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Published in:
Essays in biochemistry

DOI:
10.1042/EBC20180051

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 16-09-2023
Review Article

Collagen cross-linking mediated by lysyl hydroxylase 2: an enzymatic battlefield to combat fibrosis

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The hallmark of fibrosis is an excessive accumulation of collagen, ultimately leading to organ failure. It has become evident that the deposited collagen also exhibits qualitative modifications. A marked modification is the increased cross-linking, leading to a stabilization of the collagen network and limiting fibrosis reversibility. Not only the level of cross-linking is increased, but also the composition of cross-linking is altered: an increase is seen in hydroxallysine-derived cross-links at the expense of allysine cross-links. This results in irreversible fibrosis, as collagen cross-linked by hydroxallysine is more difficult to degrade. Hydroxallysine is derived from a hydroxylysine in the telopeptides of collagen. The expression of lysyl hydroxylase (LH) 2 (LH2), the enzyme responsible for the formation of telopeptidyl hydroxlysine, is universally up-regulated in fibrosis. It is expected that inhibition of this enzyme will lead to reversible fibrosis without interfering with the normal repair process. In this review, we discuss the molecular basis of collagen modifications and cross-linking, with an emphasis on LH2-mediated hydroxallysine cross-links, and their implications for the pathogenesis and treatment of fibrosis.

Introduction

It is estimated that fibroproliferative diseases are at the heart of more than one third of all deaths in developed countries [1,2]. So far, there is no effective treatment option that halts or even reverses fibrosis. Thus, there is an urgent need to develop effective therapies, preferably those that can be used in a variety of organs. The hallmark of organ fibrosis is an excessive accumulation of extracellular matrix (ECM), with the fibrillar collagen type I as the most abundant matrix protein. This pathological collagen accumulation ultimately leads to organ failure and subsequent death. So far, relatively little attention has been paid to develop drugs that target the matrix itself, which is remarkable, as the matrix is prominently involved in disease progression [3–7].

Collagen type I is the major constituent of the fibrotic ECM. However, it is not just the quantity of collagen that defines fibrosis. The quality of the collagen, as determined by its post-translational modifications, actively drives the disease progression. Biosynthesis of collagen is a multistep process [8], resulting in modifications throughout the molecule, such as the conversion of proline into hydroxyproline, and the conversion of lysine (Lys) into hydroxlysine (Hyl). The precursor procollagen is secreted out of the cell, its propeptides are cleaved off, and the resulting collagen molecules spontaneously segregate into well-ordered structures (fibrils) in which they are stabilized by means of intermolecular cross-links mediated by lysyl oxidase (LOX) transglutaminase (TG).

Pharmacological therapies have focused on compounds that suppress fibrosis by reduction of disease progression (suppression of inflammation, cell migration, cell proliferation, cell differentiation, viral/bacterial/parasite infections) and on drugs that suppress collagen accumulation [5]. The latter group
Lysyl hydroxylation of collagen

Fibrillar collagens consist of a triple helical domain, flanked by telopeptides at both the N- and C-terminal end of the molecule (N-telopeptide and C-telopeptide, respectively). Hydroxylation of Lys occurs both in the triple helix and the telopeptides by the enzyme LH [9]. Only the Lys in the helical sequence Gly-X-Lys is modified; a Lys in the helical sequence Gly-Lys-Y is not hydroxylated. In the last two decades, it has become clear that separate enzymes mediate lysyl hydroxylation of the triple helix and the telopeptides, which makes sense, as the primary sequence in which the hydroxylated telopeptidyl Lys is embedded is entirely different [10]. Three LHS (LH1, lysyl hydroxylase 2 (LH2) and LH3) have been discovered, which are encoded by PLOD1, PLOD2 and PLOD3, respectively. The abbreviation PLOD is derived from procollagen-lysine, 2-oxoglutarate 5-dioxygenase (which is the systematic name of LH), while the 1, 2 and 3 indicates the sequence of discovery. LH1 and LH3 exclusively hydroxylate certain Lys residues in the triple helix (helical LHs), where LH2 exclusively hydroxylates the Lys in the telopeptides (hence the name telopeptide LH) [9,10]. In addition, LH3 displays hydroxylsyl galactosyltransferase and galactosylhydroxylysyl glucosyltransferase activities, leading to the formation of glycosylated Hyl residues [9,10].

