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Tumor matrix protein collagen XIα1 in cancer

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Abstract

The extracellular matrix is increasingly recognized as an essential player in cancer development and progression. Collagens are one of the most important components of the extracellular matrix, and have themselves been implicated in many aspects of neoplastic transformation. Collagen XI is a minor collagen whose main physiologic function is to regulate the diameter of major collagen fibrils. The α1 chain of collagen XI (colXIα1), has known pathogenic roles in several musculoskeletal disorders. Recent research has highlighted the importance of colXIα1 in many types of cancer, including its roles in metastasis, angiogenesis, and drug resistance, as well as its potential utility in screening tests and as a therapeutic target. High levels of colXIα1 overexpression have been reported in multiple expression profile studies examining differences between cancerous and normal tissue, and between beginning and advanced stage cancer. Its expression has been linked to poor progression-free and overall survival. The consistency of this data across cancer types is particularly striking, including colorectal, ovarian, breast, head and neck, lung, and brain cancers. This review discusses the role of collagen XIα1 in cancer and its potential as a target for cancer therapy.

Keywords

Collagen; extracellular matrix; colXIα1; COL11A1; cancer

Introduction

The extracellular matrix (ECM) is an essential component of the cancer cell niche. The ECM is a complex macromolecular network composed of biochemically distinct elements, including polysaccharides, proteoglycans, proteins, and glycoproteins. It provides structural

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None

support for cells in the form of the basement membrane, a specialized type of matrix essential for many cellular processes. In addition, the ECM forms the interstitial matrix, which is important in structural tissue support as well as in regulating and integrating cell behavior[1,2].

The role of the ECM in tumor progression is becoming increasingly clear; a flood of recent research has illustrated that dysregulation of its various components plays an essential role in generating and maintaining the tumor microenvironment[1,2]. For example, tumor ECM is often stiffer and more highly crosslinked than normal stroma, promoting abnormal cell behavior[3–5]. Tumor cells are especially sensitive to changes in the stiffness of their environment, specifically increased collagen crosslinking, which then helps to drive the malignant phenotype[3]. A normal, functional ECM is essential for maintaining cellular architecture and polarity, which is universally lost in neoplastic growth. Abnormal ECM also promotes abnormal behavior in stromal cells, including the fibroblasts, immune cells, and endothelial cells that help make up the tumor microenvironment, and thus contributes to the formation and perpetuation of the neoplastic niche[6,7].

One of the most important components of the ECM, and the most abundant protein in the body, is collagen. Currently there are 28 known collagens, which are trimeric molecules consisting of three polypeptide alpha chains (which may or may not be identical) forming a triple helix structure common to all collagens. The collagen family is diverse, and therefore is divided into three subgroups based on molecular structure and supramolecular assemblies: fibrillar collagens, non-fibril forming collagens, and fibril-associated collagens[8–10]. Fibrillar collagens are the most abundant, and are capable of forming highly ordered fibrils in the ECM. Fibril-associated collagens, containing interrupted triple helices, associate with and help regulate fibrillar collagens. Non-fibril forming collagens, which include type IV collagen found in the basement membrane, do not form or associate with fibrils[8].

Many previous reports have revealed collagen XI as a player in human disease. Collagen XI is a minor fibrillar collagen most abundantly found in cartilage, but which has also been found in odontoblasts, trabecular bone, skeletal muscle, placenta, lung, and neoepithelium of the brain[11]. Collagen XI copolymerizes with both collagen II and collagen IX, and is essential in maintaining proper fibril diameter and function in connective tissue; absence or mutation in the alpha chain of collagen XI results in abnormally thickened cartilage fibrils[12]. Collagen XI, like all collagens, is a heterotrimer consisting of α1, α2, and α3 chains, located on different chromosomes, which are synthesized as procollagens and proteolytically cleaved to yield mature trimers[11]. The α1 and α2 chains are genetically distinct, while the α3 chain is a hyperglycosylated form of the α1 chain of collagen II. Mutations in the gene encoding the α1 chain of collagen XI (colXIα1) have been implicated in many musculoskeletal disorders, including Stickler syndrome, characterized by opthalamic, articular, orofacial, and auditory abnormalities[13,14]; fibrochondrogenesis, a lethal form of dwarfism[15]; as well as osteoarthritis[16], lumbar disc herniation[17], limbus vertebra[18], and Achilles tendinopathy[19].

