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REVIEW

Post-translational modifications of collagen and its related diseases in metabolic pathways

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Abstract As the most abundant and essential structural protein in the human body, collagen is ubiquitously present in the interstitium of nearly all solid organs, playing a crucial role in maintaining the structural integrity and functional stability of human tissues and organs. Disorders associated with collagen structure and metabolisms impose a significant burden on society and healthcare systems. Post-translational modifications (PTMs) are essential steps in collagen metabolism, and recent studies have indicated that aberrant regulation of PTMs plays a pivotal role in the pathogenesis and progress of collagen-related disorders, including liver, kidney, heart, lung, and skin fibrosis, as well as keloid. This review provides a comprehensive summary of the regulatory mechanisms of both traditional and novel PTMs in collagen metabolism and collagen-related diseases. Furthermore, we summarize the drugs that modulate PTMs and their effects, with the aim of elucidating the pathophysiology of collagen-related diseases and provide new insights for their diagnosis, prevention, and treatment.

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1. Introduction

As a highly abundant protein in the human body, collagen constitutes one-third of the total protein content and three-quarters of the skin's dry weight. Being the most abundant protein in the extracellular matrix (ECM)[1], collagen possesses unique molecular structures and a fibrous arrangement, which play a pivotal role in the formation of the extracellular scaffold. As a result, collagen serves as the primary structural component in all connective tissues and is ubiquitously present in the interstitial tissues of nearly all solid organs. The presence of collagen significantly contributes to the stability of tissues and organs, thereby ensuring the maintenance of their structural integrity[2]. The biosynthesis of collagen requires a series of complex regulatory mechanisms. Researchers have increasingly discovered close links between collagen and many diseases. Collagen is associated with diseases of the cardiovascular system, respiratory system, musculoskeletal system, immune system, skin, and tumors. Therefore, in-depth research into collagen metabolism and its related disease mechanisms is of paramount importance[3].

In addition to the diversity in the primary peptide sequences encoded by genes, selective splicing of proteins and extensive post-translational modifications (PTMs) substantially contribute to the structural and functional diversity of the cellular proteome[4]. PTMs refer to the process by which specific chemical groups are covalently attached to amino acid side chains through enzymatic or non-enzymatic chemical reactions[5]. The most extensively studied and frequently observed PTMs include enzyme-catalyzed phosphorylation, acetylation, methylation, glycosylation, as well as non-enzymatic glycation and nitrosylation[6]. PTMs can also consist of independent peptides or protein domains that are linked through isopeptide bonds. In addition to classical ubiquitination and SUMOylation, modifications by ubiquitin-like molecules are also garnering increasing attention[7]. In recent years, several novel PTMs have been identified, including butyrylation[8], succinylation[9], and lactylation[10], among others, which have been demonstrated to play distinct and crucial physiological and pathological roles in the human body. PTMs can directly or indirectly modulate cellular metabolism and function by regulating protein functionality, thereby contributing to the pathogenesis of various diseases.

The abnormality of collagen structure and metabolism can cause a variety of diseases and affect human health. The regulation of collagen metabolism involves a variety of complex and interacting signaling pathways[11-14]. The collagen synthesis process of its own PTMs includes hydroxylation, glycosylation, oxidative deamination, and covalent cross-linking. These abnormalities of PTMs can lead to collagen abnormalities and diseases[15]. In addition, numerous studies on molecules in collagen metabolism-related signaling pathways such as TGF-β/Smad[11], PI3K/AKT[16], MAPK[13], JAK/STAT[14], NF-κB[17], etc. have found that PTMs may play an important role in the physiological and pathological processes of collagen-related diseases by regulating other molecules in the upstream and downstream pathways of collagen metabolism. Thus, investigating the functional roles of PTMs in diseases is advantageous for developing innovative strategies for the effective prevention and treatment of collagen-related disorders.

In this review, we introduce the structure, synthesis, and PTMs involved in collagen. We have systematically summarized the PTMs in the relevant pathways influencing collagen metabolism, including classical phosphorylation, acetylation, ubiquitination, SUMOylation, methylation, *S*-nitrosylation, carbonylation, and *S*-glutathionylation. Emerging PTMs such as crotonylation, lactylation, succinylation, propionylation, butyrylation, β-hydroxybutyrylation, and 2-hydroxyisobutyrylation are also encompassed in this review. Moreover, we summarize the regulatory effects of drugs on these PTMs and their influence on collagen metabolism, and highlight the latest research advances in various therapeutic strategies targeting collagens for precision medicine.

2. Collagen and collagen-related disorders

2.1. *Structure of collagen*

The collagen superfamily currently comprises 28 proteins, each containing at least one triple-helical structure domain. Each triple-helical structure domain consists of three peptide chains. These three parallel peptide chains intertwine in a left-handed, polyproline type II helical conformation, forming a single-residue staggered right-handed triple helix[2,18]. This helical structure confers collagen with high tensile strength and stability within tissues. Collagen is primarily composed of amino acids, with proline, hydroxyproline, and glycine being predominant. Its characteristic amino acid sequence (Gly−X−Y) is frequently repeated in the fibrous structure, where Gly represents a glycine residue, X commonly denotes a proline residue, and Y commonly denotes a 4-hydroxyproline residue[19]. The most common collagen protein in the human body is collagen I, primarily distributed in tissues such as skin, bone, tendon, blood vessels, and cornea. It is composed of a heterotrimer consisting of two identical α1 (I) chains [COL1α1 (I)] and one α2 (I) chain [COL1α2(I)][20]. Collagen II protein is next in abundance and is primarily found in cartilage tissue, composed of three identical α1 chains. Collagen III is a homotrimer composed of three α1 (III) chains and is widely distributed in tissues containing collagen I, except for bone. It is a significant component of reticular fibers in tissues such as the lungs, liver, dermis, spleen, and vascular stroma. Collagen V and XI are heterotrimers formed by three different alpha chains (α1, α2, α3). Collagens I, II, III, V, XI, XXIV, and XXVII are referred to as fibril-forming collagens. They are characterized by their ability to assemble into highly organized supramolecular aggregates with characteristic suprastructure. Collagens IV, VI, VIII, and X are categorized as network-forming collagens. Collagens IX, XII, XIV, XVI, XIX, XX, XXI, XXII, and XXVI belong to the fibril-associated collagens with interrupted triple helices. The characteristic feature of these collagens is the presence of "collagenous domains" interrupted by short non-helical domains, and their trimeric molecules are associated with the surfaces of various fibrils. In addition, there are membrane-associated collagens with interrupted triple helices including collagens XIII, XVII, XXIII, and XXV, as well as multiple triple-helix domains and interruptions (MULTIPLEXINs) including collagens XV and XVIII. The structural differences among different types of collagen proteins enable them to fulfill specific physiological functions and tissue requirements, exerting distinct functions within the human body.

2.2. *Synthesis of collagen*

Collagen is synthesized by fibroblasts. The genes encoding collagen α chains are transcribed into RNA within the endoplasmic reticulum of fibroblasts and translated into peptide chains,

referred to as pre-α chains. Portions of peptide segments at the N- and C-termini of the peptide chain are termed propeptides[21].

After removal of the signal peptide by signal peptidase, the pro-collagen molecule undergoes several post-translational modification steps. Prolyl 3-hydroxylase, prolyl 4-hydroxylase, and lysyl hydroxylase catalyze the hydroxylation of proline residues and lysine residues. Galactosyltransferase and glucosyltransferase catalyze the transfer of galactose and glucose moieties onto the hydroxyl groups of hydroxylysine, completing glycosylation[1]. The formation of the triple helix is initiated by the binding of the C-termini of the three independent peptide chains through disulfide bonds, progressing from the C-terminus to the N-terminus in a zipper-like manner. Through this process, the α chains assemble into pro-collagen molecules, with the non-helical coil of propeptides retained at both ends[22]. Subsequently, pro-collagen is transferred to the Golgi apparatus, where it undergoes further glycosylation and is transported extracellularly *via* vesicular transport pathways. The propeptides of pro-collagen are cleaved, and the molecule is assembled into mature collagen. The N- and C-propeptides of pro-collagen are then cleaved by a group of metalloproteinases belonging to a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) and bone morphogenetic protein 1/tolloids-like proteinases, releasing mature collagen molecules. The mature collagen molecules undergo cross-linking extracellularly, where extensive covalent intermolecular cross-linking confers stability, forming collagen fibrils with mechanical functionality[23]. The complex and ordered structure of collagen endow it with the ability to provide structural support and strength within animal bodies, which is crucial for maintaining tissue health and elasticity.

Collagen synthesis and degradation represent dynamic equilibrium processes involving multiple signaling pathways. The metabolism of collagen is regulated by signaling pathways such as TGF-β/Smad, PI3K/AKT, MAPK, Wnt, NF-κB, integrin, and JAK/STAT. Some studies have shown that ion channels and cytokines also play regulatory roles in collagen metabolism. The regulation of collagen by TGF-β is the most important and involves several mechanisms: stimulating collagen mRNA expression, regulating collagen gene expression at the transcription level; inhibiting the secretion of collagenases and other metalloproteinases, and stimulating the expression of metalloproteinase inhibitors, thereby inhibiting collagen degradation; enhancing proline hydroxylation within fibroblasts, stabilizing the procollagen molecules; inhibiting lysosomal products, suppressing intracellular procollagen degradation; indirectly regulating collagen expression through autocrine signaling. Signaling molecules may act as common factors for multiple pathways or may activate or inhibit the transduction of other signaling pathways. As a result, these pathways are not mutually independent but intricately intertwined, mutually influencing one another, and collectively mediating the process of collagen metabolism (Fig. 1).

2.3. *Collagen-related disorders*

The metabolic processes of collagen synthesis and degradation play an important role in normal physiological processes and diseases, in which PTMs plays a crucial role. PTMs necessary for

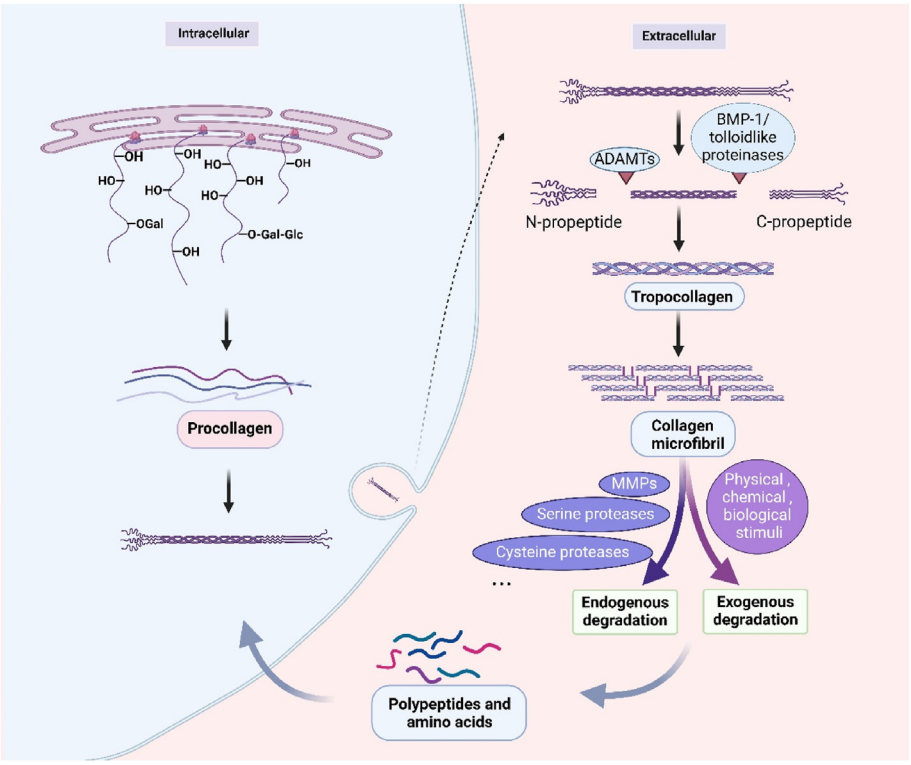


Figure 1 Collagen metabolism. The pro-α chains are synthesized on ribosomes in the rough endoplasmic reticulum, where certain proline and lysine residues undergo hydroxylation and glycosylation. Subsequently, they assemble into a triple helical structure, forming procollagen. It then moves to the extracellular space, where it is cleaved by specific proteinases to form tropocollagen. Tropocollagen undergoes covalent cross-linking to form stable collagen fibrils. After endogenous and exogenous degradation, it is decomposed into peptides and amino acids.

collagen synthesis, such as hydroxylation, glycosylation, oxidative deamination and intermolecular crosslinking, or PTMs of other relevant molecules in collagen metabolic pathway, all have important physiological and pathological effects and are closely related to the occurrence of many diseases.

