



RESEARCH ARTICLE

The Survey Looks into How Collagen Affects Extracellular Matrix, Tme, Mmps, Ddrs, Integrin, And Lox in The Growth of Cancer Cells

Salma Korbag^{1*}, Issa korbag²^{1,2}Department of Chemistry, College of Science, University of Benghazi, Al Kufra, Libya

| ARTICLE INFO | ABSTRACT |
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| Received: Apr 23, 2024 | The purpose of this research was to assess the quality of training offered to lecturers at Sudanese private universities. The study's central issue was the difficulty many universities, particularly private ones, have in offering enough professional development opportunities for their teaching staff. An analytical-descriptive methodology was used for the research. College professors made up the bulk of the study's sample group. A large-scale survey was used as a sampling strategy since the research population was quite small. The researchers devised a questionnaire to serve as a means of data collection. A total of 166 questionnaires were analyzed, and 113 (or 68%) were deemed suitable for inclusion in the research. SPSS was used to do some statistical analyses on the data for the purpose of testing the hypothesis. The purpose of this study is to test the following hypotheses: Professional development plans for teachers are planned and prepared in advance. Faculty members may further their careers in a wide variety of topics and specializations. Faculty members face challenges that prevent them from participating in professional development opportunities. The study's final results are as follows. Plans and materials for faculty professional development are prepared well in advance. Faculty members face challenges that prevent them from participating in professional development opportunities. Here are some suggestions from the research: Companies should pick the most qualified instructors to lead their training programs. |
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| Keywords | |
| Cancer | |
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| *Corresponding Author: | |
| salma.omar46@yahoo.com | |

INTRODUCTION

Collagen, a right-handed helix glycoprotein with three left-handed α -chains, forms 28 distinct types before 1971. Now, there are at least 32 genetically diverse polypeptide α -chains. Collagens are unified by the glycine-X-Y (Gly-X-Y)_n repeat, an amino acid sequence responsible for thermal stability, represented by proline (X) and hydroxyproline (Y) (Gu *et al.*, 2019). Collagens are classified into fibrillar and non-fibrillar collagens based on supramolecular organization. Fibrillar collagens, comprising ninety percent of collagen, come in various forms and are elongated, rod-like, or banded. Non-fibrillar collagens, such as transmembrane, anchoring fibrils, network-forming, and beaded filament-forming, form supramolecular structures like fibril-associated collagens (Fidle *et al.*, 2018). Collagen, a key component of the extracellular matrix (ECM), forms the base-membrane and interstitial matrix, providing mechanical support and stability for tissue and organs (Frantz *et al.*, 2010; McKee *et al.*, 2019; Xu *et al.*, 2019). Non-fibrillar collagen regulates ECM meshwork anchoring and organization, maintaining tissue structure and supporting cells, tissues, and organs with specific

functional needs. The extracellular matrix's mechanical properties influenced by its structural needs and protein content, significantly affect cell motility, proliferation, differentiation, and apoptosis, necessitating tissue composition understanding (Alberts, 2015). The tumor microenvironment (TME) is a complex mix of stromal cells, including inflammatory cells, pericytes, endothelial cells, cancer-associated fibroblasts, and extracellular matrix proteins. Tumor growth is influenced by these cells, and their role in the TME is still under investigation. Lymphocyte infiltration and collagen formation also play a role (Galon *et al.*, 2012; Drachneris *et al.*, 2023; Watterson and Coelho, 2023). Solid tumors interact with stromal, immune, and extracellular matrix cells, creating a tumor microenvironment. Lymphocyte infiltration, particularly from CD8+ T cells, affects cancer forms. Tumor-associated macrophages and cancer cells affect collagen formation, causing structural alterations in the extracellular matrix (Qiu *et al.*, 2019). Mutant genes, particularly tumor suppressor genes, significantly influence cancer cell behavior and extracellular matrix interactions, affecting collagen structure and composition. Mutant p53 and Janus kinase 2 (JaK2) signal transducers and activators of transcription 3 (STAT3) signaling affect tumor-associated collagen signature-3, leading to cancer proliferation and invasion. Arresten, an antiangiogenic component, is associated with p53 activation (Kenny *et al.*, 2017; Wörmann *et al.*, 2016). Phosphate and tension homology deleted on chromosome ten (PTEN) gene deletions or silencing can slow cancer growth by increasing cancer-associated fibroblast (CAF) recruitment and collagen production. Collagen interacts with tumor suppressor genes, facilitating cancer progression. Arresten, a collagen IV Alpha 1 chain fragment (Assadian *et al.*, 2012; Al-Khoury *et al.*, 2005; Dulińska-Litewka *et al.*, 2022; Jolly *et al.*, 2016; Gao *et al.*, 2023; Wen *et al.*, 2022), inhibits endothelial cell migration. Collagen interacts with proto-oncogene mutations, promoting cancer progression. Mutant Kras and Snail (epithelial-mesenchymal transition (EMT)) promote collagen synthesis in pancreatic cancer cells, while suppressing Kras decreases collagen I deposition in renal fibrosis (Shields *et al.*, 2013; Apte *et al.*, 2013; Liang *et al.*, 2022; Wang *et al.*, 2012).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases, consisting of 28 members, are involved in matrix turnover and remodeling ECM components like elastin, gelatin, fibrillar collagens, and proteoglycans. They are regulated by hormones, growth factors, and cytokines and are involved in ovarian functions (Kapoor *et al.*, 2016). MMPs play a crucial role in breast cancer, enhancing malignancy through TGF- β /SMAD signaling and proteolytic activation of MMP2 and 13. MMP14 is essential for malignant-promoters processes, enabling breast cancer Cytotoxic T lymphocytes (CTLs) to initiate tumors and activate motile programs under hypoxic conditions. MMPs also play a role in matrix remodeling (Kessenbrock *et al.*, 2010; Cox, 2021; Dong *et al.*, 2019).

Discoidin domain receptors (DDR) are human proteins that regulate the movement of neutrophil and fibroblasts in three-dimensional matrices. Human discoidin domain receptors (DDR) belong to the receptor tyrosine kinase (RTK) family and bind to collagen, an extracellular matrix protein, via its extracellular area, transmembrane domain (Leitinger, 2014), cytosolic juxtamembrane domain (Chua *et al.*, 2008), and C-terminal tyrosine kinase domain. They are primarily expressed in mesenchymal cells and are stimulated by collagen, an extracellular matrix protein. DDRs regulate MMP expression and activity, which can contribute to illness path physiology (Zhang *et al.*, 2013; Valiathan *et al.*, 2012; Corsa *et al.*, 2016; Ren *et al.*, 2014).

Integrins, bidirectional signaling molecules, determine receptor affinity for extracellular matrix proteins. They exist in two structural states: stretched and bent (Humphries *et al.*, 2006; Arruda Macêdo *et al.*, 2015). ECM proteins are often fibrils or have multiple recognition sites. Integrin-ligand interaction initiates downstream adhesion signaling (Franceschi *et al.*, 2015; Hamidi *et al.*, 2016; Barrow-McGee *et al.*, 2016). α 1 and α 2 integrin expression is abundant in dermal myofibroblasts. α 10 integrin is only found in cartilage and fibroblasts, making it difficult to target as a therapeutic target. Its expression in cancer is influenced by disease type and stage. Activation of transforming growth

factor- β (TGF β) can suppress tumor growth, with elevated integrin expression causing worse prognosis and cancer progression. Integrins interact with growth factor receptors (GFRs) to support cancer cell survival and stemness, accelerating tumor growth in lung and breast cancer. Elevated $\alpha\beta3$ integrin expression is linked to metastasis (Alanko *et al.*, 2015; Mai *et al.*, 2014).

Elastic collagen (ECMs) is a type of tissue that self-assembles into monomers and cross-links with lysine residues, creating mature elastic fibers (Mecham, 2018; Theocharis *et al.*, 2016). Lysyl oxidases (LOX) decrease diffusion via ECMs, and chemoresistant tumors have higher gene expression for ECM-related proteins, indicating drug transport is hindered by a tumoral environment with high cross-linking and fibrillar collagen mass (Rossow *et al.*, 2018).

This study aims to increase awareness about collagen's negative effects on cancer cell growth and development, using questionnaires to assess participants' knowledge and health knowledge to reduce cancer spread.

METHODOLOGY

A random survey of 400 participants from April 2021 to March 2024 aimed to assess public awareness of the harmful effects of collagen on various physiological systems like ECM, TME, MMPs, DDRs, integrins, and LOX. The survey for face-to-face interviews consisted of forty questions, with participant responses listed in Tables 1 and 2.

Correlated variables: Researchers utilized survey data on participants' ages and educational levels to evaluate their understanding of the risks and mechanisms of collagen action within our bodies.

