Am J Cancer Res 2026;16(4):1437-1458
www.ajcr.us /ISSN:2156-6976/ajcr0172775

Review Article

COL10A1 beyond skeletal development: a hypertrophic chondrocyte-specific collagen emerging as a potential biomarker and tumor microenvironment regulator in solid cancers

Tianxiang Zhu[1*], Yuting Liang[2,3*], Wanyu Dong[1*], Rushuang Deng[1], Wenshi Hu[1], Rong Wei[1], Qian Wang[4], Yaojuan Lu[1,5], Longwei Qiao[6,7], Tong-Chuan He[2], Qiping Zheng[1,5,8]

[1]Department of Hematology and Hematological Laboratory Science, Jiangsu Key Laboratory of Medical Science and Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang 212013, Jiangsu, China; [2]The Molecular Oncology Laboratory, Department of Orthopedic Surgery and Rehabilitation Medicine, The University of Chicago Medical Center, Chicago, Illinois 60637, USA; [3]Center for Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou 215000, Jiangsu, China; [4]Department of Human Anatomy, School of Medicine, Jiangsu University, Zhenjiang 212013, Jiangsu, China; [5]Shenzhen Walgenron Bio-Pharm Co., Ltd., Shenzhen 518118, Guangdong, China; [6]Center for Reproduction and Genetics, School of Gusu, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Nanjing Medical University, Suzhou 215002, Jiangsu, China; [7]State Key Laboratory of Genetic Engineering and MOE Engineering Research Centre of Gene Technology, School of Life Sciences, Fudan University, Shanghai 200433, China; [8]Shenzhen International Institute for Biomedical Research, Shenzhen 518110, Guangdong, China. [*]Equal contributors.

Received March 20, 2026; Accepted April 15, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Type X collagen (COL10A1) is an extracellular matrix protein primarily expressed by hypertrophic chondrocytes and is essential for endochondral ossification and skeletal mineralization. Although traditionally regarded as cartilage-specific, recent studies have reported its re-expression in a range of solid tumors. This shift in expression pattern suggests that COL10A1 may have functions beyond development, particularly within the tumor microenvironment (TME). Elevated COL10A1 levels have been reported in cancers such as breast, gastric, colorectal, and lung cancers, where both tissue expression and circulating levels are frequently associated with advanced disease stage and poor clinical outcomes. These observations support COL10A1 as a potential diagnostic and prognostic biomarker. Beyond its clinical associations, accumulating evidence indicates that COL10A1 actively contributes to tumor progression. It is involved in extracellular matrix remodeling, angiogenesis, epithelial-mesenchymal transition (EMT), and alterations in immune cell infiltration, and possibly immunotherapy response. In addition, its enrichment in specific subsets of cancer-associated fibroblasts (CAFs) highlights its essential role in tumor-stroma interactions. At the mechanistic level, COL10A1 has been linked to multiple oncogenic signaling pathways, including TGF-β1/SOX9, as well as downstream DDR2/FAK and ITGB1/PI3K/AKT pathways, which may collectively promote tumor invasion, metastasis, and therapy resistance. However, its biological functions are not yet fully defined, and tumor heterogeneity continues to complicate its clinical application. Further studies are needed to clarify how COL10A1-functions within the tumor microenvironment and to determine its clinical value as a biomarker and a potential therapeutic target in solid cancers.

Keywords: COL10A1, cancer-associated fibroblasts, biomarker, tumor microenvironment

Introduction

The extracellular matrix (ECM) is a key component of the tumor microenvironment, consisting of a complex network of structural and functional macromolecules [1]. Rather than acting merely as a static scaffold for cell adhesion, the ECM functions as a dynamic and biologically active system that influences essential cellular behaviors such as proliferation, differentiation, and migration [2]. It is composed of collagens, glycoproteins, proteoglycans, and

https://doi.org/10.62347/EVWJ6469

various polysaccharides, which together provide both mechanical support and signal transduction [3]. Under normal physiological conditions, ECM homeostasis is tightly regulated, maintaining a balance between synthesis and degradation to support tissue structure and development [4]. However, in cancer, this balance is disrupted. The ECM undergoes extensive remodeling, which is conducive to tumor initiation, progression, and therapeutic resistance [5]. These changes may involve alterations in composition and structure, abnormal collagen cross-linking, redistribution of matrix components, and increased matrix stiffness, all of which collectively reshape the tumor microenvironment [6]. This remodeling not only promotes tumor cell proliferation, invasion, and metastasis [5], but also forms a physical and biochemical barrier that hinders drug delivery and limits immune cell infiltration, ultimately reducing treatment efficacy [5, 7].

Collagen is one of the most abundant proteins in the human body and is the main structural component of the extracellular matrix [8, 9]. To date, 28 types of collagen have been identified. They all share a characteristic triple-helical structure composed of three α chains arranged in a right-handed configuration [10, 11]. These α chains are defined by repeating glycine-X-Y motifs, where X and Y are often proline and hydroxyproline, and these residues play a critical role in stabilizing the triple-helical structure [10, 12].

In addition to its well-established structural role in maintaining tissue integrity and mechanical properties, collagen is also involved in cell signal transduction. Through interactions with cell surface receptors, it can influence processes such as cell proliferation, differentiation, and intracellular signaling pathways [9, 13, 14].

Collagens are typically classified into several categories, including fibril-forming, basement membrane-associated, short-chain, and FACIT (fibril-associated collagens with interrupted triple helices) types [11]. These subclasses differ in both structure and function. Fibril-forming collagens constitute the primary tensile framework of the ECM, while FACIT collagens regulate fiber organization. Other collagen types contribute to specialized matrix structures, such as basement membranes, which are essential for maintaining tissue structure and function [15-18].

Type X collagen is a short-chain, network-structured type of collagen encoded by the *COL10A1* gene [11]. Under physiological conditions, its expression is strictly limited and serves as a marker of hypertrophic chondrocytes during endochondral ossification. During this process, COL10A1 forms a specialized ECM that supports vascular invasion and subsequent bone formation [19]. Although sequencing data indicate relatively high expression in certain non-pathological tissues (such as the gallbladder and ovaries), its levels in most normal tissues remain relatively low [20]. In contrast, COL10A1 is widely overexpressed in various solid tumors [21], suggesting its involvement in oncogenic processes. Evidence from bioinformatic analyses, functional studies, and animal models indicates that COL10A1 functions as a potent oncogene [22]. Its upregulation is not only a consequence of tumor formation but is increasingly regarded as an active driver of tumor malignant progression. Therefore, given its unique expression pattern between normal and diseased states, COL10A1 represents a promising biomarker for cancer diagnosis. This review summarizes the current understanding of COL10A1 in cancer, focusing on its expression patterns, molecular mechanisms, and role in tumor microenvironment remodeling.

