

Oncogenic mechanisms of COL10A1 in cancer and clinical challenges (Review)

QIANG YI¹, GANGFENG ZHU¹, WEIJIAN ZHU¹, JIAQI WANG¹,
XINTING OUYANG¹, KUAN YANG¹ and JINGHUA ZHONG²

¹The First Clinical Medical College, Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China;

²Department of Oncology, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China

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Abstract. Collagen type X $\alpha 1$ chain (*COL10A1*), a gene encoding the $\alpha 1$ chain of type X collagen, serves a key role in conferring tensile strength and structural integrity to tissues. Upregulation of *COL10A1* expression has been observed in different malignancies, including lung, gastric and pancreatic cancer, and is associated with poor prognosis. The present review provides an updated synthesis of the evolving biological understanding of *COL10A1*, with a particular focus on its mechanisms of action and regulatory functions within the context of tumorigenesis. For example, it has been established that increased *COL10A1* expression promotes cancer progression by activating multiple signaling pathways, including the TGF- $\beta 1$ /Smad, MEK/ERK and focal adhesion kinase signaling pathways, thereby inducing proliferation, invasion and migration. Additionally, *COL10A1* has been demonstrated to induce epithelial-mesenchymal transition and reshapes the extracellular matrix within tumor tissues. Furthermore, on the basis of methyltransferase-like 3-mediated N6-methyladenosine methylation, *COL10A1*

intricately regulates the epitranscriptomic machinery, thereby augmenting its oncogenic role. However, although *COL10A1* serves a pivotal role in gene transcription and the orchestration of tumor growth, the question of whether *COL10A1* would serve as a viable therapeutic target remains a subject of scientific hypothesis requiring rigorous examination. Variables such as distinct tumor microenvironments and treatment associations necessitate further experimental validation. Therefore, a comprehensive assessment and understanding of the functional and mechanistic roles of *COL10A1* in cancer may pave the way for the development of innovative cancer treatment strategies.

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Correspondence to: Professor Jinghua Zhong, Department of Oncology, The First Affiliated Hospital of Gannan Medical University, 128 Jinling Road, Ganzhou, Jiangxi 341000, P.R. China
E-mail: m18770738786@163.com

Abbreviations: *COL10A1*, collagen type X $\alpha 1$ chain; TUG1, taurine upregulated gene 1; NSCLC, non-small cell lung cancer; FAK, focal adhesion kinase; EMT, epithelial-mesenchymal transition; LEF1, lymphoid enhancer binding factor 1; METTL3, methyltransferase-like 3; DDR2, discoidin domain receptor tyrosine kinase 2; ECM, extracellular matrix; CAFs, cancer-associated fibroblasts; ERS, endoplasmic reticulum stress; LUAD, lung adenocarcinoma; VSNL1, visinin-like protein 1; LUSC, lung squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; LSCC, laryngeal squamous cell carcinoma; ER, endoplasmic reticulum; P4HB, prolyl 4-hydroxylase subunit β ; ceRNA, competing endogenous RNA; miRNA, microRNA

Key words: *COL10A1*, oncogenic function, mechanism, malignant cancer, biological

1. Introduction

Malignant cancers are among the most prevalent diseases, constituting a complex and dynamically evolving process. The incidence of malignant tumors is continuously increasing each year, and it is estimated that by 2050, the number of new cancer cases per year will reach 35 million (1). Since the late 1990s, molecular targeted therapy and bio-cellular immunotherapy have emerged as prevailing therapeutic modalities in the oncological landscape (2). To enhance the efficacy of tumor treatment and improve patient prognoses, there is a continual necessity to identify novel targets, thereby paving the way for the identification of novel pharmaceutical agents and combinatorial treatment strategies.

Collagen, the most abundant protein in mammals, comprises a diverse family of 28 members, which are intricately associated with the occurrence, progression and prognosis of different cancer types, including breast, colorectal, gastric, lung and cervical carcinomas (3-8). The findings of previous studies have highlighted the significance of collagen type X $\alpha 1$ chain (*COL10A1*), located on chromosome 6q22.1, as

a gene associated with disease progression. COL10A1, known as X α collagen, is a secretory, cartilage-specific short-chain collagen, serving as a principal component of the interstitial matrix (9). As a secreted protein, it is predominantly expressed in the cytoplasm and extracellular matrix (ECM), and serves a role in the development of Schmid metaphyseal chondrodysplasia (9). Upregulation of COL10A1 expression has been observed in multiple human malignancies, with its translated product primarily encompassing three structural domains: Signal peptide, collagen triple helix repeat and C1q domain (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=COL10A1&keywords=COL10A1>) (Fig. 1). Numerous studies have focused on COL10A1, making it a focal point of evaluation. Research indicates that the triple helical region of X α collagen harbors specific discoidin domain receptor tyrosine kinase 2 (DDR2) binding sites capable of receptor activation, thereby facilitating interactions with chondrocytes and other cells via the α 2 β 1 integrin (10,11). As a ligand and coactivator, COL10A1 participates in a diverse range of cellular processes, including the induction of epithelial-mesenchymal transition (EMT), modulation of the ECM, regulation of the cell cycle and proliferation (12-15). Upregulation of COL10A1 and downstream signaling pathways influences cellular biology via multiple mechanism, thereby promoting carcinogenesis. COL10A1 was initially identified, alongside MMP13, cathelicidin antimicrobial peptide and DNA damage-induced apoptosis suppressor, as one of the genes encoding proteins that were more specifically secreted in breast cancer based on differential gene expression analysis. Subsequent research has also revealed high COL10A1 expression in other human cancer types (16,17). COL10A1 has been characterized as a bidirectional communication regulator between tumor cells and cancer-associated fibroblasts (CAFs). COL10A1, as one of the ECM-associated proteins, promotes ECM deposition and remodeling in non-small cell lung cancer (NSCLC) (18). Based on the evidence obtained to date, high COL10A1 expression is associated with higher histological grades, lower overall survival rates, dysregulated apoptosis, tumor metastasis and recurrence in a range of malignant tumors. However, the precise oncogenic signaling pathways mediated by COL10A1 remain incompletely elucidated.

In humans, the upregulation of COL10A1 expression in different types of malignant tumors results in an imbalance between tumor cell proliferation and apoptosis, thereby contributing to tumorigenesis (19). However, on the basis of the considerable progress in research conducted to date, it has been established that the primary mechanistic effect of COL10A1 differs among different types of malignancies (Table I). The present comprehensive review focuses on studies that have sought to elucidate the structure, biological functions and role of COL10A1 in different types of malignant tumors.

2. Mechanisms of action of COL10A1 in tumors

Potential positive feedback regulation of COL10A1 and TGF- β signaling. The findings of research conducted to date have provided evidence to indicate that dysregulation of COL10A1 induces EMT via the TGF- β 1/SOX9 axis, thereby promoting invasion and metastasis in gastric cancer (12). The TGF- β /bone morphogenetic protein/SMAD

signaling pathway, which serves a pivotal role in cancer progression and metastasis, has been the focus of a long history of research (20-22). Upon activation by TGF- β 1, the membrane receptor serine/threonine kinase complex initiates a phosphorylation cascade of transcription factors, including Smad1, Smad2 and Smad3. Having undergone phosphorylation, these factors subsequently interact with Smad4, forming complexes that undergo nuclear translocation (23). Bierie and Moses (24) observed that TGF- β signaling modulates tumorigenesis, which is characterized by frequent alterations in the associated signaling pathway during tumor progression. SOX9, which functions as a transcription factor for COL10A1, binds directly to the COL10A1 promoter, thus activating its transcription and thereby enhancing COL10A1 expression. This process mediates tumor EMT and promotes the malignant biological behaviors of gastric cancer. Additionally, TGF- β 1 stimulation has been shown to increase the levels of SOX9, COL10A1 and phosphorylated-Smad2 in MKN45 and SGC7901 gastric cancer cells. TGF- β 1 stimulation can activate Smad2 phosphorylation, leading to changes in classical EMT markers (12) (Fig. 2). These findings provide further evidence to indicate that COL10A1 may serve an essential role downstream of the TGF- β 1/Smad2 signaling pathway (12). The importance of the TGF- β signaling pathway in EMT has been established in previous research. TGF- β signaling has been implicated in coordinating immune suppression within the tumor microenvironment and thereby contributing to cancer growth, invasion, metastasis, recurrence and resistance to treatment (25). Furthermore, TGF- β 1 stimulation has been established to induce a reduction in E-cadherin expression, and increases in vimentin, snail homolog 1 and snail homolog 2 expression, thereby promoting the migration and invasion of tumor cells (26). Conversely, the knockout of COL10A1 has been demonstrated to delay TGF- β 1-induced EMT (12). Additionally, a study has indicated that by inactivating the TGF- β /Smad signaling pathway, downregulation of COL10A1 can inhibit the proliferation, migration and EMT of HeLa and C-33A cervical cancer cells. Similarly, COL10A1 can enhance the expression of TGF- β 1 protein, modulate the phosphorylation of Smad2 and Smad3, and activate the TGF- β /Smad signaling pathway (27). Collectively, the findings of these studies tend to indicate that tumor cells induce EMT via a positive feedback loop involving the TGF- β 1/SMAD/SOX9/COL10A1 axis.