Statistical analysis: The study used EXCEL software to analyze the link between increased cancer incidence and public misconceptions about collagen risks, dividing participants into "know" and "don't know" groups for statistical analysis.

RESULT AND DISCUSSION

The study emphasizes the significance of understanding collagen's impact on cells like integrin, LOX, TME, MMPs, and DDRs for public health, addressing ignorance about its harmful effects on cancer onset and spread (refer to Tables 1 to 2).

Table1: Public perceptions of collagen's potential risks and their correlation with cancer occurrence.

| A survey was conducted to assess public perceptions of collagen's potential risks and their correlation with cancer occurrence. | | | |
|---|--|----------|----------------|
| n=400 | | | |
| NO. | Questions | Know (%) | Don't know (%) |
| 1 | Do you know the scientific definition of collagen? | 45 (11%) | 355 (89%) |
| 2 | What varieties of collagen are there? | 0 | 400 (100%) |
| 3 | What benefits does collagen provide to the body? If know, could you please give more details? | 5 (1%) | 395 (99%) |
| 4 | Are you aware of the four main functions of collagen? If know, could you please give more details? | 0 | 400 (100%) |
| 5 | What impact does higher collagen have, do you know? If so, could you please give more details? | 0 | 400 (100%) |
| 6 | In cell proliferation, what part does collagen play? If so, could you please provide more details? | 0 | 400 (100%) |
| 7 | How important is the extracellular matrix (ECM)? If you choose to answer "know," please explain. | 15 (4%) | 385 (96%) |

| | | | |
|----|---|---|------------|
| 8 | You know how much collagen is in the extracellular matrix? If so, kindly say so. | 0 | 400 (100%) |
| 9 | Can you elaborate on the recognition of collagen as an essential constituent of the extracellular matrix (ECM)? | 0 | 400 (100%) |
| 10 | In the extracellular matrix (ECM), how many different kinds of collagen are there? Could you please elaborate if you know more? | 0 | 400 (100%) |
| 11 | Does collagen contribute to the growth of tumors? Could you please provide further details if you know? | 0 | 400 (100%) |
| 12 | Does collagen support neoplasms? Could you please elaborate if you know? | 0 | 400 (100%) |
| 13 | What is the extracellular matrix (ECM) of cancer cells? Please provide more details if you are aware? | 0 | 400 (100%) |
| 14 | What is the impact of collagen on the tumor microenvironment (TME)? Would you kindly elaborate if you know? | 0 | 400 (100%) |
| 15 | Are you familiar with the components of the TME? If you are aware, kindly share it? | 0 | 400 (100%) |
| 16 | Are you aware of the significance of the TME? Please let us know if you know. | 0 | 400 (100%) |
| 17 | Are you aware of how collagen impacts the TME? Please let us know if you know. | 0 | 400 (100%) |
| 18 | Are you aware of how matrix metalloproteinases (MMPs) contribute to the onset of cancer? Please inform us if you are aware. | 0 | 400 (100%) |
| 19 | What effect do MMPs have on cancer? Please share if you are aware of it. | 0 | 400 (100%) |
| 20 | Are you aware of the impact collagen has on cancer cells? If you are aware, kindly share it. | 0 | 400 (100%) |
| 21 | Were you aware that collagen and cancer are related? If you know, kindly let us know. | 0 | 400 (100%) |
| 22 | Do you know how cancer is affected by collagenase? Please share if you are aware of it. | 0 | 400 (100%) |
| 23 | Are cancerous cells collagen-producing? Please let us know if you know. | 0 | 400 (100%) |
| 24 | Does collagen crosslinking mediated by lysyl oxidase (LOX) lead to metastasis that is increased by fibrosis? if you are aware? Tell us, please. | 0 | 400 (100%) |
| 25 | Do you know how important the discoidin domain receptors (DDR) are? Please let us know if you know. | 0 | 400 (100%) |
| 26 | Do you know anything about the DDRs pathway in cancer? If you are aware, kindly let us know. | 0 | 400 (100%) |
| 27 | What do DDRs in oncology mean? Please let us know if you know. | 0 | 400 (100%) |
| 28 | Are you aware of DDRs' goals in relation to cancer? Please let us know if you know. | 0 | 400 (100%) |
| 29 | What is the mechanism by which collagen, mesenchymal traits (EMT), and Kras interact to drive the development of cancer? Please let us know if you know. | 0 | 400 (100%) |
| 30 | What connection exists between EMT and cancer? Could you pls let us know if you know? | 0 | 400 (100%) |
| 31 | Do you know the connection between collagen III and cancer? Could you describe it if you know? | 0 | 400 (100%) |
| 32 | Are you aware of the connections between tissue fibrosis, metastasis, and the growth of primary tumors and rapid matrix deposition and remodeling? Could you explain if you know? | 0 | 400 (100%) |

| | | | |
|----|---|------------|------------|
| 33 | Collagen I is an essential component of the stroma of adipose tissue tumors and fibrosis, and it serves as a substrate for LOX. Could you explain if you know? | 0 | 400 (100%) |
| 34 | Has the Ministry of Health, the National Cancer Center, the Ministries of Education, Higher Education, and Scientific Research hosted any conferences or seminars on the dangers of collagen and its relationship to the proliferation of cancer cells? If you have, could you kindly let us know when it happened and why? | 0 | 400 (100%) |
| 35 | Have you watched any informative television programs about the dangers of collagen and how they connect to cancer's early stages? Please let us know the location and time if you witnessed it. | 0 | 400 (100%) |
| 36 | Have you already read any enlightening social media messages about the dangers of collagen and the rising rate of cancer? Please let us know where and when you read if you did. | 0 | 400 (100%) |
| 37 | Are people being informed about the risks associated with collagen and its connection to the development of cancer by the Ministries of Education and Health? Could you please let us know where, when, and whether you received it? | 0 | 400 (100%) |
| 38 | Do your loved ones or friends ever discuss the potential concerns associated with collagen? Please let us know the location and time of any discussions. | 0 | 400 (100%) |
| 39 | Have you ever seen an academic study on the link between cancer risk factors and collagen? Tell us the whereabouts and when of any sightings, please. | 0 | 400 (100%) |
| 40 | Did you think that the information you received from the survey would be helpful to you and encourage you to learn more about the hazards associated with collagen? | 400 (100%) | 0 |

Table2: Demographic Variables

| Ages (years) | n=400 | % |
|-----------------------------------|-------|----|
| <20 | 80 | 20 |
| 20-50 | 154 | 38 |
| 50-70 | 166 | 42 |
| Education level | | |
| Without formal education | 13 | 3 |
| Secondary school | 89 | 22 |
| Bachelor's degree (undergraduate) | 110 | 28 |
| Higher education | 188 | 47 |

The extracellular matrix (ECM) is a crucial part of the tumor microenvironment, influencing the progression of invasive cancer and tissue loss (Madsen and Bugge, 2015; Kader *et al.*, 2022; Madsen *et al.*, 2017). Its rigidity and density, influenced by collagen type I density, can affect cancer prognoses and malignant transformation in cells like fibroblasts, mesenchymal stem cells, and epithelial cells (Cox and Erler, 2014; Naba *et al.*, 2014; Cox *et al.*, 2013; Pickup *et al.*, 2014; Morkunas *et al.*, 2021; Li *et al.*, 2013; Puig *et al.*, 2015; Leight *et al.*, 2012). Tumors can deposit immunosuppressive proteins like osteopontin (OPN), the secreted protein acidic and rich in cysteine (SPARC), versican, and tenascin C (TN-C) (McMahon *et al.*, 2016; Papadas *et al.*, 2022; Jachetti *et al.*, 2015; Sangaletti *et al.*, 2017).