Collagen plays a very important role in the repair of bones, tendons, and ligaments. In recent years, some cutting-edge studies have found that the abnormal expression of types I, II[24], and X[25] collagen is closely related to the fibrosis of cartilage and synovium in osteoarthritis, indicating that collagen is closely related to the occurrence and development of musculoskeletal system diseases such as osteoarthritis[26]. Studies have shown that PTMs can affect cruciate ligament repair[27], growth plate cartilage development[28], and osteoporosis[29] by regulating molecules in the collagen metabolic pathway. Collagen is also involved in the growth and healing process of skin, and PTMs involve scar formation of collagen fibril and the formation of fiber tissue[30]. Studies have shown that PTMs abnormalities of molecules in many pathways affect the formation of keloids[31,32] and skin fibrosis[33].

When PTMs changes in collagen metabolic pathway cause abnormal activation of fibroblasts, collagen synthesis is abundant, resulting in excessive accumulation of fiber and insufficient degradation. At the same time, the overall composition of the extracellular matrix, especially the changes in the relative content of various types of collagens, plays a central role in the process of fibrosis[34]. The above factors can cause fibrosis of various organs and tissues such as liver[35], heart[36], kidney[37], and lung[38], and damage the normal function of the affected organs.

In addition, collagen is a major component of the tumor microenvironment and is involved in cancer fibrosis. A growing body of evidence suggests that, in addition to being a structural element, collagen is an important source of nutrients as well as a decisive growth control and immune regulatory signal. Cancer cells regulate collagen biosynthesis through transcription factors, signaling pathways, and receptors. On the contrary, PTMs changes in collagen itself and its metabolic pathway can affect the behavior of tumor cells and regulate their growth and invasion through integrins, disk domain receptors, tyrosine kinase receptors and some signaling pathways[39]. In addition, other studies have suggested that abnormalities of collagen metabolic pathway PTMs are closely related to epithelial-mesenchymal transition (EMT)[40], and that EMT is significantly associated with fibrosis and tumor development[41], suggesting that collagen and PTMs in its metabolic pathway affect tumor occurrence and development through multiple mechanisms.

3. Post-translational modifications during collagen synthesis

3.1. Intracellular modifications of collagen

3.1.1. Hydroxylation of proline and lysine

The hydroxylation of proline is catalyzed by collagen prolyl 4-hydroxylases (C-P4Hs) and prolyl 3-hydroxylases. The minimal sequence for C-P4Hs reaction with Pro is −X−Pro−gly−, while for the latter, it is −Pro−4Hyp−gly−[15]. Proline hydroxylation can regulate the flexibility of collagen molecules and provide functional sites for interacting proteins and receptors.

4-Hydroxyproline is the primary form of hydroxyproline, providing hydrogen bonds and water bridges, enhancing the stability of the triple helix structure, and influencing the formation of collagen fibrils[15]. There is regulatory linkage between hypoxia and metabolic pathways with proline hydroxylation of collagen. A study on endochondral ossification suggests that hypoxia and activation of the hypoxia-inducible factor 1 (HIF-1) induce metabolic changes, thereby regulating the hydroxylation of proline and lysine residues on collagen proteins, resulting in the accumulation of collagen matrix[42]. Additionally, the gene for the C-P4H α subunit itself is a target of HIF-1, and studies have shown that hypoxia-induced C-P4Hs are necessary to maintain normal collagen production levels in hypoxic chondrocytes[43,44]. Therefore, C-P4H-related mechanisms may play important roles in the pathogenesis of human diseases such as fibrosis and cancer.

3-Hydroxyproline residues are relatively less abundant in collagen, but inactivation mutations of prolyl 3-hydroxylase 1 can lead to severe autosomal recessive osteogenesis imperfecta, a genetic bone disorder primarily caused by mutations in the genes encoding collagen I[45]. Therefore, 3-hydroxyproline in collagen plays a crucial role in physiological and pathological processes, yet many of its biological functions remain unknown.

Biochemical analysis indicates that, compared to prolyl hydroxylation, the degree of lysine hydroxylation in collagen proteins is highly variable. Approximately 50% of proline residues in collagen are hydroxylated across various genetic types of collagens found in different tissues. However, the extent of lysine hydroxylation can vary depending on the type of collagen, ranging from 15% to 90%[46]. Lysyl hydroxylase (LH; EC 1.14.11.4) catalyzes the hydroxylation of lysine residues[47]. Mutations in the genes encoding lysyl hydroxylase can lead to abnormal levels of lysine hydroxylation in collagen, resulting in Ehlers−Danlos syndrome type VIA[48], Bruck syndrome type 2[49], and several congenital connective tissue disorders and nutritional deficiency bullous epidermolysis.

3.1.2. Glycosylation of hydroxylysine

In collagen proteins, some hydroxylated lysine residues within the helical domains undergo further modification through O-linked glycosylation, resulting in galactosyl hydroxylysine and glucosyl galactosyl hydroxylysine. These modifications are catalyzed by galactosyltransferase (GT; EC 2.4.1.50) and glucosyltransferase (GGT; EC 2.4.1.66), respectively[50]. Structural analysis of glucosyl galactosyl hydroxylysine reveals that galactose is linked to the hydroxyl group of hydroxylysine *via* a β-glycosidic bond, while glucose is linked to the C-2 of the galactose moiety *via* an α-glycosidic bond[51].

The extent of glycosylation in collagen proteins varies among different types of collagens. Fibrillar collagens such as collagen I and collagen II exhibit only minor glycosylation residues[15,52], whereas the glycosylation of network-forming collagens like collagen IV is more extensive[53].

Studies have shown that glycosylation affects the interaction of collagen with integrins $\alpha2\beta1$, $\alpha3\beta1$[54], as well as CD44[55]. Hyl glycosylation also participates in oligomerization through the collagen domain[56]. Some studies suggested that abnormalities in collagen glycosylation may be associated with the onset of diseases. *COLGALT1* gene mutations were found in two children with manifestations of cerebral small vessel anomalies and brain perforating malformations[57]. These mutations may lead to abnormal secretion of collagen IV, thus resembling the phenotype of collagen IV diseases[58]. Collagen glycosylation may also be associated with autoimmune diseases. In a mouse model of collagen-induced arthritis, comparing the arthritogenic effects of unmodified collagen with hydroxylated and glycosylated collagen confirmed the enhanced role of lysyl hydroxylation and glycosylation in eliciting immune responses to collagen[59].

3.2. Extracellular modifications of collagen

3.2.1. Oxidative deamination of lysine and hydroxylysine by LOX

The procollagen molecule is secreted into the extracellular space, where during the process of fiber formation, specific lysine and hydroxylysine residues in the N- and C-terminal peptides are oxidatively deaminated by lysyl oxidase (LOX). These reactive aldehydes spontaneously form covalent intramolecular and intermolecular cross-links with other aldehydes or lysine and hydroxylysine residues' ϵ-amino groups in collagen and elastin proteins. This is the first step in the development of final cross-linking reactions in collagen proteins and is crucial for tissue stability[60].

Previous studies have indicated that the LOX family not only plays a role in cross-linking collagen but also has diverse biological functions, including involvement in tissue development and regeneration, inhibition of tumors or promotion of metastasis, and participation in fibrotic processes. The enhanced synthesis and deposition of collagen during cardiac fibrosis following myocardial injury may be associated with increased expression and activity of LOX and LOXL2, followed by enhanced collagen cross-linking[61,62]. In Ehlers−Danlos and Bruck syndrome, alterations in the cross-linking process mediated by LOX affect the formation of bone structure[63]. The development and metastasis of cancer are associated with the tumor microenvironment, where LOX can influence the ECM, thereby impacting tumor initiation and progression. Previous studies have identified the functional role of LOX in breast cancer, colorectal cancer, prostate cancer, gastric cancer, pancreatic cancer, head and neck squamous cell carcinoma, renal clear cell carcinoma, melanoma, oral and pharyngeal squamous cell carcinoma, as well as basal and squamous cell skin carcinomas[64].

3.2.2. Covalent intra- and inter-molecular cross-linking

The final step in the biosynthesis of collagen I is the formation of covalent cross-links, which are crucial for its biomechanical function. After the initial intra- and inter-molecular cross-linking mediated by LOX, further multivalent cross-links occur involving additional amino acid residues, including peptidyl lysines[65].

The formation of cross-links is associated with a series of post-translational modifications of collagen preceding it. Since cross-linking is initiated by the formation of aldehydes in the telopeptides catalyzed by LOX (possibly LOXLs), the expression and activity of LOX are critical for controlling the quantity of cross-links. The degree of lysine hydroxylation in the N-terminal or C-terminal telopeptides and adjacent triple helical domains is a key determinant, hence the level and activity of lysyl hydroxylase isoenzymes are crucial for controlling the quality of cross-links[50].

4. Post-translational modifications in collagen-related disorders

4.1. Phosphorylation

Protein phosphorylation (P) is the most abundant and common PTM in humans. It primarily occurs on serine (Ser; S), threonine (Thr; T), and tyrosine (Tyr; Y) residues, occasionally also on histidine (His; H) and lysine (Lys; K) residues[66]. Protein phosphorylation and dephosphorylation are catalyzed by kinases and phosphatases, respectively. Phosphorylation is involved in regulating important physiological processes such as cell cycle control, growth signal response, extracellular matrix regulation, cell migration, and plays a crucial role in collagen and related diseases.

4.1.1. TGF-β/Smad signaling pathway

The transforming growth factor-beta (TGF-β) pathway regulates cell proliferation, differentiation, and apoptosis in organisms. In mammals, three isoforms exist: TGF-β1, TGF-β2, and TGF-β3[11]. Smad proteins transmit TGF-β signals from the cell membrane to the nucleus. They are categorized as Receptor-regulated Smads (R-Smads, including Smad1, 2, 3, 5, and 8), Co-Smad (Smad4), and Inhibitory Smads (I-Smads, Smad6 and 7). Upon TGF-β binding, receptors phosphorylate R-Smads, which then form a complex with Smad4 and enter the nucleus to regulate gene transcription, promoting connective tissue growth factor and collagen mRNA synthesis. Overexpression of TGF-β leads to tissue fibrosis due to increased collagen deposition. I-Smads block signal transduction, maintaining pathway balance[67].

Research shows that fisetin inhibit Smad3 phosphorylation induced by TGF-β1, leading to reduced synthesis of collagen and α-SMA, and alleviating renal fibrosis[37]. The activity of Smad3 is regulated by phosphorylation of its ligand (MH1) and MH2 domains. Smad3-EPSM mutants mutated four phosphorylation sites in the junction region, significantly enhancing TGF-β1-induced EMT deficits[68]. Furthermore, research has found that phosphorylation of T388 in the Smad3 MH2 domain is also an important mechanism regulating the TGF-β/Smad3 signaling pathway promoting renal fibrosis[69]. In a study on pulmonary fibrosis, pan-phosphodiesterase inhibitors were found to alleviate TGF-β-induced fibrotic phenotype in lung alveolar type II epithelial cells by downregulating Smad-2 phosphorylation, reducing the expression of fibrosis markers such as collagen I[70]. Similar mechanisms have been observed in liver fibrosis, where propolin G and TF-SC were found to protect the liver from fibrosis by eliminating TGF-β-induced Smad2/3 phosphorylation[35,71]. The important role of Smad phosphorylation has also been discovered in collagen overproduction-related skin diseases such as keloids and scleroderma[33]. Previous studies have shown that overexpression of DKK3[31] or gene knockout of elF3a[32], IRF3[72], NLRC5[73], FOXM1[74] can downregulate the phosphorylation levels of Smad2 and Smad3, inhibit fibroblast proliferation, and suppress collagen synthesis. Furthermore, Smad7, acting as a negative feedback regulator, plays a role in keloids. Overexpression of TIEG1 in keloids can downregulate Smad7 expression, thereby promoting Smad2 phosphorylation, contributing to the development of keloids[75] (Fig. 2A).