The biology and pathobiology of type X collagen

Molecular structure and physiological function

Type X collagen is a homotrimer composed of three identical α1 (X) chains, which are encoded by the *COL10A1* gene [23]. Its structure consists of a short central triple-helical collagenous domain, with an N-terminal NC2 domain on one side and a spherical C-terminal NC1 domain on the other [24]. The highly conserved NC1 domain is crucial for initiating and stabilizing trimer assembly [25, 26]. This collagen is specifically produced by hypertrophic chondrocytes in the growth plate [19]. In the process of ECM remodeling, the intact trimeric NC1 domain is secreted into the circulation. This fragment, referred to as the colla-

Table 1. MCDS-related pathogenic mutations in the COL10A1 gene

Mutation position	Variant type	Molecular consequence	Ref.
52	G>A (p.Gly18Arg)	Missense variant	[167]
1293-1296	dup (p.Pro433fs)	Frameshift variant	/
1772	G>T (p.Cys591Phe)	Missense variant	/
1790	A>G (p.Tyr597Cys)	Missense variant	[168]
1833	G>A (p.Trp611Ter)	Nonsense	/
1841	T>C (p.Leu614Pro)	Missense variant	[169]
1853-1866	del (p.Gly618fs)	Frameshift variant	/
1857-1869	del (p.Val621fs)	Frameshift variant	[40]
1858-1859	del (p.Pro620fs)	Frameshift variant	[170]
1859	del (p.Pro620fs)	Frameshift variant	[171]
1884	C>G (p.Tyr628Ter)	Nonsense	[170]
1900	del (p.Asp634fs)	Frameshift variant	/
1945	C>T (p.Gln649Ter)	Nonsense	/
1951-1952	dup (p.Trp651fs)	Frameshift variant	/
1952-153	insA (p.Trp651Ter)	Nonsense	/
1989	C>A (p.Tyr663Ter)	Nonsense	[172]
1989	C>G (p.Tyr663Ter)	Nonsense	[44]

gen X marker (CXM), is a serum biomarker used to evaluate bone growth rate in children [27, 28].

Type X collagen plays a critical role in endochondral skeletal development. It is involved in matrix formation, proteoglycan accumulation, and initiation of mineralization [29-31]. During this process, mesenchymal cells differentiate into chondrocytes, which undergo hypertrophy after proliferation [32]. At this stage, chondrocytes secrete large amounts of type X collagen [33]. Mechanistically, collagen X regulates calcification by binding to matrix vesicles and promoting calcium influx [34, 35]. It also forms a pericellular network that gathers key components (including matrix vesicles and proteoglycans) in the hypertrophic zone [36]. This spatial organization ensures proper initiation and control of mineralization, which is essential for normal ossification [36].

The importance of these functions is supported by genetic models. Early collagen X-null mice exhibited minimal phenotypic abnormalities [37], which might be due to compensatory mechanisms. However, other models demonstrate its importance. Collagen X deficient mice show abnormal matrix distribution and impaired trabecular bone formation [36]. Transgenic mice expressing mutant collagen X develop skeletal deformities, including growth plate compression and reduced bone formation [38]. Moreover, COL10A1 knockdown in mesenchymal stem cells disrupts ECM synthesis during cartilage differentiation and significantly impairs bone formation in transplantation models [39]. In summary, these studies emphasize the essential role of collagen X in the process of cartilage differentiation and endochondral ossification.

Dysregulation and associated diseases

Metaphyseal chondrodysplasia, Schmid type (MCDS), is an autosomal dominant skeletal disorder caused by *COL10A1* mutations [40, 41]. Patients typically present with short stature, coxa vara, genu varum, and a waddling gait [40, 42]. Most mutations are located in the NC1 region, which is critical for trimerization and stability of collagen X [26, 43]. These mutations, including missense, nonsense, and frameshift variants, often produce misfolded α chains that accumulate in hypertrophic chondrocytes (**Table 1**) [44]. This accumulation induces endoplasmic reticulum (ER) stress and activates the unfolded protein response [45], leading to impaired chondrocyte differentiation and degradation of mutant proteins, ultimately resulting in functional haploinsufficiency [46]. In some cases, missense mutations exert dominant-negative effects by incorporating into collagen trimers and disrupting wild-type chain function [47]. These mechanisms disrupt growth plate organization and endochondral ossification, resulting in the characteristic abnormalities of MCDS [48]. Recently, the FDA-approved antiepileptic drug carbamazepine (CBZ) has emerged as a potential therapeutic option for MCDS [49]. Studies show that CBZ promotes clearance of misfolded proteins and alleviates ER stress in model systems, and it has progressed to clinical trials [50-52].

Elucidating the regulatory mechanisms of COL10A1 expression is essential for under-

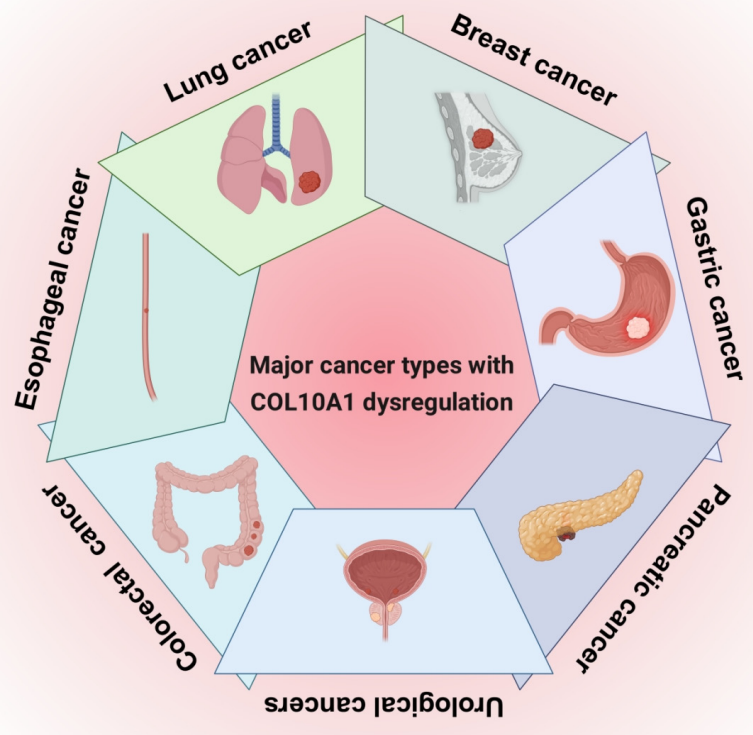

Figure 1. Major cancer types characterized by COL10A1 dysregulation. COL10A1 expression is aberrantly elevated across multiple human malignancies, including breast, gastric, pancreatic, urological, colorectal, esophageal, and lung cancers.

standing chondrocyte hypertrophy. Under physiological conditions, COL10A1 transcription is tightly regulated by multiple factors. HIF-2α directly binds to hypoxia response elements in its promoter to activate transcription [53], while RUNX2 promotes expression through interaction with cis-regulatory elements [54]. Additional transcription factors, including DLX5, MEF2A, DDX5, and the inhibitory regulator TBX5, also participate in its regulation [55, 56]. Notably, SOX9 suppresses RUNX2 expression and inhibits the transition from proliferative to hypertrophic chondrocytes [57, 58]. However, in the hypertrophic zone, SOX9 cooperates with MEF2C to promote COL10A1 expression [57]. MicroRNAs also contribute to this regulation: miR-218 targets RUNX2, MEF2C, and COL10A1 to inhibit hypertrophic differentiation [59], while miR-26 suppresses COL10A1 production and maintains cartilage matrix stability [60].