Activation of COL10A1 triggers the focal adhesion kinase (FAK) signaling pathway. DDRs, including discoidin domain receptor tyrosine kinase 1 and DDR2, constitute a unique class of receptor tyrosine kinases activated by collagen at the cell-matrix interface. These receptors are widely expressed in fetal and adult tissues, and both experimental and clinical evidence indicates their dysregulation in cancer (28). FAK, known for its regulatory role in cellular survival, proliferation and migratory processes, has been demonstrated to be upregulated in diverse cancer types, including breast cancer (29). Disruption of DDR2 has been found to alter focal adhesion orientation and subsequent ECM organization, thereby modulating FAK and Yes1-associated transcriptional regulator and WW domain-containing transcriptional regulator 1-mediated mesenchymal lineage cell signaling (30). It has been reported

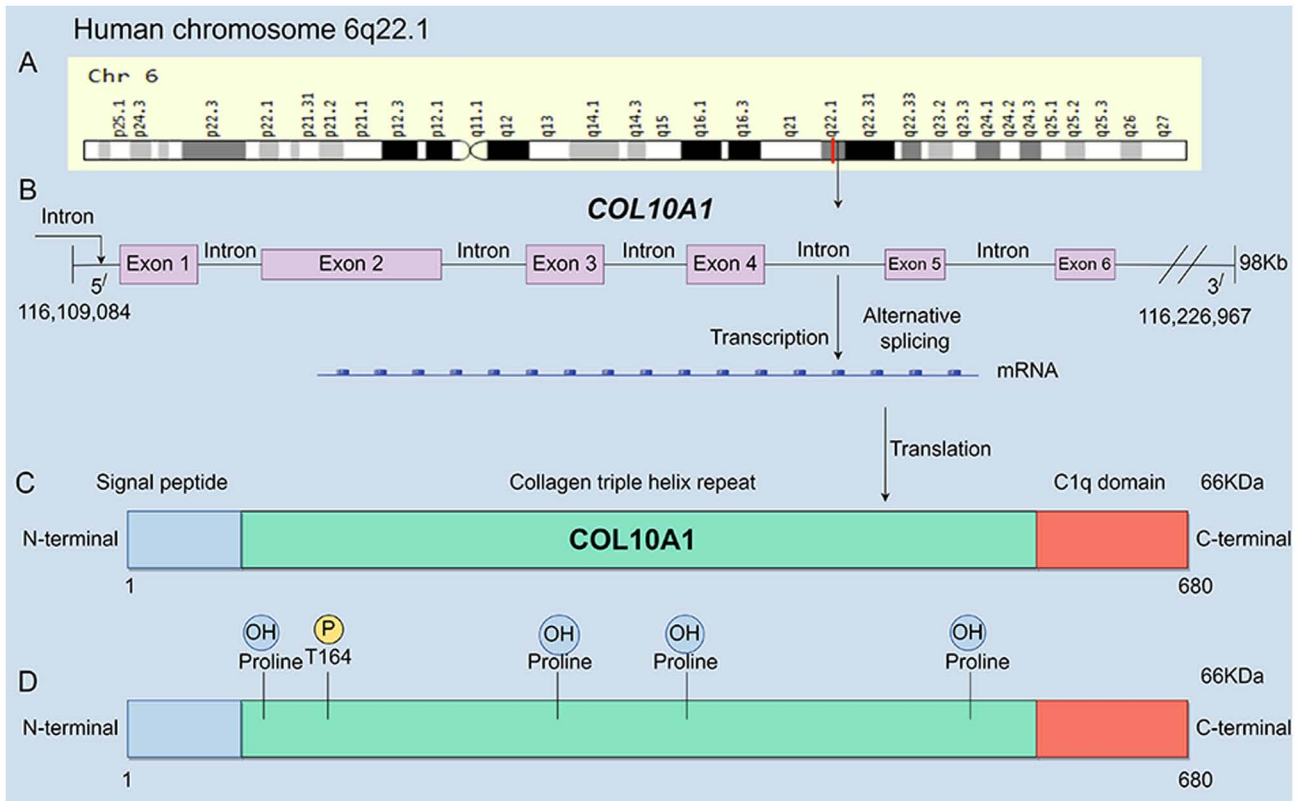


Figure 1. Map of the gene, functional domains and phosphorylation sites of COL10A1 according to data from the Uniprot (<https://www.uniprot.org/>), Genecards (<https://www.genecards.org/>), PhosphoSitePlus (<https://www.phosphosite.org/>) and neXtProt (<https://www.nextprot.org/>) databases. (A) COL10A1 is located on chromosome 6q22.1. (B) COL10A1 consists of six exons. (C) The COL10A1 structural domain has a signal peptide, a collagen triple helix repeat sequence that provides structural stability and a C1q structural domain that may be involved in protein interactions. (D) Phosphorylation site and possible hydroxylation sites on COL10A1. The figure was generated using Figdraw (<https://www.figdraw.com/static/index.html#/>). COL10A1, collagen type X $\alpha 1$ chain; OH, hydroxylation; P, phosphorylation.

that DDR2 and integrin $\beta 1$ can interact with COL10A1 (11), and Chaney *et al* (31) found that the end-binding protein EB1 limits breast cancer cell invasive pseudopod formation and matrix protein degradation via FAK. Another study has identified COL10A1 as a ligand for DDR2, with the interaction between COL10A1 and DDR2 promoting DDR2 phosphorylation, and thus, influencing downstream FAK signaling, which contributes to the regulation of the malignant progression of lung adenocarcinoma (LUAD) cells (13). Furthermore, integrins have been established to induce EMT and activate non-canonical FAK-independent signaling pathways, thereby preventing cancer cells from undergoing integrin-mediated death, and thus, promoting cancer cell metastasis (32). It is hypothesized that COL10A1 induces EMT via its interaction with DDR2, which, once activated, phosphorylates FAK, the expression levels of which are thus maintained (Fig. 3A). As a consequence, expression of the epithelial marker E-cadherin is downregulated, whereas mesenchymal markers, such as N-cadherin and vimentin, are upregulated, thereby promoting tumor cell migration and proliferation. Furthermore, knockdown of COL10A1 in LUAD cells has been demonstrated to result in a reduction in FAK expression, whereas ectopic expression of COL10A1 leads to a marked increase in FAK expression (13). These findings indicate that COL10A1 contributes to malignant progression by remodeling the ECM via the integrin/FAK signaling pathway.

COL10A1 regulates gene expression through epitranscriptomic mechanisms. Cancer is a complex disease caused by genetic and epitranscriptomic alterations in cell division control (33). Epitranscriptomics delineates the realm of genetic modifications that have the capacity to influence gene expression, whilst preserving the fundamental sequence of DNA nucleotides (34). In lung squamous cell carcinoma (LUSC), cancer-associated fibroblasts (CAFs) have been shown to upregulate COL10A1 expression. This regulation occurs through the enhancement of methyltransferase-like 3 (METTL3) expression, which subsequently stabilizes COL10A1 expression within CAFs via N6-methyladenosine (m6A) modification. This stabilization facilitates the subsequent delivery of COL10A1 into LUSC cells, thus promoting cell proliferation and suppressing oxidative stress-induced apoptosis. Simultaneously, CAF-produced METTL3 promotes lung cancer cell proliferation by mediating the m6A methylation of COL10A1 (35) (Fig. 3B). This process contributes to enhancing the levels of superoxide dismutase and glutathione peroxidase, whilst reducing the rates of cell apoptosis and reactive oxygen species production (35). m6A has been identified as the predominant type of mRNA modification, catalyzed by the methyltransferase complex. Within this complex, METTL3 assumes the exclusive role of the catalytic subunit (36,37). METTL3 has been extensively studied in the context of cancer, including its role in regulating VGF nerve growth factor inducible expression in LUAD cells, mediated by both

Table I. Expression and function of COL10A1 in human malignant tumors.

First author/s, year	Tumor type	COL10A1 expression	Function in tumors	Mechanism	(Refs.)
Liang <i>et al.</i> , 2020	Lung cancer	Upregulation	Reconstructs the ECM, and governs the proliferation and metastasis of LUAD cells	COL10A1/DDR2/FAK axis	(13)
Li <i>et al.</i> , 2022		Upregulation	Stimulates the proliferation of LUSC cells and impedes apoptosis-induced oxidative stress	Cancer-associated fibroblasts undergo m6A methylation of COL10A1 mediated by METTL3	(35)
Guo <i>et al.</i> , 2019		Upregulation	Promotes cell proliferation, and inhibits apoptosis and autophagy in NSCLC cells	miR-384	(60)
Li <i>et al.</i> , 2018	Gastric cancer	Upregulation	Facilitates EMT, and promotes cell migration, invasion and metastasis	TGF- β 1/SOX9 axis	(12)
Zhang <i>et al.</i> , 2022		Upregulation	Contributes to an unfavorable prognosis in gastric cancer	Upregulation of LEF1 and Wnt2	(15)
Li <i>et al.</i> , 2020		Upregulation	Facilitates the proliferation, migration and invasion of gastric cancer cells	miR-26a-5p	(59)
Aktas <i>et al.</i> , 2022		Upregulation	Contributes to the progression of the tumor	Interactions between the COL10A1 and SOX9 genes	(68)
Wen <i>et al.</i> , 2022	Pancreatic cancer	Upregulation	Enhances the proliferation and migration of PDAC cells, resulting in EMT and accelerating the progression of pancreatic cancer	Activation of the MEK/ERK signaling pathway via the COL10A1/DDR2 axis	(50)
Xu <i>et al.</i> , 2023		Upregulation	Promotes cell proliferation, migration and invasion	Regulates CD276	(73)
Zhang <i>et al.</i> , 2023		Upregulation	Promotes the progression of pancreatic cancer	Upregulation of COL10A1/FAP/FN1, activating the PI3K/AKT signaling pathway	(76)
Liu <i>et al.</i> , 2022		Upregulation	Facilitates immune infiltration in pancreatic cancer	TUG1/miR-144-3p axis	(57)
Ma <i>et al.</i> , 2020	Breast cancer	Upregulation	Facilitates the proliferation, migration and invasion of breast cancer cells	Upregulates the expression of P4HB	(54)
Vishnubalaji <i>et al.</i> , 2019		Upregulation	Associated with the HR ⁺ /HER2 ⁺ breast cancer molecular subtype	TGF β and FAK signal transduction	(107)
Cen <i>et al.</i> , 2023	Prostate cancer	Upregulation	Exerts a considerable impact on cancer proliferation, metastasis, immune therapy, and resistance to radiotherapy and chemotherapy	Activates the endoplasmic reticulum stress mechanism	(87)
He <i>et al.</i> , 2022	Colorectal cancer	Upregulation	Promotes the proliferation, migration and invasion of colorectal cancer	VSNL1/COL10A1 axis	(95)

Table I. Continued.