4.1.2. PI3K/AKT signaling pathway

The PI3K/AKT pathway is a major signaling pathway involved in cellular functions such as proliferation, differentiation, and apoptosis. Upon receiving extracellular signals, the catalytic subunit of PI3K converts the substrate PIP2 into PIP3. PIP3 then binds to intracellular signaling proteins AKT and PDK1, leading to the phosphorylation of AKT protein at Ser473 and Thr308 by PDK1, thereby fully activating the pathway.

When fibroblasts adhere to collagen, AKT is phosphorylated, providing a survival signal. Conversely, under the mechanical force generated during collagen contraction, AKT is dephosphorylated, leading to fibroblast apoptosis. Integrin-linked kinase (ILK) is associated with β1 integrin in focal adhesion complexes. ILK activity decreases with collagen matrix contraction, which is

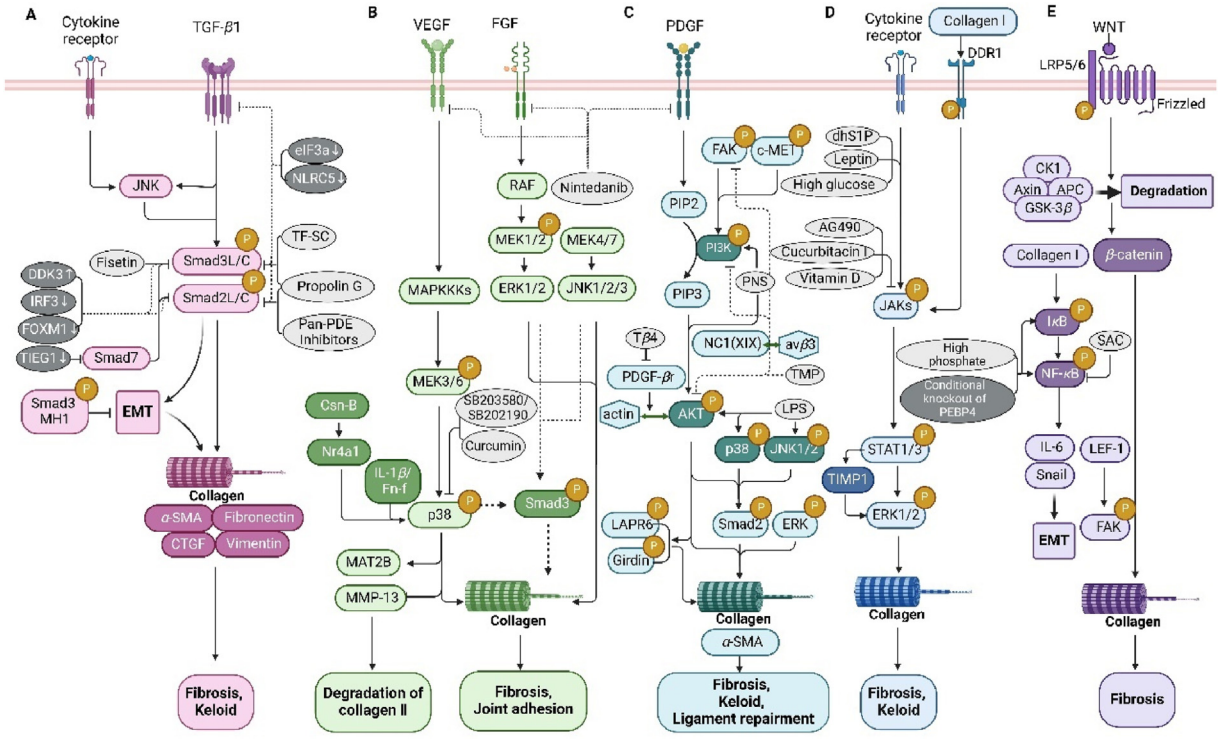


Figure 2 Phosphorylation and collagen-related diseases. In the figure, the green arrow represents the promoting effect and the red line represents the inhibiting effect, showing the role of different drugs and genes in regulating protein phosphorylation levels in various pathways (A). TGF-β binds to the receptor to activate the downstream pathway, and phosphorylation of different Smads in the pathway promotes or inhibits collagen synthesis. (B) Phosphorylation of FAK, PI3K, c-MET, AKT, p38, JNK, ERK, and other proteins in the PI3K/AKT signaling pathway regulates collagen synthesis. (C) Phosphorylation of MEK, p38, ERK, JNK, PI3K, AKT, and other proteins in the MAPK signaling pathway regulates collagen synthesis. (D) Phosphorylation of JAKs, STAT, ERK, and other proteins in the JAK/STAT signaling pathway regulates collagen synthesis. (E) Phosphorylation of LRP5/6, IκB, NF-κB, FAK, and other proteins in NF-κB and Wnt signaling pathways regulates collagen synthesis.

associated with AKT dephosphorylation and induction of fibroblast apoptosis[76].

Thymosin-β4 inhibits AKT binding by chelating with actin, suppressing its phosphorylation and preventing hepatic stellate cell differentiation and excessive collagen synthesis, thereby preventing liver fibrosis[16]. Lipopolysaccharide activates the non-canonical Smad pathway *via* PI3K/AKT and MAPK, leading to Smad2 phosphorylation and collagen I and α-SMA overexpression in HSC-T6 cells, promoting fibrosis[12]. *Panax notoginseng* saponins, derived from the traditional Chinese medicine Sanqi (*P. notoginseng*), promote the proliferation and migration of fibroblasts in the anterior cruciate ligament by enhancing phosphorylation of the PI3K/AKT pathway, thereby increasing the expression levels of collagen and fibronectin[27]. Tetramethylpyrazine, the main active component of the traditional Chinese medicine Chuanxiong (*Ligusticum wallichii*), reduces the phosphorylation level of AKT and downregulates the expression of fibrotic-related molecules. It inhibits the proliferation of fibroblasts in scars and activates apoptosis in cells[77]. Hepatocyte growth factor is involved in keloid pathogenesis through activated c-Met receptor, correlated with keloid size, Ki-67 expression, and collagen I expression, and associated with AKT and ERK phosphorylation, leading to keloid fibroblast proliferation, migration, and invasion[78].

The phosphorylation of downstream pathways of the PI3K/AKT cascade also affects collagen and related diseases. AKT-mediated Girdin phosphorylation affects angiogenesis and neointima formation. In Girdin S1416A knock-in mice, reduced collagen deposition impairs cardiac repair, leading to increased rupture and mortality[79]. La ribonucleoprotein domain family member 6 (LARP6) is an RNA-binding protein. The phosphorylation of LARP6 follows a hierarchical sequence; phosphorylation at S451 is a prerequisite for other serine phosphorylations. Inhibition of the PI3K/AKT pathway reduces the phosphorylation of LARP6 but has no effect on the S451A mutant, indicating that the PI3K/AKT pathway targets S451. This suggests that phosphorylation of LARP6 at the S451 site is crucial for regulating the translation and folding of collagen peptides, making it a key step in the synthesis of collagen I[80].

Collagen XIX, associated with the basement membrane, contains a non-collagenous domain (NC1) that binds to $\alpha v\beta 3$ integrin, reducing PI3K/AKT/mTOR pathway protein phosphorylation and increasing GSK3β activity, exhibiting anti-tumor migration and invasion properties[81,82] (Fig. 2B).

4.1.3. MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) pathway is a crucial signaling pathway that connects the cytoplasm with the nucleus, playing a significant regulatory role in various cellular physiological processes.

The MAPK pathway plays a significant regulatory role in collagen metabolism. Research has shown that phosphorylated

p38 MAPK is involved in mediating the synthesis of Matrix Metalloproteinase 13 (MMP13) in chondrocytes, which can lead to the degradation of collagen II[13]. Fibroblast growth factors promote fibroblast proliferation and collagen regeneration *via* phosphorylation of target proteins like Raf-1 and ERK1, exerting anti-aging effects[83]. In renal interstitial fibrosis models, downregulation of nuclear receptor subfamily 4 group A member 1 (Nr4a1) prevents TGF-β1-induced fibronectin and collagen I expression, as well as p38 MAPK activation, suggesting Nr4a1's role in promoting fibrosis[84]. Specific p38 MAPK inhibitors such as SB203580 or SB202190 can suppress p38, eliminating the upregulation of collagen I or fibronectin expression in systemic sclerosis (SSc) fibroblasts. This suggests that the p38 MAPK signal plays a regulatory role in TGF-β-mediated regulation of the human α2 (I) collagen gene in normal skin fibroblasts and contributes to the constitutive upregulation of collagen I and fibronectin expression in SSc fibroblasts[85]. Similar mechanisms have been found in studies investigating the therapeutic effects of the active polyphenol curcumin on liver fibrosis. Curcumin, long known for its anti-inflammatory properties, has been found to downregulate MAT2B expression by blocking p38 MAPK. This contributes to the inhibition of mouse hepatic stellate cell (HSC) activation and collagen expression, revealing the inhibitory effect of curcumin on HSC activation and fibrosis[86]. Nintedanib is a receptor tyrosine kinase inhibitor that targets vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptors. Studies have found that nintedanib can antagonize various signaling pathways associated with VEGF-R, FGF-R, PDGF-R, and TGF-β-R, thereby blocking the phosphorylation of multiple kinases including p38, JNK, ERK, STAT3, and Smad, and enhancing receptor internalization to inhibit proliferation, migration, and collagen synthesis of keloid fibroblasts[87].

As research progresses, the connection between the MAPK pathway and the Smad pathway has been gradually uncovered. Unlike the traditional carboxy-terminal phosphorylation mediated by TGF-β receptors, activation of MAPK and potentially other kinases by growth factors and hormones can lead to phosphorylation of the linker region of r-Smad. This linker region lies between the MH1 DNA-binding domain and the MH2 C-terminal phosphorylation domain. In various cell types, three major MAPKs, ERK 1/2, p38, and JNK, have been shown to phosphorylate Smads in the cytoplasm[88] (Fig. 2C).

4.1.4. *JAK/STAT signaling pathway*

The initiation of JAK/STAT signaling typically occurs when cell surface receptors are activated. When activated, JAKs phosphorylate STAT proteins, inducing a conformational change that leads to dimerization.

Previous studies have consistently observed enhanced expression of phosphorylated STAT3 (Tyr705 phospho-STAT3) in keloid tissue and keloid fibroblasts[89,90], selective inhibitors of JAK2, such as cucurbitacin I and AG490, have been shown to inhibit STAT3 phosphorylation, confirming the hypothesis that JAK2 mediates STAT3 phosphorylation[91]. Cucurbitacin I serves as a natural selective inhibitor of the JAK2/STAT3 pathway, while AG490 acts as a tyrosine kinase inhibitor of JAK2, selectively inactivating it. Additionally, lipoprotein metabolite analog dihydrosphingosine-1-phosphate, a mimic of high-density lipoprotein lipid metabolism, increases STAT1 and STAT3 phosphorylation in the JAK/STAT pathway, resulting in elevated tissue inhibitor of metalloproteinases 1 (TIMP1), increased collagen synthesis in neonatal cardiac fibroblasts, and cardiomyocyte hypertrophy[92]. Another study found that high glucose can enhance the protein expression of phosphorylated STAT1 and STAT3 in cardiac fibroblasts, inducing increased proliferation and collagen deposition in CFs *in vitro*[93]. In patients with idiopathic pulmonary fibrosis and in the lungs of fibrotic mice induced by bleomycin (BLM), increased phosphorylation of STAT-3 was observed in lung biopsies. Moreover, there may be cross-regulation between the STAT pathway and the TGF-β/SMAD pathway. Stimulation of lung fibroblasts by TGF-β leads to STAT-3 phosphorylation in a SMAD2/SMAD3-dependent manner[14]. In rat mesangial cells under high-glucose conditions, VD treatment can inhibit the tyrosine phosphorylation of JAK2, STAT1, and STAT3, thereby suppressing the expression of downstream proteins encoded by JAK/STAT signaling pathway genes, including collagen IV, protecting mesangial cells from high-glucose-induced damage[94]. Elevation in the phosphorylation levels of the breakpoint cluster region of discoidin domain receptor 1, activated by collagen, and the subsequent upregulation of STAT3 phosphorylation, results in renal fibrosis in mice[95]. Leptin, a protein hormone secreted by adipose tissue, has been found in multiple studies to be associated with collagen synthesis. A study on ATDC5 cells found that leptin increased the phosphorylation of ERK1/2, p38, and STAT3 in a time- and dose-dependent manner, stimulating an increase in mRNA levels of collagen X and promoting the development of growth plate cartilage[28]. Leptin can activate JAK1 and JAK2, as well as phosphorylation of STAT3 and STAT5, leading to the transcription of the TIMP-1 gene, promoting the activation of hepatic stellate cells, and resulting in collagen deposition and fibrosis[96] (Fig. 2D).