COL10A1 and its fragments also have important roles in bone development and joint diseases. The collagen X marker, which corresponds to the trimeric NC1 domain, is released into circulation during endochondral ossification [61, 62]. CXM serves as a real-time indicator of bone growth and height velocity in children [28, 61], and abnormal levels reflect impaired ossification in conditions such as osteogenesis imperfecta, skeletal dysplasia, achondroplasia, and fracture healing [61, 63-66].

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive cartilage degeneration, leading to pain, stiffness, and functional impairment [67-69]. OA chondrocytes undergo hypertrophic transformation, marked by increased collagen X expression and reduced cartilage-specific markers [70, 71]. This process triggers matrix degradation, pathological calcification, and vascular invasion [72, 73]. Additionally, a collagen X neo-epitope (Col10neo) has been identified as a potential diagnostic biomarker for knee OA [74]. The C-Col10 assay further shows that serum collagen X levels are elevated in early OA and correlate with cartilage degeneration [75].

Targeting aberrant chondrocyte hypertrophy has gained attention as a potential therapeutic approach for osteoarthritis. A number of regulatory pathways involved in this process have been identified. For example, undercarboxylated osteocalcin (ucOCN) has been shown to suppress hypertrophic markers such as COL10A1 and MMP13, while promoting autophagy through the GPRC6A/HIF-1α pathway [76]. Similarly, the neuronal guidance molecule Sema3A can inhibit hypertrophic changes via PI3K signaling [77].

Emerging evidence also highlights a role for extracellular vesicles in modulating disease progression. Exosomal miR-26b-5p has been reported to reduce chondrocyte hypertrophy and influence macrophage polarization [78]. In parallel, targeting key transcription factors such as DLX5 and RUNX2 can attenuate OA

Table 2. COL10A1 expression and its biological roles in breast and gynecologic tumors

Cancer type	Sample type	Exp.	Research content	Ref.
Breast cancer	Tissue	↑	The upregulated COL10A1 promotes the progression of BRCA and is associated with poor prognosis and disease stage.	[92, 93, 173]
		↑	COL10A1 promotes the malignant progression of BRCA by upregulating the expression of P4HB.	[174]
		↑	COL10A1 promotes the progression of TNBC through the Wnt/β-catenin signaling pathway. Its high expression leads to poorer outcomes in terms of OS and RFS.	[113]
		↑	Increased expression of COL10A1 and low levels of TILs are associated with poor pathological response in ER+/HER2+ breast tumors.	[127]
		↑	COL10A1 increased from pure DCIS to DCIS of DCIS/IBC mixed tumors.	[175]
		↑	Tumors with high expression of COL10A1 may possess higher EMT ability and metastasis potential.	[176]
		↑	COL10A1 regulates EMT and BRCA brain metastasis.	[146]
		↑	The specific expression of COL10A1 in tumors and its localization in blood vessels.	[21]
		↑	COL10A1 directly interacts with ITGB1, activating the PI3K/AKT signaling pathway, and promoting the growth and metastasis of TNBC.	[162]
		/	LncRNA HAGLROS binds to miR-135-3p, thereby alleviating its repressive effect on COL10A1 expression.	[122]
		/	COL10A1 is correlated with LINC01614 and the small molecule inhibitions of TGF-β or FAK signaling suppress LINC01614 expression.	[177]
		/	Urchin-Like magnetic nanoparticles loaded with COL10A1 siRNA and stattic for TNBC therapy.	[178]
	Blood	↑	The combination containing COL10A1 can distinguish between BC patients and benign diseases.	[108]
Cervical cancer	Tissue	↑	COL10A1 promotes the proliferation, invasion and EMT of cervical cancer by activating the TGF-β/SMAD signaling pathway.	[155]

Abbreviations: BRCA, breast cancer; DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; OS, overall survival; RFS, recurrence-free survival; TNBC, triple-negative breast cancer.

progression, at least in part by downregulating COL10A1 expression [79, 80].

Additional signaling axes have also been implicated. Inhibition of the AMPK-β-catenin-Runx2 pathway has been shown to reduce downstream matrix metalloproteinase activity [81]. Furthermore, studies examining the role of leptin in age-related OA, along with the identification of aging-associated biomarkers, provide new perspectives on disease mechanisms and potential therapeutic targets [82, 83].

Dual-platform biomarker: from tissue to liquid biopsy

As the global burden of cancer continues to increase, there is a growing need for methods that enable early detection and real-time disease monitoring [84]. Although tissue biopsy remains the standard approach for histological diagnosis, its invasive nature and susceptibility to sampling bias limit its suitability for repeated assessment [85].

Liquid biopsy has emerged as an alternative strategy, allowing the detection of tumor-derived components from small volumes of body fluids and enabling longitudinal monitoring [86, 87]. While COL10A1 was originally studied in the context of cartilage development, accumulating evidence indicates that it is upregulated across a range of malignancies (**Figure 1**; **Tables 2**-**5**) [22, 88-90]. Notably, COL10A1 can also be detected in circulation, supporting its potential use as a non-invasive serum biomarker [89, 91].

