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RESEARCH ARTICLE

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

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ABSTRACT

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.

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-Khouri *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 (DDRs) are human proteins that regulate the movement of neutrophil and fibroblasts in three-dimensional matrices. Human discoidin domain receptors (DDRs) 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). α1 and α2 integrin expression is abundant in dermal myofibroblasts. α10 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 (TGFβ) 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 αvβ3 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 (DDRs) 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-κB) is a cellular signaling pathway that plays a crucial role in various functions such as immunity, memory, learning, apoptosis, cell proliferation, and inflammation. NF-κB family comprises five subunits, with nuclear localization signal in RHD of p50/p65 dimers obscured by κB inhibitors, preventing nuclear translocation. Target gene expression is facilitated by IκBα phosphorylation by IKK complex, mediated by NIK. NF-κB, 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-κB 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 COLI, COLII, and COLIV degradation (Chang *et al*., 2015). NF-κB 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-Trypuć *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 (DDRs) 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. COLI upregulate N-cadherin be in PDAC cells, stimulating MMP14, collagen, and EMT development in breast cancer and epithelial to mesenchymal traits through phosphorylation, activation, and blocking GSK 3β (Favreau *et al*., 2014; Huang *et al.,* 2016; Rada *et al.,* 2018; Oliveira-Ferrer *et al.,* 2014; Procacci *et al*., 2018). COLI inhibit E-cadherin in PDAC, affecting liver metastasis and EMT. This effect is associated with CCL7 and CCLIV-regulating chemokines. COLIV 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 β1 integrin signaling complexes, radiation-induced breast cancer cells using β1 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/β1 integrin signaling pathway reduces cell stiffness and increases motility, affecting cell movement in melanoma. PI3K activation through α2β1 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.

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