Recent progress has highlighted an important role for collagen XI in many aspects of neoplastic transformation. This review will focus on the role of collagen XIα1 in cancer.

Dysregulation of collagen XIα1 in cancer

Normal, physiologic expression of collagen XI is very low or nonexistent in most tissues[20–22]. Therefore, changes in collagen XIα1 (colXIα1) expression associated with cancer are excellent putative markers both of neoplastic change and disease progression.

ColXIα1 was found to be the most highly overexpressed gene in high-stage (versus low-stage) cancer in a meta-analysis of microarray data from multiple cancers[23]. This analysis generated a metastasis-associated gene expression signature of which colXIα1 was the top hit, and which was common to multiple cancers, including ovarian, colon, breast, and lung[23]. This metastasis-associated gene expression signature corresponds to a stromal desmoplastic reaction commonly produced by tumor-associated fibroblasts (TAFs). This reaction is frequently present in high stage cancers either in the process of or which have already invaded into the surrounding tissues and/or metastasized to distant sites. Specifically, colXIα1 mRNA expression correlated with cancer staging in this group of cancers, suggesting that it alone can be used as a proxy for the metastasis-associated gene expression signature. Expression of this metastasis-associated gene signature by primary tumors may be an early marker for invasive potential[23,24]. To validate this data, human neuroblastoma cells were xenografted into immunocompromised mice. The resulting tumors also expressed high levels of colXIα1 as assessed by quantitative PCR, as well as the other epithelial-to-mesenchymal transition (EMT)-associated genes in the signature[24]. This signature was only expressed by the xenografted human cells, and not the surrounding mouse stroma, suggesting that signals for EMT derive specifically from the tumor[24]. A subset of murine adipocyte markers was downregulated in association with the upregulation of EMT signature genes, implicating adipocytes in the development of cancer cell invasion. Similarly, highly migratory human glioma cells were used to assess markers for cell invasion and their epigenetic controls, as compared to non-migratory breast cancer cells. ColXIα1 mRNA was highly upregulated in the glioma cells as compared to the breast cancer cells. This was associated with both hyperacetylation and methylation of specific lysine residues on histone 3, both of which are markers for transcriptional activation[25]. ColXIα1 is also highly expressed at the protein level in human gliomas versus paired normal tissue[26].

Colorectal carcinoma

The role of colXIα1 in cancer was first identified in sporadic colorectal cancer, which expresses high levels of colXIα1 mRNA, while there is no expression in normal colonic tissue. In this setting, colXIα1 seems to be co-expressed with collagen Vα2, the other minor fibrillar collagen with which collagen XI shares a high degree of sequence homology, and which is also not expressed in normal adult colon[20]. ColXIα1 is also overexpressed in colon polyps from patients with familial adenomatous polyposis, an inherited mutation in the tumor suppressor APC which causes colorectal carcinoma. The authors suggest that colXIα1 overexpression could be related to the APC/β-catenin pathway, which is dysregulated not only in familial adenomatous polyposis but also in the majority of sporadic colorectal cancers[21]. This aberrant expression has been linked to a mutation in exon 54 in the colXIα1 gene, discovered by analyzing mutations in exfoliated tumor cells from the stool of

colorectal cancer patients. The mutation may act as a potential non-invasive screening test for colorectal cancer[27].