The presence of COL10A1 in both tumor tissues and blood samples suggests that it may

Table 3. COL10A1 expression and its biological roles in digestive system tumors

Cancer type	Sample type	Exp.	Research content	Ref.
Gastric cancer	Tissue	↑	COL10A1 is related to the staging and prognosis of GC.	[95, 96]
		↑	COL10A1 is associated with GC metastasis and reduced survival period and the TGF-β1-SOX9 axis induces the expression of COL10A1.	[114]
		↑	Overexpression of COL10A1 promotes the invasiveness of GC through EMT.	[145]
		↑	Knockdown of COL10A1 inhibits the proliferation and migration of GC cells while promoting their apoptosis.	[179]
		↑	COL10A1 is identified as a tumor-specific ECM protein through the decellularization technology.	[135]
		/	The N110T and H165R mutants of SOX9 promote tumor progression by enhancing the binding affinity of the COL10A1-SOX9 complex.	[180]
		/	COL10A1 is a potential mRNA vaccine candidate for STAD.	[181]
		/	COL10A1 is one of the hub genes in the circRNA-miRNA-mRNA regulatory network and overexpression of COL10A1 is associated with a lower OS rate in STAD.	[182]
	Blood	↑	Elevated plasma levels of COL10A1 are associated with poor survival in patients.	[89]
		↑	High expression of COL10A1 is associated with gastrointestinal tumorigenesis and can be detected in the blood.	[183]
		↑	The inclusion of COL10A1 in a panel of biomarkers enhances the early diagnosis of gastric cancer and improves the distinction between benign and malignant gastric diseases.	[109]
Colorectal cancer	Tissue	↑	High expression of COL10A1 is an independent risk factor for prognosis and overall survival in CRC patients.	[98]
		↑	COL10A1 is a potential diagnostic biomarker associated with deficient mismatch repair and immune infiltration in colon cancer.	[125]
		↑	The abundance of COL10A1 in CRC tissues predicts metastatic and immunogenic properties and it may mediate the interaction between cancer cells and TME.	[99]
		/	COL10A1 is upregulated in FAP-positive CAFs.	[184]
		/	The COL10A1+Fib subpopulation is associated with the progression of colorectal cancer and poor prognosis of patients.	[118]
		/	SYNPO2L promotes the secretion of COL10A1 and the infiltration of tumor-associated fibroblasts, thereby facilitating EMT.	[185]
	Blood	↑	Serum COL10A1 serve as a potential diagnostic candidate for detecting adenomatous lesions and colorectal neoplasms.	[106]
Pancreatic cancer	Tissue	↑	Patients with high COL10A1 expression exhibits worse RFS and OS.	[107]
		↑	COL10A1 promotes pancreatic adenocarcinoma tumorigenesis by regulating CD276.	[100]
	Blood	↑	Serum COL10A1 has high sensitivity and specificity for the diagnosis of PDAC.	[107]
Esophageal cancer	Tissue	↑	COL10A1 is a potential diagnostic and prognostic biomarker in ESCC.	[186]
		↑	The potential of COL10A1 as a molecular biomarker for early diagnosis of ESCC.	[187]
		/	COL10A1Var1 is a novel and recurrent transcript variant associated with Esophageal Adenocarcinoma, and it has potential tumor-promoting functions.	[188]
Hepatocellular carcinoma	Tissue	↑	COL10A1 serves as a diagnostic biomarker for differentiating MASLD from MASL-HCC.	[189]
Cholangiocarcinoma	Tissue	↓	COL10A1 is a down-regulated differentially expressed gene.	[190]

Abbreviations: CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; PDAC, pancreatic ductal adenocarcinoma; STAD, stomach adenocarcinoma.

provide clinically relevant information on tumor progression and could assist in guiding patient.

Prognostic indicator across multiple tumors

COL10A1 is highly expressed in various cancers and is associated with poor prognosis. In breast cancer (**Table 2**), its expression is particularly elevated in aggressive subtypes, including invasive lobular and ductal carcinoma [21, 92]. Tissue microarray-based immunohistochemistry further demonstrates that high COL10A1 expression correlates with advanced stage and unfavorable outcomes [92, 93]. In

Table 4. COL10A1 expression and its biological roles in tumors of respiratory and urinary systems

Cancer type	Sample type	Exp.	Research content	Ref.
Lung Cancer	Tissue	↑	Potential diagnostic value of COL10A1 in IPF and NSCLC.	[191]
		↑	miR-384 reduces the level of COL10A1, thereby inhibiting cell proliferation and promoting apoptosis and autophagy in NSCLC cells.	[192]
		↑	COL10A1 is identified as a key hub gene linking ECM remodeling and tumor progression across COPD, LUAD, and LUSC.	[193]
		↑	The COL10A1/DDR2/FAK axis regulates the proliferation and metastasis of LUAD cells.	[101]
		/	COL10A1 secreted by CAFs promotes LUSC cell proliferation and suppresses apoptosis induced by oxidative stress through METTL3-mediated m^6A modification of its mRNA, thereby accelerating Tumor growth.	[194]
	Blood	↑	COL10A1 levels are elevated in lung cancer patients compared to healthy heavy smokers.	[91]
Nasopharyngeal carcinoma	Tissue	↑	COL10A1 may serve as a prognostic and diagnostic marker for nasopharyngeal carcinoma.	[195]
Prostate Cancer	Tissue	↑	COL10A1 is related to tumor prognosis and tumor prediction.	[102, 123]
		↑	COL10A1 directly interacts with INHBA and activates the PI3K/AKT signaling pathway.	[164]
		/	COL10A1 may be involved in predicting bone metastasis of prostate cancer.	[196]
		/	COL10A1 is involved in predicting the biochemical recurrence of prostate cancer patients.	[197]
Bladder cancer	Tissue	↑	COL10A1 is upregulated in the BLCA samples, and increased expression of COL10A1 is associated with a lower overall survival rate.	[100]
		↑	COL10A1 is one of the markers for preoperative prediction of lymph node metastasis in BLCA.	[198]

Abbreviations: BLCA, bladder cancer; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NSCLC, non-small cell lung cancer; OS, overall survival.

basal cell carcinoma (BCC), COL10A1 is not uniformly expressed across all high-risk subtypes but is enriched in the stroma of sclerotic/infiltrative and basosquamous variants [94], suggesting its value in subtype classification and prognosis.

Similar patterns are observed in digestive and urologic malignancies. In gastric cancer (**Table 3**), COL10A1 expression is higher in tumor tissues than in adjacent normal tissues [95] and is associated with lymph node metastasis and reduced overall survival [89, 95]. It is also linked to immune infiltration within the tumor microenvironment [96, 97]. In colorectal cancer, elevated COL10A1 predicts poorer overall and disease-free survival [98, 99]. Likewise, in bladder cancer, its upregulation is associated with shorter survival, supporting its role as a prognostic biomarker [100].

COL10A1 also shows prognostic significance in other adenocarcinomas. In lung adenocarcinoma (**Table 4**), its expression is elevated and positively correlates with lymph node metastasis, serving as an independent predictor of poor prognosis [101]. In prostate cancer, COL10A1 expression is increased and associated with clinical features, demonstrating both diagnostic and prognostic value [102]. In pancreatic cancer, COL10A1 overexpression correlates with advanced clinicopathological features, supporting its potential as an early diagnostic and prognostic marker [103]. Additionally, COL10A1 is upregulated in laryngeal squamous cell carcinoma and oral cancer (**Table 5**) [104, 105].