First author/s, year	Tumor type	COL10A1 expression	Function in tumors	Mechanism	(Refs.)
Sun <i>et al</i> , 2022	Cervical cancer	Upregulation	Promotes cell proliferation, migration and EMT in cervical cancer	Activates the TGF- β /Smad signaling pathway	(27)
Karagoz <i>et al</i> , 2016	Esophageal squamous cell carcinoma	Upregulation	Facilitates the occurrence and development of esophageal squamous cell carcinoma	Metabolic dysfunction in arachidonic acid metabolism and steroid hormone biosynthesis pathways	(100)
Xie <i>et al</i> , 2019	Ovarian cancer	Upregulation	Stimulates the proliferation, invasion and migration of oral cancer cells	miR-101-3p in extracellular vesicles from human bone marrow mesenchymal stem cells	(105)
Guo <i>et al</i> , 2021	Nasopharyngeal carcinoma	Upregulation	Promotes the development of nasopharyngeal carcinoma cells	NF- κ B signaling pathway and extra-cellular matrix organization	(106)

COL10A1, collagen type X α 1 chain; DDR2, discoidin domain receptor tyrosine kinase 2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; FAP, fibroblast activation protein; FN1, fibronectin 1; HR, hormone receptor; LEF1, lymphoid enhancer binding factor 1; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; m6A, N6-methyladenosine; METTL3, methyltransferase-like 3; miR, microRNA; NSCLC, non-small cell lung cancer; P4HB, prolyl 4-hydroxylase subunit β ; PDAC, pancreatic ductal adenocarcinoma; TUG1, taurine upregulated gene 1; VSNL1, visinin-like protein 1.

transcriptional (via histone modification) and post-transcriptional (via m6A modification) mechanisms in a spatiotemporal manner (38). In this regard, Wang *et al* (39) reported that elevated METTL3 expression promotes tumor angiogenesis and glycolysis in gastric cancer, thereby enhancing tumor cell invasiveness. Additionally, Guo *et al* (40) demonstrated that a multi-omics model, specifically involving COL10A1, exhibited superior prognostic accuracy for gastric cancer compared with single-omics models. This model integrates data on mutations, copy number variations, transcription, methylation and clinicopathological changes, providing a more comprehensive approach to prognosis prediction. In summary, the aforementioned findings indicate that the functional activity of COL10A1 involves epitranscriptomic mechanisms, via which it activates gene transcription, thereby serving a pivotal role in cancer initiation and progression by engaging CAFs within the tumor microenvironment.

COL10A1 activates the MAPK signaling pathway. Upregulated DDR2 expression has been detected in a range of cancer cell types, in which it serves as a primary regulator of EMT, promoting EMT processes in cancer types such as hepatocellular carcinoma (41,42), gastric cancer (43,44), breast cancer (45), and head and neck squamous cell carcinoma (46). EMT is recognized as a key regulatory process in tumor metastasis, endowing cells with an invasive phenotype (47). The MEK/ERK signaling pathway is a well-characterized MAPK signaling pathway, and genetic alterations in this are among the most common genetic alterations observed in human cancer (48). Cancer cells activate the MEK/ERK signaling pathway to induce EMT, whereby ERK signal transduction regulates key cellular processes such as proliferation, migration and invasion (49). Research has indicated that COL10A1 regulates PANC-1 and CFPAC-1 pancreatic ductal adenocarcinoma (PDAC) cell proliferation and the MEK/ERK signaling pathway by binding to DDR2, thereby promoting migration, invasion and EMT (50). In PDAC cells, COL10A1, through its binding to and phosphorylation of DDR2, has been demonstrated to activate the MEK/ERK signaling pathway, with the subsequent phosphorylation of MEK and ERK leading to increases in the protein levels of EMT pathway markers (E-cadherin, N-cadherin, vimentin and snail homolog 1), thereby promoting the malignant biological behaviors of these cells, resulting in poor patient prognosis. Furthermore, Wen *et al* (50) demonstrated that upregulation of COL10A1 expression leads to a reduction in the expression levels of the epithelial marker E-cadherin, and increases in the expression levels of the mesenchymal markers N-cadherin and vimentin. However, treatment with the ERK inhibitor SCH772984 was observed to reverse EMT in PDAC cells in the group with COL10A1 overexpression. These findings indicate an association between COL10A1-DDR2 expression and the MEK/ERK signaling pathway (Fig. 3C).

COL10A1 targets prolyl 4-hydroxylase subunit β (P4HB) to promote tumor cell migration and invasion. P4HB is a human chromosomal gene that encodes an endoplasmic reticulum (ER) molecular chaperone protein with oxidoreductase, co-chaperone and isomerase activities (51). P4HB has been demonstrated to serve roles in carcinogenesis and cancer

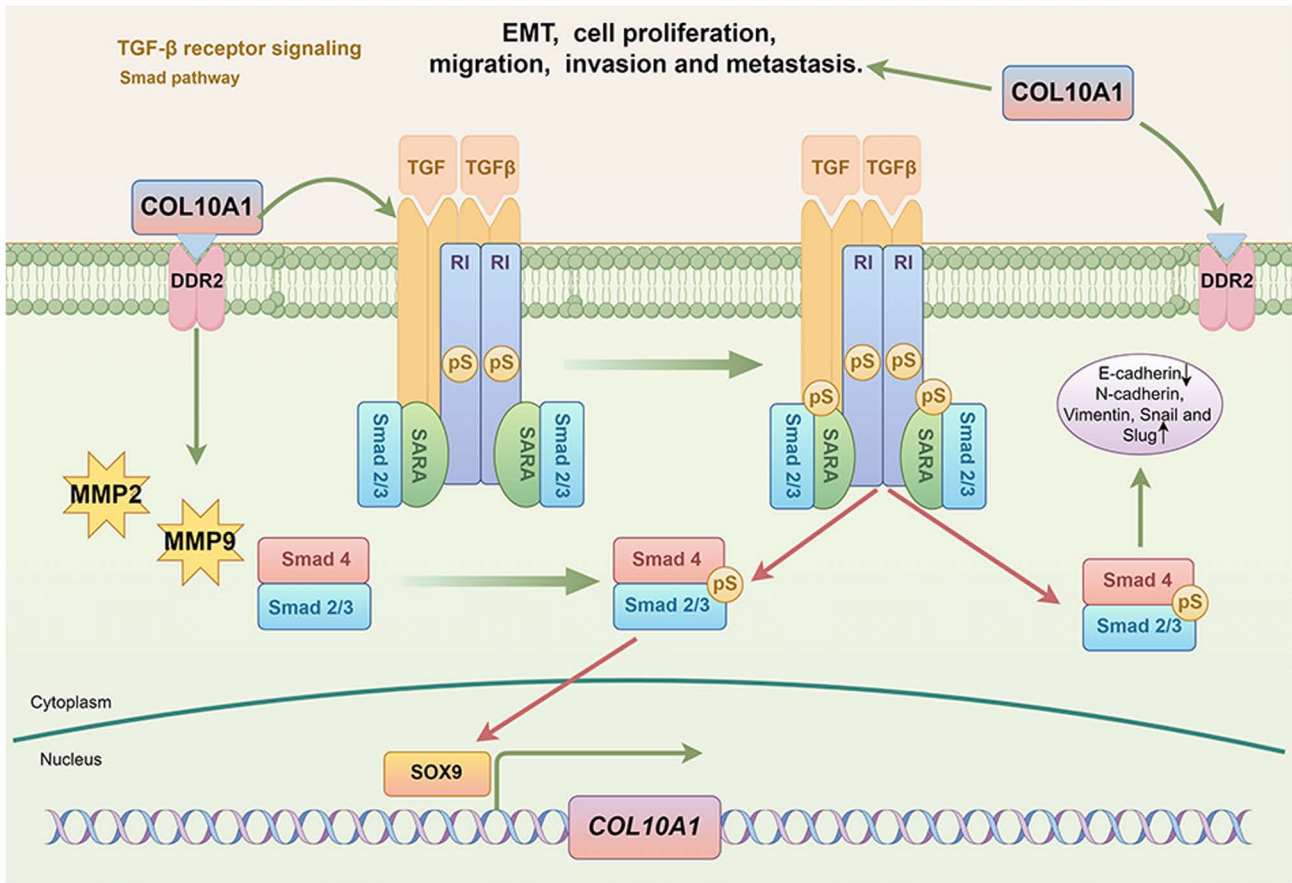


Figure 2. COL10A1 regulates EMT, tumor cell proliferation and metastasis by phosphorylating Smad in conjunction with DDR2 and activating the TGF- β signaling pathway. The figure was generated using Figdraw. COL10A1, collagen type X α 1 chain; DDR2, discoidin domain receptor tyrosine kinase 2; EMT, epithelial-mesenchymal transition; pS, phosphoserine; RI, receptor I; SARA, Smad anchor for receptor activation.

progression (52); for example, by acting as an inhibitor of ferroptosis, thereby promoting tumor cell proliferation (53). Ma *et al* (54) found that EMT and the β -catenin/Snail signaling pathway influence the regulatory role of P4HB in the chemoresistance of hepatocellular carcinoma, and their study has provided evidence indicating an important role for P4HB in the progression of cancer. Furthermore, by positively regulating P4HB expression, the upregulation of COL10A1 enhances the proliferation and clonogenicity of MCF-7 and MDA-MB-231 breast cancer cells, and promotes breast cancer cell migration and invasion (55). Using rescue experiments, it has been demonstrated that downregulating P4HB suppresses the promotive effects of overexpression of COL10A1 on the proliferation, migration and invasion of breast cancer cells (55). In summary, by regulating P4HB, COL10A1 can contribute to the control of tumor cell phenotypes (Fig. 4). In breast cancer cells, COL10A1 enhances cell proliferation, migration and invasion by targeting P4HB. However, further in-depth research is required to identify the signaling pathway associated with the COL10A1/P4HB axis and its transcriptional regulation.

Competing endogenous RNA (ceRNA) network and microRNA (miRNA/miR) regulation of COL10A1. COL10A1 can undergo gene silencing by binding with miRNAs, whereas long non-coding RNAs (lncRNAs) can modulate the occurrence, invasion and metastasis of tumors by competitively binding

to miRNAs. The ceRNA network connects the functions of protein-coding mRNAs with those of non-coding RNAs (such as miRNAs, lncRNAs, pseudogene RNAs and circular RNAs), and dysregulation of the ceRNA network is implicated in a range of human diseases, including cancer (56). Using bioinformatics analysis, Liu *et al* (57) found that lncRNA taurine upregulated gene 1 (TUG1) participates in the miR-144-3p/COL10A1 axis, promoting immune cell infiltration in pancreatic cancer. However, this involvement has yet to be experimentally validated and has only been assessed at the level of data analysis. Liu *et al* (58) constructed a circular RNA-miRNA-mRNA regulatory network, thereby providing a novel perspective for elucidating the ceRNA regulatory mechanisms of COL10A1 in stomach adenocarcinoma. Additionally, a study has indicated that by targeting COL10A1, miR-26a-5p can enhance the proliferation, migration and invasion of MKN-45 gastric cancer cells (59). Furthermore, miR-26a-5p has been found to inhibit the occurrence and development of gastric cancer by reducing the expression levels of COL10A1, and dual-luciferase assays have further confirmed the targeting relationship between miR-26a-5p and COL10A1 (59). In addition, Guo *et al* (60) found that miR-384 can downregulate COL10A1 levels, thereby inhibiting NSCLC cell proliferation, and promoting apoptosis and autophagy. Collectively, these findings indicate that COL10A1 can be regulated by miRNAs, thereby influencing the development of tumor cells in different diseases (Fig. 4).