Collagen cross-linking by lysyl oxidase

Enzymatic collagen cross-linking by means of LOXs is a final step in the biosynthesis of collagen and essential for the physical and mechanical properties of collagen fibrils [11,12]. The formation of these cross-links starts with the oxidative deamination of the ε-amino group of specific Lys or Hyl residues within the C- and N-terminal telopeptides by a family of five LOXs (LOX and LOX-like 1-4 (LOXL1-4)), leading to the formation of the aldehydes allysine (ε-aminoacidipic acid-δ-semialdehyde = Lysald) and hydroxyallysine ( = hydroxy-ε-aminoacidipic acid-δ-semialdehyde = Hylald). The reactive aldehyde condensates either with another aldehyde in the same molecule or with Lys, Hyl or histidine (His) residues in neighboring collagen molecules, in order to form intra- and/or intermolecular cross-links. Collagen cross-links can be divided into two classes: (i) cross-links formed via the Lysald pathway (i.e. derived from a Lys in the telopeptide) and (ii) cross-links formed via the Hylald pathway (i.e. derived from a Hyl in the telopeptide) [13,14]. The relative abundance of the two cross-link pathways varies from tissue to tissue, depending on the hydroxylation state of the telopeptide Lys. For example, collagen deposited in skin and cornea is mainly cross-linked via the Lysald pathway with almost no Hylald cross-links present in these tissues [15,16]. In bone, cartilage, tendon, dentin and ligaments, collagen cross-links mainly derive from the Hylald pathway [15]. The Lysald route gives rise to divalent and tetravalent cross-links (recently, it has been proposed that the reported trivalent cross-link histidinohydroxylysinoorleucine is a laboratory artifact [17]), whereas the Hylald route gives rise to divalent and trivalent cross-links [13,14] (Figure 1).

The reactive telopeptide Hylald can pair with a helical Lys or a helical Hyl to form divalent cross-links. These divalent cross-links further mature either into the respective lysylpyridinoline (LP) or hydroxylysylpyridinoline (HP) cross-links or into the respective deoxypyrrrolic (d-PRL) and pyrrrolic (PRL) cross-links. The trivalent pyridinoline and pyrrrolic cross-links differ with respect to the hydroxylation state of the second telopeptide Lys residue. HP and LP cross-links are derived from two telopeptide Hylald residues and a helical Hyl or Lys residue, respectively, whereas...
Figure 1. Schematic representation of cross-links derived from the allysine (Lys\(^{\text{ald}}\)) and hydroxallysine (Hyl\(^{\text{ald}}\)) pathway

Amino acids from the telopeptide and the triple helix are marked in green and blue, respectively, enzymes are marked in red, whereas the cross-links are shown in white boxes. The Lys in the telopeptides can be converted into Hyl by lysyl hydroxylase 2 (LH2). The Lys and Hyl in the telopeptides can be converted into the aldehydes Lys\(^{\text{ald}}\) and Hyl\(^{\text{ald}}\) by lysyl oxidase (LOX) and/or LOX-like 1-4 (LOXL). The next step for Lys\(^{\text{ald}}\) is the reaction with another Lys\(^{\text{ald}}\) from the telopeptides to form an aldol condensation product (ACP), or to react with a Lys or Hyl from the triple helix. The reaction with a Lys or Hyl results in the divalent cross-link dehydro-lysino-5-keto-norleucine (deH-LNL) and dehydro-hydroxylysino-5-keto-norleucine (deH-HLNL), respectively, whereas the ACP reacts with a His and finally with a Hyl in the triple helix, leading to the tetravalent cross-link dehydro-histidino-5-keto-merodesmosine (deH-HHMD). The first step for the Hyl\(^{\text{ald}}\) is the reaction with a Lys or a Hyl in the triple helix. The resulting divalent iminium cross-links deH-HLNL and dehydro-dihydroxylysino-5-keto-norleucine (deH-DHLNL) undergo a spontaneous Amadori rearrangement, leading to the more stable divalent keto-imines lysino-5-keto-norleucine (LKNL) and hydroxylysino-5-keto-norleucine (HLKNL), respectively. The keto-amines finally react with either a Lys\(^{\text{ald}}\) or a Hyl\(^{\text{ald}}\) from the telopeptides, resulting in the trivalent pyrrolic cross-links (d-PRL = deoxypyrrole; PRL = pyrrole) or trivalent pyridinoline cross-links (HP, hydroxylsypyrrolidine; LP, lysylpyridinoline).