Serum biomarker in tumors

Circulating COL10A1 has gained attention as a potential biomarker across multiple cancer types. Its presence in blood, together with its association with disease progression, makes it an attractive candidate for minimally invasive and repeatable monitoring. In gastric cancer, elevated circulating COL10A1 levels have been linked to poorer survival outcomes, suggesting

Table 5. COL10A1 expression and its biological roles in other carcinomas and sarcomas

Cancer type	Sample type	Exp.	Research content	Ref.
Basal cell carcinoma	Tissue	↑	COL10A1 is a marker for high-risk basal cell carcinoma.	[94]
Laryngeal squamous cell carcinoma	Tissue	↑	COL10A1 may serve as a potential drug target for Laryngeal squamous cell carcinoma.	[104]
Oral cancer	Tissue	↑	The exosomes derived from hBMSCs contain miR-101-3p, which targets COL10A1 and inhibits the progression of oral cancer.	[105]
Thyroid carcinoma	Tissue	/	COL10A1 may serve as a novel candidate diagnostic marker for TCPTC.	[199]
Osteosarcoma	Tissue	/	COL10A1 is a potential procollagen substrate of PCOLCE and is positively correlated with TWIST1, a key molecule in metastasis.	[200]
		/	LncRNA TTTY14 may influence the development of osteosarcoma by co-expressing with COL10A1.	[201]
Chondrosarcoma	Tissue	/	COL10A1 expression is higher in both Chondrosarcoma tissue and 3D cultures than in 2D cultures.	[202]
		/	Depsipeptide inhibits the growth of chondrosarcoma cells by inducing cell cycle arrest and/or apoptosis. Long-term treatment with low-dose depsipeptide leads to differentiation into a hypertrophic phenotype, characterized by increased COL10A1 expression in chondrosarcoma cells.	[203]

Abbreviations: TCPTC, tall cell variant papillary thyroid carcinoma.

potential value for both early detection and prognostic assessment [89]. A similar trend has been reported in colorectal disease, where increased serum COL10A1 can distinguish patients with colon cancer or adenomas from cancer-free individuals, supporting its role in early diagnosis [106].

In pancreatic ductal adenocarcinoma, COL10A1 overexpression has been observed in both tumor tissues and plasma, with higher levels correlating with disease progression and reduced survival, indicating both diagnostic and prognostic relevance [107]. In non-small cell lung cancer, plasma COL10A1 concentrations are elevated compared with those in healthy heavy smokers [91], although current evidence does not show a clear relationship with clinical stage or survival [91].

Despite these findings, the diagnostic performance of individual circulating biomarkers remains limited. To improve accuracy, combined biomarker approaches have been explored. For instance, integrating COL10A1 with COL11A1 and COMP significantly enhances the ability to distinguish breast cancer from benign breast conditions [108]. Similarly, multimarker models incorporating COL10A1 have shown improved performance in early detection and in differentiating malignant from benign tumors [109].

The consistent elevation of circulating COL10A1 across different malignancies suggests that common underlying processes may be involved. Increased tumor expression, together with active extracellular matrix remodeling, likely contributes to the release of collagen X fragments into the bloodstream. In this context, circulating COL10A1 may serve as an indirect indicator of ECM turnover in cancer, analogous to its role in skeletal development.

The emerging role of COL10A1 in the tumor microenvironment

The tumor microenvironment (TME) regulates cancer development, therapeutic response, and patient prognosis through complex interactions between cells and molecules [110, 111]. The extracellular matrix has evolved from a passive scaffold into an active regulator of tumor progression, engaging in bidirectional crosstalk with malignant and stromal cells [112]. In this context, short-chain collagen type X has become an important functional component of the TME. In various cancers, the abnormal expression of COL10A1 is not only a consequence of tumor growth but also a driving factor

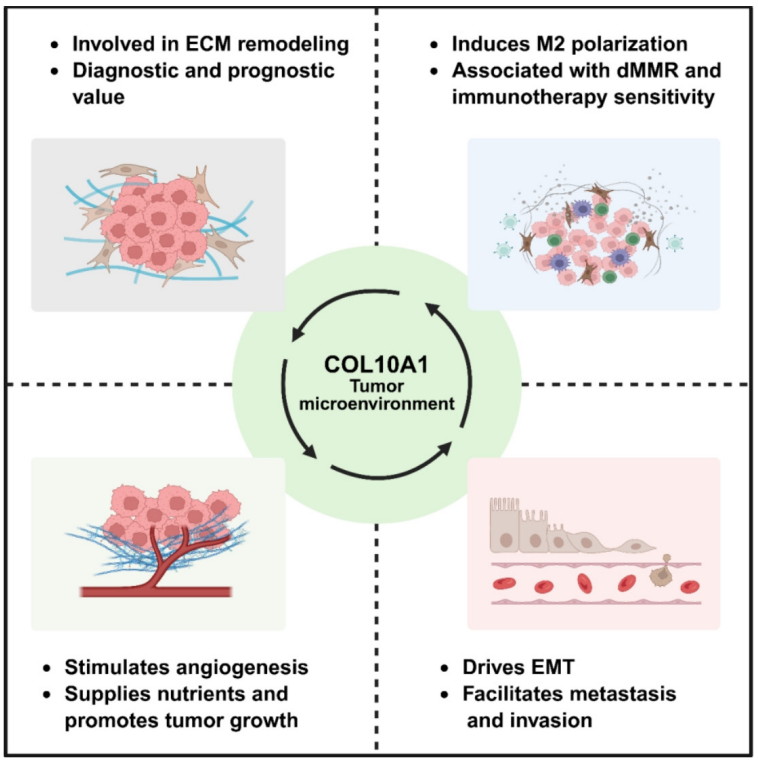

Figure 2. The emerging role of COL10A1 in the tumor microenvironment. COL10A1 participates in extracellular matrix (ECM) remodeling and functions as a dual biomarker in both tissue and serum. It promotes tumor progression by inducing epithelial-mesenchymal transition (EMT), angiogenesis, metastasis, and M2 macrophage polarization.

for malignancy. COL10A1 promotes a tumor-supportive environment by regulating cancer-associated fibroblasts (CAFs), immune cell infiltration, and ECM architecture [99, 101]. In addition, it enhances tumor progression by inducing epithelial-mesenchymal transition (EMT) and stimulating angiogenesis (**Figure 2**) [113, 114].

Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) are a heterogeneous population that regulates tumor growth, invasion, and therapeutic resistance [115, 116]. Multi-omics analyses have identified a distinct CAF subpopulation characterized by COL10A1 expression [90, 117]. These "COL10A1-positive fibroblasts" are associated with colorectal cancer progression and poor prognosis [118]. Mechanistically, COL10A1 directly induces EMT in tumor cells and promotes macrophage polarization toward the M2 phenotype through activation of the CD18/JAK1/STAT3 axis [118]. Importantly, M2 macrophages further enhance COL10A1 expression in fibroblasts via the TGF-β/RUNX2 pathway, forming a positive feedback loop that sustains tumor progression [118].