Nuclear factor kappa-light-chain enhancer of activated B-cells (NF- κ B) is a cellular signaling pathway that plays a crucial role in various functions such as immunity, memory, learning, apoptosis, cell proliferation, and inflammation. NF- κ B family comprises five subunits, with nuclear localization signal in RHD of p50/p65 dimers obscured by κ B inhibitors, preventing nuclear translocation. Target gene expression is facilitated by I κ B α phosphorylation by IKK complex, mediated by NIK. NF- κ B, a

key player in various malignancies, affects tumor growth and therapeutic resistance through its anti-inflammatory functions (Shen *et al.*, 2014; Hoesel *et al.*, 2013; Kaltschmidt *et al.*, 2018; Riedlinger *et al.*, 2018; Baud *et al.*, 2016; Taniguchi and Karin, 2018; Lawrence and Fong, 2010; Yoshida *et al.*, 2013). Collagen expression is regulated by NF- κ B and STATs, potentially causing cancer. Combining AZD1480 with gemcitabine improves collagen fiber direction in pancreatic cancer treatment by modifying collagen through TGF- β /Smad signaling. Collagen fibers convert pancreatic epithelium into fibrotic tissue, reversing cancer cell activities (Bray *et al.*, 2018; Laklai *et al.*, 2016). Collagen stiffness promotes melanoma differentiation, but TGF- β and Ras-Raf-MEK-ERK inhibits YAP/pax3/MITF production, leading to dedifferentiation. Melanoma cells increase collagen production, activating p38, resulting in protumorigenic extracellular matrix (Miskolczi *et al.*, 2018; Jenkins *et al.*, 2015; Clarke *et al.*, 2016). Tyrosine kinase receptors, specifically FGFR4-R388, are key collagen-related receptors in various cancers, notably increasing MMP14 protein production and regulating COL1, COL2, and COL4 degradation (Chang *et al.*, 2015). NF- κ B targets epithelial-to-mesenchymal transition (EMT) in cancer stem cells (CSCs), suppressing epithelial phenotype and increasing cancer invasiveness. This induces mesenchymal markers like Vimentin, MMP2 and MMP9. Human mammary epithelial cells can undergo EMT, producing stem cells with enhanced potential. High stiffness in cancer cells promotes EMT, invasion, and metastasis (Wei *et al.*, 2015; Sipes *et al.*, 2011; Yamazaki *et al.*, 2009; Meng *et al.*, 2018). Rho-associated coiled-coil kinase (ROCK)/Rho signaling regulates cancer cell behavior, affecting migratory motility and cell proliferation. It also promotes COL1A1 gene promoter acetylation in breast cancer cells. PDAC suppression hinders collagen, fibroblast proliferation, and survival. MMP10 and MMP13 levels increase due to collagen matrix alteration by PDAC cells (Vennin *et al.*, 2017; Rath *et al.*, 2017).

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases with 28 members divided into subfamilies based on substrate specificity. These include collagenases (MMP1, MMP8, MMP13, and MMP18), matrilysins (MMP7 and MMP26), gelatinases (MMP2 and MMP9), stromelysins (MMP3, MMP10, and MMP11), and membrane-type MMPs (MT-MMPs) (Cui *et al.*, 2017). Glycosylphosphatidylinositol-associated membrane metalloproteinases (MMP17 and MMP25) are essential enzymes in membrane metalloproteinase production, along with secreted-type matrix metalloproteinases like MMP12, MMP19, MMP20, MMP21, MMP22, MMP23, MMP27, and MMP28 (Jabłońska-Trypuc *et al.*, 2016; Fallata *et al.*, 2019). MMP family members share a standard structure with a flexible hinge region linking hemopexin to catalytic domain. MMP production is regulated by endogenous and tissue inhibitors, but overexpression in cancer lead to extracellular matrix breakdown (Verovenko *et al.*, 2024; Newby, 2016). MMP1, 8, and 13 prefer collagen I, II, and III, while MMP3, 7, 10, and 11 break down extracellular matrix components. Interstitial collagenase MMP13 is crucial in cancer initiation and progression, overexpressed in cancers and CSCs (Peng *et al.*, 2012; Xu *et al.*, 2015). Discoidin domain receptor tyrosine kinases (DDR) are involved in the binding of collagen to tumor cells, breaking various ECM components in cancers and CSCs.

DDR1 and DDR2 receptors in the tyrosine kinases subfamily are homologous, and collagens share similar DDRs. Akt activation increases myeloid leukemia cell mobility and adhesion. COL1 upregulate N-cadherin in PDAC cells, stimulating MMP14, collagen, and EMT development in breast cancer and epithelial to mesenchymal traits through phosphorylation, activation, and blocking GSK 3 β (Favreau *et al.*, 2014; Huang *et al.*, 2016; Rada *et al.*, 2018; Oliveira-Ferrer *et al.*, 2014; Procacci *et al.*, 2018). COL1 inhibit E-cadherin in PDAC, affecting liver metastasis and EMT. This effect is associated with CCL7 and CCL14-regulating chemokines. COL4 stimulates ERK1/2 and FAK during EMT, promoting Snail1, Snail2, and Sip1 expression, MMP2 secretion and cell migration. Changes in protein expression are linked to collagen mediating prostate cancer spread (Vaniotis *et al.*, 2018; Espinosa Neira *et al.*, 2012; Spivey *et al.*, 2012).

Integrin, a common adhesion protein in cancer cells, regulates cell activity by interacting with collagen. In squamous cell carcinoma, it promotes cell growth and invasion through various signaling

pathways. Collagen deposition is promoted by cutaneous SCC development, and altered collagen-integrin interactions affect cancer cell behavior, particularly ovarian cancer cells. Acidic, cysteine-rich proteins are associated with melanoma cells, promoting invasiveness (Hayashido *et al.*, 2014; Ibbetson *et al.*, 2013; Shen *et al.*, 2012; Girotti *et al.*, 2011). EMT changes, decreased differentiation, elevated clonogenicity, and colorectal cancer stem cell proliferation are resulting from melanoma cells activating various pathways. The formation of $\beta 1$ integrin signaling complexes, radiation-induced breast cancer cells using $\beta 1$ integrin-FAK signaling, and the COLIV basement membrane causing collagen destruction are all involved (Smith *et al.*, 2012; Blockhuys *et al.*, 2013; Artym *et al.*, 2015; Yan *et al.*, 2018). The COLIV/ $\beta 1$ integrin signaling pathway reduces cell stiffness and increases motility, affecting cell movement in melanoma. PI3K activation through $\alpha 2\beta 1$ integrin influences adhesion, survival, aggregation, and migration in soft-tissue sarcoma, oral squamous cell carcinoma, glioblastoma, and breast cancer (Chen *et al.*, 2014; Cattaruzza *et al.*, 2013; Zhang *et al.*, 2018; Stawikowski *et al.*, 2014). Collagen stimulates cancer cell signaling pathways, reducing phospho-STAT5 and ERK1/2 expression, enhancing tumor proliferation, and altering caspase-3/PI3K/AKT pathways. In cervical cancer, collagen fiber-containing protein COLI causes invasive protrusions, reducing Akt and ERK1/2 phosphorylation and resistance to inhibitors. Collagen glycation and carbamylation impact cancer cell spread, and TNF receptor 2/p38 MAPK signaling inhibits tumor growth (Liu *et al.*, 2017; Shea *et al.*, 2018; Barcus *et al.*, 2017; Yamazaki *et al.*, 2018; Brown *et al.*, 2015; Liu *et al.*, 2017). Triple-negative breast cancer cell types exhibit crosslinking with prol-yl-4-hydroxylase alpha 1 and alpha 2, promoting chemoresistance. Mutant p53 blocks transcriptional activity, preventing COL7A1 expression. Collagen crosslinking, interfibril branching, and matrix stiffness affect vascular growth and integrity. Imatinib treatment enhances tumor stromal oxygen levels and blood flow recovery (Goggins *et al.*, 2018; Xiong *et al.*, 2018; Amelio *et al.*, 2018; Bordeleau *et al.*, 2017; Burmakin *et al.*, 2017). Metastases cause 90% of cancer fatalities, necessitating rapid intervention and understanding of molecular colonization mechanisms. The activation of harmful signaling pathways in ECM remodeling and the microenvironment significantly impacts tumor development, metastasis, and survival (Kitamura *et al.*, 2015; McAllister *et al.*, 2014; Gupta *et al.*, 2014).

Extracellular amine oxidase, also known as lysyl oxidase (LOX), is an essential enzyme that modifies collagen and elastin to catalyze the process of fiber crosslinking. It stabilizes collagen fibers and fibrils; also, organ fibrosis and tumor stroma depend on collagen I, a substrate of LOX. Organ fibrosis may result from fibroblasts producing more ECM proteins (Osawa *et al.*, 2013; Antar *et al.*, 2023; Yamazaki *et al.*, 2012). Participants are unaware of the detrimental consequences of collagen I, a crucial tumor component that is connected to metastases, a poor prognosis for breast cancer, cell invasion, and the development of malignancy.

CONCLUSION

People are unaware of collagen risks, including tissue loss and cancer growth. Collagen type I density triggers malignant transformation, and overexpression of MMP causes matrix breakdown in cancer. LOX dysregulation can lead to fibrous processes, tumor growth, metastasis, neurological disorders, and cardiovascular problems.

DISCLOSURE STATEMENT

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AUTHORS' CONTRIBUTIONS

All authors contributed to data analysis, drafting, and revising of the article and agreed to be responsible for all the aspects of this work.