4.1.5. *NF-κB signaling pathway*

Nuclear factor kappa B (NF-κB) is a family of transcription factor proteins that reside in the cytoplasm in an inactive state, forming a complex with inhibitor of NF-κB (IκB), preventing NF-κB from entering the nucleus.

In a mouse model, conditional knockout of PEBP4 in hepatocytes activated the NF-κB signaling pathway, increasing phosphorylation of NF-κB p65 and IκB-α, exacerbating CCl_4-induced liver fibrosis and deposition of collagen I and collagen III[17]. In a study investigating the effects of a high phosphate diet on the heart, phosphoproteomic analysis revealed that high blood phosphate significantly increased the phosphorylation levels of proteins related to NF-κB and STAT3 signaling pathways. This led to increased activity of atrial fibroblasts and mitochondrial oxidative stress, along with increased expression of collagen proteins[97]. *S*-Allyl-L-cysteine (SAC) is a neuroprotective drug known for its preventive effects against cognitive decline and is one of the major bioactive compounds found in garlic. In mice with pulmonary fibrosis induced by BLM, SAC dose-dependently reduces inflammatory cell infiltration, lung injury, and collagen deposition. This effect involves the downregulation of fibrotic genes including α-smooth muscle actin (α-SMA), fibronectin, collagen I, and collagen III at both mRNA and protein levels. SAC achieves this by reducing the phosphorylation levels of AKT and NF-κB p65 in BLM-stimulated mice[98].

In some cases, collagen can also influence the phosphorylation process of the NF-κB pathway. In studies investigating the mechanism of EMT, it has been found that collagen I can lead to ILK-dependent phosphorylation of IκB and subsequent nuclear translocation of active NF-κB. This, in turn, promotes increased expression of transcription factors Snail and LEF-1, thereby

facilitating EMT[40]. In addition, EMT is also associated with tumor invasion and metastasis[41]. Furthermore, studies have found that collagen I significantly promotes the production and release of interleukin-6 through nuclear translocation of NF-κB p65. It also involves the phosphorylation of focal adhesion kinase (FAK) associated with NF-κB p65 nuclear translocation, enhancing the migration and myogenic differentiation of mouse C2C12 myoblasts, but without affecting cell proliferation[99] (Fig. 2E).

4.1.6. *Wnt signaling pathway*

The Wnt signaling pathway is associated with processes such as cell differentiation, growth, and apoptosis, among others, and consists mainly of three intracellular transduction pathways: Wnt/β-catenin, Wnt/Ca^{2+}, and Wnt/PCP. Among them, the Wnt/β-catenin pathway is the most classical signaling pathway. The Wnt protein serves as the initiating factor of this pathway, binding to Frizzled receptors and co-receptors low-density lipoprotein receptor-related protein 5/6 (LRP5/6) on the cell surface to initiate signal transduction. In the absence of Wnt signaling, a complex composed of Axin, adenomatous polyposis coli, and glycogen synthase kinase 3β phosphorylates β-catenin, leading to its degradation. However, upon activation of Wnt signaling, binding of Wnt protein to its receptors results in the phosphorylation of the LRP5/6 receptor. This prevents the formation of the Axin complex and reduces phosphorylation of β-catenin at residues S33, S37, T41, and S45. Unphosphorylated β-catenin evades degradation and enters the nucleus, where it binds to TCF/LEF transcription factors, activating the transcription of Wnt-responsive genes. Phosphorylation plays a crucial regulatory role in the Wnt signaling pathway[100]. An increasing number of studies have found correlations between Wnt activation and the pathogenesis of EMT, excessive ECM accumulation, as well as fibrosis in the kidneys, liver, lungs, and heart[101] (Table 1, Fig. 2E).

4.2. *Acetylation*

Protein acetylation (Ac) plays a crucial role in various biological processes, such as gene transcription, DNA damage repair, cell signaling, and metabolism, including both histone and non-histone acetylation. It also plays an important biological role in collagen metabolism and related diseases. Lysine acetyltransferases (KATs) catalyze the transfer of acetyl groups to lysine residues, including the GCN5 family, p300 family, MYST family, and unclassified KATs. Although there are various types of KATs, many share the same catalytic site; for example, CREB-binding protein (CBP) and p300 can catalyze the acetylation of histone H3K18 and H3K27, while GCN5 and p300/CBP-associated factor can catalyze the acetylation of H3K9. In contrast to KATs, lysine deacetylases catalyze the removal of acetyl groups and are divided into two major classes: zinc-dependent classical histone deacetylases (HDACs) and NAD^+-dependent sirtuin deacetylases (SIRTs).

4.2.1. *Histone acetylation*

In the fibrosis processes of various organs and tissues, histone acetylation also plays a crucial role, as different acetylation sites on histones have distinct effects on the transcription or inhibition of collagen genes. Studies have found that after myocardial infarction, TGF-β binds to its receptor, forming a complex of phosphorylated Smad2/3 in the cytoplasm, which then binds to Smad4. After the formation of the complex, it is transported into the nucleus and specifically binds to the promoter region of collagen genes[102,103]. Subsequently, this complex recruits p300, which can promote histone H3K9 acetylation, ultimately enhancing collagen gene transcription and leading to the development of cardiac fibrosis. A characteristic feature of systemic sclerosis is sustained fibroblast activation triggered by TGF-β. During this process, TGF-β enhances the recruitment of p300 and histone H4 acetylation at the COL1A2 site, leading to increased transcriptional activity of collagen I[104]. Histone deacetylase inhibitors (HDACi) such as suberoylanilide hydroxamic acid (SAHA) elevate the levels of histone H3 and H4 acetylation in idiopathic pulmonary fibrosis (IPF) cells. They significantly reduce the increased expression of *COL3A1* in IPF fibroblasts, alleviating the excessive deposition of collagen[38]. In a mouse model of peritoneal fibrosis, subcutaneous injection of SAHA upregulated the acetylation levels of H3K9, thereby inhibiting the thickening of the subendothelium and the accumulation of collagen III induced by chlorhexidine gluconate injection[105]. Sodium valproate is a first-line medication used to treat epilepsy and migraines, and it is also recognized as a histone deacetylase inhibitor. Valproate treatment significantly reduces the overexpression of HDAC4/5/7 induced by diabetes in a dose-dependent manner, restoring the decreased acetylation of histone H3. This treatment also markedly decreases the overexpression of TGF-β1, fibronectin, α-SMA, and collagen I induced by diabetes, thereby improving the balance between fibrotic and anti-fibrotic proteins[106]. Blueberry anthocyanins extracted from blueberries have been found to promote histone acetylation. In rats with liver fibrosis induced by carbon tetrachloride, intervention with blueberry anthocyanins led to an upregulation of acetylation levels of H3K9, H3K14, and H3K18. Consequently, this intervention resulted in reduced expression of collagen I and TIMP1, thereby improving liver fibrosis in the rats[107].

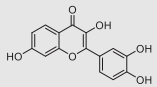
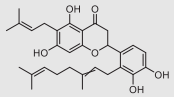
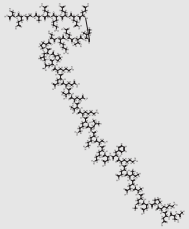
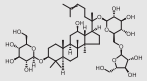
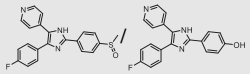
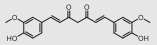
Many studies have found that histone acetylation plays a crucial role in the skeletal system. In cartilage tissue, MicroRNA-455-3p inhibits the expression of HDAC2/8 by directly targeting them. This inhibition promotes histone H3 acetylation at the *COL2A1* promoter, playing a critical role in cartilage formation[108]. Prenatal nicotine exposure induces increased expression of Snail and HDAC1/2 in male offspring mice, resulting in decreased levels of histone acetylation (H3K9/H3K14) at the promoter regions of growth plate genes *ACAN* and *COL2A1*. This leads to reduced collagen synthesis and delayed development of fetal growth plate cartilage[109]. The HDAC inhibitor trichostatin A enhances histone H3 acetylation at promoter and enhancer regions in chondrosarcoma cells, resulting in increased expression of *COL2A1* and regulating the differentiation of chondrosarcoma cells[110]. In osteosarcoma (OS), c-Jun bound p300 increases the acetylation level of H3K27 in the *COL6A1*gene promoter region, resulting in the upregulation of *COL6A1* in OS. The overexpression of *COL6A1* interacts with SOCS5, leading to the ubiquitination and proteasomal degradation of STAT1 expression and activation, thereby promoting the migration and invasion of OS cells[111] (Fig. 3A).

4.2.2. *Non-histone acetylation*

In addition to histone acetylation, it has been found that acetylation of some non-histone proteins also plays a significant role in the regulation of collagen.

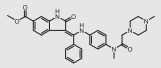
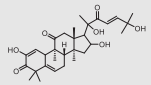
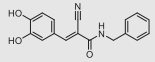
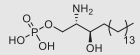
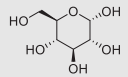
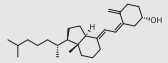
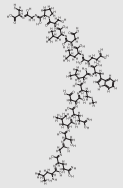
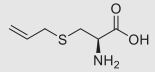
The decreased expression of SIRTs has been found to play a role in many collagen expression abnormalities and fibrotic diseases. In a study utilizing an IL-1β-induced chondrocyte culture model of cartilage degradation, an increased ratio of acetylated lysine residues on FOXO4 protein was observed in CH, leading to

Table 1 Drugs targeting phosphorylation to regulate collagen metabolism.

Drug	Modified protein	Activation or inhibition	Disease/Physiological process	The effect on diseases
Fisetin 	SMAD3	Inhibition	Renal fibrosis	Renal interstitial collagen deposition was reduced and renal fibrosis was inhibited
Pan-phosphodiesterase inhibitors	SMAD2	Inhibition	Pulmonary fibrosis	The pro-fibrotic phenotype of type II alveolar epithelial cells induced by TGF-β was reduced, and the expression of fibrotic markers such as collagen I was decreased
Propolin G 	SMAD2/SMAD3	Inhibition	Liver fibrosis	The α-SMA and collagen expression and proliferation of HSC-T6 cells after TGF-β treatment were inhibited, and the liver was protected from fibrosis
TF-SC	SMAD3	Inhibition	Liver fibrosis	The expressions of α-SMA, collagen I, and fibronectin were decreased, and liver fibrosis was inhibited
Thymosin-β4 (43AA) 	AKT	Inhibition	Liver fibrosis	Cell proliferation and migration were decreased, the expressions of PDGF-βr, α-SMA, and collagen were decreased, and liver fibrosis was inhibited
Lipopolysaccharides	Smad2	Activation	Liver fibrosis	Collagen I, α-SMA, and MMP-9 are upregulated, promoting liver fibrosis
Panax notoginseng saponins (PNS) 	PI3K, AKT, ERK	Activation	Cruciate ligament injury	The expression of collagen I and III and fibronectin increased, and the proliferation and migration of anterior cruciate ligament fibroblasts increased
Tetramethylpyrazine 	AKT	Inhibition	Hypertrophic scar	The expressions of collagen I and III and fibronectin were reduced, and hypertrophic scars were inhibited
SB203580/SB202190 	p38	Inhibition	Systemic sclerosis	The up-regulation of collagen I or fibronectin in SSc fibroblasts is eliminated
Curcumin 	P38	Inhibition	Liver fibrosis	The expression of MAT2B was down-regulated, and the liver HSC activation and collagen expression

(*continued on next page*)

Table 1 (*continued*)