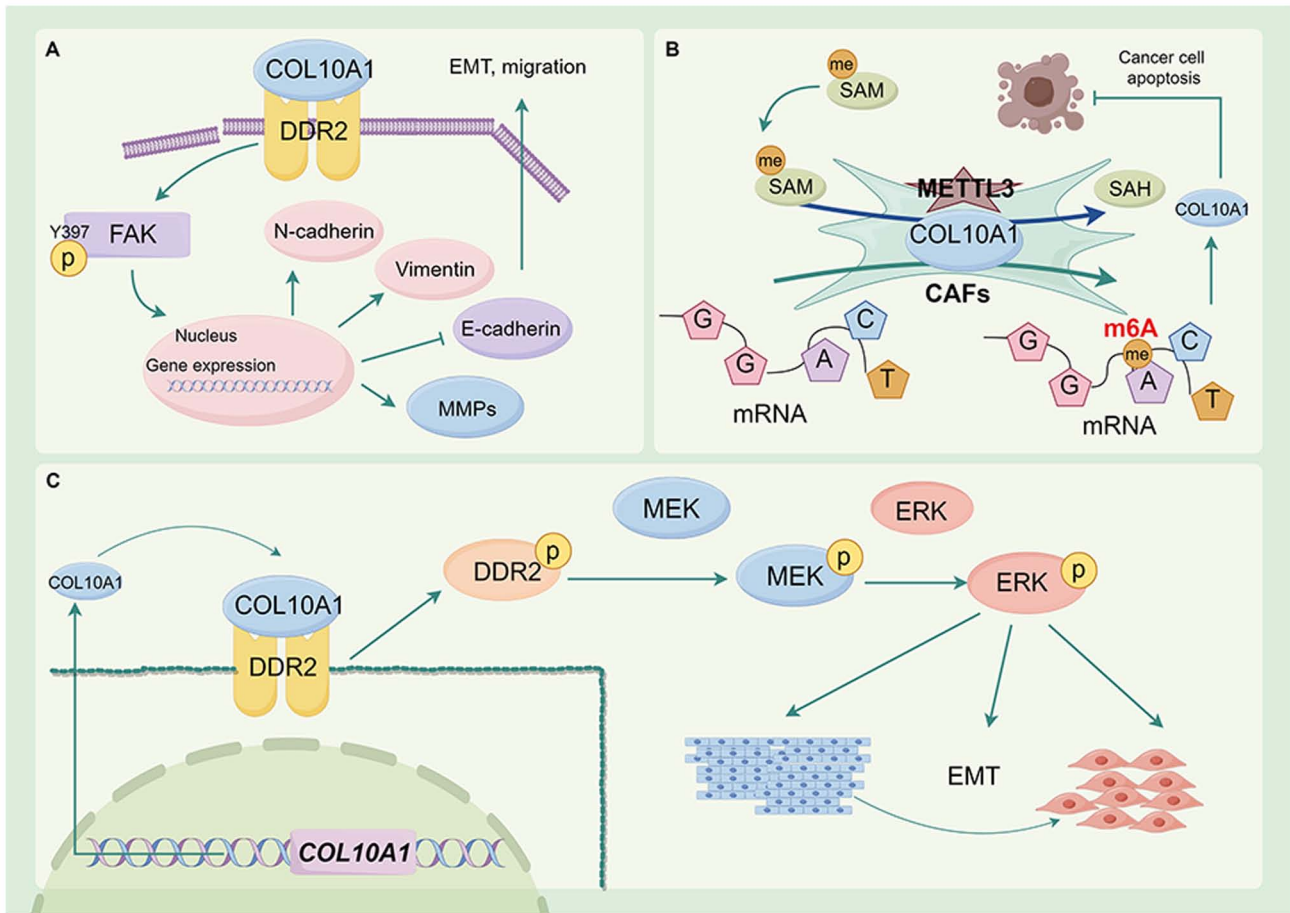


Figure 3. COL10A1 activates signaling pathways and regulates gene expression. (A) COL10A1 activates the FAK signaling pathway. (B) COL10A1 regulates gene expression via epitranscriptomic mechanisms. (C) COL10A1 regulates the MAPK-related pathway. COL10A1 activates phosphorylated MEK and ERK molecules by binding to DDR2 and subsequently activates a cascade reaction. The figure was generated using Figdraw. CAFs, cancer-associated fibroblasts; COL10A1, collagen type X α 1 chain; DDR2, discoidin domain receptor tyrosine kinase 2; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; m6A, N6-methyladenosine; me, methylation; METTL3, methyltransferase-like 3; p, phosphorylation; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine.

3. Function of COL10A1 in tumors

Lung cancer. As the most commonly diagnosed cancer, lung cancer is a leading cause of cancer incidence and mortality in both men and women (1). With the development of numerous effective targeted therapies and immunotherapies, immune checkpoint inhibitors have shown benefits in the treatment of lung cancer. Currently, these inhibitors are used as a first-line treatment for metastatic disease and consolidative therapy for unresectable locally advanced disease post-chemoradiotherapy, as well as adjuvant therapy for resectable tumors following surgery and chemotherapy (61). In patients with LUAD, variations in the expression levels of COL10A1 have been observed, with higher levels of COL10A1 mRNA being associated with a shorter overall survival, and upregulation of COL10A1 is positively associated with white blood cell transendothelial migration, vascular smooth muscle contraction and ECM-receptor interaction in LUAD (62). Wu *et al* (63) discerned notable distinctions in the interplay between COL10A1 and different cellular pathways within the context of NSCLC, including the inositol phosphate metabolism pathway, focal adhesion signaling pathway, vascular smooth muscle contraction signaling pathway, peroxisome

proliferator-activated receptor signaling pathway and calcium signaling pathway. A further study has indicated that the diversity of interactions is attributed to the regulation of LUAD cell proliferation and migration by the COL10A1/DDR2/FAK axis, and elevated levels of COL10A1 promote remodeling of the ECM, exhibiting a positive association with lymph node metastasis (13). Research has also confirmed that COL10A1, COL11A1 and secreted phosphoprotein 1, as core genes originating from the embryonic mesoderm, serve pivotal roles in the ECM-receptor interaction and cell adhesion signaling pathways, potentially forming networks in lung and gastric cancer (64). Furthermore, miR-384 has been shown to down-regulate COL10A1 levels, thereby inhibiting NSCLC cell proliferation, and promoting apoptosis and autophagy (60). CAFs, via METTL3-mediated mRNA methylation modification, promote the secretion of COL10A1, the upregulation of which promotes SW900 and LOU-NH91 LUSC cell proliferation and inhibits apoptosis-induced oxidative stress (35). As a soluble factor associated with tumor-stroma crosstalk, COL10A1 may also serve as a potential marker to distinguish patients with lung cancer from heavy smokers (18). Upregulation of COL10A1 expression has been established to be closely associated with LUAD lymph node metastasis

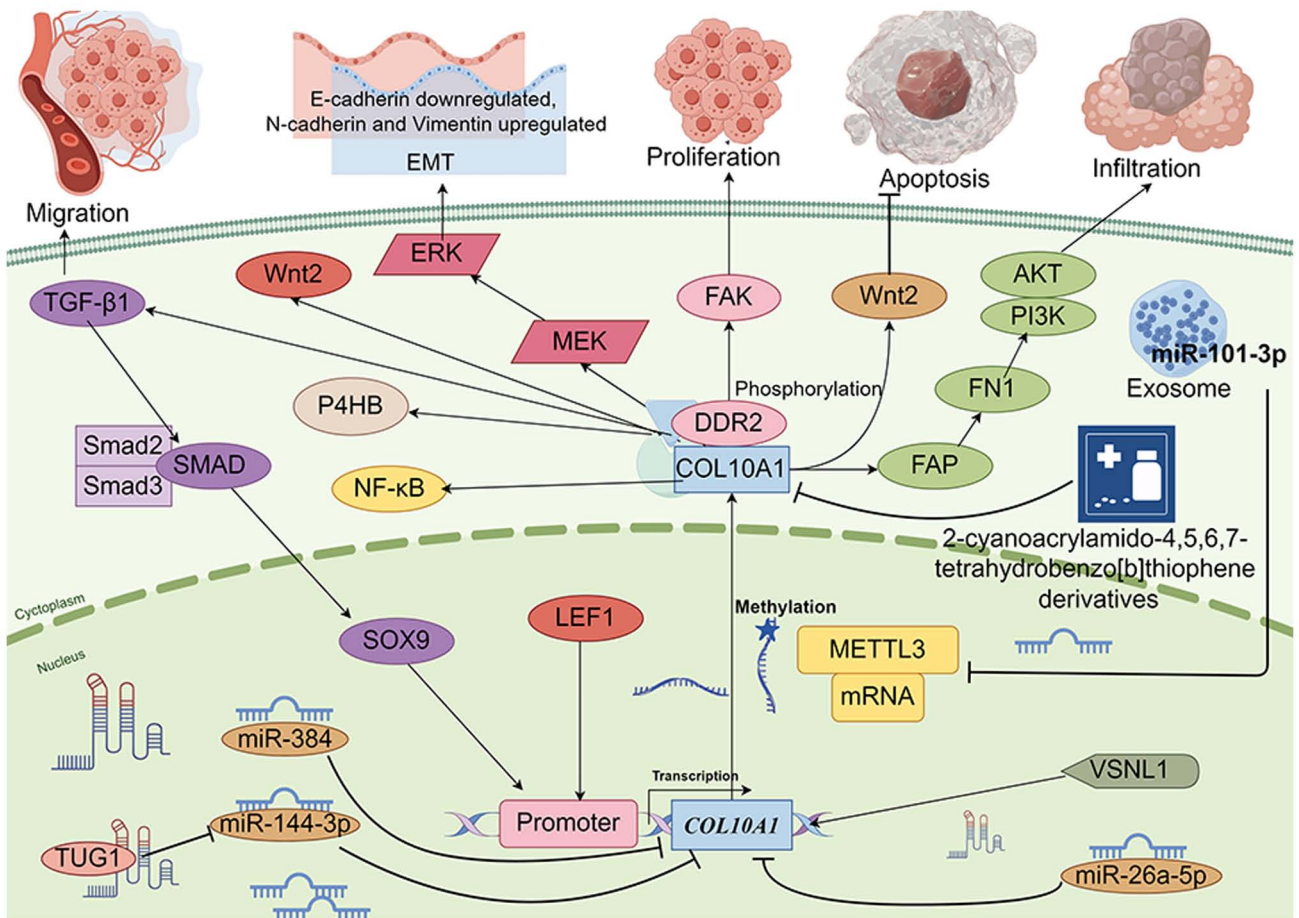


Figure 4. Role of COL10A1 in malignant tumors. TUG1 inhibits miR-144-3p to enhance COL10A1 transcription, while miR-384 and extracellular vesicle-contained miR-101-3p suppress COL10A1 transcription. COL10A1, via the TGF- β 1/SMAD, FAK, MAPK and Wnt2 signaling pathways, and targeted action against P4HB, promotes tumor cell proliferation. Additionally, COL10A1 promotes METTL3 expression, which upregulates the methylation of COL10A1 itself, thereby further facilitating tumorigenesis. The figure was generated using Figdraw. COL10A1, collagen type X α 1 chain; DDR2, discoidin domain receptor tyrosine kinase 2; EMT, epithelial-mesenchymal transition; FAK, focal adhesion kinase; FAP, fibroblast activation protein; FN1, fibronectin 1; LEF1, lymphoid enhancer binding factor 1; METTL3, methyltransferase-like 3; miR, microRNA; P4HB, prolyl 4-hydroxylase subunit β ; TUG1, taurine upregulated gene 1; VSNL1, visinin-like protein 1.

positivity, thereby serving as an independent prognostic marker for poor outcomes in patients with lung cancer.