The role of COL10A1 in CAF biology extends beyond gastrointestinal cancers. In basal cell carcinoma, COL10A1 is highly expressed in the stroma of high-risk subtypes and is associated with a specific subset of ECM-producing fibroblasts adjacent to invasive tumors [94]. This CAF population exhibits strong ECM remodeling activity, suggesting that COL10A1 may serve as a potential therapeutic target in high-risk BCC [94].

Similarly, in breast cancer, particularly the triple-negative subtype, COL10A1 is part of a CAF-associated gene signature. The CAF+ subtype, enriched with COL10A1, is associated with worse overall survival and an immunosuppressive TME [117]. In pancreatic ductal adenocarcinoma (PDAC), COL10A1 is mainly expressed in myofibroblast CAFs (myCAFs) [90], which are characterized by high α-SMA and low interleukin-6 (IL-6) expression and are linked to metastasis and immunosuppression [119]. This non-canonical collagen profile is deregulated across multiple cancers and is frequently associated with poor prognosis [90].

Immune microenvironment

The immune landscape of the tumor microenvironment (TME) is a key determinant of tumor progression, although many tumors develop mechanisms to evade immune surveillance and dampen cytotoxic responses [120]. Interactions between cancer-associated fibroblasts (CAFs) and immune cells contribute to the establishment of an immunosuppressive milieu [121]. In this context, COL10A1 expression has been linked to specific patterns of immune infiltration, particularly the polarization of macrophages toward the M2 phenotype [102, 118].

Experimental evidence indicates that COL10A1-positive fibroblasts can promote the polarization of M2-type macrophages, which in turn may reinforce COL10A1 expression through a feedback mechanism within the microenvironment [118]. Additional regulatory pathways have also been implicated. For instance, the lncRNA HAGLROS has been shown to promote the development of breast cancer through the miR-135b-3p/COL10A1 axis while simultaneously promoting M2 polarization, although the exact contribution of COL10A1 remains to be fully defined [122].

Similar orrelations have been observed in different types of tumors. For instance, in prostate cancer, elevated COL10A1 expression is associated with increased infiltration of M2-type macrophages, indicating its conserved role in shaping an immunosuppressive environment [102, 123]. In bladder cancer, COL10A1 expression is associated with broader immune cell infiltration and may influence immune cell recruitment and function [100]. A prognostic model based on macrophages has shown predictive value for patient outcomes [124]. In gastric cancer, COL10A1 levels correlate with infiltration by multiple immune cell populations, including $CD8^+$ T cells, cytotoxic lymphocytes, regulatory T cells, and natural killer cells [96].

The potential role of COL10A1 in the response to immunotherapy is receiving increasing attention. In colorectal cancer, its expression has been associated with immune infiltration and deficient mismatch repair status [125], a feature linked to responsiveness to immune checkpoint blockade therapy [125, 126]. Some studies also suggest that higher COL10A1 levels may be associated with increased sensitivity to anti-PD-1 therapy [125]. In contrast, in $ER^+/HER2^+$ breast cancer, elevated COL10A1 expression combined with low levels of tumor-infiltrating lymphocytes (TILs) has been associated with a reduced response to neoadjuvant treatment [127]. Pan-cancer analyses further indicate associations between COL10A1 and genomic features such as tumor mutational burden (TMB) and microsatellite instability (MSI) [123].

Extracellular matrix remodeling

In addition to providing structural support, the extracellular matrix also influences tumor behavior through both biochemical signaling and mechanical properties [128, 129]. The continuous remodeling of the ECM is a significant feature of tumor progression and plays a central role in facilitating metastasis, making it an attractive therapeutic target [130]. In this setting, COL10A1 is considered an active contributor to ECM reorganization.

In lung adenocarcinoma (LUAD), elevated COL10A1 expression has been linked to ECM remodeling, which is achieved by activating the COL10A1/DDR2/FAK signaling axis. This signaling axis can promote tumor cell proliferation and invasion [101]. Mechanistically, COL10A1 can function as a ligand for discoidin domain receptor 2 (DDR2), a collagen-activated receptor tyrosine kinase located at the cell-matrix interface [131, 132]. Binding to DDR2 leads to downstream activation of focal adhesion kinase (FAK), which is a key regulator of cell adhesion and signaling and is also associated with immune modulation and enhanced responses to combination immunotherapy strategies [133].

Integrin-mediated interactions further promote this process by coordinating cell-ECM communication and maintaining tissue integrity [134]. Supporting these findings, decellularization studies have identified COL10A1 as a tumor-associated ECM component that is largely absent from adjacent normal tissues [135]. In colorectal cancer, its expression correlates with CAF-related transcriptional programs, highlighting its role in mediating tumor-stroma interactions [99].

Overall, these observations suggest that COL10A1 functions not only as a structural ECM protein but also as a regulator of matrix remodeling, contributing to the formation of a microenvironment that supports tumor invasion and progression.

Tumor angiogenesis

The ECM plays a central role in all stages of angiogenesis [136]. Its remodeling regulates vessel formation, pericyte recruitment, endothelial basement membrane assembly, and the availability of angiogenic factors [136]. In tumors, this process drives pathological angiogenesis, which supports tumor growth and

metastasis [137, 138]. COL10A1 is specifically enriched in tumor vasculature and is largely absent in normal vessels [21]. Its association with angiogenesis is also observed in endochondral ossification, osteoarthritis-related neovascularization, and age-related macular degeneration [32, 139-141]. These findings suggest that COL10A1 functions as both a structural and signaling regulator of angiogenesis. In triple-negative breast cancer, COL10A1 promotes angiogenesis through paracrine mechanisms, as conditioned medium from COL10A1-overexpressing cells induces denser and more complex endothelial tubular networks with increased junctions and tube length [113].

