagen type III, the strength of the connective tissue may be altered to the point of causing problems (Fig. 1). For example, a study has shown that a decrease in the ratio of collagen type I/III, by way of an increase in collagen type III content, plays a role in the development of incisional hernias [42]. Additionally, studies have shown that an increase in the collagen I/III ratio may play a role in the stiffening of the heart that subsequently leads to cardiomyopathy [43,44]. This is due to the different properties of types I and III collagen that arise from their different structures. Collagen type I composes strong, rigid fibrils, while collagen type III fibrils are regarded as immature, weak, and elastic [45]. Thus, through the manipulation of the type I/III ratio, increased degradation of type I collagen or increased deposition of type III collagen could be useful in combating excess rigidity of the interstitial matrix in tissues. Not only this, but endogenous bioactive peptides would also be released to aid in facilitating the various functions found in Table 1. However, depending on the tissue, either increasing or decreasing the collagen type I/III ratio may cause more harm than good. For example, an increased deposition of collagen type III has been linked to an increased risk of developing colonic diverticulosis [46]. So, although a clinical route toward the improved healing of wounds and concomitant stabilization of tissue function is through the activation of certain MMPs to produce endogenous collagen I peptide fragments, the collagen ratios found within tissues is sensitive, and needs to be delicately maintained.

The wound healing process of tissues involves a wide range of factors, cells, and moieties that communicate and regulate one another to produce the response to injury, whether physiological or pathological. Some strategies in combating excessive fibrosis involve the general degradation of the ECM through treatment with exogenous collagenases [47]. However, this also has the potential of targeting important ECM collagens that preserve structural support for tissues [47]. Other strategies involve utilizing mesenchymal stem cells (MSCs) for the regeneration of tissue and attenuation of abnormal accumulation of ECM components [48]. However, due to the infancy of the field of regenerative medicine, risks associated with stem cell therapies are still prominent. These risks include unwanted in vivo differentiation, immune responses, use of immune suppressors in therapies, or the irreversibility of the treatment [49]. Utilizing bioactive collagen fragments to manipulate cellular processes bypasses many of these risks associated with cellular therapies. Thus, bioactive ECM fragments as clinical therapeutics is a promising field of study. However, there is still information lacking regarding the specific fragment sequences that can be generated, as well as their potential effects on tissue structure-function. Also, if therapies opt for the route of MMP manipulation, excessive degradation of ECM collagens is as severe a problem as excessive accumulation of ECM collagens, and the delicate balance of collagen types in tissues needs to be maintained if the collagen peptide therapy is to procure benefits.

Conflict of interest

There are no competing interests.

Acknowledgements

The authors wish to thank Madaniah Zakari for her input during discussions.

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