REFERENCES

1. L. Gu, T. Shan, Y. X. Ma, F.R. Tay, L. Niu, 2019. Novel Biomedical Applications of Crosslinked Collagen. *Trends in biotechnology*, 37(5), 464–491. <https://doi.org/10.1016/j.tibtech.2018.10.007>
2. L. Fidler, S. P. Boudko, A. Rokas, B. G. Hudson. The triple helix of collagens - an ancient protein structure that enabled animal multicellularity and tissue evolution. *Journal of cell science*, 131(7), jcs203950. <https://doi.org/10.1242/jcs.203950>
3. C. Frantz, K. M. Stewart, V. M. Weaver, 2010. The extracellular matrix at a glance. *Journal of cell science*, 123(Pt 24), 4195–4200. <https://doi.org/10.1242/jcs.023820>
4. T. J. McKee, G. Perlman, M. Morris, S. V. Komarova, 2019. Extracellular matrix composition of connective tissues: a systematic review and meta-analysis. *Scientific reports*, 9(1), 10542. <https://doi.org/10.1038/s41598-019-46896-0>
5. S. Xu, H. Xu, W. Wang, S. Li, H. Li, T. Li, W. Zhang, X. Yu, L. Liu, 2019. The role of collagen in cancer: from bench to bedside. *Journal of translational medicine*, 17(1), 309. <https://doi.org/10.1186/s12967-019-2058-1>
6. B. Alberts, 2015. *Molecular Biology of the Cell* (6th ed.). W.W. Norton & Company, <https://doi.org/10.1201/9781315735368>
7. J. Galon, F. Pagès, F. M. Marincola, H. K. Angell, M. Thurin, A. Lugli, I. Zlobec, A. Berger, C. Bifulco, G. Botti, F. Tatangelo, C. M. Britten, S. Kreiter, L. Chouchane, P. Delrio, H. Arndt, M. Asslaber, M. Maio, G. V. Masucci, M. Mihm, B. A. Fox, 2012. Cancer classification using the Immunoscore: a worldwide task force. *Journal of translational medicine*, 10, 205. <https://doi.org/10.1186/1479-5876-10-205>
8. J. Drachneris, A. Rasmusson, M. Morkunas, M. Fabijonavicius, A. Cekauskas, F. Jankevicius, A. Laurinavicius, 2023. CD8+ Cell Density Gradient across the Tumor Epithelium-Stromal Interface of Non-Muscle Invasive Papillary Urothelial Carcinoma Predicts Recurrence-Free Survival after BCG Immunotherapy. *Cancers*, 15(4), 1205. <https://doi.org/10.3390/cancers15041205>
9. A. Watterson, M. A. Coelho, 2023. Cancer immune evasion through KRAS and PD-L1 and potential therapeutic interventions. *Cell communication and signaling: CCS*, 21(1), 45. <https://doi.org/10.1186/s12964-023-01063-x>
10. S. Qiu, L. Deng, X. Liao, L. Nie, F. Qi, K. Jin, X. Tu, X. Zheng, J. Li, L. Liu, Z. Liu, Y. Bao, J. Ai, T. Lin, L. Yang, Q. Wei, 2019. Tumor-associated macrophages promote bladder tumor growth through PI3K/AKT signal induced by collagen. *Cancer science*, 110(7), 2110–2118. <https://doi.org/10.1111/cas.14078>
11. T. C. Kenny, H. Schmidt, K. Adelson, Y. Hoshida, A. P. Koh, N. Shah, J. Mandeli, J. Ting, D. Germain, 2017. Patient-derived Interstitial Fluids and Predisposition to Aggressive Sporadic Breast Cancer through Collagen Remodeling and Inactivation of p53. *Clinical cancer research: an official journal of the American Association for Cancer Research*, 23(18), 5446–5459. <https://doi.org/10.1158/1078-0432.CCR-17-0342>
12. S. M. Wörmann, L. Song, J. Ai, K. N. Diakopoulos, M. U. Kurkowski, K. Görgülü, D. Ruess, A. Campbell, C. Doglioni, D. Jodrell, A. Neesse, I. E. Demir, A. P. Karpathaki, M. Barenboim, T. Hagemann, S. Rose-John, O. Sansom, M. Schmid, M. P. Protti, M. Lesina, H. Algül, 2016. Loss of P53 Function Activates JAK2-STAT3 Signaling to Promote Pancreatic Tumor Growth, Stroma Modification, and Gemcitabine Resistance in Mice and Is Associated With Patient Survival. *Gastroenterology*, 151(1), 180–193.e12. <https://doi.org/10.1053/j.gastro.2016.03.010>

13. S. Assadian, W. El-Assaad, X. Q. Wang, P. O. Gannon, V. Barrès, M. Latour, A. M. Mes-Masson, F. Saad, Y. Sado, J. Dostie, J. G. Teodoro, 2012. p53 inhibits angiogenesis by inducing the production of Arresten. *Cancer research*, 72(5), 1270–1279. <https://doi.org/10.1158/0008-5472.CAN-11-2348>
14. A. M. Al-Khoury, Y. Ma, S. H. Togo, S. Williams, T. Mustelin, 2005. Cooperative phosphorylation of the tumor suppressor phosphatase and tensin homologue (PTEN) by casein kinases and glycogen synthase kinase 3beta. *The Journal of biological chemistry*, 280(42), 35195–35202. <https://doi.org/10.1074/jbc.M503045200>
15. J. Dulińska-Litewka, D. Felkle, K. Dykas, Z. Handziuk, M. Krzysztolik, B. Gąsioriewicz, 2022. The role of cyclins in the development and progression of prostate cancer. *Biomedicine & pharmacotherapy*, 155, 113742. <https://doi.org/10.1016/j.biopha.2022.113742>
16. L. A. Jolly, S. Novitskiy, P. Owens, N. Massoll, N. Cheng, W. Fang, H. L. Moses, A. T. Franco, 2016. Fibroblast-Mediated Collagen Remodeling Within the Tumor Microenvironment Facilitates Progression of Thyroid Cancers Driven by BrafV600E and Pten Loss. *Cancer research*, 76(7), 1804–1813. <https://doi.org/10.1158/0008-5472.CAN-15-2351>
17. C. Gao, F. Liu, Q. Ye, A. Guo, 2023. Cancer-Associated Fibroblasts Affect Tumor Metabolism and Immune Microenvironment in Gastric Cancer and Identification of Its Characteristic Genes. *Journal of oncology*, 2023, 1424589. <https://doi.org/10.1155/2023/1424589>
18. Z. Wen, J. Sun, J. Luo, Y. Fu, Y. Qiu, Y. Li, Y. Xu, H. Wu, Q. Zhang, 2022. COL10A1-DDR2 axis promotes the progression of pancreatic cancer by regulating MEK/ERK signal transduction. *Frontiers in oncology*, 12, 1049345. <https://doi.org/10.3389/fonc.2022.1049345>
19. M. A. Shields, K. Ebine, V. Sahai, K. Kumar, K. Siddiqui, R. F. Hwang, P. J. Grippo, H. G. Munshi, 2013. Snail cooperates with KrasG12D to promote pancreatic fibrosis. *Molecular cancer research: MCR*, 11(9), 1078–1087. <https://doi.org/10.1158/1541-7786.MCR-12-0637>
20. M. V. Apte, J. S. Wilson, A. Lugea, S. J. Pandol, 2013. A starring role for stellate cells in the pancreatic cancer microenvironment. *Gastroenterology*, 144(6), 1210–1219. <https://doi.org/10.1053/j.gastro.2012.11.037>
21. Z. Liang, S. Tang, R. He, W. Luo, S. Qin, H. Jiang, 2022. The effect and mechanism of miR-30e-5p targeting SNAI1 to regulate epithelial-mesenchymal transition on pancreatic cancer. *Bioengineered*, 13(4), 8013–8028. <https://doi.org/10.1080/21655979.2022.2050880>
22. J. H. Wang, L. J. Newbury, A. S. Knisely, B. Monia, B. M. Hendry, C. C. Sharpe, 2012. Antisense knockdown of Kras inhibits fibrosis in a rat model of unilateral ureteric obstruction. *The American journal of pathology*, 180(1), 82–90. <https://doi.org/10.1016/j.ajpath.2011.09.036>
23. C. Kapoor, S. Vaidya, V. Wadhwan, Hitesh, G. Kaur, A. Pathak, 2016. Seesaw of matrix metalloproteinases (MMPs). *Journal of cancer research and therapeutics*, 12(1), 28–35. <https://doi.org/10.4103/0973-1482.157337>
24. K. Kessenbrock, V. Plaks, Z. Werb, 2010. Matrix metalloproteinases: regulators of the tumor microenvironment. *Cell*, 141(1), 52–67. <https://doi.org/10.1016/j.cell.2010.03.015>
25. T. R. Cox, 2021. The matrix in cancer. *Nature reviews. Cancer*, 21(4), 217–238. <https://doi.org/10.1038/s41568-020-00329-7>
26. H. Dong, H. Diao, Y. Zhao, H. Xu, S. Pei, J. Gao, J. Wang, T. Hussain, D. Zhao, X. Zhou, D. Lin, 2019. Overexpression of matrix metalloproteinase-9 in breast cancer cell lines remarkably increases the cell malignancy largely via activation of transforming growth factor

