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Tumor Microenvironment in Colorectal Cancer Development: A Review of 3D Study Analysis

Rebecca Noerjani Angka [1,2*], Aru Wisaksono Sudoyo [3], Nurjati Chairani Siregar [4], Wifanto Saditya Jeo [5], Radiana Dhewayani Antarianto [6,7]

[1] Doctoral Program of Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2] Department of Anatomical Pathology, Faculty of Medicine and Health Sciences, Krida Wacana Christian University (UKRIDA), Jakarta, Indonesia
[3] Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[4] Department of Anatomical Pathology, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[5] Department of Surgery, Digestive Division, Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[6] Department of Histology, Faculty of Medicine, Universitas Indonesia, Indonesia
[7] Stem Cell and Tissue Engineering Research Cluster IMERI, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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*Corresponding author:
Rebecca Noerjani Angka
Department of Anatomical Pathology, Faculty of Medicine and Health Sciences, Krida Wacana Christian University (UKRIDA), Jakarta, Indonesia
rnah2904@gmail.com

ABSTRACT

Background: Colorectal cancer is the third most common cancer in 2020, with a high mortality rate. Colorectal cancer treatment has made many advances. However, many factors in the tumor microenvironment still have not been reached but significantly affect the success of treatment. This literature review was conducted to search for research articles that analyze factors in the tumor microenvironment, how they interact through studies primarily conducted in 3D, and how to prepare for 3D research on colorectal cancer will be briefly discussed. The aim of this systematic review is to study the components of the tumor microenvironment in colorectal cancer development as assessed by 3D studies.

Methods: Article searches were conducted through Embase, Scopus and PubMed. From the 110 articles found at the beginning of the search, after going through several screening stages, 27 articles were determined that met the inclusion criteria. The inclusion criteria used were journals containing research articles on colorectal cancer in the last five years with topics regarding the tumor microenvironment and according to keywords.

Results: Microenvironment components in colorectal cancer, consisting of cellular and non-cellular components, have the most significant effect on cancer development and ultimately affect metastasis, response to treatment, and prognosis.

Conclusions: This literature review proves that the components of the tumor microenvironment are very diverse, making colorectal cancer heterogeneous. It still requires a lot of research to prove the existence of other components that affect the effectiveness of the treatment.

INTRODUCTION

Global Cancer Observatory (GLOBOCAN) 2021 reported 19.3 million new cancer cases with nearly 10.0 million cancer deaths. More than 1.9 million new colorectal cancer cases were reported, with 935,000 colorectal cancer deaths in 2020. This makes colorectal cancer the third most frequently diagnosed cancer case under breast cancer in women and lung cancer, while for causes of death due to cancer, colorectal cancer is under lung cancer cases [1]. The cause of colorectal cancer death is generally due to metastasis, the process of which is influenced by the tumor microenvironment and ultimately affects the prognosis [2].

The studies that have been carried out reveal that the cause of colorectal cancer is related to multiple

factors, including colonic inflammation and tumor microenvironment factors, which have an enormous influence [3,4]. The tumor microenvironment is the environment associated with tumor pathology, consisting of the extracellular matrix, tumor cells, stromal cells, immune cells, and other bioactive factors that control the interactions between stromal cells and tumor cells and between these cells with the extracellular matrix. The extracellular matrix also controls tumor cells' proliferation, differentiation, and metastasis and acts as a natural defense [5,6].

The number of factors in the tumor microenvironment has not been clearly understood. This literature review aims to analyze the factors in the microenvironment and how they interact through studies that are mainly carried out in 3D. We chose 3D analysis because it can better describe the actual conditions inside the human body and observe cells' growth, differentiation, and function [7]. This systematic review aims to study the components of the tumor microenvironment in colorectal cancer development as assessed by 3D studies. How to do 3D research on colorectal cancer will be briefly discussed.

METHODS

The international literature search method was carried out through Embase, Scopus, and PubMed data using keywords: 3D, cell-matrix interaction, colorectal cancer, and microenvironment. The inclusion criteria in this article are journals containing research articles on colorectal cancer in the last five years with topics regarding the tumor microenvironment and according to keywords. The exclusion criteria used were journals discussing the types of colorectal and other cancers and the therapy carried out. Of the 110 articles found during the initial search, after the final selection stage, 27 articles were determined to meet the inclusion criteria (**Figure 1**).

RESULTS

Microenvironment components in colorectal cancer have the most significant effect on cancer development and ultimately affect invasion, metastasis, response to treatment, and prognosis. Below are some research studies about microenvironment components (**Table 1**).