Ovarian carcinoma

In a study looking at gene expression in human epithelial ovarian cancer tissue samples, colXIα1 was the most highly expressed of the studied genes, and expression correlated with stage of disease[28]. High colXIα1 at both the mRNA and protein level was also associated with cancer recurrence or persistence, as well as lower overall and disease-free survival[28,29]. ColXIα1 was similarly identified as part of a 10-gene panel from 403 high-grade serous ovarian cancer samples predictive of poor clinical outcome[30]. Furthermore, colXIα1 expression (both mRNA and protein) differs by tumor site and stage: the lowest levels were expressed in primary ovarian cancer samples, moderate levels in concurrent metastases, and highest levels in recurrent/persistent metastases from the same patient[30]. ColXIα1 was also the most highly overexpressed gene in a microarray study of metastatic versus primary ovarian serous papillary carcinoma, where it was upregulated by an average of 8.23-fold in omental metastases[31]. ColXIα1 was identified as one of 12 genes highly expressed in ovarian tumor vasculature, and may serve as a tumor biomarker[32]. Markers of tumor blood supply may act as important drug targets, following in the footsteps of the VEGF inhibitor bevacizumab, which has been successful as part of a multi-therapy regimen in treating many types of solid tumors.

Breast carcinoma

Multiple studies have found that colXIα1 is much more highly expressed in invasive ductal carcinoma than its precursor, the premalignant lesion ductal carcinoma in situ, indicating that it may play a role in local invasion of cancer cells[33–35]. Additionally, increased colXIα1 expression has been reported in primary breast tumors compared to paired lymph node metastases[36,37]. Overexpression of colXIα1, along with other similar extracellular matrix genes, at primary tumor sites suggests that it is important in modulating the ECM to facilitate tumor cell dissemination and therefore metastasis; this is in agreement with the findings from the metastasis-associated gene signature discussed above. ColXIα1 was also overexpressed in a “high risk” group of breast cancer patients, who were axillary lymph node-positive and had distant metastases within follow up time (43 months), versus those in the “low risk” group, who were also node-positive but had no metastases within this time[36]. However, another study found that colXIα1 protein was actually downregulated in primary breast tumors that had metastasized versus those that had not[38]. The apparent discrepancy may be due to the use of immunohistochemistry to assess protein level, versus the study describing higher expression in primary tumors, which was based on mRNA data.

Aerodigestive tract tumors

Similar to the above findings, in a microarray study of head and neck squamous cell carcinoma (HNSCC), colXIα1 was one of two genes of 12,000 studied found to be highly upregulated (by an average of 476-fold) in all HNSCC samples studied, and had no expression in normal tissue, making it an ideal marker for HNSCC[39]. This finding was confirmed by another study in which colXIα1 was upregulated by an average of 6.63 fold in HNSCC tumors versus normal adjacent tissue[40]. An additional study demonstrated a 7.5-

fold increase in colXI α1 mRNA levels in metastatic HNSCC tumors compared to non-metastatic tumors[41]. A genome-wide analysis examining chromosomal alterations occurring in environmental insult-initiated esophageal squamous cell carcinoma found significant amplification of colXIα1 gene compared to matched normal tissue, which may be used as an early biomarker for esophageal cancer[42]. Single nucleotide polymorphisms in the colXIα1 gene have been linked to papillary thyroid cancer, with certain alleles conferring a protective effect[43].

ColXIα1 is also overexpressed in non-small cell lung cancer, as well as correlating with pathological stage, presence of lymph node metastasis, and poor prognosis[44]. In transitional cell carcinoma of the bladder, colXIα1 is one of seven genes with differential expression between superficial and muscle-invasive tumors[45]. ColXIα1 expression is also capable of differentiating premalignant from malignant stomach cancers[46]. See Table 1 for a summary of colXIα1 dysregulation across cancer types.