- beta/SMAD signalling. *Cell proliferation*, 52(5), e12633. <https://doi.org/10.1111/cpr.12633>
27. B. Leitinger, 2014. Discoidin domain receptor functions in physiological and pathological conditions. *International review of cell and molecular biology*, 310, 39–87. <https://doi.org/10.1016/B978-0-12-800180-6.00002-5>
 28. H. H. Chua, T. H. Yeh, Y. P. Wang, Y. T. Huang, T. S. Sheen, Y. C. Lo, Y. C. Chou, C. H. Tsai, 2008. Upregulation of discoidin domain receptor 2 in nasopharyngeal carcinoma. *Head & neck*, 30(4), 427–436. <https://doi.org/10.1002/hed.20724>
 29. K. Zhang, C. A. Corsa, S. M. Ponik, J. L. Prior, D. Piwnica-Worms, K. W. Eliceiri, P. J. Keely, G. D. Longmore, 2013. The collagen receptor discoidin domain receptor 2 stabilizes SNAIL1 to facilitate breast cancer metastasis. *Nature cell biology*, 15(6), 677–687. <https://doi.org/10.1038/ncb2743>
 30. R. R. Valiathan, M. Marco, B. Leitinger, C. G. Kleer, R. Fridman, 2012. Discoidin domain receptor tyrosine kinases: new players in cancer progression. *Cancer metastasis reviews*, 31(1-2), 295–321. <https://doi.org/10.1007/s10555-012-9346-z>
 31. C. A. Corsa, A. Brenot, W. R. Grither, S. Van Hove, A. J. Loza, K. Zhang, S. M. Ponik, Y. Liu, D. G. DeNardo, K. W. Eliceiri, P. J. Keely, G. D. Longmore, 2016. The Action of Discoidin Domain Receptor 2 in Basal Tumor Cells and Stromal Cancer-Associated Fibroblasts Is Critical for Breast Cancer Metastasis. *Cell reports*, 15(11), 2510–2523. <https://doi.org/10.1016/j.celrep.2016.05.033>
 32. T. Ren, W. Zhang, X. Liu, H. Zhao, J. Zhang, J. Zhang, X. Li, Y. Zhang, X. Bu, M. Shi, L. Yao, J. Su, 2014. Discoidin domain receptor 2 (DDR2) promotes breast cancer cell metastasis and the mechanism implicates epithelial-mesenchymal transition programme under hypoxia. *The Journal of pathology*, 234(4), 526–537. <https://doi.org/10.1002/path.4415>
 33. J. D. Humphries, A. Byron, M. J. Humphries. Integrin ligands at a glance. *Journal of cell science*, **2006**, 119(Pt 19), 3901–3903. <https://doi.org/10.1242/jcs.03098>
 34. J. K. Arruda Macêdo, J. W. Fox, M. de Souza Castro, 2015. Disintegrins from snake venoms and their applications in cancer research and therapy. *Current protein & peptide science*, 16(6), 532–548. <https://doi.org/10.2174/1389203716666150515125002>
 35. N. De Franceschi, H. Hamidi, J. Alanko, P. Sahgal, J. Ivaska, 2015. Integrin traffic - the update. *Journal of cell science*, 128(5), 839–852. <https://doi.org/10.1242/jcs.161653>
 36. H. Hamidi, M. Pietilä, J. Ivaska, 2016. The complexity of integrins in cancer and new scopes for therapeutic targeting. *British journal of cancer*, 115(9), 1017–1023. <https://doi.org/10.1038/bjc.2016.312>
 37. R. Barrow-McGee, N. Kishi, C. Joffre, L. Ménard, A. Hervieu, B. A. Bakhouche, A. J. Noval, A. Mai, C. Guzmán, L. Robbez-Masson, X. Iturrioz, J. Hult, C. H. Brennan, I. R. Hart, P. J. Parker, J. Ivaska, S. Kermorgant, 2016. Corrigendum: Beta 1-integrin-c-Met cooperation reveals an inside-in survival signalling on autophagy-related endomembranes. *Nature communications*, 7, 12392. <https://doi.org/10.1038/ncomms12392>
 38. J. Alanko, A. Mai, G. Jacquemet, K. Schauer, R. Kaukonen, M. Saari, B. Goud, J. Ivaska, 2015. Integrin endosomal signalling suppresses anoikis. *Nature cell biology*, 17(11), 1412–1421 <https://doi.org/10.1038/ncb3250>
 39. A. Mai, G. Muharram, R. Barrow-McGee, H. Baghirov, J. Rantala, S. Kermorgant, J. Ivaska, 2014. Distinct c-Met activation mechanisms induce cell rounding or invasion through pathways involving integrins, RhoA and HIP1. *Journal of cell science*, 127(Pt 9), 1938–1952. <https://doi.org/10.1242/jcs.140657>
 40. R. P. Mecham, 2018. Elastin in lung development and disease pathogenesis. *Matrix biology: journal of the International Society for Matrix Biology*, 73, 6–20. <https://doi.org/10.1016/j.matbio.2018.01.005>

41. A. D. Theocharis, S. S. Skandalis, C. Gialeli, N. K. Karamanos, 2016. Extracellular matrix structure. *Advanced drug delivery reviews*, 97, 4–27. <https://doi.org/10.1016/j.addr.2015.11.001>
42. L. Rossow, S. Veitl, S. Vorlová, J. K. Wax, A. E. Kuhn, V. Maltzahn, B. Upcin, F. Karl, H. Hoffmann, S. Gätzner, M. Kallius, R. Nandigama, D. Scheld, S. Irmak, S. Herterich, A. Zernecke, S. Ergün, E. Henke, 2018. LOX-catalyzed collagen stabilization is a proximal cause for intrinsic resistance to chemotherapy. *Oncogene*, 37(36), 4921–4940. <https://doi.org/10.1038/s41388-018-0320-2>
43. D. H. Madsen, T. H. Bugge, 2015. The source of matrix-degrading enzymes in human cancer: Problems of research reproducibility and possible solutions. *The Journal of cell biology*, 209(2), 195–198. <https://doi.org/10.1083/jcb.201501034>
44. A. Kader, J. O. Kaufmann, D. B. Mangarova, J. Moeckel, L. C. Adams, J. Brangsch, J. L. Heyl, J. Zhao, C. Verlemann, U. Karst, F. Collettini, T. A. Auer, B. Hamm, M. R. Makowski, 2022. Collagen-Specific Molecular Magnetic Resonance Imaging of Prostate Cancer. *International journal of molecular sciences*, 24(1), 711. <https://doi.org/10.3390/ijms24010711>
45. D. H. Madsen, H. J. Jürgensen, M. S. Siersbæk, D. E. Kuczek, L. Grey Cloud, S. Liu, N. Behrendt, L. Grøntved, R. Weigert, T. H. Bugge, 2017. Tumor-Associated Macrophages Derived from Circulating Inflammatory Monocytes Degrade Collagen through Cellular Uptake. *Cell reports*, 21(13), 3662–3671. <https://doi.org/10.1016/j.celrep.2017.12.011>
46. T. R. Cox, J. T. Erler, 2014. Molecular pathways: connecting fibrosis and solid tumor metastasis. *Clinical cancer research: an official journal of the American Association for Cancer Research*, 20(14), 3637–3643. <https://doi.org/10.1158/1078-0432.CCR-13-1059>
47. A. Naba, K. R. Clauser, J. M. Lamar, S. A. Carr, R. O. Hynes, 2014. Extracellular matrix signatures of human mammary carcinoma identify novel metastasis promoters. *eLife*, 3, e01308. <https://doi.org/10.7554/eLife.01308>
48. T. R. Cox, D. Bird, A. M. Baker, H. E. Barker, M. W. Ho, G. Lang, J. T. Erler, 2013. LOX-mediated collagen crosslinking is responsible for fibrosis-enhanced metastasis. *Cancer research*, 73(6), 1721–1732. <https://doi.org/10.1158/0008-5472.CAN-12-2233>
49. M. W. Pickup, J. K. Mouw, V. M. Weaver, 2014. The extracellular matrix modulates the hallmarks of cancer. *EMBO reports*, 15(12), 1243–1253. <https://doi.org/10.15252/embr.201439246>
50. M. Morkunas, D. Zilenaite, A. Laurinaviciene, P. Treigys, A. Laurinavicius, 2021. Tumor collagen framework from bright-field histology images predicts overall survival of breast carcinoma patients. *Scientific reports*, 11(1), 15474. <https://doi.org/10.1038/s41598-021-94862-6>
51. H. X. Li, J. H. Zheng, H. X. Fan, H. P. Li, Z. X. Gao, D. Chen, 2013. Expression of $\alpha\text{v}\beta 6$ integrin and collagen fibre in oral squamous cell carcinoma: association with clinical outcomes and prognostic implications. *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 42(7), 547–556. <https://doi.org/10.1111/jop.12044>
52. M. Puig, R. Lugo, M. Gabasa, A. Giménez, A. Velásquez, R. Galgoczy, J. Ramírez, A. Gómez-Caro, Ó. Busnadiego, F. Rodríguez-Pascual, P. Gascón, N. Reguart, J. Alcaraz, 2015. Matrix stiffening and $\beta 1$ integrin drive subtype-specific fibroblast accumulation in lung cancer. *Molecular cancer research: MCR*, 13(1), 161–173. <https://doi.org/10.1158/1541-7786.MCR-14-0155>
53. J. L. Leight, M. A. Wozniak, S. Chen, M. L. Lynch, C. S. Chen, 2012. Matrix rigidity regulates a switch between TGF- $\beta 1$ -induced apoptosis and epithelial-mesenchymal transition.