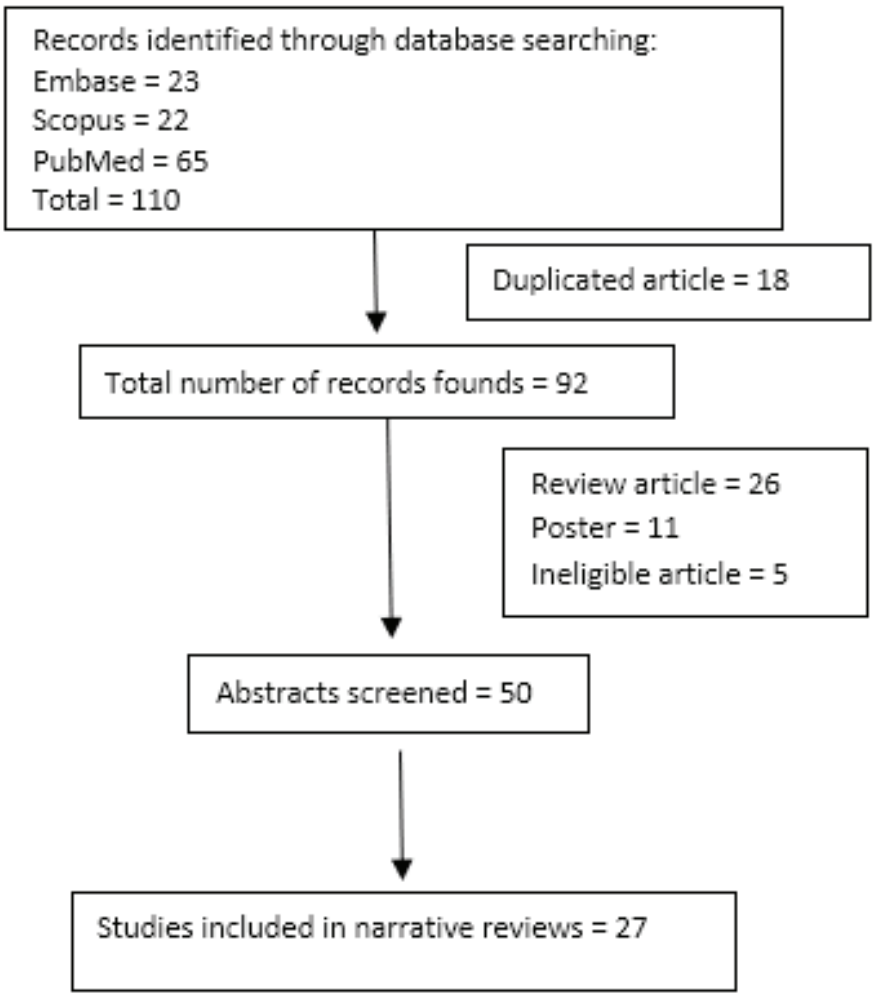

Figure 1. PRISMA flow diagram

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Table 1. List of articles about the tumor microenvironment

Author	Methods	Output	Sample	Results
Ciszewski WM, et al. 2017 [8]	In vitro	Cancer progression	Adenocarcinoma cancer cell lines LS180 and LoVo	TGF-β2 induces mesenchymal transdifferentiation from Human Microvascular Endothelial Cells (HMEC-1 cells) into Cancer-Associated Fibroblast (CAF)-like cells in association with elongated cell morphology, modulation of stress fiber organization, high levels of α-SMA protein and activation of the RhoA and Rac-1 pathways.
Piccoli M, et al. 2017 [9]	In vitro	The best techniques for 3D research	28 pairs of normal mucosa and cancer tissue from colorectal cancer patients	3D in vitro obtained by the decellularization method using enzymatic treatment of detergents, small molecules, and peptides is a good model for screening and drug delivery research.
Tsai CW, et al. 2018 [10]	In vitro	Cancer model to know drug effectiveness	The 3A6 cell line	Co-cultured cells on chitosan, 3A6 and Hs68 cells were always located in the spheroid nucleus and completely enveloped by SW620 cells due to N-cadherin protein expression. Nuclear cells can be a feeder layer to stimulate the SW620. Shell cells to increase mitochondrial activity.
Hsu YL, et al. 2018 [11]	In vitro and in vivo	Colorectal cancer progression	Dendritic cells from colorectal cancer patients	Tumor-associated dendritic cells (TADCs) secreting CXCL1 enhance metastatic capacity by enhancing cell migration, MMP-7 expression and EMT.
Manfredonia C, et al. 2019 [12]	In vitro	Colorectal cancer progression and response to treatment	Primary colorectal cancer cells	Fresh tissue cultures from colorectal cancer patients in bioreactors under perfusion can maintain the entire live tumor tissue, including cancer cells with mesenchymal stromal cells and immune cell components, for some time and allow the assessment of cancer drug response.
Zoetemelk M, et al. 2019 [13]	In vitro	Treatment optimization	Colorectal cancer cell lines	Effect of fibroblasts and endothelial cells on cancer cells on treatment.
Landskron G, et al. 2019 [14]	In vitro	Metastasis	HT29 and HCT116 adenocarcinoma cell lines	Increased tumor IL-33 and decreased stromal ST2 were associated with greater desmoplasia in left colon tumors, which ultimately contributed to the development of lymphatic metastases.
Pape J, et al. 2019 [15]	In vitro	Invasion and metastasis	Human adenocarsinoma cell lines HT29 and HCT116	Invasive cancer affects blood vessels more than less invasive cancer, which is directly related to cancer development.
Fuhr L, et al. 2019 [16]	In vitro	Carcinogenesis process	CaCo2, HCT116, HT29, LIM1215, RKO, SW480 and SW 620 cell lines	The interaction between colon cancer cells and tumor-associated fibroblasts affects the molecular clock and appears to exacerbate the cancer cell phenotype.
Drev D, et al. 2019 [17]	In vitro, retrospective	Overall survival	466 colorectal patients stage II and III	Stromal SPARC can be a predictive factor for recurrence.
Unterleuthner D, et al. 2019 [18]	In vitro	Angiogenesis	Primary human umbilical vein endothelial cells and cancer-associated fibroblasts (CAFs) from colorectal cancer patients.	Wingless-type MMTV integration site family member 2 (WNT2) increases endothelial cell migration.