Gastric cancer. Gastric cancer ranks fifth globally in terms of incidence and fifth in terms of mortality among all cancer types (1). Despite recent therapeutic advances that have reduced the incidence and associated mortality, the prognosis of gastric cancer remains poor, with a 5-year survival rate of 20-30% (65). Upregulation of COL10A1 expression has been identified as an adverse prognostic indicator in gastric cancer, being associated with tumor occurrence or pathological grading in gastrointestinal cancer (66,67). COL10A1 has been found to regulate gastric cancer progression via a number of mechanisms. First, the TGF- β 1/SOX9 axis promotes upregulation of COL10A1, thereby contributing to invasive and metastatic tendencies in gastric cancer via EMT (12,68). Second, the transcription factor lymphoid enhancer-binding factor 1 (LEF1) upregulates COL10A1 expression, which is associated with reduced survival rates in patients with gastric cancer exhibiting high COL10A1 levels compared with those with lower levels. This upregulation contributes to a poorer prognosis

by driving the Wnt2 signaling pathway (15). Third, by attenuating the expression of COL10A1, miR-26a-5p has inhibitory effects on gastric cancer cell proliferation, migration and invasion (59). Fourth, COL10A1 may influence tumor T staging and pathological staging by regulating immune infiltration within the late-stage gastric cancer microenvironment (69). The ECM serves an undisputed role in tissue homeostasis, an imbalance of which can lead to changes in mechanical and biochemical cues influencing cancer initiation and progression (70). As a soluble ECM protein, increases in the plasma levels of COL10A1 have been detected in patients with gastric adenocarcinoma, and these elevated levels have been demonstrated to be associated with cancer progression (71), which was validated by Li *et al* (67), who used comprehensive bioinformatics methods to identify a COL10A1 model protein-protein interaction network involving ECM-receptor interactions. In summary, upregulation of COL10A1 expression is associated with clinical stage, and lymph node and distant metastasis in gastric cancer, and thus, COL10A1 expression is an independent prognostic factor for patients with gastric cancer.

Pancreatic cancer. Pancreatic cancer is among the most invasive, high-mortality and poorly treatable types of tumors (72). COL10A1 is associated with the malignant characteristics of pancreatic cancer. Increased COL10A1 expression in pancreatic cancer tissues has been established to enhance the proliferation and migration of PDAC cells. The COL10A1/DDR2 axis activates the MEK/ERK pathway, leading to EMT and accelerating the progression of pancreatic cancer (50). Using bioinformatics analysis, Liu *et al* (57) identified the TUG1/miR-144-3p signaling pathway as the most likely upstream non-coding RNA pathway for COL10A1, although further research is needed, including experimental verification using luciferase assays. Additionally, COL10A1 has been demonstrated to serve a key role in regulating CD276 in Panc-1 pancreatic cancer cell viability, migration, and invasion (73), with the knockdown of COL10A1 reducing CD276 expression, and upregulation of CD276 expression in cells reversing the inhibition of proliferation and migration induced by COL10A1 knockdown. In recent research, COL10A1, specific to myofibroblast CAFs, has been observed to be elevated in different solid tumor types and was associated with poor survival (74). In related gastroenteropancreatic neuroendocrine tumors, it has been demonstrated that COL10A1 can also be used to differentiate between primary and metastatic gastroenteropancreatic neuroendocrine neoplasms with different antitumor phenotypes (75). Collectively, these findings highlight the pivotal role of COL10A1 in the occurrence and development of pancreatic cancer. Zhang *et al* (76) also reported that the upregulation of characteristic genes (COL10A1/fibroblast-activation protein/fibronectin 1) in Coronavirus Disease 2019 may promote the progression of pancreatic cancer by activating the PI3K/AKT signaling pathway. In conclusion, upregulation of COL10A1 appears to be closely associated with increased proliferation and migratory potential of pancreatic cancer cells.

Breast cancer. Breast cancer is the most common type of cancer in women and the second leading cause of cancer-related deaths in women worldwide (77). Although treatment options for breast cancer have undergone improvement, late-stage breast cancer and triple-negative breast cancer continue to present challenges (78). Although current immunotherapy and molecular targeted therapies have contributed to a substantial improvement in patient survival, challenges such as immune escape, drug resistance and poor apoptosis still need to be addressed (79). As attention turns to the therapeutic potential of targeting COL10A1 in breast cancer, it has been found that knocking down this collagen protein can disrupt the interaction between COL10A1 and P4HB, thereby inhibiting the proliferation, migration and invasion of breast cancer cells (54). A bioinformatics investigation has revealed a favorable association between COL10A1 expression and estrogen receptor, progesterone receptor and HER-2 status, as well as lymph node status in breast cancer samples. In tumor tissues, COL10A1 levels have been shown to be inversely associated with age, Scarff-Bloom-Richardson grade, basal-like status and triple-negative status, whereas these associations were not observed in normal tissues (80). In addition, the down-regulation of COL14A1 has been found to be associated with invasive, basal-like and Her-2/neu breast cancer subtypes (81).

Brodsky *et al* (82) demonstrated that an increase in stromal COL10A1 expression is associated with poor pathological response in estrogen receptor-positive/HER2⁺ breast tumors and low tumor-infiltrating lymphocyte levels. Furthermore, COL10A1 has been found to be associated with immune cell infiltration, being positively associated with $\gamma\delta$ T cells and M1 macrophages, and being negatively associated with CD8 T cells, monocytes and follicular helper T cells (83,84). In addition, the findings of a study have provided evidence to indicate that COL10A1 is associated with markers of CAF subtypes, with CAF⁺ cells being particularly enriched in the ECM pathway (85). Changes in the quantity and composition of the ECM are considered markers of tumor development, and in this regard, protein imprinting analysis has revealed an increase in the molecular levels of COL10A1 in conditioned normal human dermal fibroblast cell lysates and supernatants, potentially contributing to the diagnostic assessment of suspicious breast nodules (86). Furthermore, Zhang *et al* (80) conducted bioinformatics Gene Set Enrichment Analysis to assess the significance of COL10A1 in breast cancer prognosis, and observed enrichment of this protein in the TGF- β signaling pathway, which may promote the migration and invasion of tumor cells via this pathway. Consequently, targeting of COL10A1 could emerge as a novel strategy in the clinical treatment of breast cancer. Taken together, the evidence obtained to date indicates that COL10A1 positively regulates the malignant progression of breast cancer cells, and the development of therapies targeting COL10A1 could provide novel strategies for the treatment of invasive breast cancer.

Prostate cancer. Endoplasmic reticulum stress (ERS) has been established to affect tumor growth, metastasis, immune therapy, and resistance to radiotherapy and chemotherapy. COL10A1 has been found to serve a key role in ERS in prostate cancer (87), where its high expression is associated with poor patient prognosis. Analysis of the immune relevance of COL10A1 in different cancer types has revealed an association with tumor mutation burden, microsatellite instability and immune cell infiltration. Additionally, knockdown of COL10A1 has been demonstrated to be associated with a substantial reduction in the proliferation, migration and invasion of prostate cancer cells (88). Further research has indicated that COL10A1 may be involved in M2 macrophage polarization in prostate cancer (89). Additionally, network analysis, based on weighted gene co-expression network analysis modules, has been used to predict the occurrence of bone metastasis in prostate cancer, with the results indicating that the upregulation of COL10A1 expression in prostate cancer is associated with disease progression (90). However, given the limited research on the involvement of COL10A1 in prostate cancer, further clinical trials are required to validate these findings.

Colorectal cancer. Colorectal cancer is the third most common type of cancer and the fourth leading cause of cancer-related death (91). COL10A1 expression is frequently upregulated in most colorectal cancers, in which it is considered to serve a carcinogenic role in progression, maintenance and metastasis (92). For example, colorectal cancer progression and EMT processes have been shown to be associated with the aberrant expression of COL10A1 (93). As a consequence of EMT,

cancer cells acquire stronger migratory capacities, thereby facilitating a dissociation from the primary tumor and the subsequent establishment of distant metastatic foci. Research has indicated a strong positive association between COL10A1 and the transcriptional characteristics of CAFs and immune cell clusters (such as those of B cells and macrophages), thereby providing evidence that COL10A1 transcription may mediate the interaction between tumor cells and their stromal microenvironment (94). Furthermore, the levels of COL10A1 expression have been found to be associated with mismatch repair defects and immune infiltration (95). He *et al* (95) reported that visinin-like protein 1 (VSNL1) could promote the proliferation, migration and invasion of colorectal cancer cells by targeting COL10A1, whereas the upregulation of COL10A1 could enhance the proliferation, migration and invasion of colorectal cells, and reverse the effects of VSNL1 knockdown on SW480 and LoVo colorectal cancer cells. 2-cyanoacrylamido-4,5,6,7-tetrahydrobenzo[b]thiophene derivatives, a novel class of compounds, have been found to downregulate COL10A1 expression and show promising anticancer activity in the treatment of colon cancer (96). Accordingly, although it has been established that COL10A1 serves a prominent role in the occurrence and development of colorectal cancer, research on targeting of COL10A1 for treatment remains limited.