- Molecular biology of the cell*, 23(5), 781–791. <https://doi.org/10.1091/mbc.E11-06-0537>
54. M. McMahon, S. Ye, L. Izzard, D. Dlugolenski, R. A. Tripp, A. G. Bean, D. R. McCulloch, J. Stambas, 2016. ADAMTS5 Is a Critical Regulator of Virus-Specific T Cell Immunity. *PLoS biology*, 14(11), e1002580. <https://doi.org/10.1371/journal.pbio.1002580>
 55. A. Papadas, G. Deb, A. Cicala, A. Officer, C. Hope, A. Pagenkopf, E. Flietner, Z. T. Morrow, P. Emmerich, J. Wiesner, G. Arauz, V. Bansal, K. Esbona, C. M. Capitini, K. A. Matkowskyj, D. A. Deming, K. Politi, S. I. Abrams, O. Harismendy, F. Asimakopoulos, 2022. Stromal remodeling regulates dendritic cell abundance and activity in the tumor microenvironment. *Cell reports*, 40(7), 111201. <https://doi.org/10.1016/j.celrep.2022.111201>
 56. E. Jachetti, S. Caputo, S. Mazzoleni, C. S. Brambillasca, S. M. Parigi, M. Grioni, I. S. Piras, U. Restuccia, A. Calcinotto, M. Freschi, A. Bach., R. Galli, M. Bellone, 2015. Tenascin-C Protects Cancer Stem-like Cells from Immune Surveillance by Arresting T-cell Activation. *Cancer research*, 75(10), 2095–2108. <https://doi.org/10.1158/0008-5472.CAN-14-2346>
 57. S. Sangaletti, C. Chiodoni, C. Tripodo, M. P. Colombo, 2017. Common extracellular matrix regulation of myeloid cell activity in the bone marrow and tumor microenvironments. *Cancer immunology, immunotherapy: CII*, 66(8), 1059–1067. <https://doi.org/10.1007/s00262-017-2014-y>
 58. Y. Xia, S. Shen, I. M. Verma, 2014. NF- κ B, an active player in human cancers. *Cancer immunology research*, 2(9), 823–830. <https://doi.org/10.1158/2326-6066.CIR-14-0112>
 59. B. Hoesel, J. A. Schmid, 2013. The complexity of NF- κ B signaling in inflammation and cancer. *Molecular cancer*, 12, 1–15. <https://doi.org/10.1186/1476-4598-12-86>
 60. B. Kaltschmidt, J. F. Greiner, H. M. Kadhim, C. Kaltschmidt, 2018. Subunit-specific role of NF- κ B in cancer. *Biomedicines*, 6(2), 44. <https://doi.org/10.3390/biomedicines6020044>
 61. T. Riedlinger, J. Haas, J. Busch, B. Van de Sluis, M. Kracht, M. L. Schmitz, 2018. The direct and indirect roles of NF- κ B in cancer: Lessons from oncogenic fusion proteins and knock-in mice. *Biomedicines*, 6(1), 36. <https://doi.org/10.3390/biomedicines6010036>
 62. V. Baud, D. Collares, 2016. Post-translational modifications of RelB NF- κ B subunit and associated functions. *Cells*, 5(2), 22. <https://doi.org/10.3390/cells5020022>
 63. K. Taniguchi, M. Karin, 2018. NF- κ B, inflammation, immunity and cancer: coming of age. *Nature Reviews Immunology*, 18(5), 309–324. <https://doi.org/10.1038/nri.2017.142>
 64. T. Lawrence, C. Fong, 2010. The resolution of inflammation: anti-inflammatory roles for NF- κ B. *The international journal of biochemistry & cell biology*, 42(4), 519–523. <https://doi.org/10.1016/j.biocel.2009.12.016>
 65. T. Yoshida, M. Hashimura, T. Kuwata, T. Matsumoto, E. Suzuki, Y. Tazo, H. Nakajima, M. Inukai, M. Saegusa, 2013. Transcriptional regulation of the alpha-1 type II collagen gene by nuclear factor B/p65 and Sox9 in the chondrocytic phenotype of uterine carcinosarcomas. *Human pathology*, 44(9), 1780–1788. <https://doi.org/10.1016/j.humpath.2012.12.019>
 66. F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, A. Jemal, 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, 68(6), 394–424. <https://doi.org/10.3322/caac.21492>
 67. H. Laklai, Y. A. Miroshnikova, M. W. Pickup, E. A. Collisson, G. E. Kim, A. S. Barrett, R. C. Hill, J. N. Lakin, D. D. Schlaepfer, J. K. Mouw, V. S. LeBleu, N. Roy, S. V. Novitskiy, J. S. Johansen, V. Poli, R. Kalluri, C. A. Iacobuzio-Donahue, L. D. Wood, M. Hebrok, K. Hansen, V. M. Weaver, 2016. Genotype tunes pancreatic ductal adenocarcinoma tissue tension to

- induce matricellular fibrosis and tumor progression. *Nature medicine*, 22(5), 497–505. <https://doi.org/10.1038/nm.4082>
68. Z. Miskolczi, M. P. Smith, E. J. Rowling, J. Ferguson, J. Barriuso, C. Wellbrock, 2018. Collagen abundance controls melanoma phenotypes through lineage-specific microenvironment sensing. *Oncogene*, 37(23), 3166–3182. <https://doi.org/10.1038/s41388-018-0209-0>
 69. M. H. Jenkins, W. Croteau, D. W. Mullins, C. E. Brinckerhoff, 2015. The BRAF(V600E) inhibitor, PLX4032, increases type I collagen synthesis in melanoma cells. *Matrix biology: journal of the International Society for Matrix Biology*, 48, 66–77. <https://doi.org/10.1016/j.matbio.2015.05.007>
 70. C. J. Clarke, T. J. Berg, J. Birch, D. Ennis, L. Mitchell, C. Cloix, A. Campbell, D. Sumpton, C. Nixon, K. Campbell, V. L. Bridgeman, P. B. Vermeulen, S. Foo, E. Kostaras, J. L. Jones, L. Haywood, E. Pulleine, H. Yin, D. Strathdee, O. Sansom, J. C. Norman, 2016. The Initiator Methionine tRNA Drives Secretion of Type II Collagen from Stromal Fibroblasts to Promote Tumor Growth and Angiogenesis. *Current biology: CB*, 26(6), 755–765. <https://doi.org/10.1016/j.cub.2016.01.045>
 71. C. C. Chang, T. L. Hsieh, T. Y. Tjong, C. H. Hsiao, A. T. Ji, W. T. Hsu, O. K. Lee, J. H. Ho, 2015. Regulation of metastatic ability and drug resistance in pulmonary adenocarcinoma by matrix rigidity via activating c-Met and EGFR. *Biomaterials*, 60, 141–150. <https://doi.org/10.1016/j.biomaterials.2015.04.058>
 72. S. C. Wei, L. Fattet, J. H. Tsai, Y. Guo, V. H. Pai, H. E. Majeski, A. C. Chen, R. L. Sah, S. S. Taylor, A. J. Engler, J. Yang, 2015. Matrix stiffness drives epithelial-mesenchymal transition and tumour metastasis through a TWIST1-G3BP2 mechanotransduction pathway. *Nature cell biology*, 17(5), 678–688. <https://doi.org/10.1038/ncb3157>
 73. C. Meng, Y. He, Z. Wei, Y. Lu, F. Du, G. Ou, N. Wang, X. G. Luo, W. Ma, T. C. Zhang, H. He, 2018. MRTF-A mediates the activation of COL1A1 expression stimulated by multiple signaling pathways in human breast cancer cells. *Biomedicine & pharmacotherapy*, 104, 718–728. <https://doi.org/10.1016/j.biopha.2018.05.092>
 74. C. Vennin, V. T. Chin, S. C. Warren, M. C. Lucas, D. Herrmann, A. Magenau, P. Melenec, S. N. Walters, G. Del Monte-Nieto, J. R. Conway, M. Nobis, A. H. Allam, R. A. McCloy, N. Currey, M. Pinese, A. Boulghourjian, A. Zaratzian, A. A. Adam, C. Heu, A. M. Nagrial, P. Timpson, 2017. Transient tissue priming via ROCK inhibition uncouples pancreatic cancer progression, sensitivity to chemotherapy, and metastasis. *Science translational medicine*, 9(384), eaai8504. <https://doi.org/10.1126/scitranslmed.aai8504>
 75. N. Rath, J. P. Morton, L. Julian, L. Helbig, S. Kadir, E. J. McGhee, K. I. Anderson, G. Kalna, M. Mullin, A. V. Pinho, I. Rooman, M. S. Samuel, M. F. Olson, 2017. ROCK signaling promotes collagen remodeling to facilitate invasive pancreatic ductal adenocarcinoma tumor cell growth. *EMBO molecular medicine*, 9(2), 198–218. <https://doi.org/10.15252/emmm.201606743>
 76. N. Cui, M. Hu, R. A. Khalil, 2017. Biochemical and Biological Attributes of Matrix Metalloproteinases. *Progress in molecular biology and translational science*, 147, 1–73. <https://doi.org/10.1016/bs.pmbts.2017.02.005>
 77. A. Jabłońska-Trypuć, M. Matejczyk, S. Rosochacki, 2016. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. *Journal of enzyme inhibition and medicinal chemistry*, 31(sup1), 177–183. <https://doi.org/10.3109/14756366.2016.1161620>
 78. A. M. Fallata, R. A. Wyatt, J. M. Levesque, A. Dufour, C. M. Overall, B. D. Crawford, 2019. Intracellular Localization in Zebrafish Muscle and Conserved Sequence Features