Author	Methods	Output	Sample	Results
Germann M, et al. 2019 [19]	In vitro and in vivo	Tumor micro-environment and response to immunotherapy	APC mice and blood samples of colorectal cancer patients	In vivo mouse colon tumors: infiltrating neutrophils have a remarkable potential to suppress T cells in the tumor microenvironment. In humans, it has been shown that suppression of T cells through TGF-β.
Qi L, et al. 2020 [20]	In vitro	Survival analysis	566 colorectal cancer cases from The Gene Expression Omnibus (GEO) database	The extracellular matrix, which is the tumor microenvironment, is closely related to the occurrence of invasion and metastasis.
Li ZL, et al. 2020 [5]	In vitro and in vivo	Tumor development	Colorectal cancer tissue from 60 patients	The structure and composition of the extracellular matrix is disorganized during tumor development, creating a conducive environment for tumor development.
Kiyasu Y, et al. 2020 [21]	In vivo	Tumor development	C57BL/6 wild-type mice or C57BL/6 Ccr1-/- mice	MC38 and CMT93 stimulate the recruitment of CCR1+ myeloid cells to tumors, and genetic deficiency of CCR1 and/or pharmacological inhibition of CCR1 with anti-CCR1 mAB may exhibit anti-tumor effects on tumor growth and metastasis.
Devarasetty M, et al. 2020 [22]	In vitro and in vivo	Tumor development	Human hepatic stellate cells, LX2, and HCT116 Human colorectal cancer tissue sample	Experimental animal models are not accurate for capturing human tumor architecture.
Le CC, et al. 2020 [23]	In vitro	Colorectal cancer progression	LS174T, HT-29, and RKO cell lines	DDR1 leads to the proliferation and apoptosis of colon cancer cells.
Kim MS, et al. 2020 [6]	In vitro	Tumor development	Human colon cancer epithelial cells DLD-1, HCT116 and colon myofibroblast cells CCD-18co	PDGFRβ and THBS4 overexpression in tumor tissues of colorectal cancer patients and increased PDGF-D expression after treatment with TGFβ in DLD-1 colon cancer survivor cells.
Chen H, et al. 2020 [24]	In vitro	Tumor development	HCT116 cell lines and 2 normal stroma cell types (HUVECs and HELFs)	The successful development of a 3D tumor tissue model so that it can study tumor physiology metabolism and tumor malignancy transformation.
Garzon JFG, et al. 2020 [25]	In vitro	Tumor development	Mouse colonic adenocarcinoma cells, which express GFP and CT26 cells	Mouse colon adenocarcinoma cells destroyed with HIF-1α produce smaller and more hypoxic tumors.
Dominijanni A, et al. 2020 [26]	In vitro	Tumor cell interaction	Tumor organoid model (HSCs dan HCT116)	Manipulating the extracellular matrix of tumor organoids can study the interactions of the extracellular matrix of tumor cells and better understand the response to chemotherapy.
McCarthy B, et al. 2021 [27]	In vitro	Matrix cell/ nanoparticle interaction	Mouse colorectal cancer cell lines	Semiconductor polymer nanoparticles in a 3D tumor-like organ model successfully demonstrate target ablation.
Chiang CT, et al. 2021 [28]	In vitro	Cancer development	Human colorectal cancer cell lines HCT116 and HT 29	Tumor cells were grown in a variety of biochemical and biomechanical microenvironmental contexts, including varying oxygen and drug concentrations and growth on conventional rigid plastics, softer matrices, and biologically engineered acellular liver extracellular matrix. Growth rate analysis under these conditions was carried out through cell phenotype digitizer (CellPD).