Other types of malignant tumors. Research has revealed that COL10A1 expression is upregulated in a range of different malignant tumor types, exerting multiple pro-tumor effects on cell proliferation and invasion. In cervical cancer, COL10A1 facilitates cell proliferation, migration and the EMT process via modulation of the TGF- β /Smad signaling pathway, and silencing of COL10A1 has been demonstrated to reduce TGF- β 1 protein levels and downregulate the phosphorylation of Smad2 and Smad3 (27). Additionally, as an ECM-related protein, COL10A1 has been established to be associated with immune cells, overall survival and bladder cancer recurrence (97,98). For example, Wu *et al* (99) demonstrated the efficacy of a bladder cancer-associated COL10A1 genomic model in predicting preoperative lymph node status, transurethral resection T stage and lymphovascular invasion status. Upregulation of COL10A1 expression is also associated with histological grading, tumor metastasis and poor survival in esophageal squamous cell carcinoma, suggesting that this protein may be a potential drug treatment target (100-103). Similarly, Lapa *et al* (104) revealed that COL10A1 could serve as a drug target for laryngeal squamous cell carcinoma (LSCC). By interacting with high-mobility group box DNA-binding protein 1, COL10A1 modulates the cell cycle, and its abnormal expression may regulate LSCC cell proliferation and survival (14). The findings of a further study have indicated that extracellular vesicles derived from human bone marrow mesenchymal stem cells and carrying miR-101-3p effectively restrain the proliferation, invasion and migration of TCA8113 oral cancer cells, which is mediated via downregulation of COL10A1 (105). Therefore, COL10A1 may function as a key regulatory factor in the development of oral cancer. Furthermore, COL10A1 may participate in the occurrence of nasopharyngeal carcinoma via the NF- κ B signaling pathway and ECM organization, and could thus

serve as a molecular biomarker for the early diagnosis of this cancer (106). However, research on the involvement of COL10A1 in these aforementioned tumors is currently limited, and thus, further clinical trials are required.

4. Analysis and future prospects

The present review provides a comprehensive overview of the mechanisms and functions of COL10A1 in different cancer types, including lung, gastric, pancreatic, breast, prostate and colorectal cancer, and highlights the potential application of COL10A1 as a promising biomarker for cancer diagnosis and in therapeutic targeting. COL10A1 is implicated in tumor growth, invasion, migration and EMT in multiple cancer types, involving the TGF- β 1/Smad, MEK/ERK and FAK signaling pathways, and P4HB protein regulation. Additionally, by regulating COL10A1, miR-26a-5p and miR-384 may serve important roles in influencing the development of tumor cells in diseases. Preliminary findings suggest that COL10A1 could serve as a diagnostic biomarker or therapeutic target for cancer, but further *in vivo* studies and clinical trials are necessary to confirm these roles. Furthermore, on the basis of METTL3-mediated m6A methylation, COL10A1 has been established to serve pivotal roles in the epitranscriptomic mechanisms associated with different malignancies, thereby providing novel therapeutic avenues for cancer.

However, despite these promising therapeutic applications, it should be emphasized that much of the data reviewed in the present review is based on bioinformatics analyses, highlighting the necessity for further experimental studies to establish an optimal overview and minimize unnecessary batch effects, whilst retaining biological signals. For example, the specific interactions between COL10A1 and its transcription factor LEF1, and the underlying regulatory mechanisms, as well as their roles in oncogenesis, remain unclear. Furthermore, the characteristics and involvement of the TUG1/miR-144-3p/COL10A1 axis warrant further elucidation, and additional efforts are required to develop specific inhibitors for COL10A1. Furthermore, given that the pathological role served by COL10A1 in cancer development appears to be dependent on the cell type and microenvironment, it will be necessary to develop novel COL10A1 subtype mouse models. Nevertheless, COL10A1 remains a promising onco-promoter, with considerable therapeutic potential in the diagnosis and treatment of malignant tumors.

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Authors' contributions

QY conceived the project and drafted the manuscript. GZ, WZ, JW, XO and KY contributed to data analysis, manuscript revision, discussions and language editing, and JZ revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

References

- Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
- Min HY and Lee HY: Molecular targeted therapy for anticancer treatment. *Exp Mol Med* 54: 1670-1694, 2022.
- Ricard-Blum S: The collagen family. *Cold Spring Harb Perspect Biol* 3: a004978, 2011.
- Salimian N, Peymani M, Ghaedi K, Hashemi M and Rahimi E: Collagen 1A1 (COL1A1) and Collagen11A1(COL11A1) as diagnostic biomarkers in Breast, colorectal and gastric cancers. *Gene* 92: 147867, 2024.
- Wu X, Cai J, Zuo Z and Li J: Collagen facilitates the colorectal cancer stemness and metastasis through an integrin/PI3K/AKT/Snail signaling pathway. *Biomed Pharmacother* 114: 108708, 2019.
- Sun H, Wang Y, Wang S, Xie Y, Sun K, Li S, Cui W and Wang K: The involvement of collagen family genes in tumor enlargement of gastric cancer. *Sci Rep* 13: 100, 2023.
- Zeltz C, Khalil M, Navab R and Tsao MS: Collagen Type XI inhibits lung cancer-associated fibroblast functions and restrains the integrin binding site availability on collagen type I matrix. *Int J Mol Sci* 23: 11722, 2022.
- Padežnik T, Oleksy A, Cokan A, Takač I and Sobočan M: Changes in the extracellular matrix in endometrial and cervical cancer: A systematic review. *Int J Mol Sci* 24: 5463, 2023.
- Zhang X, Liang H, Liu W, Li X, Zhang W and Shang X: A novel sequence variant in COL10A1 causing spondylometaphyseal dysplasia accompanied with coxa valga: A case report. *Medicine (Baltimore)* 98: e16485, 2019.
- Leitinger B and Kwan AP: The discoidin domain receptor DDR2 is a receptor for type X collagen. *Matrix Biol* 25: 355-364, 2006.
- Luckman SP, Rees E and Kwan AP: Partial characterization of cell-type X collagen interactions. *Biochem J* 372: 485-493, 2003.
- Li T, Huang H, Shi G, Zhao L, Li T, Zhang Z, Liu R, Hu Y, Liu H, Yu J and Li G: TGF- β 1-SOX9 axis-inducible COL10A1 promotes invasion and metastasis in gastric cancer via epithelial-to-mesenchymal transition. *Cell Death Dis* 9: 849, 2018.
- Liang Y, Xia W, Zhang T, Chen B, Wang H, Song X, Zhang Z, Xu L, Dong G and Jiang F: Upregulated collagen COL10A1 remodels the extracellular matrix and promotes malignant progression in lung adenocarcinoma. *Front Oncol* 10: 573534, 2020.
- Wu JY, Lan XL, Yan DM, Fang YY, Peng YX, Liang FF, Jiang L, Huang SN, Mo M, Lin CX, *et al*: The clinical significance of transcription factor WD repeat and HMG-box DNA binding protein 1 in laryngeal squamous cell carcinoma and its potential molecular mechanism. *Pathol Res Pract* 230: 153751, 2022.
- Zhang M, Jin M, Gao Z, Yu W and Zhang W: High COL10A1 expression potentially contributes to poor outcomes in gastric cancer with the help of LEF1 and Wnt2. *J Clin Lab Anal* 36: e24612, 2022.
- Chang HJ, Yang MJ, Yang YH, Hou MF, Hsueh EJ and Lin SR: MMP13 is potentially a new tumor marker for breast cancer diagnosis. *Oncol Rep* 22: 1119-1127, 2009.
- Sun Y, Wang L, Jiang M, Huang J, Liu Z and Wolf S: Secreted phosphoprotein 1 upstream invasive network construction and analysis of lung adenocarcinoma compared with human normal adjacent tissues by integrative biocomputation. *Cell Biochem Biophys* 56: 59-71, 2010.
- Andriani F, Landoni E, Mensah M, Facchinetti F, Miceli R, Tagliabue E, Giussani M, Callari M, De Cecco L, Colombo MP, *et al*: Diagnostic role of circulating extracellular matrix-related proteins in non-small cell lung cancer. *BMC Cancer* 18: 899, 2018.
- Patra R, Das NC and Mukherjee S: Exploring the differential expression and prognostic significance of the COL11A1 gene in human colorectal carcinoma: An integrated bioinformatics approach. *Front Genet* 12: 608313, 2021.
- Jung B, Staudacher JJ and Beauchamp D: Transforming growth factor β superfamily signaling in development of colorectal cancer. *Gastroenterology* 152: 36-52, 2017.
- Liu R, Yin G, Tuo H, Guo Y, Zhu Y, Zhang L, Yang W, Liu Q and Wang Y: METTL3-induced lncRNA GBAP1 promotes hepatocellular carcinoma progression by activating BMP/SMAD pathway. *Biol Direct* 18: 53, 2023.
- Iyengar PV, Marvin DL, Lama D, Tan TZ, Suriyamurthy S, Xie F, van Dinther M, Mei H, Verma CS, Zhang L, *et al*: TRAF4 inhibits bladder cancer progression by promoting BMP/SMAD signaling. *Mol Cancer Res* 20: 1516-1531, 2022.
- Shi Y and Massagué J: Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* 113: 685-700, 2003.
- Bierie B and Moses HL: TGF-beta and cancer. *Cytokine Growth Factor Rev* 17: 29-40, 2006.
- Shi X, Yang J, Deng S, Xu H, Wu D, Zeng Q, Wang S, Hu T, Wu F and Zhou H: TGF- β signaling in the tumor metabolic microenvironment and targeted therapies. *J Hematol Oncol* 15: 135, 2022.
- Yang H, Yue GG, Yuen KK, Gao S, Leung PC, Wong CK and Lau CB: Mechanistic insights into the anti-tumor and anti-metastatic effects of *Patrinia villosa* aqueous extract in colon cancer via modulation of TGF- β R1-smad2/3-E-cadherin and FAK-RhoA-cofilin pathways. *Phytomedicine* 117: 154900, 2023.
- Sun Y, Ling J and Liu L: Collagen type X alpha 1 promotes proliferation, invasion and epithelial-mesenchymal transition of cervical cancer through activation of TGF- β /Smad signaling. *Physiol Int*: May 18. 2022 doi: 10.1556/2060.2022.00006 (Epub ahead of print).
- Trono P, Ottavi F and Rosano L: Novel insights into the role of Discoidin domain receptor 2 (DDR2) in cancer progression: A new avenue of therapeutic intervention. *Matrix Biol* 125: 31-39, 2024.
- Lv PC, Jiang AQ, Zhang WM and Zhu HL: FAK inhibitors in cancer, a patent review. *Expert Opin Ther Pat* 28: 139-145, 2018.
- Pagani CA, Bancroft AC, Tower RJ, Livingston N, Sun Y, Hong JY, Kent RN III, Strong AL, Nunez JH, Medrano JMR, *et al*: Discoidin domain receptor 2 regulates aberrant mesenchymal lineage cell fate and matrix organization. *Sci Adv* 8: eabq6152, 2022.
- Chanez B, Ostacolo K, Badache A and Thuault S: EB1 restricts breast cancer cell invadopodia formation and matrix proteolysis via FAK. *Cells* 10: 388, 2021.
- Li M, Wang Y, Li M, Wu X, Setrerrahmane S and Xu H: Integrins as attractive targets for cancer therapeutics. *Acta Pharm Sin B* 11: 2726-2737, 2021.
- Recillas-Targa F: Cancer epigenetics: An overview. *Arch Med Res* 53: 732-740, 2022.
- Zhou S, Zeng H, Huang J, Lei L, Tong X, Li S, Zhou Y, Guo H, Khan M, Luo L, *et al*: Epigenetic regulation of melanogenesis. *Ageing Res Rev* 69: 101349, 2021.
- Li Y, Li X, Deng M, Ye C, Peng Y and Lu Y: Cancer-associated fibroblasts hinder lung squamous cell carcinoma oxidative stress-induced apoptosis via METTL3 mediated m6A methylation of COL10A1. *Oxid Med Cell Longev* 2022: 4320809, 2022.
- Zeng C, Huang W, Li Y and Weng H: Roles of METTL3 in cancer: Mechanisms and therapeutic targeting. *J Hematol Oncol* 13: 117, 2020.