Pyrrolic cross-links are derived from a telopeptide Hyl\(^{\text{ald}}\), a telopeptide Lys\(^{\text{ald}}\), and a helical Lys or Hyl residue (deoxy-pyrrole or pyrrole, respectively) [13,14].

Fibrotic tissues show increase Hyl\(^{\text{ald}}\) cross-link levels

In wound healing of the skin, such as in hypertrophic scarring, large amounts of Hyl\(^{\text{ald}}\) cross-links are present [18–23]. A predominance of such cross-links is also found in collagen that is produced in the damaged corneal stroma; the resulting scar shows markedly increased levels of Hyl\(^{\text{ald}}\) derived cross-links at the expense of Lys\(^{\text{ald}}\) cross-links [24]. The pioneering studies on elevated Hyl\(^{\text{ald}}\) derived cross-links in abnormal scarring were later confirmed [25–29], followed by reports on increased Hyl\(^{\text{ald}}\) derived cross-links in other fibrotic disorders, such as various lung diseases (respiratory distress syndrome, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, respiratory bronchiolitis, silicosis and bleomycin-induced lung fibrosis) [30–39], chronic adriamycin nephropathy (an experimental model resulting in non-immunologic glomerulosclerosis and interstitial fibrosis) [40], infarct scar of the myocardium [41,42], joint contractures [43], vessel luminal narrowing [44]; lipodermatosclerosis [45,46], annulo-aortic ectasia [47], fibrotic lesions of Dupuytren’s disease [48], skin of patients with lipid proteinosis [49], diabetes [50,51], skin fibrosis...
due to chromoblastomycosis infection [52,53], skeletal muscle abnormalities [54–56], systemic sclerosis [57], uterine fibroids [58], vein graft disease [59] and various liver diseases such as in alveolar echinococcosis (a dense and irreversible fibrosis), hepatocellular carcinoma, alcoholic cirrhosis or cirrhotic livers induced by CCl4, viral hepatitis or by *Schistosoma mansoni* [60–69].

The presence or absence of LH2 regulates the abundance of Hylald cross-links. In recent years, it has been suggested that the relative (and absolute) amount of Hylald cross-links are adequate biomarkers for the accumulation of pathological collagen in lung and liver fibrosis [30,32–35,37–39,61–63]. As the same is observed in other fibrotic tissues including skin and kidney, it was actually stated that "It is possible that organ fibrosis is a unique process ultimately associated with a change in cross-linking whereby the proportion of the allysine cross-links decreases in favor of the hydroxyallysine-derived crosslinks" [45]. Thus, Hylald cross-links are implicated in the pathogenesis of fibrosis.

**Telopeptide LH exhibits two splice variants**

The abundance of data on elevated Hylald cross-link levels in fibrotic tissues strongly support an up-regulation of telopeptidyl lysyl hydroxylation in fibrotic lesions, which is indeed the case. *PLOD2* encodes two different splice variants, LH2a and LH2b (LH2b contains an extra insert, encoded by exon 13A). LH2b is expressed in a wide variety of tissues and organs, including bone, cartilage and skin, whereas LH2a is only present in the frontal lobe, spleen, kidney, liver and placenta [70–72]. Overexpression of LH2a and LH2b revealed that only LH2b hydroxylates the telopeptides, as overexpression of LH2a does not induce pyridinoline cross-link formation *in vitro* [72], a conclusion that is confirmed by a Bruck syndrome type 2 patient that only expresses LH2a [73]. The inability of LH2a to induce pyridinoline cross-links together with increased levels of LH2b in fibrotic tissues suggests that LH2b is the likely culprit in pathogenic collagen cross-linking [74]. Meanwhile, the exact functions of LH2a remain unclear.