- Suggest Roles for Gelatinase A *Moonlighting in Sarcomere Maintenance. Biomedicines*, 7(4), 93. <https://doi.org/10.3390/biomedicines7040093>
79. V. Verovenko, S. Tennstedt, M. Kleinecke, T. Kessler, H. Schunkert, J. Erdmann, S. Ensminger, Z. Aherrahrou, 2024. Identification of a functional missense variant in the matrix metalloproteinase 10 (MMP10) gene in two families with premature myocardial infarction. *Scientific reports*, 14(1), 12212. <https://doi.org/10.1038/s41598-024-62878-3>
 80. A. C. Newby, 2016. Metalloproteinase production from macrophages-a perfect storm leading to atherosclerotic plaque rupture and myocardial infarction. *Experimental physiology*, 101(11), 1327–1337. <https://doi.org/10.1113/EP085567>
 81. W. J. Peng, J. Q. Zhang, B. X. Wang, H. F. Pan, M. M. Lu, J. Wang, 2012. Prognostic value of matrix metalloproteinase 9 expression in patients with non-small cell lung cancer. *Clinica chimica acta; international journal of clinical chemistry*, 413(13-14), 1121–1126. <https://doi.org/10.1016/j.cca.2012.03.012>
 82. Y. Xu, Z. Li, P. Jiang, G. Wu, K. Chen, X. Zhang, X. Li, 2015. The co-expression of MMP-9 and Tenascin-C is significantly associated with the progression and prognosis of pancreatic cancer. *Diagnostic pathology*, 10, 211. <https://doi.org/10.1186/s13000-015-0445-3>
 83. A. J. Favreau, C. P. Vary, P. C. Brooks, P. Sathyanarayana, 2014. Cryptic collagen IV promotes cell migration and adhesion in myeloid leukemia. *Cancer medicine*, 3(2), 265–272. <https://doi.org/10.1002/cam4.203>
 84. H. Huang, R. A. Svoboda, A. J. Lazenby, J. Saowapa, N. Chaika, K. Ding, M. J. Wheelock, K. R. Johnson, 2016. Up-regulation of N-cadherin by Collagen I-activated Discoidin Domain Receptor 1 in Pancreatic Cancer Requires the Adaptor Molecule Shc1. *The Journal of biological chemistry*, 291(44), 23208–23223. <https://doi.org/10.1074/jbc.M116.740605>
 85. M. Rada, S. Nallanthighal, J. Cha, K. Ryan, J. Sage, C. Eldred, M. Ullo, S. Orsulic, D. J. Cheon, 2018. Inhibitor of apoptosis proteins (IAPs) mediate collagen type XI alpha 1-driven cisplatin resistance in ovarian cancer. *Oncogene*, 37(35), 4809–4820. <https://doi.org/10.1038/s41388-018-0297-x>
 86. L. Oliveira-Ferrer, K. Rößler, V. Haustein, C. Schröder, D. Wicklein, D. Maltseva, N. Khaustova, T. Samatov, A. Tonevitsky, S. Mahner, F. Jänicke, U. Schumacher, K. Milde-Langosch, 2014. c-FOS suppresses ovarian cancer progression by changing adhesion. *British journal of cancer*, 110(3), 753–763. <https://doi.org/10.1038/bjc.2013.774>
 87. P. Procacci, C. Moscheni, P. Sartori, M. Sommariva, N. Gagliano, 2018. Tumor-Stroma Cross-Talk in Human Pancreatic Ductal Adenocarcinoma: A Focus on the Effect of the Extracellular Matrix on Tumor Cell Phenotype and Invasive Potential. *Cells*, 7(10), 158. <https://doi.org/10.3390/cells7100158>
 88. G. Vaniotis, R. F. Rayes, S. Qi, S. Milette, N. Wang, S. Perrino, F. Bourdeau, H. Nyström, Y. He, N. Lamarche-Vane, P. Brodt, 2018. Collagen IV-conveyed signals can regulate chemokine production and promote liver metastasis. *Oncogene*, 37(28), 3790–3805. <https://doi.org/10.1038/s41388-018-0242-z>
 89. R. Espinosa Neira, E. P. Salazar, 2012. Native type IV collagen induces an epithelial to mesenchymal transition-like process in mammary epithelial cells MCF10A. *The international journal of biochemistry & cell biology*, 44(12), 2194–2203. <https://doi.org/10.1016/j.biocel.2012.08.018>
 90. K. A. Spivey, I. Chung, J. Banyard, I. Adini, H. A. Feldman, B. R. Zetter, 2012. A role for collagen XXIII in cancer cell adhesion, anchorage-independence and metastasis. *Oncogene*, 31(18), 2362–2372. <https://doi.org/10.1038/onc.2011.406>

91. Y. Hayashido, H. Kitano, T. Sakaue, T. Fujii, M. Suematsu, S. Sakurai, T. Okamoto, 2014. Overexpression of integrin α v facilitates proliferation and invasion of oral squamous cell carcinoma cells via MEK/ERK signaling pathway that is activated by interaction of integrin α v β 8 with type I collagen. *International journal of oncology*, 45(5), 1875–1882. <https://doi.org/10.3892/ijo.2014.2642>
92. S. J. Ibbetson, N. T. Pyne, A. N. Pollard, M. F. Olson, M. S. Samuel, 2013. Mechanotransduction pathways promoting tumor progression are activated in invasive human squamous cell carcinoma. *The American journal of pathology*, 183(3), 930–937. <https://doi.org/10.1016/j.ajpath.2013.05.014>
93. Y. Shen, R. Shen, L. Ge, Q. Zhu, F. Li, 2012. Fibrillar type I collagen matrices enhance metastasis/invasion of ovarian epithelial cancer via β 1 integrin and PTEN signals. *International journal of gynecological cancer: official journal of the International Gynecological Cancer Society*, 22(8), 1316–1324. <https://doi.org/10.1097/IGC.0b013e318263ef34>
94. S. D. Smith, M. Enge, W. Bao, M. Thullberg, T. D. Costa, H. Olofsson, B. Gashi, G. Selivanova, S. Strömblad, 2012. Protein kinase α (PKC α) regulates p53 localization and melanoma cell survival downstream of integrin α v in three-dimensional collagen and in vivo. *The Journal of biological chemistry*, 287(35), 29336–29347. <https://doi.org/10.1074/jbc.M112.341917>
95. S. Blockhuys, B. Van Rompaye, R. De Rycke, K. Lambein, K. Claes, M. Bracke, C. De Wagter, O. De Wever, 2013. Radiation-induced myosin IIA expression stimulates collagen type I matrix reorganization. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*, 108(1), 162–167. <https://doi.org/10.1016/j.radonc.2013.04.001>
96. V. V. Artym, S. Swatkoski, K. Matsumoto, C. B. Campbell, R. J. Petrie, E. K. Dimitriadis, X. Li, S. C. Mueller, T. H. Bugge, M. Gucuk, K. M. Yamada, 2015. Dense fibrillar collagen is a potent inducer of invadopodia via a specific signaling network. *The Journal of cell biology*, 208(3), 331–350. <https://doi.org/10.1083/jcb.201405099>
97. T. Yan, A. Zhang, F. Shi, F. Chang, J. Mei, Y. Liu, Y. Zhu, 2018. Integrin α v β 3-associated DAAM1 is essential for collagen-induced invadopodia extension and cell haptotaxis in breast cancer cells. *The Journal of biological chemistry*, 293(26), 10172–10185. <https://doi.org/10.1074/jbc.RA117.000327>
98. S. Y. Chen, J. S. Lin, B. C. Yang, 2014. Modulation of tumor cell stiffness and migration by type IV collagen through direct activation of integrin signaling pathway. *Archives of biochemistry and biophysics*, 555–556, 1–8. <https://doi.org/10.1016/j.abb.2014.05.004>
99. S. Cattaruzza, P. A. Nicolosi, P. Braghetta, L. Pazzaglia, M. S. Benassi, P. Picci, K. Lacrima, D. Zanocco, E. Rizzo, W. B. Stallcup, A. Colombatti, R. Perris, 2013. NG2/CSPG4-collagen type VI interplays putatively involved in the microenvironmental control of tumour engraftment and local expansion. *Journal of molecular cell biology*, 5(3), 176–193. <https://doi.org/10.1093/jmcb/mjt010>
100. H. Zhang, T. Fredericks, G. Xiong, Y. Qi, P. G. Rychahou, J. D. Li, T. Pihlajaniemi, W. Xu, R. Xu, 2018. Membrane associated collagen XIII promotes cancer metastasis and enhances anoikis resistance. *Breast cancer research: BCR*, 20(1), 116. <https://doi.org/10.1186/s13058-018-1030-y>
101. M. J. Stawikowski, B. Auksz, R. Stawikowska, M. Cudic, G. B. Fields, 2014. Glycosylation modulates melanoma cell α 2 β 1 and α 3 β 1 integrin interactions with type IV collagen. *The Journal of biological chemistry*, 289(31), 21591–21604. <https://doi.org/10.1074/jbc.M114.572073>