ColXIα1 and tumor-associated stroma

TAFs are the most abundant cell type within the stroma of many solid malignancies. ColXIα1 was found to be more highly expressed by TAFs isolated from HNSCC explants than in normal fibroblasts derived from cancer-free patients[40]. Immunohistochemical studies in pancreatic cancer have also suggested that colXIα1 may be a marker capable of differentiating TAFs from normal activated fibroblasts, a distinction which has been elusive so far[47]. In ovarian cancer studies, colXIα1 expression was mainly confined to stromal cells, specifically to the intra/peritumoral stromal cells, and not expressed >1 mm from epithelial tumor cells, indicating again that colXIα1 is a specific marker for TAFs, and potentially for malignant cells undergoing EMT[30]. Taken together, this strongly implicates stroma-secreted colXIα1 in the ECM modulation that is critical in facilitating tumor spread.

ColXIα1 is highly expressed in the stroma of breast cancer, with anti-procolXIα1 antibodies capable of recognizing invasive ductal carcinoma-associated TAFs and therefore differentiating breast malignancies from benign lesions, which have very little or no procolXIα1 expression[48,49]. Similarly, resection margins from gastric carcinoma patients exhibit high colXIα1 levels[50]. Expression is also limited to stroma in colorectal cancer[20]. However, in several of the studies discussed above, the source of increased colXIα1 was the epithelial compartment, not the surrounding stroma, suggesting a complex interplay between these two factors in facilitating tumor invasion.

ColXIα1 as a therapeutic target

Although colXIα1 is clearly active in promoting cancer progression and metastasis, descriptive studies, even with human tissue, are limited in terms of functional or mechanistic significance. Thus it is noteworthy that functional studies in various cancer types have confirmed that dysregulation of colXIα1 expression is indeed playing a relevant role in neoplastic progression (Figure 1). ColXIα1 siRNA-mediated knockdown in both ovarian cancer cell lines and HNSCC cell lines significantly suppressed invasion and slowed proliferation. This effect was not observed when normal, non-cancerous cells were transfected with colXIα1 siRNA, further confirming its potential as a therapeutic target[28,40].

In the ovarian cancer cell lines, colXIα1 knockdown was associated with decreased matrix metalloproteinase (MMP) 3 mRNA expression and activity. This effect was mediated through Ets-1, a transcription factor that regulates expression of many matrix-modulating genes, including several MMPs, and which is known to be expressed in many types of cancer. ColXIα1 knockdown decreased Ets-1 binding to the MMP3 promoter, indicating that the effect of colXIα1 on cell invasion may be mediated through MMP3 upregulation[28]. When colXIα1-knockdown cells were inoculated into mice, they showed impaired tumor spread and invasion compared to mice injected with cells expressing wild-type colXIα1[28,30]. One study in a mouse model of pancreatic cancer suggests that colXIα1 may be a downstream target of the Hedgehog signaling pathway, which is activated in most pancreatic cancers. In pancreatic cancer cells, overexpression of Gli1, the major transcription factor activated by the Hedgehog pathway, resulted in increased expression of colXIα1[51]. Studies in pancreatic and ovarian cancer have also suggested that colXIα1 is a downstream target of the TGF-β signaling pathway, which is itself regulated by the ECM and is commonly dysregulated in cancer. TGF-β upregulates colXIα1 expression through transcription factor NF-Y[28,30,52]. Treatment with TGF-β inhibitors drastically reduced colXIα1 expression in ovarian cancer cell lines, as well as cell invasion[28].

ColXIα1 has also been linked with therapeutic resistance, which is a significant problem across cancer types. The stroma is often hypothesized as the source of resistance to many targeted therapies that seem promising in vitro but fail in clinical trials. The colXIα1-driven metastasis-associated gene expression signature discussed above was also associated with resistance to neoadjuvant chemotherapy in breast cancer[23]. High levels of colXIα1 protein secretion have been linked with resistance to platinum-based therapies in ovarian cancer[29]. Therefore, therapeutic strategies targeting collagen XI may help sensitize cells to conventional treatments.