**TG-mediated cross-links in fibrosis**

The other enzymatically mediated cross-link in collagen is catalyzed by TGs. TGs comprise a family of isozymes that catalyze the formation of covalent bonds between glutamine and Lys in a variety of proteins [75,76]. Increasing the level of γ-glutamyl-ε-lysine cross-links by adding TG to collagen *in vitro*, makes collagen more resistant toward proteinases [77–79]. It is widely believed that TG promotes fibrosis by increasing the number of TG cross-links in collagen [79–84]. However, not a single report quantitatively measured the level of TG cross-links per collagen molecule. Apart from that, TG is far from being specific for collagen, as many other substrates have been identified [85,86]. The only data supporting the hypothesis is the increased staining in fibrotic tissue with an antibody toward TG or TG-mediated cross-links. Paradoxically, this increase always correlates with increased collagen levels. Hence, it is very well possible that the number of TG cross-links in normal and fibrotic collagen molecules is the same. That would be in sharp contrast with Hylald cross-links: there is an abundance of data demonstrating elevated Hylald cross-links in collagen molecules from fibrotic tissues. Although inhibition of TG can result in an attenuation of fibrosis [76–84], this cannot automatically be attributed to a higher degradability of collagen, as TG is involved in many other intracellular and extracellular processes, often in a transamidase-independent manner [75,76]. In fact, studies in TG2 knockout mice showed that TG2 deficiency had no measurable effect on the stability of the fibrotic ECM (e.g. solubility of collagen toward pepsin) or in reversibility of hepatic fibrosis *in vivo* in two hepatotoxin-induced models [87]. Thus, *in vivo* collagen degradability and irreversibility does not seem to be regulated by TG2. Therefore, the concept that TG cross-links are elevated in fibrotic collagen molecules probably needs to be revisited [87,88]. In contrast, inhibition of LOX-mediated collagen cross-linking results in a higher solubility of collagen toward pepsin, and enhances spontaneous fibrosis reversal [89,90].

**Collagen containing Lysald or Hylald cross-links show different degradation profiles**

An important aspect of fibrosis is the problem of irreversibility of collagen deposition. Remarkably, the effects of the type of cross-links on the susceptibility of collagen to proteolytic enzymes has hardly been investigated, despite the fact that the presence of Hylald cross-links is indicative for irreversible collagen deposition.

It is generally accepted that an increase in LOX derived collagen cross-links results in a higher resistance toward collagenases [91]. An increase of ∼0.1 LOX-mediated cross-link per collagen molecule already results in a 2-3-fold resistance to human collagenase compared with uncross-linked collagen [92]. In fibrosis, we see an increase in the number of Hylald and Lysald cross-links, due to higher LOX activity. In addition, lysyl hydroxylation levels of the telopeptides are increased, which automatically means that the ratio of Hylald and Lysald cross-links is changed, in...
Figure 2. Position of the cross-links derived from the allysine and hydroxyallysine pathway in collagen type I

(A) Collagen molecules are packed in a quarter-staggered array in fibrils. Shown are the positions of the cross-links between the N- and C-terminal telopeptides with the triple helix of collagen. The cleavage site of MMP1 (between residue 775 and 776) is opposite the position of the cross-links of an adjacent staggered molecule; the presence of Hylαd crosslinks inhibits cleavage of the peptide bond between 775 and 776 by MMP1. The residues involved in cross-linking is as follows: the α1(9N) residue from the N-telopeptide (or the 5N residue from the α2 chain) reacts with either the α1(930) or the α2(933) residue from the triple helix. The α1(16C) residue from the C-telopeptide reacts with the α1(87) or α2(87) residue from the triple helix; there is no Lys or Hyl present in the C-telopeptide of the α2 chain. (B) Structure of the deH−HLNL and the HP cross-link; the position shown is the N-telopeptide. Note that deH−HLNL can be formed between α1(telo) and α1(helix) (shown in the figure), but also between the α1(telo) and α2(helix), or between α2(telo) and α1(helix) or α2(helix). (C) Structure of the hydroxylysylpyridinoline (HP) cross-link; the position shown is the N-telopeptide. As is the case with figure B, several combinations of α1 and α2 are possible.