Drug	Modified protein	Activation or inhibition	Disease/Physiological process	The effect on diseases
				were inhibited
Nintedanib 	p38, JNK, ERK, STAT3, Smad	Inhibition	Keloid	Cell proliferation, migration, and collagen production of keloid fibroblasts were significantly inhibited
Cucurbitacin I 	STAT3	Inhibition	Keloid	Collagen I production in keloid cells is inhibited
AG490 	STAT3	Inhibition	Keloid	Excessive proliferation of keloid cells and inhibition of collagen I and II production
Dihydrosphingosine-1-phosphate 	STAT1, STAT3	Activation	Cardiac fibrosis	Collagen synthesis was increased in cardiac fibroblasts and new cardiomyocytes became hypertrophic
High glucose 	STAT1, STAT3	Activation	Cardiac fibrosis	CFs proliferation and collagen deposition increased
Vitamin D 	JAK2, STAT1, STAT3	Inhibition	Diabetic nephropathy	The expression of SOCS1, SOCS3, and collagen IV is inhibited, protecting mesangial cells from hyperglycemia-induced damage
Leptin (167AA) 	ERK1/2, p38, STAT3	Activation	Growth-plate cartilage development	The mRNA level of collagen X was increased, and the development of growth plate cartilage was promoted
Leptin (167AA)	JAK1, JAK2, STAT3, STAT5	Activation	Liver fibrosis	*TIMP-1* gene transcription is stimulated and hepatic stellate cells are activated, leading to collagen deposition and fibrosis
S-Allyl-L-cysteine 	p65, AKT	Inhibition	Pulmonary fibrosis	The mRNA expression levels of α-smooth muscle actin (α-SMA), fibronectin, collagen I and III and the protein levels of α-SMA were down-regulated, and the pulmonary fibrosis of mice was inhibited

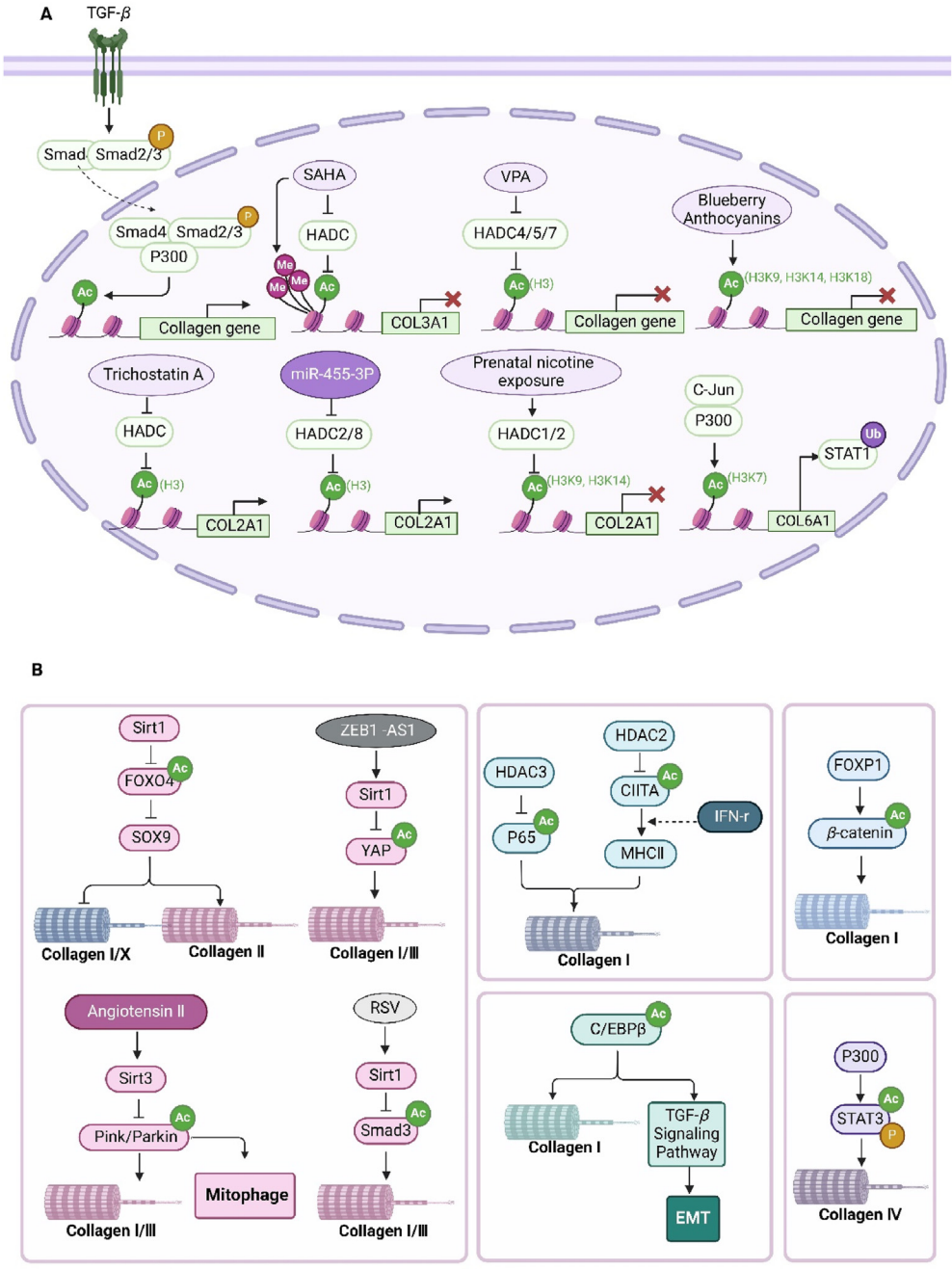


Figure 3 Acetylation and collagen-related diseases. (A) Histone acetylation. When TGF-β binds to its receptor, it forms a complex with phosphorylated Smad2/3 in the cytoplasm, which subsequently binds to Smad4. This complex recruits p300, promoting histone acetylation and ultimately facilitating collagen gene transcription. Suberoylanilide hydroxamic acid (SAHA) inhibits HDAC, and increases histone acetylation levels, while also elevating histone methylation levels, leading to the inhibition of collagen gene transcription. Valproic acid inhibits HDAC4/5/7, elevating histone H3 acetylation levels and suppressing collagen gene *COL3A1* transcription. Blueberry anthocyanins increase histone acetylation levels, suppressing collagen gene transcription. Trichostatin A inhibits HDAC, elevating histone H3K9, H3K14, and H3K18 acetylation levels, thereby promoting collagen gene *COL2A1* transcription. MicroRNA-455-3p inhibits the expression of HDAC2/8, promoting histone acetylation and collagen gene *COL2A1* transcription. Prenatal nicotine exposure increases the expression of HDAC1/2, leading to reduced histone H3K9/H3K14 acetylation levels and inhibition of collagen gene *COL2A1* transcription. c-Jun bound p300 increases the acetylation level of H3K27 in the promoter region of the *COL6A1* gene, promoting its transcription. Overexpression of *COL6A1* suppresses the expression and activation of STAT1 through ubiquitination and proteasomal degradation. (B) Non-histone acetylation and collagen-related diseases. SIRT1 inhibits the acetylation of FOXO4 protein, thereby promoting the expression of SOX9 protein, increasing the expression of type II collagen, and reducing the expression of type I and type X collagens. ZEB1-AS1 reduces the expression of type I and type III collagens in cells by mediating the deacetylation of Yes-associated protein *via* SIRT1. Resveratrol upregulates SIRT1, inhibiting the acetylation of Smad3 and the consequent expression of collagen I/III. Angiotensin II promotes SIRT3 expression, leading to decreased acetylation of Pink/Parkin and reduced expression of collagen I/III. HDAC2

decreased expression of SOX9 protein. This process was reversed upon overexpression of SIRT1, concomitant with increased expression of collagen II and aggrecan, and decreased expression of collagen I, collagen X, MMP-13, and ADAMTS-5 mRNA, thus favoring the maintenance of ECM stability in cartilage[112]. In a dilated cardiomyopathy rat model, decreased expression of SIRT1 resulted in reduced direct binding between SIRT1 and Smad3, leading to a significant increase in acetylated Smad3 (Ac-Smad3) in dilated cardiomyopathy. This upregulation of Ac-Smad3 was associated with elevated expression of collagen I and collagen III, promoting myocardial fibrosis. However, Resveratrol significantly increased SIRT1 mRNA levels, facilitated direct binding between SIRT1 and Smad3, and markedly reduced the acetylation of Smad3. Consequently, the expression of collagen I and collagen III in the myocardium was decreased, effectively ameliorating myocardial fibrosis and cardiac function[36]. In studies on angiogenesis, it was found that angiotensin II infusion in mice led to overexpression of SIRT3 in cardiac microvascular endothelial cells. This resulted in decreased acetylation levels of Pink/Parkin, which reduced the expression of collagen I and collagen III while enhancing Pink/Parkin-mediated mitochondrial autophagy. Consequently, this alleviated angiogenesis and cardiac fibrosis[113]. However, other reports suggest that SIRT3-mediated activation of the Pink1/Parkin pathway primarily depends on FOXO3A deacetylation[114]. Research conducted on human cardiac fibroblasts treated with high glucose revealed that long non-coding RNA zinc finger E-box binding homeobox 1 antisense 1 (ZEB1-AS1) can deacetylate Yes-associated protein through SIRT1 mediation. This process led to a reduction in the levels of collagen I, collagen III, α-SMA, and fibronectin in cells, thereby inhibiting high glucose-induced fibrosis in human cardiac fibroblasts and alleviating myocardial fibrosis in diabetic mice[115].

In the process of atherosclerosis formation, the synthesis and secretion of collagen by aortic smooth muscle cells and the presentation of major histocompatibility complex II (MHC II) by macrophages are important pathological processes. In macrophages and smooth muscle cells, HDAC2 mediates the deacetylation of the MHC II transactivator, thereby regulating interferon-gamma (IFN-γ)-induced MHC II activation and suppressing the activation of collagen I promoter, resulting in decreased expression of collagen I. This suggests that HDAC2 plays an anti-atherosclerotic role[116]. HDAC3 mediates the deacetylation of the p65 subunit of the NF-κB transcription complex, leading to reduced DNA binding and transcriptional activity. Consequently, the expression of *COL1A1* and other related genes is decreased, resulting in inhibition of alkaline phosphatase, collagen I, and osteocalcin expression, thereby modulating the coupling between bone resorption and bone formation[117]. In endometriotic stromal cells, higher levels of FOXP1 have been observed, which subsequently upregulates the acetylation of β-catenin, a protein associated with the Wnt pathway. This enhances fibrosis during endometriosis, increasing the expression of connective tissue growth factor, collagen I, α-smooth muscle actin, and fibronectin, as well as collagen contraction, cell proliferation, and migration[118]. Additionally, research has found that overexpression of p300 significantly increases the acetylation of STAT3 at Lys685 and phosphorylation of STAT3 at Tyr705 in renal tubular epithelial cells. This overexpression also enhances the expression of collagen IV and fibronectin, promoting fibrosis in renal tubular epithelial cells[119]. CCAAT/enhancer binding protein beta (C/EBPβ) is a leucine zipper transcription factor, and immunohistochemistry has shown its presence in alveolar epithelial cells and small airway epithelium. Acetylation at Lys39 of C/EBPβ regulates its transcriptional activation, and acetylation of C/EBPβ may play an important role in pulmonary fibrosis. Studies have confirmed that deacetylation of C/EBPβ in alveolar epithelial cells reverses the decrease in α-SMA expression and excessive collagen I accumulation, successfully ameliorating TGF-β1-induced EMT[120] (Fig. 3B—Table 2).

4.3. *Ubiquitination*

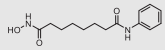
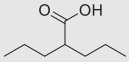
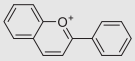
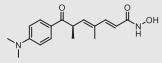
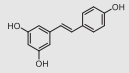
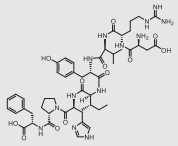
Protein ubiquitination (Ub) plays a wide range of physiological functions, including protein degradation, signal transduction, DNA damage repair, and protein localization. Ubiquitin (Ub) undergoes a series of enzyme-catalyzed reactions involving activation (E1), conjugation (E2), and ligation (E3) enzymes to covalently link to lysine residues on target proteins. These three enzymes act sequentially. Ubiquitin is first activated by E1, then transferred to the E2 conjugating enzyme. Subsequently, the E3 ubiquitin ligase interacts with both the Ub-loaded E2 and the substrate protein, mediating the formation of an isopeptide bond between the C-terminus of Ub and the lysine residue of the substrate, thereby completing the ubiquitination process[121].