Precisely how colXIα1 is mediating these effects is unknown. Limited research has identified integrin α2β1 and the discoidin domain receptor family as putative collagen XI receptors; however, very little is known about downstream signaling[53,54]. One potential colXIα1 binding partner is nucleolin, a nuclear transport protein which also has autolytic activity. This activity results in cleavage products capable of post-transcriptionally regulating MMP9, which, like MMP3, may be involved in colXIα1-mediated cell invasion[55]. Overall, development of approaches to target colXIα1 would be therapeutically beneficial. Approaches including antisense targeting or modulation of transcription or translation for colXIα1 may hold the most promise.

Conclusion

The expression pattern of colXIα1 in cancer is obviously complex and incompletely understood. While most studies point to a direct relationship between colXIα1 expression and cancer progression, specifically as it pertains to metastasis, there are some seemingly discordant findings. The expression of colXIα1 changes as the tumor evolves, and differences in study timepoints and the source of the colXIα1, whether it be the tumor itself or the surrounding stroma, may account for large expression differences. A limited number of functional studies confirm that colXIα1 is playing a role in cancer proliferation, invasion,

and metastasis, as well as in resistance to therapeutics. More in-depth studies are needed to determine mechanisms through which colXIα1 influences cancer cell behavior. What data is available suggests that collagen XIα1, with its low expression in normal tissue and high expression in cancer, and its mechanistic significance, may be an ideal target for future therapies across multiple cancer types.

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Highlights

- Collagen XI is a minor collagen with pathogenic roles in musculoskeletal diseases
- ColXIα1 is overexpressed at mRNA and protein levels in many cancer types
- ColXIα1 is highly expressed in tumor stroma, especially by tumor-associated fibroblasts
- ColXIα1 has functional roles in cancer development and may be a therapeutic target

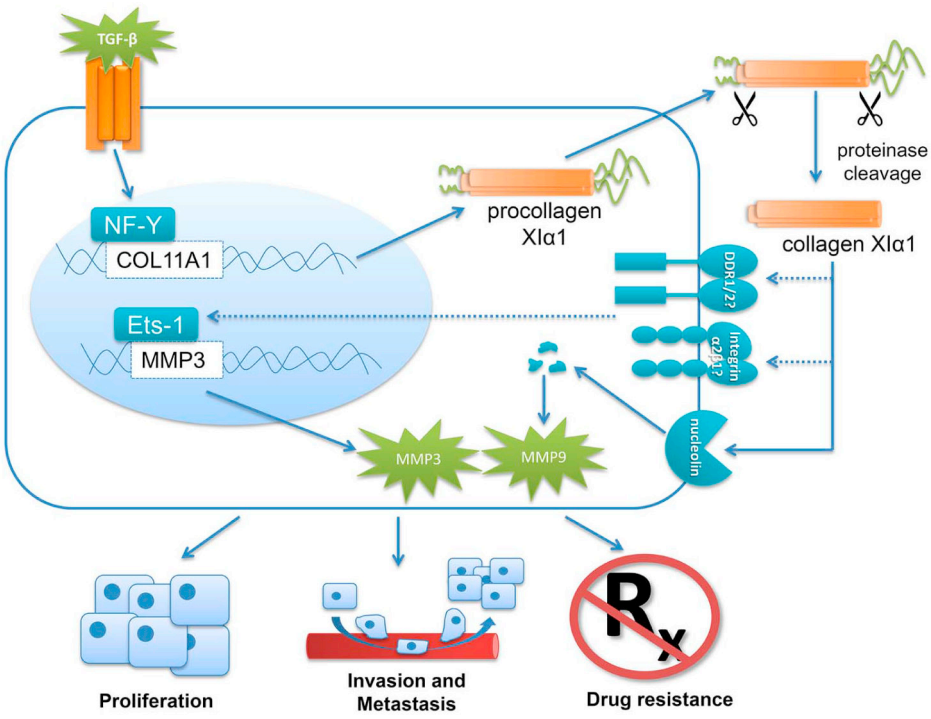

Figure 1.