Epithelial-mesenchymal transition

Epithelial-mesenchymal transition (EMT) enables epithelial cells to acquire mesenchymal characteristics [142]. In cancer, EMT promotes invasion, metastasis, and therapy resistance [143, 144]. Among ECM components, COL10A1 not only induces EMT-associated phenotypic changes but also links ECM remodeling to tumor progression. In gastric cancer, the TGF-β1/SOX9/COL10A1 axis acts as a key inducer of EMT and is strongly associated with patient survival [114]. Mechanistically, TGF-β1 increases Smad2 phosphorylation and upregulates SOX9 and COL10A1 expression, while SOX9 directly activates COL10A1 transcription [114]. COL10A1 overexpression promotes EMT by upregulating mesenchymal markers (N-cadherin, vimentin, Snail/Slug) and downregulating epithelial markers (E-cadherin, β-catenin) [145]. In colorectal cancer, COL10A1+CAFs promote EMT through COL10A1 secretion [118]. Similarly, COL10A1 enhances EMT via activation of the Wnt/β-catenin pathway in triple-negative breast cancer [113]. Knockout studies further show that COL10A1 promotes breast cancer cell invasiveness and may facilitate penetration of the blood-brain barrier, contributing to intracranial metastasis [146]. Overall, COL10A1 promotes EMT and enhances tumor cell proliferation, migration, and invasion, suggesting that it may serve as a key molecular link between local invasion and distant metastasis, as well as a potential therapeutic target.

Signaling mechanisms of COL10A1 in cancer

In cancer, the TGF-β/Smad signaling pathway promotes COL10A1 expression. Elevated COL10A1 further drives tumor progression through two major signaling axes: the COL10A1/DDR2/FAK axis, which promotes EMT and metastasis, and the COL10A1/ITGB1/PI3K/AKT axis, which enhances tumor cell proliferation and invasion (**Figure 3**).

TGF-β/Smad signaling pathway

Transforming growth factor-β (TGF-β) signaling is critical for embryonic development, tissue homeostasis, and tumor progression [147, 148]. In advanced cancer, this pathway often shifts from a tumor suppressor to a metastasis-promoting factor [149]. Its oncogenic effects involve EMT induction, abnormal ECM deposition, and CAF activation [147, 150]. Binding of TGF-β to its cell surface receptors activates the canonical TGF-β/Smad pathway [151], triggering a phosphorylation cascade that activates Smad2 and Smad3 [151]. These proteins form a complex with Smad4, translocate into the nucleus, and regulate downstream gene transcription [151, 152]. Within this network, COL10A1 has been identified as a key ECM component [135] and a downstream effector of TGF-β1 signaling [114]. Mechanistically, TGF-β1 enhances Smad2 phosphorylation, leading to increased expression of the transcription factor SOX9 [114]. SOX9 then directly binds to the COL10A1 promoter to activate its transcription [114]. The role of TGF-β signaling in EMT regulation is well established [150, 153, 154]. In gastric cancer, TGF-β1 reduces epithelial marker E-cadherin while increasing the mesenchymal marker vimentin and activating transcription factors such as Snail and Slug, thereby enhancing migration and invasion [114]. Notably, COL10A1 knockdown attenuates TGF-β1-induced EMT [114]. In addition, COL10A1 knockdown in cervical cancer cells reduces TGF-β1 levels and decreases phosphorylation of Smad2 and Smad3 [155]. Overall, TGF-β/Smad signaling promotes tumor progression partly through COL10A1, which is essential for EMT induction and maintenance of a tumor-permissive microenvironment.

COL10A1/DDR2/FAK signaling axis

Discoidin domain receptors (DDR1 and DDR2) are a class of receptor tyrosine kinases activated by collagen binding in the extracellular matrix [156]. DDR2 preferentially binds specific

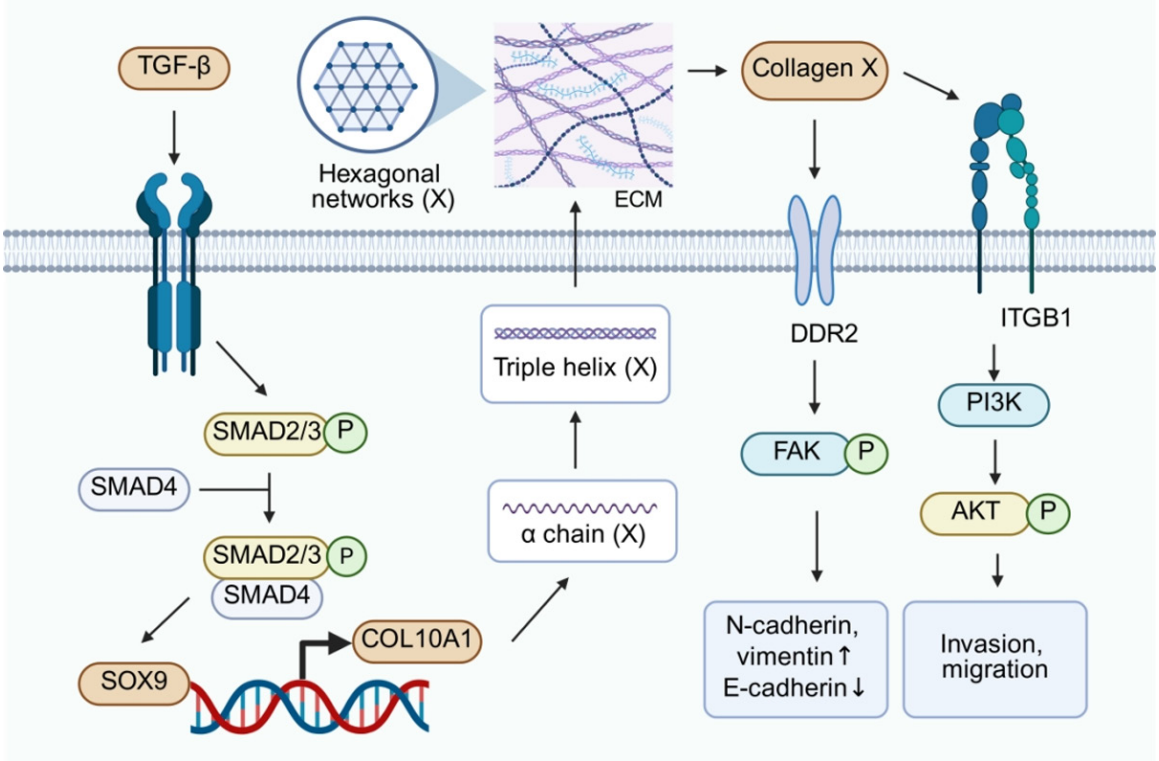

Figure 3. Signaling mechanisms of COL10A1 in cancer. The TGF-β/SMAD signaling pathway activates SOX9, which in turn promotes COL10A1 expression. Three identical type X α chains form a triple helix that assembles into hexagonal networks within the extracellular matrix (ECM). COL10A1 binds to DDR2 to activate FAK and interacts with ITGB1 to stimulate the PI3K/AKT pathway. These signaling events induce epithelial-mesenchymal transition (EMT) and enhance tumor cell invasion and migration.

collagens, including type II and type X (COL10A1) [132]. Functional studies have identified focal adhesion kinase (FAK) as a key downstream effector of the COL10A1/DDR2 axis [101]. FAK is a non-receptor tyrosine kinase that regulates adhesion signaling, cell migration, and angiogenesis [133, 157]. In lung cancer cells, COL10A1 binds DDR2 and induces its phosphorylation (p-DDR2), which subsequently activates FAK phosphorylation (p-FAK) and downstream signaling [101].