In favor of Hylαd. Thus, in fibrosis, we not only see an increase in cross-links, but also a shift in the type of cross-link. A variety of profibrotic cytokines up-regulates both collagen and the three LHs. Interestingly, LH2 levels are increased far more than collagen itself, thus changing the ratio between LH2 and collagen [93,94]. This may explain the increase of Hylαd cross-links at the expense of Lysαd cross-links.

Collagen cross-linked through Hylαd is much more difficult to degrade by matrix metalloproteinases (MMPs) than collagen cross-linked by Lysαd [95,96]. The same goes for degradation by non-MMPs, such as pepsin [96]. Indeed, collagen in Bruck syndrome bone lacking Hylαd cross-links is easily released by pepsin, and these patients present highly osteoporotic bone due to high degradation rates in vivo [97]. In long bones with high levels of Hylαd cross-links, osteoclasts use cathepsin K to degrade collagen, whereas in the calvaria, with low Hylαd cross-links, osteoclasts use MMPs to degrade collagen [96]. The most probable reason for this observation is that cathepsin K cleaves Hylαd cross-linked collagen more efficiently than MMPs do, as cathepsin K cleaves collagen at multiple sites [98]. In contrast, MMP1 cleaves collagen only between amino acids 775 and 776, which is sterically in the vicinity of the cross-link sites when collagen molecules are packed into fibrils (Figure 2). In cartilage, collagen type II shows the highest Hylαd level seen of all fibrillar collagens, and this collagen is hardly degraded (it has an estimated half-life of >100 years) [99]. The
pathological degradation of collagen type II in osteoarthritis is mainly caused by MMP13 [100,101], which is, as is the case with cathepsin K, able to cleave collagen at more than one position [102]. Finally, in HIF prolyl hydroxylase-2 (PHD2)-deficient mice that have a higher Hylald level of collagen type II compared with wild-type mice, the collagen was less susceptible toward MMPs [103]. Taken together, these findings indicate that collagen containing increased Hylald cross-links is more difficult to degrade.

**Reversibility of fibrosis is hampered by Hylald cross-links**

The resistance of Hylald cross-linked collagen toward degradation by proteinases is an important feature of irreversible collagen accumulation in fibrosis. In fact, Hylald cross-link levels might be an important criterion in assessing the irreversibility of fibrosis. The validity of this hypothesis is strengthened by cross-link patterns seen in self-limiting and progressive forms of fibrosis. Collagen produced in response to an injury of skin is initially stabilized by dehydro-dihydroxylsinosinonorleucine [18–22], a cross-link derived from Hylald. In the early stages of wound healing, the collagen of both forms of fibrosis possess dehydro-dihydroxylsinosinonorleucine as the major cross-link type, but after a few months there is an approximately equal proportion of Lys ald cross-links. Subsequently, self-limiting and progressive fibrosis follow a different course. In hypertrophic scars, a progressive form of skin fibrosis, the 1:1 ratio of the two cross-links is retained. In contrast, the cross-link pattern in the self-limiting form of fibrosis gradually reverts to normal, i.e. there is a virtual disappearance of Hylald cross-links and replacement by Lys ald cross-links [20,22,23].

In another set-up, the authors found that osteoarthritis-related fibrosis induced by connective tissue growth factor (CTGF) did not result in increased Hylald cross-links, and was transient in nature [104,105]. A bleomycin-induced skin fibrosis model was also transient in nature [95,106], and also this model did not show an increase in Hylald cross-links [95]. In contrast, transforming growth factor (TGFP-β1) induces persistent osteoarthritis-related fibrosis, which coincides with increased Hylald cross-link levels [104,105]. This is in agreement with the observation that the tissue level of pyridinoline correlates to the severity and reversibility of the fibrotic process, where the highest level is found in irreversible fibrosis [53,61–63].