Collagen XIα1 in cancer promotion. ColXIα1 is a downstream target of the TGF-β pathway, acting through transcription factor NF-Y. Once translated, procolXIα1 is transported into the ECM, where its N and C termini are cleaved by proteinases. Mature colXIα1 can then regulate MMP3 expression through transcription factor Ets-1, perhaps through putative cell surface receptors integrin α2β1 and/or DDR1/2. ColXIα1 also binds nucleolin, a cell surface receptor, which autolytically degrades itself into fragments which post-transcriptionally regulate MMP9. Ultimately, colXIα1 promotes cell proliferation, invasion and metastasis, and therapeutic resistance.

Table 1

Dysregulation of colXIα1 in cancer.

Cancer type	Sample type	Dysregulation	Control	Clinical association	Measurement level	Reference
Bladder	muscle-invasive transitional cell carcinoma	Overexpressed	papillary transitional cell carcinoma tissue	muscle invasion	mRNA	45
Breast	IDC	Underexpressed	nonmetastasized primary tumor	metastasis	protein	38
Breast	tumor stroma	Underexpressed	normal stroma	tumor stroma	protein	38
Breast	IDC	Overexpressed	DCIS, normal breast tissue, mouse breast carcinomas	local invasion	mRNA	34
Breast	IDC	Overexpressed	paired lymph node metastases	primary tumor; high risk of metastasis	mRNA	36
Breast	IDC	Overexpressed	DCIS and normal adjacent stroma	local invasion	mRNA	33
Breast	Multiple breast cancer types	Overexpressed	normal breast tissue	tumor-associated fibroblasts	Protein	49
Colorectal	sloughed tumor cells	Mutation	none	malignancy	DNA	27
Colorectal (inherited)	FAP polyps	Overexpressed	paired normal colon tissue	malignancy	mRNA	21
Colorectal (sporadic)	multiple CRC types	Overexpressed	Normal colon tissue	malignancy	mRNA	20
Gastric	tumor resection margins	Overexpressed	gastric tumor and normal gastric tissue	resection margin	protein	50
Gastric	multiple gastric cancer types	Overexpressed	paired premalignant and normal gastric tissue	malignancy	mRNA	46
Glioma	gliobastoma	Overexpressed	paired normal neural tissue	malignancy	mRNA, protein	26
Glioma	tumor cells	Overexpressed	non-migratory tumor cells	motility	mRNA	25
HNSCC	HNSCC, multiple sites	Overexpressed	paired normal mucosal tissue	malignancy	mRNA	39
HNSCC	HNSCC, multiple sites	Overexpressed	paired normal mucosal tissue	malignancy, metastasis	mRNA	40
HNSCC	oral cavity/oropharynx SCC	Overexpressed	nonmetastatic HNSCC, normal mucosa	metastasis	mRNA	41
HNSCC	esophageal SCC	DNA amplification	paired normal tissue	malignancy	DNA	42
Lung	NSCLC	Overexpressed	normal lung tissue	pathological stage; lymph node metastasis, poor prognosis	mRNA	44
Ovarian	epithelial ovarian cancer	Overexpressed	internal	pathological stage; lower overall survival, lower progression-free survival	mRNA	28
Ovarian	serous and endometrioid ovarian cancer	Overexpressed	internal	poor prognosis	mRNA	31
Ovarian	tumor cells	Overexpressed	non-resistant cell lines	drug resistance	protein	29

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Cancer type	Sample type	Dysregulation	Control	Clinical association	Measurement level	Reference
Ovarian	serous ovarian cancer	Overexpressed	internal	metastasis; lower overall survival	mRNA, protein	30
Ovarian	epithelial ovarian cancer vasculature	Overexpressed	healthy ovarian vascular tissue	angiogenesis	mRNA, protein	32
Pancreatic	PDAC	Overexpressed	chronic pancreatitis and normal pancreas tissue	tumor-associated fibroblasts	mRNA, protein	47
Thyroid	peripheral blood	SNP	peripheral blood from healthy subjects	increased/reduced cancer risk	DNA	43