37. Xu Y, Song M, Hong Z, Chen W, Zhang Q, Zhou J, Yang C, He Z, Yu J, Peng X, *et al.*: The N6-methyladenosine METTL3 regulates tumorigenesis and glycolysis by mediating m6A methylation of the tumor suppressor LATS1 in breast cancer. *J Exp Clin Cancer Res* 42: 10, 2023.
38. Shi K, Sa R, Dou L, Wu Y, Dong Z, Fu X and Yu H: Correction: METTL3 exerts synergistic effects on m6A methylation and histone modification to regulate the function of VGF in lung adenocarcinoma. *Clin Epigenetics* 16: 2, 2024.
39. Wang Q, Chen C, Ding Q, Zhao Y, Wang Z, Chen J, Jiang Z, Zhang Y, Xu G, Zhang J, *et al.*: METTL3-mediated m⁶A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance. *Gut* 69: 1193-1205, 2020.
40. Guo S, Wang E, Wang B, Xue Y, Kuang Y and Liu H: Comprehensive multiomics analyses establish the optimal prognostic model for resectable gastric cancer: Prognosis prediction for resectable GC. *Ann Surg Oncol* 31: 2078-2089, 2024.
41. Cai Y, Lyu T, Li H, Liu C, Xie K, Xu L, Li W, Liu H, Zhu J, Lyu Y, *et al.*: LncRNA CEBPA-DT promotes liver cancer metastasis through DDR2/ β -catenin activation via interacting with hnRNPC. *J Exp Clin Cancer Res* 41: 335, 2022.
42. Xie B, Lin W, Ye J, Wang X, Zhang B, Xiong S, Li H and Tan G: DDR2 facilitates hepatocellular carcinoma invasion and metastasis via activating ERK signaling and stabilizing SNAI1. *J Exp Clin Cancer Res* 34: 101, 2015.
43. Ren L, Ren Q, Wang J, He Y, Deng H, Wang X and Liu C: miR-199a-3p promotes gastric cancer progression by promoting its stemness potential via DDR2 mediation. *Cell Signal* 106: 110636, 2023.
44. Wang YG, Xu L, Jia RR, Wu Q, Wang T, Wei J, Ma JL, Shi M and Li ZS: DDR2 induces gastric cancer cell activities via activating mTORC2 signaling and is associated with clinicopathological characteristics of gastric cancer. *Dig Dis Sci* 61: 2272-2283, 2016.
45. Ren T, Zhang W, Liu X, Zhao H, Zhang J, Zhang J, Li X, Zhang Y, Bu X, Shi M, *et al.*: Discoidin domain receptor 2 (DDR2) promotes breast cancer cell metastasis and the mechanism implicates epithelial-mesenchymal transition programme under hypoxia. *J Pathol* 234: 526-537, 2014.
46. Xu J, Lu W, Zhang S, Zhu C, Ren T, Zhu T, Zhao H, Liu Y and Su J: Overexpression of DDR2 contributes to cell invasion and migration in head and neck squamous cell carcinoma. *Cancer Biol Ther* 15: 612-622, 2014.
47. Davis FM, Stewart TA, Thompson EW and Monteith GR: Targeting EMT in cancer: Opportunities for pharmacological intervention. *Trends Pharmacol Sci* 35: 479-488, 2014.
48. Ullah R, Yin Q, Snell AH and Wan L: RAF-MEK-ERK pathway in cancer evolution and treatment. *Semin Cancer Biol* 85: 123-154, 2022.
49. Zheng F, Wu J, Zhao S, Luo Q, Tang Q, Yang L, Li L, Wu W and Hann SS: Baicalein increases the expression and reciprocal interplay of RUNX3 and FOXO3a through crosstalk of AMPK α and MEK/ERK1/2 signaling pathways in human non-small cell lung cancer cells. *J Exp Clin Cancer Res* 34: 41, 2015.
50. Wen Z, Sun J, Luo J, Fu Y, Qiu Y, Li Y, Xu Y, Wu H and Zhang Q: COL10A1-DDR2 axis promotes the progression of pancreatic cancer by regulating MEK/ERK signal transduction. *Front Oncol* 12: 1049345, 2022.
51. Wang F, Yu Z, Liu X, Hu F, Liu X, Fu X, Liu Y and Zou Z: A meta-analysis and bioinformatics analysis of P4HB expression levels in the prognosis of cancer patients. *Pathol Res Pract* 245: 154474, 2023.
52. Feng D, Wang J, Li D, Wu R, Tuo Z, Yu Q, Ye L, Miyamoto A, Yoo KH, Wang C, *et al.*: Targeting Prolyl 4-hydroxylase subunit beta (P4HB) in cancer: New roads to travel. *Aging Dis*: Nov 26, 2023.
53. Feng D, Li L, Li D, Wu R, Zhu W, Wang J, Ye L and Han P: Prolyl 4-hydroxylase subunit beta (P4HB) could serve as a prognostic and radiosensitivity biomarker for prostate cancer patients. *Eur J Med Res* 28: 245, 2023.
54. Ma X, Wang J, Zhuang J, Ma X, Zheng N, Song Y and Xia W: P4HB modulates epithelial-mesenchymal transition and the β -catenin/Snai1 pathway influencing chemoresistance in liver cancer cells. *Oncol Lett* 20: 257-265, 2020.
55. Yang W, Wu X and Zhou F: Collagen Type X Alpha 1 (COL10A1) Contributes to cell proliferation, migration, and invasion by targeting Prolyl 4-hydroxylase beta polypeptide (P4HB) in breast cancer. *Med Sci Monit* 27: e928919, 2021.
56. Qi X, Zhang DH, Wu N, Xiao JH, Wang X and Ma W: ceRNA in cancer: Possible functions and clinical implications. *J Med Genet* 52: 710-718, 2015.
57. Liu Q, Zhao H, Guo Y, Zhang K, Shang F and Liu T: Bioinformatics-based analysis: Noncoding RNA-Mediated COL10A1 is associated with poor prognosis and immune cell infiltration in pancreatic cancer. *J Healthc Eng* 2022: 7904982, 2022.
58. Liu Q, Zhang W, Wu Z, Liu H, Hu H, Shi H, Li S and Zhang X: Construction of a circular RNA-microRNA-messengerRNA regulatory network in stomach adenocarcinoma. *J Cell Biochem* 121: 1317-1331, 2020.
59. Li HH, Wang JD, Wang W, Wang HF and Lv JQ: Effect of miR-26a-5p on gastric cancer cell proliferation, migration and invasion by targeting COL10A1. *Eur Rev Med Pharmacol Sci* 24: 1186-1194, 2020.
60. Guo Q, Zheng M, Xu Y, Wang N and Zhao W: MiR-384 induces apoptosis and autophagy of non-small cell lung cancer cells through the negative regulation of Collagen α -1(X) chain gene. *Biosci Rep* 392019.
61. Mamdani H, Matosevic S, Khalid AB, Durm G and Jalal SI: Immunotherapy in lung cancer: Current landscape and future directions. *Front Immunol* 13: 823618, 2022.
62. Liu X, Li L, Xie X, Zhuang D and Hu C: Integrated bioinformatics analysis of microarray data from the GEO database to identify the candidate genes linked to poor prognosis in lung adenocarcinoma. *Technol Health Care* 31: 579-592, 2023.
63. Wu X, Zhang W, Hu Y and Yi X: Bioinformatics approach reveals systematic mechanism underlying lung adenocarcinoma. *Tumori* 101: 281-286, 2015.
64. Shi Y, Chang D, Li W, Zhao F, Ren X and Hou B: Identification of core genes and clinical outcomes in tumors originated from endoderm (gastric cancer and lung carcinoma) via bioinformatics analysis. *Medicine (Baltimore)* 100: e25154, 2021.
65. Díaz Del Arco C, Ortega Medina L, Estrada Muñoz L, García Gómez de Las Heras S and Fernández Aceñero MJ: Is there still a place for conventional histopathology in the age of molecular medicine? Laurén classification, inflammatory infiltration and other current topics in gastric cancer diagnosis and prognosis. *Histol Histopathol* 36: 587-613, 2021.
66. Cai Z, Wei Y, Chen S, Gong Y, Fu Y, Dai X, Zhou Y, Yang H, Tang L and Liu H: Screening and identification of key biomarkers in alimentary tract cancers: A bioinformatic analysis. *Cancer Biomark* 29: 221-233, 2020.
67. Li Y, Luo Y, Tian Q, Lai Y, Xu L, Yun H, Liang Y, Liao D, Gu R, Liu L, *et al.*: Integrated bioinformatics analysis for identifying the significant genes as poor prognostic markers in gastric adenocarcinoma. *J Oncol* 2022: 9080460, 2022.
68. Aktas SH, Taskin-Tok T, Al-Khafaji K and Akın-Balı DF: A detailed understanding of the COL10A1 and SOX9 genes interaction based on potentially damaging mutations in gastric cancer using computational techniques. *J Biomol Struct Dyn* 40: 11533-11544, 2022.
69. Shen N, Zhu S, Zhang Z and Yong X: High Expression of COL10A1 is an independent predictive poor prognostic biomarker and associated with immune infiltration in advanced gastric cancer microenvironment. *J Oncol* 2022: 1463316, 2022.
70. Moreira AM, Ferreira RM, Carneiro P, Figueiredo J, Osório H, Barbosa J, Preto J, Pinto-do-Ó P, Carneiro F and Seruca R: Proteomic identification of a gastric tumor ECM signature associated with cancer progression. *Front Mol Biosci* 9: 818552, 2022.
71. Necula L, Matei L, Dragu D, Pitică I, Neagu AI, Bleotu C, Dima S, Popescu I, Diaconu CC and Chivu-Economescu M: High plasma levels of COL10A1 are associated with advanced tumor stage in gastric cancer patients. *World J Gastroenterol* 26: 3024-3033, 2020.
72. Chen L, Zhang X, Zhang Q, Zhang T, Xie J, Wei W, Wang Y, Yu H and Zhou H: A necroptosis related prognostic model of pancreatic cancer based on single cell sequencing analysis and transcriptome analysis. *Front Immunol* 13: 1022420, 2022.
73. Xu Q, Zheng J, Su Z, Chen B and Gu S: COL10A1 promotes tumorigenesis by modulating CD276 in pancreatic adenocarcinoma. *BMC Gastroenterol* 23: 397, 2023.
74. Thorlacius-Ussing J, Jensen C, Nissen NI, Cox TR, Kalluri R, Karsdal M and Willumsen N: The collagen landscape in cancer: Profiling collagens in tumors and in circulation reveals novel markers of cancer-associated fibroblast subtypes. *J Pathol* 262: 22-36, 2024.
75. Lou X, Gao H, Xu X, Ye Z, Zhang W, Wang F, Chen J, Zhang Y, Chen X, Qin Y, *et al.*: The Interplay of four main pathways recomposes immune landscape in primary and metastatic Gastroenteropancreatic neuroendocrine tumors. *Front Oncol* 12: 808448, 2022.