Ubiquitination of certain collagen proteins can mark the protein itself, directing it towards the protein degradation pathway. The antioxidant *S*-adenosyl-L-methionine (SAMe) has been demonstrated to effectively alleviate liver damage in various animal models of liver injury. Studies have shown that treatment with SAMe in activated hepatic stellate cells significantly increases the ubiquitination of collagen I protein, thereby inhibiting its processing and secretion. This may represent an important mechanism by which SAMe suppresses liver fibrosis[122]. During pregnancy, collagen III protein in the amniotic membrane contributes to its tensile strength. Cortisol can increase the ubiquitination of COL3A1 protein in the amniotic tissue, activating the proteasome pathway to reduce the abundance of collagen III protein. The decrease in COL3A1 protein by cortisol can be blocked by the ubiquitin-activating enzyme inhibitor PYR-41. Therefore, the regeneration of cortisol in amniotic fibroblasts may reduce collagen III through the ubiquitin-proteasome pathway, which is associated with membrane rupture during delivery[123].

The ubiquitination levels of other proteins also impact collagen synthesis and degradation. Smurf2 is a homologous member of the E3 ubiquitin ligase E6-AP carboxyl terminus family. Smurf2 is recruited to the TGF-β1 receptor complex through Smad7, leading to the ubiquitination of TGF-β1 receptors and subsequent degradation[124,125]. Previous studies have shown that the expression of Smurf2 gradually increases in proliferative scar fibroblasts treated with TGF-β1. Transfection of Smurf2 small interfering RNA into proliferative

deacetylates the major histocompatibility complex class II transactivator (CIITA), inducing MHC II activation and reducing the expression of collagen I through IFN-γ induction. HDAC3 deacetylates the p65 subunit of the NF-κB transcription complex, leading to reduced expression of collagen I. P300 increases STAT3 acetylation and phosphorylation and enhances the expression of collagen IV. FOXP1 upregulates β-catenin acetylation, increasing the expression of collagen I. Acetylation of C/EBPβ promotes the expression of collagen I and facilitates TGF-β1-induced epithelial-mesenchymal transition (EMT).

Table 2 Drugs targeting acetylation to regulate collagen metabolism.

Drug	Modified site	Activation or inhibition	Disease/Physiological process	The effect on diseases
Suberoylanilide hydroxamic acid (SAHA) 	Histone H3, H4	Activation	Pulmonary fibrosis	Collagen III was significantly reduced and pulmonary fibrosis was inhibited in mice
Valproic acid 	Histone H3	Activation	Diabetic nephropathy	The overexpression of TGF-β1, fibronectin, α-SMA, and collagen I induced by diabetes was significantly reduced, and the balance of pro-fibrotic and anti-fibrotic proteins in the kidneys of rats was improved
Blueberry anthocyanins 	Histone H3K9, H3K14, H3K18	Activation	Liver fibrosis	The expression of collagen I and TIMP1 decreased, and the liver fibrosis of rats was improved
Trichostatin A 	Histone H3	Activation	Differentiation in chondrosarcoma cells	The expression of *COL2A1* was increased, and the differentiation of chondrosarcoma cells was regulated
Resveratrol 	Smad3	Inhibition	Cardiac fibrosis	The expression of collagen I and collagen III in rat myocardium was decreased, myocardial fibrosis and cardiac function were improved
Angiotensin II 	Pink/Parkin	Inhibition	Cardiac fibrosis	In mice, the expression of collagen I and collagen III was decreased, Pink/Parkin-mediated mitochondrial phagocytosis was enhanced, and angiogenesis and cardiac fibrosis were reduced

scar fibroblasts significantly reduces TGF-β1 production, inhibits α-SMA levels, and suppresses collagen I synthesis. Therefore, the upregulation of Smurf2 expression is associated with proliferative scar formation[126]. TRIM13, a well-defined E3 ubiquitin ligase, is downregulated in mesangial cells of diabetic nephropathy mouse models, while the expression of C/EBP homologous protein (CHOP) is upregulated. CHOP is a protein known to play a crucial role in kidney injury associated with diabetic nephropathy. Research has confirmed that TRIM13 promotes the ubiquitination and degradation of CHOP, thereby inhibiting the expression of collagen-related factors (including COL1A2, TGF-β1, and COL1A4) in diabetic nephropathy kidney tissues to suppress collagen synthesis[127]. Membrane-type 1 matrix metalloproteinase (MT1-MMP, MMP14) is a zinc-dependent type I transmembrane metalloproteinase that plays a crucial role in ECM degradation and cell migration. Its elevated expression is associated with poor prognosis in cancer. The intracellular domain of MT1-MMP is monoubiquitinated at Lys581, a modification that promotes its degradation of collagen I and enhances the invasive capacity of cancer cells[128] (Fig. 4A).

4.4. *SUMOylation*

SUMOylation (SUMO) is a series of enzymatic reactions catalyzed by E1 activating enzymes, E2 conjugating enzymes, and E3 SUMO ligases. Five SUMO isoforms have been identified in humans, among which SUMO 1, 2, and 3 are the most prevalent. Because SUMOylation predominantly occurs in the nucleus, SUMO participates in numerous nuclear processes such as DNA damage response, genome integrity, transcriptional regulation, as well as regulation of protein stability and subcellular localization of substrate proteins[129].

In a study on liver fibrosis, significant upregulation of Ubc9 protein (the sole SUMO E2 conjugating enzyme) and its mRNA expression levels were observed in LX-2 hepatic fibrosis cell line as well as HepG2 and SMMC-7721 HCC cell lines. Interestingly, in activated LX-2 cells, silencing of Ubc9 expression mediated by UBC9-shRNA plasmid led to reduced expression of fibrotic markers such as α-SMA and collagen I, as well as decreased secretion of pro-fibrotic cytokines IL-6 and TNF. Moreover, downregulation of UBC9 could promote apoptosis in activated human LX-2 hepatic stellate cells by inhibiting the NF-κB signaling pathway[130]. In a study on skin fibrosis, it was also found that UBC9 silencing could inhibit sumoylation, exerting a potent anti-fibrotic effect and preventing dermal thickening, myofibroblast differentiation, and collagen accumulation induced by bleomycin or constitutively active TGF-β receptor type I in experimental models. Furthermore, in experimental fibrosis, downregulation of Ubc9 reduced the accumulation of phosphorylated Smad3, suggesting that inhibition of sumoylation may normalize the typical TGF-β/Smad signaling pathway *in vivo*[131].

Another study found that the deSUMOylating protease family member SENP2 is a key protein in alleviating CCl_4-induced liver fibrosis in mice. In the CCl_4-induced liver fibrosis mouse model, the expression levels of SENP2 protein and mRNA in activated hepatic stellate cells (HSCs) were decreased both *in vitro* and *in vivo*. Overexpression of SENP2 *in vitro* resulted in reduced expression of α-SMA and COL1A1 proteins in TGF-β-activated HSC lines, along with decreased cell viability, favoring cell cycle arrest in the G0/G1 phase, and inducing apoptosis in TGF-β-activated HSCs *in vitro*. Conversely, siRNA-mediated knockdown of SENP2 induced expression of α-SMA and COL1A1 proteins in TGF-β-activated HSCs, stimulating cell proliferation and reducing

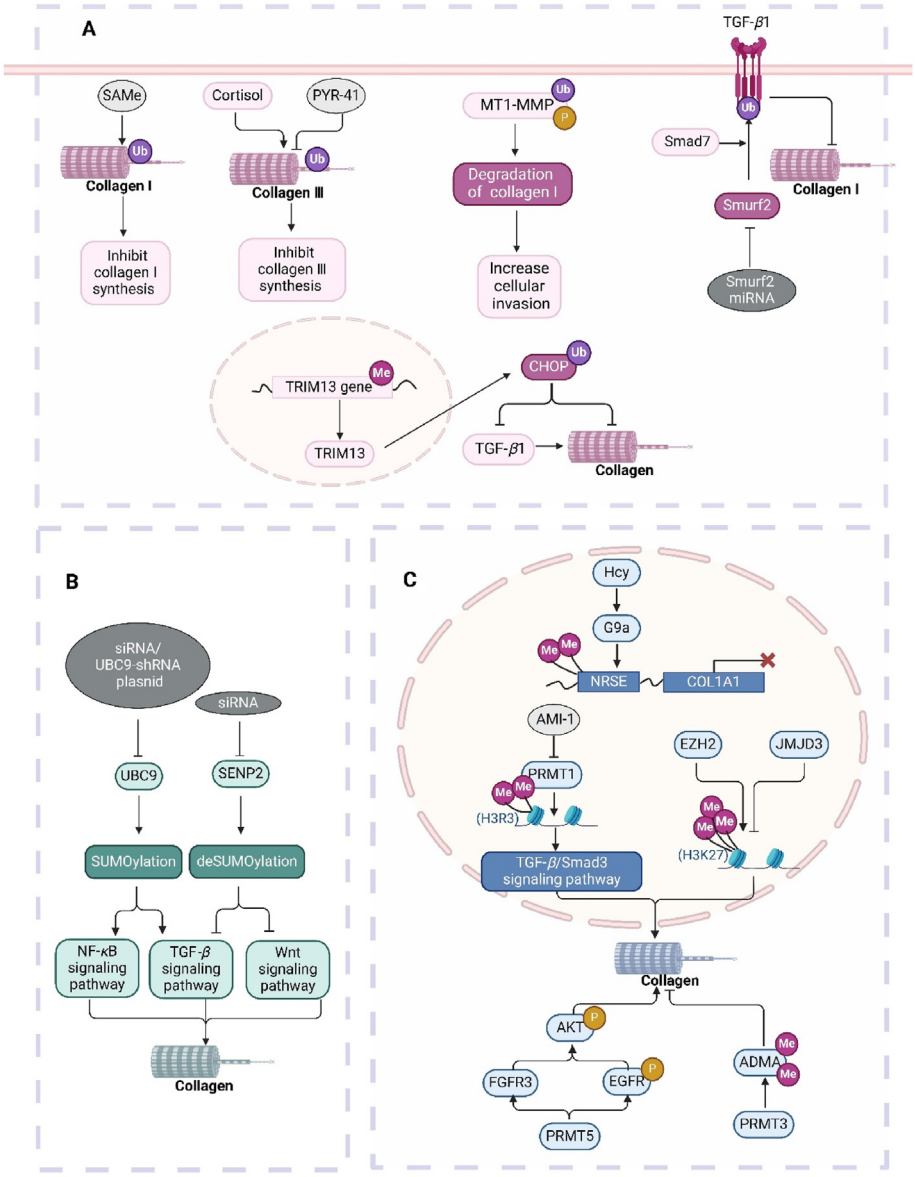


Figure 4 Ubiquitination, SUMOylation, methylation and collagen-related diseases. (A) *S*-Adenosyl-L-methionine (SAMe) increases the polyubiquitination of collagen I, thereby inhibiting its synthesis. Cortisol promotes the ubiquitination of COL3A1. This process can be blocked by the ubiquitin-activating enzyme inhibitor PYR-41. Smurf2 is recruited to the TGF-β1 receptor complex *via* Smad7, leading to the ubiquitination and degradation of the TGF-β1 receptor, thereby inhibiting the synthesis of collagen I. TRIM13 promotes the ubiquitination and degradation of CHOP, directly inhibiting collagen synthesis and indirectly inhibiting it by suppressing the TGF-β pathway. Monoubiquitination of MT1-MMP enhances its degradation of collagen I and increases cell invasion. (B) UBC9 can promote collagen expression through the TGF-β and NF-κB signaling pathways, while UBC9-shRNA plasmid and siRNA can inhibit this process. Overexpression of SENP2 reduces collagen expression by inhibiting the TGF-β and Wnt signaling pathways. Conversely, siRNA-mediated SENP2 silencing can reverse this process. (C) AMI-1 reduces PRMT1 levels, thereby decreasing histone H4R3 methylation, and inhibiting collagen expression. PRMT3 increases the levels of asymmetric dimethylarginine in the cytoplasm, leading to decreased expression of collagen I. PRMT5 can increase collagen I expression through the PRMT5/FGFR3/Akt pathway and the PRMT5/EGFR/AKT/β-catenin pathway, promoting cancer cell EMT. G9a binds to the Neuron-Restrictive Silencer Element on the COL1A1 promoter, catalyzing histone H3K9 dimethylation and reducing collagen I expression. Homocysteine (Hcy) down-regulates G9a expression, reversing this process. EZH2 promotes histone H3K27 methylation, thereby enhancing collagen synthesis. Conversely, JMJD3 inhibits this process.

apoptosis. Finally, in TGF-β-activated HSCs, overexpression of SENP2 led to downregulation of members of the Wnt/β-catenin pathway, suggesting a therapeutic role for SENP2 in liver fibrosis[132] (Fig. 4B).