The COL10A1/DDR2 axis regulates FAK through a dual mechanism, promoting both its phosphorylation and basal expression. COL10A1 expression positively correlates with FAK protein levels, as its upregulation increases FAK expression, whereas downregulation reduces FAK levels [101]. Activated FAK promotes EMT, characterized by decreased E-cadherin and increased N-cadherin and vimentin, thereby enhancing tumor cell migration and invasion [101]. Functional studies further indicate that the migration-promoting effect of COL10A1 depends on FAK signaling, as FAK inhibition reverses this effect [101]. Thus, targeting the COL10A1/DDR2/FAK axis, particularly with DDR2 or FAK inhibitors, may represent a promising anticancer strategy.

ITGB1/PI3K/AKT signaling axis

Integrins are heterodimeric transmembrane receptors composed of α and β subunits that connect the extracellular matrix to the cytoskeleton and mediate both cell adhesion and signal transduction [158, 159]. Among them, integrin β1 (ITGB1) plays an important role in sensing extracellular mechanical cues and has been implicated in processes such as angiogenesis, neuronal development, and tumor progression [160].

The PI3K/AKT pathway is a central regulator of malignant phenotypes, including cell survival, proliferation, and invasion, primarily through

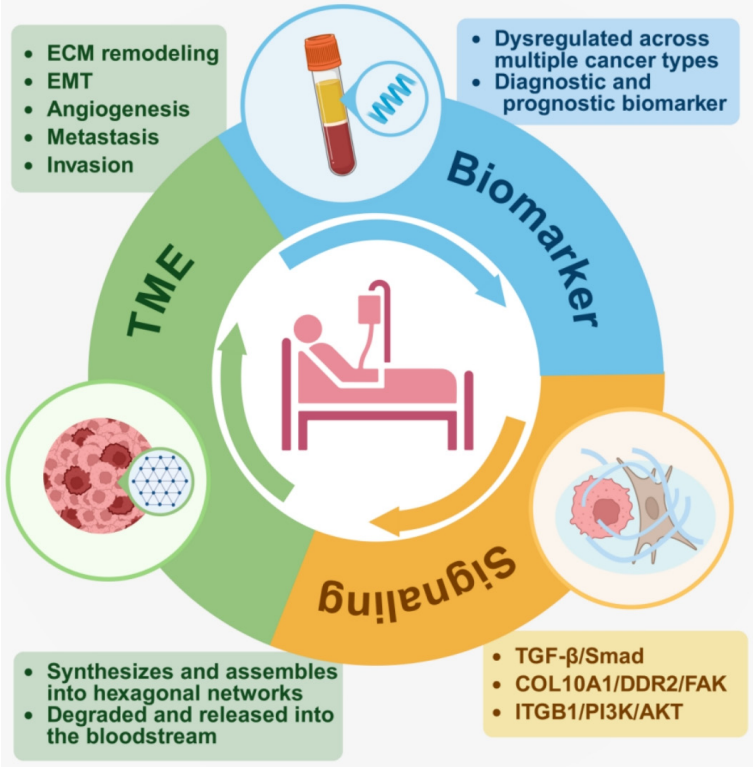

Figure 4. Functional and regulatory landscape of COL10A1 in cancer. COL10A1 promotes tumor progression by inducing ECM remodeling, EMT, and angiogenesis. COL10A1 is synthesized and assembled into hexagonal networks within the ECM, and its degradation products can be released into the circulation. COL10A1 is dysregulated in multiple cancers and functions as a dual tissue and serum biomarker for diagnosis and prognosis. In addition, COL10A1 drives tumor progression through the TGF-β/Smad, COL10A1/DDR2/FAK, and ITGB1/PI3K/AKT signaling axes.

activation of AKT by phosphorylation [161]. Evidence suggests that COL10A1 can interact directly with ITGB1, leading to activation of its intracellular signaling domain and subsequent recruitment of PI3K [162, 163]. Activated PI3K generates PIP3, which facilitates the localization of AKT to the plasma membrane and promotes its phosphorylation, thereby initiating downstream signaling events [162].

Consistent with this mechanism, COL10A1 expression has been shown to correlate positively with AKT phosphorylation levels. Overexpression of COL10A1 enhances cancer cell proliferation, migration, and invasion, whereas these effects can be attenuated by PI3K/AKT inhibitors or by silencing ITGB1 [162]. Similar inhibitory effects are also observed in COL10A1-deficient cells, further supporting the functional link between COL10A1 and this pathway [162].

In addition, COL10A1 has been reported to interact with INHBA in prostate cancer, contributing to activation of PI3K/AKT signaling [164]. INHBA, a member of the TGF-β superfamily, is known to promote tumor progression [165]. Its suppression inhibits TGF-β signaling and reduces tumor cell migration and invasion [165, 166].

Overall, these findings suggest that activation of the PI3K/AKT pathway is a major mechanism underlying the tumor-promoting effects of COL10A1. Disrupting COL10A1-mediated signaling or targeting downstream components of this pathway may therefore represent a potential therapeutic approach.

Conclusion and future perspectives

The extracellular matrix protein COL10A1 shows elevated expression in various solid tumors, and its expression is strongly associated with poor patient prognosis, highlighting its potential as both a histopathological and circulating biomarker for diagnosis and prognostic assessment (**Figure 4**) [21].

Currently, many findings regarding COL10A1 are derived from tumor transcriptomic analyses based on public databases. Therefore, the clinical translational potential of COL10A1 as a tissue or circulating biomarker still requires validation through large-scale prospective clinical studies. In addition, the mechanisms linking dynamic changes in circulating COL10A1 (or its fragments) with tumor burden, disease progression, and treatment response remain insufficiently understood. Further investigation into these relationships will be essential to facilitate the clinical translation of COL10A1 as a standardized liquid biopsy biomarker.

Acknowledgements

The reported study was supported in part by Postgraduate Research & Practice Innovation

Program of Jiangsu Province (KYCX25_4296 to RD).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qiping Zheng, Department of Hematological Laboratory Science, School of Medicine, Jiangsu University, Zhenjiang 212013, Jiangsu, China. E-mail: qp_zheng@hotmail.com; Dr. Longwei Qiao, Center for Reproduction and Genetics, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou 215002, Jiangsu, China. E-mail: qiaolongwei1@126.com; Dr. Tong-Chuan He, The Molecular Oncology Laboratory, Department of Orthopedic Surgery and Rehabilitation Medicine, The University of Chicago Medical Center, Chicago, Illinois 60637, USA. E-mail: tche@uchicago.edu

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