76. Zhang X, Chen B, Liu K, Ma Y, Liu Y, Zhou H and Wei P: Infection with COVID-19 promotes the progression of pancreatic cancer through the PI3K-AKT signaling pathway. *Discov Oncol* 14: 225, 2023.
77. Abdi E, Latifi-Navid S and Latifi-Navid H: LncRNA polymorphisms and breast cancer risk. *Pathol Res Pract* 229: 153729, 2022.
78. Won KA and Spruck C: Triple-negative breast cancer therapy: Current and future perspectives (Review). *Int J Oncol* 57: 1245-1261, 2020.
79. Onkar SS, Carleton NM, Lucas PC, Bruno TC, Lee AV, Vignali DAA and Oesterreich S: The great immune escape: Understanding the divergent immune response in breast cancer subtypes. *Cancer Discov* 13: 23-40, 2023.
80. Zhang M, Chen H, Wang M, Bai F and Wu K: Bioinformatics analysis of prognostic significance of COL10A1 in breast cancer. *Biosci Rep* 40: BSR20193286, 2020.
81. Malvia S, Chintamani C, Sarin R, Dubey US, Saxena S and Bagadi SAR: Aberrant expression of COL14A1, CELRS3, and CTHRC1 in breast cancer cells. *Exp Oncol* 45: 28-43, 2023.
82. Brodsky AS, Xiong J, Yang D, Schorl C, Fenton MA, Graves TA, Sikov WM, Resnick MB and Wang Y: Identification of stromal ColXα1 and tumor-infiltrating lymphocytes as putative predictive markers of neoadjuvant therapy in estrogen receptor-positive/HER2-positive breast cancer. *BMC Cancer* 16: 274, 2016.
83. Zhou W, Li Y, Gu D, Xu J, Wang R, Wang H and Liu C: High expression COL10A1 promotes breast cancer progression and predicts poor prognosis. *Heliyon* 8: e11083, 2022.
84. Bao S and He G: Identification of key genes and key pathways in breast cancer based on machine learning. *Med Sci Monit* 28: e935515, 2022.
85. Wang M, Feng R, Chen Z, Shi W, Li C, Liu H, Wu K, Li D and Li X: Identification of cancer-associated fibroblast subtype of triple-negative breast cancer. *J Oncol* 2022: 6452636, 2022.
86. Giussani M, Landoni E, Merlino G, Turdo F, Veneroni S, Paolini B, Cappelletti V, Miceli R, Orlandi R, Triulzi T and Tagliabue E: Extracellular matrix proteins as diagnostic markers of breast carcinoma. *J Cell Physiol* 233: 6280-6290, 2018.
87. Cen S, Jiang D, Lv D, Xu R, Hou J, Yang Z, Wu P, Xiong X and Gao X: Comprehensive analysis of the biological functions of endoplasmic reticulum stress in prostate cancer. *Front Endocrinol (Lausanne)* 14: 1090277, 2023.
88. Xu S, Liu D, Qin Z, Liang Z, Xie H, Yi B, Wang K, Lin G, Liu R, Yang K, *et al*: Experimental validation and pan-cancer analysis identified COL10A1 as a novel oncogene and potential therapeutic target in prostate cancer. *Aging (Albany NY)* 15: 15134-15160, 2023.
89. Wang C, Wang J, Chen S, Li K, Wan S and Yang L: COL10A1 as a prognostic biomarker in association with immune infiltration in prostate cancer. *Curr Cancer Drug Targets* 24: 340-353, 2023.
90. Zhao J, Wang R, Sun X, Huang K, Jin J, Lan L, Jian Y, Xu Z, Wu H, Wang S and Wang J: An integrative multi-omics analysis based on nomogram for predicting prostate cancer bone metastasis incidence. *Genet Res (Camb)* 2022: 8213723, 2022.
91. Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E and Rodriguez Yoldi MJ: Colorectal carcinoma: A general overview and future perspectives in colorectal cancer. *Int J Mol Sci* 18: 197, 2017.
92. Solé X, Crous-Bou M, Cordero D, Olivares D, Guinó E, Sanz-Pamplona R, Rodriguez-Moranta F, Sanjuan X, de Oca J, Salazar R and Moreno V: Discovery and validation of new potential biomarkers for early detection of colon cancer. *PLoS One* 9: e106748, 2014.
93. Huang H, Li T, Ye G, Zhao L, Zhang Z, Mo D, Wang Y, Zhang C, Deng H, Li G and Liu H: High expression of COL10A1 is associated with poor prognosis in colorectal cancer. *Onco Targets Ther* 11: 1571-1581, 2018.
94. Kahlert UD, Shi W, Strecker M, Scherpinski LA, Wartmann T, Dölling M, Perrakis A, Relja B, Mengoni M, Braun A and Croner RS: COL10A1 allows stratification of invasiveness of colon cancer and associates to extracellular matrix and immune cell enrichment in the tumor parenchyma. *Front Oncol* 12: 1007514, 2022.
95. He C, Liu W, Xiong Y, Pan L, Luo L, Tu Y, Song R and Chen W: VSNL1 promotes cell proliferation, migration, and invasion in colorectal cancer by binding with COL10A1. *Ann Clin Lab Sci* 52: 60-72, 2022.
96. Sroor FM, Aboelenin MM, Mahrous KF, Mahmoud K, Elwahy AHM and Abdelhamid IA: Novel 2-cyanoacrylamido-4,5,6,7-tetrahydrobenzo[b]thiophene derivatives as anticancer agents. *Arch Pharm (Weinheim)* 353: e2000069, 2020.
97. Zhao H, Chen Z, Fang Y, Su M, Xu Y, Wang Z, Gyamfi MA and Zhao J: Prediction of prognosis and recurrence of bladder cancer by ECM-Related genes. *J Immunol Res* 2022: 1793005, 2022.
98. Liu Q, Diao R, Feng G, Mu X and Li A: Risk score based on three mRNA expression predicts the survival of bladder cancer. *Oncotarget* 8: 61583-61591, 2017.
99. Wu SX, Huang J, Liu ZW, Chen HG, Guo P, Cai QQ, Zheng JJ, Qin HD, Zheng ZS, Chen X, *et al*: A Genomic-clinicopathologic Nomogram for the preoperative prediction of lymph node metastasis in bladder cancer. *EBioMedicine* 31: 54-65, 2018.
100. Karagoz K, Lehman HL, Stairs DB, Sinha R and Arga KY: Proteomic and metabolic signatures of esophageal squamous cell carcinoma. *Curr Cancer Drug Targets*: Feb 2, 2016 (Epub ahead of print).
101. Li J, Wang X, Zheng K, Liu Y, Li J, Wang S, Liu K, Song X, Li N, Xie S and Wang S: The clinical significance of collagen family gene expression in esophageal squamous cell carcinoma. *PeerJ* 7: e7705, 2019.
102. Li Y, Wang X, Shi L, Xu J and Sun B: Predictions for high COL1A1 and COL10A1 expression resulting in a poor prognosis in esophageal squamous cell carcinoma by bioinformatics analyses. *Transl Cancer Res* 9: 85-94, 2020.
103. Song Y, Wang X, Wang F, Peng X, Li P, Liu S and Zhang D: Identification of four genes and biological characteristics of esophageal squamous cell carcinoma by integrated bioinformatics analysis. *Cancer Cell Int* 21: 123, 2021.
104. Lapa RML, Barros-Filho MC, Marchi FA, Domingues MAC, de Carvalho GB, Drigo SA, Kowalski LP and Rogatto SR: Integrated miRNA and mRNA expression analysis uncovers drug targets in laryngeal squamous cell carcinoma patients. *Oral Oncol* 93: 76-84, 2019.
105. Xie C, Du LY, Guo F, Li X and Cheng B: Exosomes derived from microRNA-101-3p-overexpressing human bone marrow mesenchymal stem cells suppress oral cancer cell proliferation, invasion, and migration. *Mol Cell Biochem* 458: 11-26, 2019.
106. Guo W, Zheng X, Hua L, Zheng X, Zhang Y, Sun B, Tao Z and Gao J: Screening and bioinformatical analysis of differentially expressed genes in nasopharyngeal carcinoma. *J Cancer* 12: 1867-1883, 2021.
107. Vishnubalaji R, Shaath H, Elkord E and Alajez NM: Long non-coding RNA (lncRNA) transcriptional landscape in breast cancer identifies LINC01614 as non-favorable prognostic biomarker regulated by TGFβ and focal adhesion kinase (FAK) signaling. *Cell Death Discov* 5: 109, 2019.



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