102. S. Liu, G. Liao, G. Li, 2017. Regulatory effects of COL1A1 on apoptosis induced by radiation in cervical cancer cells. *Cancer cell international*, 17, 73. <https://doi.org/10.1186/s12935-017-0443-5>
103. M. P. Shea, K. A. O'Leary, K. A. Wegner, C. M. Vezina, L. A. Schuler, 2018. High collagen density augments mTOR-dependent cancer stem cells in ER α + mammary carcinomas, and increases mTOR-independent lung metastases. *Cancer letters*, 433, 1–9. <https://doi.org/10.1016/j.canlet.2018.06.025>
104. C. E. Barcus, K. A. O'Leary, J. L. Brockman, D. E. Rugowski, Y. Liu, N. Garcia, M. Yu, P. J. Keely, K. W. Eliceiri, L. A. Schuler, 2017. Elevated collagen-I augments tumor progressive signals, intravasation and metastasis of prolactin-induced estrogen receptor alpha positive mammary tumor cells. *Breast cancer research: BCR*, 19(1), 9. <https://doi.org/10.1186/s13058-017-0801-1>
105. S. Yamazaki, Y. Higuchi, M. Ishibashi, H. Hashimoto, M. Yasunaga, Y. Matsumura, K. Tsuchihara, M. Tsuboi, K. Goto, A. Ochiai, G. Ishii, 2018. Collagen type I induces EGFR-TKI resistance in EGFR-mutated cancer cells by mTOR activation through Akt-independent pathway. *Cancer science*, 109(6), 2063–2073. <https://doi.org/10.1111/cas.13624>
106. C. W. Brown, A. S. Brodsky, R. N. Freiman, 2015. Notch3 overexpression promotes anoikis resistance in epithelial ovarian cancer via upregulation of COL4A2. *Molecular cancer research: MCR*, 13(1), 78–85. <https://doi.org/10.1158/1541-7786.MCR-14-0334>
107. J Liu, S. G Kang, P Wang, Y Wang, X Lv, Y Liu, F Wang, Z Gu, Z Yang, J. K Weber, N Tao, Z Qin, Q Miao, C Chen, R. Zhou, Y. Zhao, 2018. Molecular mechanism of Gd@C82(OH)22 increasing collagen expression: Implication for encaging tumor. *Biomaterials*, 152, 24–36. <https://doi.org/10.1016/j.biomaterials.2017.10.027>
108. E. Goggins, S. Kakkad, Y. Mironchik, D. Jacob, F. Wildes, B. Krishnamachary, Z. M. Bhujwalla, 2018. Hypoxia Inducible Factors Modify Collagen I Fibers in MDA-MB-231 Triple Negative Breast Cancer Xenografts. *Neoplasia (New York, N.Y.)*, 20(2), 131–139. <https://doi.org/10.1016/j.neo.2017.11.010>
109. G Xiong, R. L Stewart, J Chen, T Gao, T. L Scott, L. M Samayoa, K O'Connor, A. N Lane, R Xu, 2018. Collagen prolyl 4-hydroxylase 1 is essential for HIF-1 α stabilization and TNBC chemoresistance. *Nature communications*, 9(1), 4456. <https://doi.org/10.1038/s41467-018-06893-9>
110. I. Amelio, M. Mancini, V. Petrova, R. A. Cairns, P. Vikhrev, S. Nicolai, A. Marini, A. A. Antonov, J. Le Quesne, J. D. Baena Acevedo, K. Dudek, G. Sozzi, U. Pastorino, R. A. Knight, T. W. Mak, G. Melino, 2018. p53 mutants cooperate with HIF-1 in transcriptional regulation of extracellular matrix components to promote tumor progression. *Proceedings of the National Academy of Sciences of the United States of America*, 115(46), E10869–E10878. <https://doi.org/10.1073/pnas.1808314115>
111. F. Bordeleau, B. N. Mason, E. M. Lollis, M. Mazzola, M. R. Zanutelli, S. Somasegar, J. P. Califano, C. Montague, D. J. LaValley, J. Huynh, N. Mencia-Trinchant, Negrón Y. L. Abril, D. C. Hassane, L. J. Bonassar, J. T. Butcher, R. S. Weiss, C. A. Reinhart-King, 2017. Matrix stiffening promotes a tumor vasculature phenotype. *Proceedings of the National Academy of Sciences of the United States of America*, 114(3), 492–497. <https://doi.org/10.1073/pnas.1613855114>
112. M. Burmakin, T. van Wieringen, P. O. Olsson, L. Stühr, A. Åhgren, C. H. Heldin, R. K. Reed, K. Rubin, C. Hellberg, 2017. Imatinib increases oxygen delivery in extracellular matrix-rich but not in matrix-poor experimental carcinoma. *Journal of translational medicine*, 15(1), 47. <https://doi.org/10.1186/s12967-017-1142-7>
113. T. Kitamura, B. Z. Qian, J. W. Pollard, 2015. Immune cell promotion of metastasis. *Nature reviews. Immunology*, 15(2), 73–86. <https://doi.org/10.1038/nri3789>

114. S. S. McAllister, R. A. Weinberg, 2014. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. *Nature cell biology*, 16(8), 717–727. <https://doi.org/10.1038/ncb3015>
115. D. K. Gupta, N. Singh, D. K. Sahu, 2014. TGF- β Mediated Crosstalk Between Malignant Hepatocyte and Tumor Microenvironment in Hepatocellular Carcinoma. *Cancer growth and metastasis*, 7, 1–8. <https://doi.org/10.4137/CGM.S14205>
116. T. Osawa, N. Ohga, K. Akiyama, Y. Hida, K. Kitayama, T. Kawamoto, K. Yamamoto, N. Maishi, M. Kondoh, Y. Onodera, M. Fujie, N. Shinohara, K. Nonomura, M. Shindoh, K. Hida, 2013. Lysyl oxidase secreted by tumour endothelial cells promotes angiogenesis and metastasis. *British journal of cancer*, 109(8), 2237–2247. <https://doi.org/10.1038/bjc.2013.535>
117. S. A. Antar, N. A. Ashour, M. E. Marawan, A. A. Al-Karmalawy, 2023. Fibrosis: Types, Effects, Markers, Mechanisms for Disease Progression, and Its Relation with Oxidative Stress, Immunity, and Inflammation. *International journal of molecular sciences*, 24(4), 4004. <https://doi.org/10.3390/ijms24044004>
118. Y. Yamazaki, Y. Mikami, M. Yuguchi, Y. Namba, K. Isokawa, 2012. Development of collagen fibres and lysyl oxidase expression in the presumptive dermis of chick limb bud. *Anatomia, histologia, embryologia*, 41(1), 68–74. <https://doi.org/10.1111/j.1439-0264.2011.01103.x>