4.5. *Methylation*

Methylation (Me) primarily occurs on arginine, lysine, and histidine residues but can also occur on the carboxyl group of glutamic

acid and aspartic acid residues. It is PTM that plays a wide range of biological functions. Methylation is involved in the regulation of protein−protein interactions and has significant impacts on transcriptional regulation, cellular localization, intracellular signaling pathways, protein stability, and various other critical cellular events[6].

4.5.1. *Arginine methylation*

Eukaryotes possess three forms of methylated arginine residues, including monomethylarginine, asymmetric dimethylarginine, and symmetric dimethylarginine. Protein arginine methyltransferases (PRMTs) are enzymes responsible for arginine methylation.

Protein arginine methyltransferase 1 (PRMT1) primarily induces asymmetric arginine methylation of histones and non-histone proteins. In a mouse model of renal fibrosis induced by unilateral ureteral obstruction (UUO), the expression of PRMT1 and asymmetric dimethylation of histone 4 arginine 3 (H4R3Me2a) are upregulated, leading to increased expression of α-SMA, collagen I, and fibronectin. Treatment with AMI-1 (a selective inhibitor of PRMT1) reduces the expression of PRMT1 and H4R3Me2a, attenuates the deposition of ECM proteins, and inhibits the activation and proliferation of renal fibroblasts. Additionally, it suppresses phosphorylation of Smad3 and expression of TGF-β receptor I, indicating that PRMT1 may mediate the activation of renal fibroblasts and the development of renal fibrosis by activating the TGF-β/Smad3 signaling pathway[133]. Research has shown that the deficiency of miR-19a in airway smooth muscle cells of asthma patients leads to constitutive enhancement in the production and activity of ERK1/2 MAPK, thereby increasing the expression of PRMT1 in asthma patients. The enhanced PRMT1 exacerbates airway remodeling in the lungs of asthma patients by inducing ASMC proliferation, migration, and expression of collagen I and fibronectin[134].

PRMT3 is upregulated in the kidneys of UUO mice. Unlike PRMT1, the downstream effects of PRMT3 in UUO kidneys are not mediated through H4R3me2a-mediated epigenetic gene regulation. Instead, PRMT3 exerts its effects by increasing the levels of asymmetric dimethylarginine in the cytoplasm, reducing the expression of α-SMA and collagen I, and suppressing renal tubulointerstitial fibrosis[135]. In studies on lung cancer[136] and pancreatic cancer[137], PRMT5 has been found to increase the expression of vimentin, collagen I, and β-catenin through the PRMT5/FGFR3/Akt pathway and the PRMT5/EGFR/AKT/β-catenin pathway, promoting EMT in lung cancer and pancreatic cancer cells, thus facilitating tumor growth, migration, and invasion.

4.5.2. *Lysine methylation*

Protein lysine methyltransferases (PKMTs) catalyze the mono-, di-, and trimethylation of lysine residues and are categorized into SET domain-containing families and non-SET domain-containing families. To date, over 50 PKMTs have been identified, including lysine methyltransferase 9 (KMT9/G9a, also known as EHMT2), EZH2, SMYD2, SMYD3, NSD2, NSD3, SETD7, SETD1A, SETDB1, and EHMT1, among others.

G9a specifically catalyzes the methylation of histone H3 at lysine 9 (H3K9me2). G9a binds to the neuron-restrictive silencer element on the COL1A1 promoter, thereby reducing the expression of collagen I. In cases of hyperhomocysteinemia (HHcy), the expression of G9a is downregulated by homocysteine (Hcy) in human liver cells and liver tissues of HHcy mice. This downregulation decreases the binding of G9a and the levels of H3K9me2 on the promoter of the collagen I gene, resulting in upregulation of collagen I expression, thereby promoting liver fibrosis[138]. Similarly, inhibiting G9a can suppress peritoneal fibrosis[139] and pulmonary fibrosis[140] by reducing H3K9 methylation.

EZH2 functions as a histone methyltransferase targeting histone H3 at lysine 27 (H3K27), while JMJD3 serves as a demethylase. Numerous studies have implicated EZH2 in various fibrotic diseases. Research has shown that EZH2 is upregulated in activated hepatic stellate cells (HSCs). Inhibiting EZH2 with DZNep or silencing Ezh2RNA through siRNAs can downregulate H3K27me3 levels, subsequently reducing the expression of α-SMA and COL1A, decreasing collagen deposition in the liver, and enhancing HSC apoptosis. Overexpression of JMJD3 has also demonstrated similar effects[141]. EZH2 overexpression has been observed in renal fibrosis[142], IPF[143], SSc[144], and hypertrophic scars[145]. Inhibition of EZH2 expression by various means has led to suppression of collagen expression and fibrosis in these conditions (Fig. 4C).

4.6. *S-Nitrosylation*

Nitric oxide (NO) is a signaling molecule that plays a crucial role in various physiological processes. In *S*-nitrosylation (S−NO), the NO group is covalently added to the sulfur atom of cysteine residues in proteins, playing an important role in cellular signal transduction and redox regulation[146].

NO signaling is vital for the normal function of the vascular system. Under physiological conditions, NO is mainly produced by endothelial nitric oxide synthase (eNOS) and participates in the regulation of vascular tone. During inflammation, the generation of NO increases dramatically through the activation of inducible nitric oxide synthase (iNOS). iNOS activation leads to increased protein nitrosylation and *S*-nitrosylation. A study conducted in a rat model of acute hypertension induced by transverse aortic constriction (TAC) found that activation of iNOS in adventitial fibroblasts increased protein nitrosylation and *S*-nitrosylation levels, as well as the deposition of collagen I and III, exacerbating vascular fibrosis[147].

4.7. *Carbonylation*

Protein carbonylation (CO) is an irreversible oxidative modification associated with loss of function, increased toxicity, enhanced thermal sensitivity, or increased hydrophobicity, and is considered an early hallmark of oxidative stress-related diseases[148].

Studies have found that α-dicarbonyl compound methylglyoxal treatment leads to carbonylation of porcine dermal collagen I in a concentration- and time-dependent manner, resulting in morphological and functional changes in collagen in the skin. Accumulation of carbonylated collagen may lead to fibroblast apoptosis, decreased skin elasticity, and promote aging[149]. The ECM of intervertebral discs is composed of collagen, proteoglycans, and non-collagenous proteins. Matrix proteins isolated from intervertebral discs of aged mice exhibit carbonylation and glycation associated with oxidative damage, increasing the level of protein aggregation, and are related to structural changes and rupture of collagen and other proteins[148].

4.8. *S-Glutathionylation*

Protein *S*-glutathionylation (SSG) is a reversible post-translational modification related to redox signaling. Reduced or oxidized glutathione reacts with oxidized protein thiols or thiocyanate anions to

form PSSG modifications through several enzymatic and non-enzymatic mechanisms. PSSG can be reversed by glutaredoxin-1 (GLRX)[150].

Studies have found a significant decrease in GLRX enzyme activity and an increase in PSSG in fibrotic lungs, where endogenous GLRX is inactivated through oxidation mechanisms. Direct application of GLRX protein to the airways has been shown to enhance GLRX activity, reversing collagen accumulation induced by TGFB1 or bleomycin in mice, thereby alleviating lung fibrosis[151]. The absence of GLRX also promotes spontaneous activation of the TGF-β pathway in airway basal cells, increases expression of interstitial genes, promotes expression of *COL1A1* and fibronectin, and is associated with airway remodeling in fibrosis[152].

5. Novel post-translational modifications and collagen-related disorders

5.1. Crotonylation

Lysine crotonylation (Cr) is a novel post-translational modification of proteins. Lysine crotonylation is extensively involved in various pathophysiological processes, including cardiac remodeling[153], endodermal differentiation, and DNA repair[154]. P300/CBP, GCN5, and MYSTs mediate histone crotonylation, while HDAC1-3 and SIRT1−3 are the major executors of histone de-crotonylation. Additionally, short-chain enoyl-CoA hydratase 1 and chromodomain Y-like protein serve as the direct suppliers of crotonyl-CoA for regulating protein lysine crotonylation levels, thus negatively modulating protein lysine crotonylation[155].

Studies have found a decrease in total lysine crotonylation (Kcr) in the fibrotic livers of mice. Oral administration of the anti-fibrotic drug Sorafenib reversed the decreased levels of crotonylation, particularly at the levels of H2BK12cr and H3K18cr. The expression of lysine crotonylation was negatively correlated with serum biochemical indicators of fibrosis, such as type III procollagen, hyaluronic acid, and laminin. Additionally, Sorafenib inhibited the accumulation of α-SMA and collagen I induced by CCl in the liver. Furthermore, blocking the deacetylases HDAC1 and HDAC3 to increase total lysine crotonylation levels suppressed liver cancer cell proliferation. These pieces of evidence collectively suggest a potential role of lysine crotonylation in liver fibrosis[156]. Another study found that site-specific Kcr of mitochondrial protein IDH3a (isocitrate dehydrogenase 3 [NAD^+] alpha) and cytoskeletal protein TPM1 (tropomyosin alpha-1 chain), or enhancement of general Kcr by sodium crotonate, not only protected cardiomyocytes from apoptosis but also inhibited fibrosis after ischemia-reperfusion[157].

5.2. Lactylation

During protein lactylation (Lac), P300/MOF/GCN5 act as lactyltransferases, while Class I HDACs (HDAC1-3), SIRT1 and SIRT2 serve as histone lysine lactyl deacylases. Enhanced glycolysis and lactate uptake lead to increased intracellular lactate levels. Lactate is converted to lacyl-CoA through an unknown mechanism and serves as a donor to promote lactylation of both histone and non-histone proteins[10].

Bone marrow mesenchymal stem cells isolated from osteoporosis patients exhibit downregulation of histone H3K18 lactylation (H3K18la) and reduced expression of target genes, including collagen I alpha 2 chain (COL1A2), cartilage oligomeric matrix protein, ectonucleotide pyrophosphatase/phosphodiesterase 1, and transcription factor 7-like 2. Increasing exogenous lactate enhances H3K18la lactylation levels and directly stimulates the transcription of the aforementioned genes, suggesting that lactylation regulates the expression of osteogenic genes such as the collagen I gene, thereby participating in the differentiation of bone marrow mesenchymal stem cells into osteoblasts[29].

Another set of studies has found associations between lactylation and pulmonary fibrosis. Enhanced glycolysis in fibrotic lungs increases lactate production, leading to the promotion of pro-fibrotic genes in alveolar macrophages through non-cell-autonomous histone lactylation[158]. Additionally, levels of lactate are elevated in lung tissues of patients with IPF, which may promote myofibroblast differentiation through pH-dependent activation of latent TGF-β[159].

5.3. Succinylation

Succinyl-CoA, one of the most abundant acyl-CoA molecules in tissues, is an essential intermediate metabolite at the central node of the TCA cycle, hence succinylation(Suc) commonly occurs in mitochondrial proteins. P300/CBP or GCN5 can add succinyl groups on lysine residues, while SIRT5 serves as a desuccinylase[160].

Research has found that in a mouse model of TAC-induced heart failure, SIRT5 plays a crucial role in cardiac stress response. Mice with SIRT5 gene knockout (SIRT5KO) exhibited more severe cardiac dysfunction, cardiac hypertrophy, and myocardial fibrosis[161]. Conversely, mice overexpressing SIRT5 (SIRT5OE) showed significant protection against TAC-induced left ventricular dilation, subsequent functional decline, and fibrosis[162].

Additionally, research has found that in TAC mice, quercetin promotes the expression of SIRT5, thereby increasing the desuccinylation of $NADP^+$-dependent isocitrate dehydrogenase 2. This regulation helps to maintain redox balance, preserve mitochondrial homeostasis, suppress inflammation, and protect cardiomyocytes. Simultaneously, it inhibits the expression of fibroblast differentiation markers, collagenI and III, reducing the level of myocardial fibrosis injury and restoring cardiac function[163].