**Inhibition of LH 2 to ameliorate fibrosis**

The reduced proteolytic turnover of Hylald cross-linked collagen explains, at least in part, the irreversibility of collagen deposition. This resistance toward proteolytic enzymes is most probably caused by a changed packing of collagen molecules within the fibrils. Indeed, the type of cross-links dictate the mode of packing of collagen molecules within the fibrils [107–110]. Altogether, the above mentioned data indicate that the type of cross-links provide a mechanism for the regulation of the rate of collagen catabolism: collagen with Hylald cross-links are less susceptible to proteolytic degradation than collagen cross-linked by Lys ald residues. Thus, inhibition of LH2 (to enhance the formation of Lys ald cross-links at the expense of Hylald cross-links) is an attractive strategy to attenuate fibrosis. Since the up-regulation of LH2 is seen in all organs, a drug that specifically inhibits LH2 activity can be used in a wide range of fibrotic disorders. Furthermore, since LH2 catalyzes only a single reaction downstream in the fibrogenic cascade (namely the formation of unwanted cross-links in collagen of the fibrotic lesions), little (if any) side-effects are expected, as the deposited collagen in the wound area is expected to be normally modified, and thus have the properties (e.g. with respect to tensile strength) required for a normal function of the repaired tissue. In addition, the collagens that normally contain Hylald cross-links, such as in tendons, ligaments, bone and cartilage, show a half-life of several years to several decades [111–113]. It is, therefore, unlikely that treatments that even span several months will significantly affect such tissues.

The improved comprehension of the pathogenesis of fibrogenesis in relation to Hylald cross-linking opens the way to develop novel therapies. Unfortunately, no specific inhibitors for LH2 currently exist. In order to be active, LH2 needs to form homodimers. Remarkably, mutations in the gene FKBP10, encoding the immunophilin FKBP65, gives rise to Bruck syndrome type 1, which shows the same biochemical defect as Bruck syndrome type 2 (in which LH2 is mutated), namely a lack of Hylald cross-links in bone [114]. Recently, we found that the mutated FKBP65 prevents the formation of LH2 homodimers [115]. Thus, inhibiting FKBP65 activity is a tool to inhibit LH2 activity, albeit indirectly. Interestingly, inhibition of FKBP65 results in less fibrosis [116,117]. The availability of a 3D model of human LH2 [118] based on the crystal structure of human LH3 [119], might accelerate rational drug design. Equally important, the recent development of a high-throughput assay to measure LH activity enabled a screen of 65000 compounds, identifying ~30 possible LH2 inhibitors [120]. Thus, steps are currently taken to develop specific anti-fibrotic agents that can slow down or arrest fibrogenesis, or even reverse its progression, by giving matrix-degrading enzymes the opportunity to break down the scars. Interestingly, it has recently been shown that fibrosis also plays an important role in regulating the hallmark features of cancer [121]. Thus, inhibiting the formation of Hylald cross-links may also have potential therapeutic value in the field of cancer biology.
Summary

- A common denominator of fibrotic collagen is an increased level of Hylald cross-links in favor of Lysald cross-links, resulting in collagen that show a high resistance toward MMPs, and as a consequence inhibiting resolution of fibrosis.

- LH2 is responsible for the conversion of Lys into Hyl in the telopeptides of collagen, leading to the formation of Hylald cross-links by LOXs.

- Normalizing the cross-link pattern by selectively inhibiting LH2 (and thus Hylald cross-linking) alters the balance of collagen degradation; it is expected that this results in reversible fibrosis.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Author Contribution

B.P. and R.B. wrote the manuscript and designed the figures.

Abbreviations

ECM, extracellular matrix; FKBP, FK506-binding protein; HP, hydroxylysylpyridinoline; Hyl, hydroxylysine; Hylald, hydroxyallysine; LH, lysyl hydroxylase; LH2, lysyl hydroxylase 2; LP, lysylpyridinoline; LOX, lysyl oxidase; LOXL, LOX-like; Lys, lysine; Lysald, allysine; MMP, matrix metalloproteinase; PLOD, procollagen-lysine, 2-oxoglutarate 5-dioxygenase; TG, transglutaminase.

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Iredale, J.P. and Pellicoro, A. (2011) “It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast: it keeps him young” (Konrad Lorenz, 1903-1989).


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