5.4. Propionylation

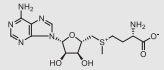
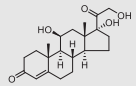
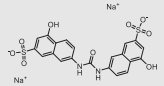
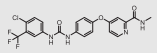
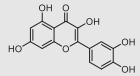
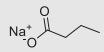
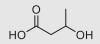
P300/CBP, GCN5 (KAT2A), and MYSTs catalyze protein propionylation (Pr), while SIRT1−3 can remove propionyl groups from lysine residues in histones. Lysine 14 of histone H3 (H3K14) is a common propionylation site, and propionylation at other sites has also been discovered. Histone propionylation is mainly enriched at gene promoters to drive high transcriptional output[164].

The propionyl coenzyme A, a propionylation donor, is produced as an intermediate of branched-chain amino acid (BCAA) oxidation in the nucleus. In one study, it was found that in mice subjected to pressure overload on the heart, compared to mice on a standard BCAA diet, those on a BCAA-deficient diet exhibited decreased H3K23Pr at promoters, resulting in reduced expression of *COL1A1* and fibrosis during cardiac hypertrophy. Additionally, it reversed the downregulation of ETC I−V subunits, enhanced mitochondrial respiration, and suppressed the progression of cardiac hypertrophy[165].

5.5. Butyrylation

Similar to acetylation, P300/CBP is a common butyryltransferase (Bu), and SIRT1−3 can mediate de-butyrylation processes.

Table 3 Drugs targeting novel PTMs to regulate collagen metabolism.

Drug	PTM	Modified site	Activation or inhibition	Disease/ Physiological process	The effect on diseases
S-Adenosyl-L-methionine(SAMe) 	Ubiquitination	Collagen I	Activation	Liver fibrosis	Collagen I processing and secretion and hepatic fibrosis were inhibited
Cortisol 	Ubiquitination	COL3A1	Activation	Amniotic rupture	The abundance of collagen III in amniotic tissue was decreased
AMI-1 	Methylation	Histone H4R3	Inhibition	Renal fibrosis	The expression of α-SMA, collagen I, and fibronectin is decreased, and the development of renal fibrosis is inhibited
Sorafenib 	Crotonylation	Histone H2BK12, H3K18	Activation	Liver fibrosis	The expression of α-SMA, collagen I, serum biochemical indexes of fibrosis (type III procollagen (PC-III), hyaluronic acid (HA), laminin (LN), etc.) were decreased, and the liver fibrosis of rats was inhibited
Lactate 	Lactylation	Histone H3K18	Activation	Osteoporosis	Transcription of *COL1A2*, COMP, ectonucleotide pyrophosphatase/ phosphodiesterase 1 and transcription factor 7-like 2 genes was increased, and osteoporosis was improved
Quercetin 	Succinylation	Isocitrate dehydrogenase 2	Activation	Diabetic nephropathy	The expression of collagens I and III was decreased, and the damage of myocardial fibrosis was decreased
Sodium butyrate 	Butyrylation	Histone H3K9	Activation	Renal fibrosis	Diabetic kidney inflammation is improved, glomerular collagen IV deposition is reduced, and renal fibrosis is alleviated
β-hydroxybutyrate (BHB) 	β-hydroxybutyrylation	Histone H3K9	Activation	Diabetic nephropathy	The production of MMP-2 increased, the content of COLIV decreased, and glomerular fibrosis was improved in diabetic rats

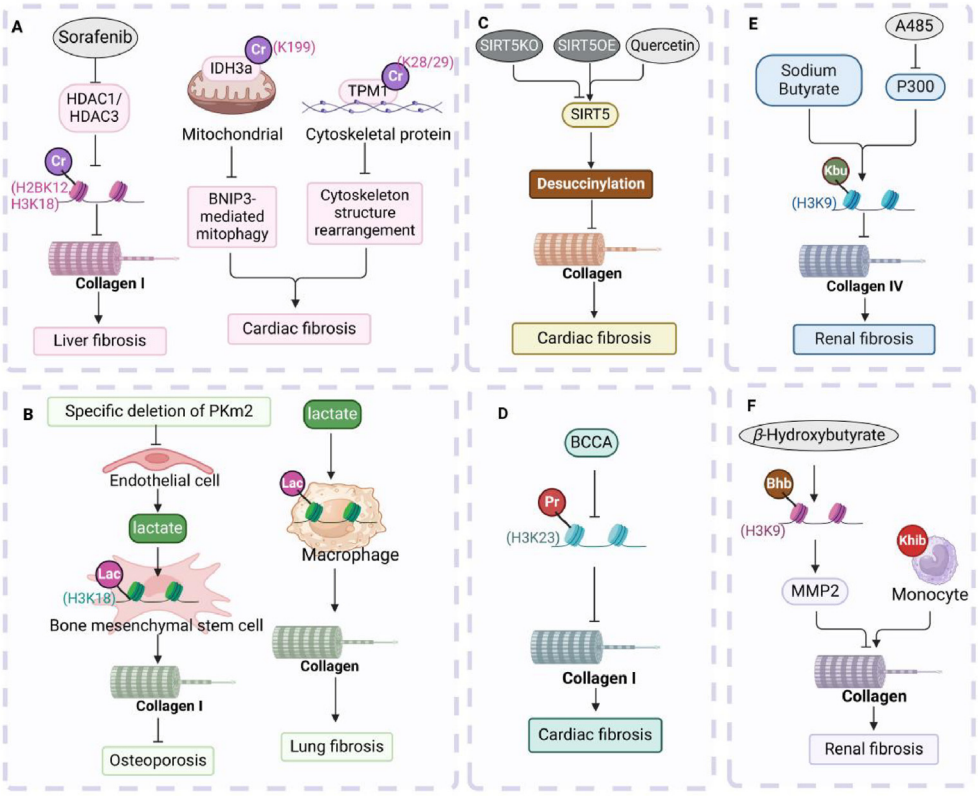


Figure 5 Novel PTMs and collagen-related disorders. (A) Sorafenib blocks HDAC1 and HDAC3, increasing levels of crotonylation on histone H2BK12 and H3K18, inhibiting hepatic collagen accumulation and liver fibrosis; crotonylation of mitochondrial protein IDH3a (Isocitrate dehydrogenase 3 [NAD^+] alpha) and cytoskeletal protein TPM1 (Tropomyosin alpha-1 chain) suppresses cardiac fibrosis. (B) Lactic acid derived from endothelial cells can reduce the level of histone lactylation in bone marrow mesenchymal stem cells, inhibiting the development of osteoporosis, while specific deletion of Pkm2 can reverse this process. Lactic acid promotes histone lactylation in alveolar macrophages, leading to pulmonary fibrosis. (C) SIRT5 reduces the level of myocardial fibrosis injury by promoting the desuccinylation process. (D) Branched-chain amino acids (BCAAs) promote propionylation of histone H3K23 at the promoter, inhibiting type I collagen production and cardiac fibrosis. (E) Butyrate induces an increase in the level of histone H3K9butyrylation, which can alleviate renal fibrosis by reducing collagen fiber IV deposition in the glomerulus. However, the histone modification enzyme p300 inhibitor A485 can reverse this process. (F) β-Hydroxybutyrate (BHB) significantly increases H3K9 β-hydroxybutyrylation at the matrix metalloproteinase-2 (MMP-2) promoter, reducing collagen content and alleviating glomerular fibrosis. In peripheral blood mononuclear cells of end-stage renal disease (ESRD) patients, widespread 2-hydroxyisobutyrylation sites are present.

Butyrate, induced by acetyl-CoA synthetase 2, is the corresponding substrate for histone butyrylation, making it crucial for histone butyrylation[8]. Research has found that H3K9bu is a major histone butyrylation mark enriched at transcription start sites. Inducing histone H3K9bu levels with butyrate supplementation, both *in vitro* and *in vivo*, can ameliorate diabetic kidney inflammation and reduce glomerular collagen IV deposition, thus alleviating kidney fibrosis. Conversely, inhibiting histone butyrylation with the histone modifier p300 inhibitor A485 reverses the anti-inflammatory and anti-fibrotic effects of butyrate. This suggests that butyrate-induced histone Kbu may be an important molecular mechanism in the pathogenesis of diabetic kidney disease[166].

5.6. *β-Hydroxybutyrylation, 2-hydroxyisobutyrylation*

In β-hydroxybutyrylation (Bhb), P300 can add intracellular β-hydroxybutyryl-CoA to histones in a concentration-dependent manner, a process that can be reversed by SIRT3[167]. 2-Hydroxyisobutyrate is an isomer of β-hydroxybutyrate, derived from microbial degradation of dietary proteins. It is converted to 2-hydroxyisobutyryl-CoA, the donor for lysine 2-hydroxyisobutyrylation (Khib). Tip60, TmcA, and p300 can mediate Khib, while HDAC1−3 serve as its removal enzymes[168].

Treatment with β-hydroxybutyrate salts in diabetic rats significantly increases H3K9bhb at the MMP-2 promoter, upregulating MMP-2 production and concentration-dependently decreasing COLIV content, thus improving renal biochemical markers and alleviating glomerular fibrosis in diabetic rats[169]. Additionally, it has been found that Khib sites are widely present in peripheral blood mononuclear cells of end-stage renal disease (ESRD) patients, while the Rho/ROCK signaling pathway is significantly upregulated in ESRD, suggesting a potential involvement of Khib in renal fibrosis in ESRD patients[168] (Table 3, Fig. 5).

6. Conclusions

In summary, collagen is an indispensable structural protein ubiquitously expressed in diverse tissues and organs of the human body, playing a pivotal role in the structure and function of multiple systems. Aberrations in collagen structure or quantity

have been implicated in a broad spectrum of diseases across various systems in the human body.

Although the factors contributing to collagen-related diseases necessitate further elucidation, investigations into various types of diseases consistently suggest that structural or quantitative abnormalities of collagen related to PTMs are crucial determinants. This article provides an overview of the PTMs occurring during collagen synthesis, such as hydroxylation and glycosylation, as well as PTMs in collagen-related diseases, including fibrosis, scars, and tumors.

In addition to classical modifications such as phosphorylation, acetylation, and ubiquitination, this article also explores the roles of recently identified novel PTMs in the pathogenesis and progression of collagen-related diseases, including crotonylation, lactylation, succinylation, propionylation, butyrylation, hydroxybutyrylation, and hydroxyethylbutyrylation, offering new insights and evidence for elucidating the pathogenic mechanisms of these diseases. The modifying enzymes, de-modifying enzymes, modified targets, and PTM-related drugs associated with various types of PTMs are also discussed in detail, providing potential novel therapeutic strategies for clinical application.

Furthermore, the crosstalk of PTMs in collagen-related diseases remains to be investigated. The sequence and timing of protein modifications may be crucial for specific cellular processes. For example, phosphorylation following ubiquitination can target proteins for degradation, while acetylation following phosphorylation can alter protein−protein interactions. Therefore, in-depth studies on the crosstalk of PTMs are of significant importance for understanding the relationship between epigenetic modifications and physiological/pathological processes. Additionally, numerous studies suggest that epithelial−mesenchymal transition is closely associated with fibrosis and tumorigenesis. The complex interplay between EMT and collagen, as well as the role of PTMs in this process, also warrant further exploration.

The advancement in PTM identification techniques, algorithms, and mass spectrometry technologies has significantly facilitated and influenced the in-depth exploration of post-translational modifications in collagen and its related diseases. As more and more novel post-translational modifications are continuously being discovered, their relationship with collagen awaits further investigation. However, the detection of post-translational modifications related to collagen-related diseases remains challenging and incomplete in clinical trials. This aspect may become a crucial direction for future clinical research and an important target for clinical therapy.

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Author contributions

Linghong Guo and Weiyi Xiang contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. Linghong Guo: Conceptualization, Methodology, Writing-Original draft preparation. Weiyi Xiang: Visualization, Writing-Original draft preparation. Zhaoping Pan: Visualization. He Gu: Writing-Reviewing and Editing. Xian Jiang: Supervision, Writing-Reviewing and Editing.

Conflicts of interest

The authors declare no competing financial interest.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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