Author	Methods	Output	Sample	Results
Huang Z, et al. 2021 [29]	In silico	Prognosis	The Oncomine and UALCAN databases	In colorectal cancer, ADAM12 plays an important role in regulating the extracellular matrix and immune cell recruitment.
Xu H, Pan Y. 2021 [30]	In vitro	Overall survival (OS)	375 sample tumor	Signs associated with fibroblasts can predict a patient's prognosis.
Zhang HP, et al. 2022 [31]	In silico	Pathogenesis tumor	The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO)	SPARCL1 inherited in colorectal cancer tissue and showed high accuracy for diagnosis of primary colorectal cancer.
Yang W, et al. 2022 [4]	In vivo	Cancer development	Mice Il1f9+/- and Il1f5+/- , block paraffin colorectal cancer	IL-36γ and IL-36Ra reciprocally regulate tumor progression directly through modulation of cell-matrix adhesion to indirectly regulate Wnt signaling.

DISCUSSION

The interaction and role of cells in the tumor microenvironment play a role in the development of cancer, which is not easily proven by 2D research, so studies must be carried out using techniques that can maintain the biological conditions of the factors to be studied. Several 3D culture models that have been carried out will be described in this article. The decellularization method using detergent-enzymatic treatment (DET) is one of the research methods that can maintain the original structure, ultrastructure, architecture, and protein composition to be studied [9].

The growth and development of cancer in patients over the years often without causing symptoms and complaints. The relationship between the components of the extracellular matrix and how to control the response of cancer cells through changes in the tumor microenvironment to chemotherapy and radiation can be studied more through 3D research than using experimental animals. Experimental animal models cannot provide accurate architecture of human cancer conditions [22]. The 3D scaffold used in this study was manufactured using a custom-built electro-hydrodynamic (E-jet) 3D printing system consisting of a 3D collection platform, a liquid feed system, a high-voltage power supply, and an observation system [24]. A 3D study with chitosan prepared from deacetylation of chitin was carried out by Tsai CW to prove the expression of N-cadherin, E-cadherin, P-cadherin and ultimately to observe the cytotoxic effect of chemotherapy drugs [10].

Another tumor microenvironment study was carried out using a perfused bioreactor-based 3D culture system. The new colorectal cancer sections were placed between 2 collagen-like sandwiches and cultured in a bioreactor tube with continuous perfusion [12]. The 3D scaffold allows direct interactions between cells showing the same physiological status as in vivo conditions and can be evaluated continuously over a period of time [12,24]. Research with 3D culture systems can also see the cytotoxic effects and optimization of chemotherapy drug treatment, although implementation in drug discovery is still far from expected. The combination of drugs given at low doses will provide different results when given at high doses in metastatic colorectal cancer cell cultures [13]. Several studies have been carried out, and research using the 3D method, both with chitosan and perfused bioreactor, provides more apparent results to find out the actual mechanism that occurs in the body. Furthermore, this literature review will discuss the results of research using 2D and 3D methods regarding the tumor microenvironment.

Non-cellular components

Inflammation and hypoxia influence the tumor microenvironment in the process of tumorigenesis, progression, and invasiveness of colorectal cancer. The necrosis factor receptor-associated factor 6 (TRAF6) protein is an intracellular protein that stabilizes HIF-1α in colon cancer cells. The response of tumor cells to increased hypoxia in the colon leads to the promotion of nonfunctional angiogenesis, which is regulated by the hypoxia pathway and TRAF6. Colonic adenocarcinoma cells attenuated to hypoxia produce smaller tumors than control cells [25]. Chiang CT demonstrated that the growth of highly aggressive colorectal cancer is affected by oxygen levels, as well as response to chemotherapy in which hypoxia has a protective effect against oxaliplatin-induced cytotoxicity in the plastics and liver extracellular matrix used [28].

Another cellular matrix glycoprotein in the tumor stroma is the secreted protein acidic and rich in cysteine (SPARC) produced by many organs in rapid proliferation. In colorectal cancer, it is produced by CAFs with tumor suppressor function. Stromal SPARC is a factor that suppresses focal adhesion kinase phosphorylation,

migration, and invasion of tumor cells so that it can indicate tumor aggressiveness and poor outcome [17]. Secreted protein acidic and rich in cysteine-like 1 (SPARCL1) plays an important role in regulating cell adhesion, migration, and proliferation and is associated with a poor prognosis. Low expression of SPARCL1 was detected in primary colorectal cancer compared to normal colorectal and in liver metastases compared to primary. Zhang et al. [31] proved a significant relationship between SPARCL1 and clinicopathological features, overall survival, distant metastases, tumor differentiation, and tumor microenvironment in colorectal cancer.

Disintegrin and metalloproteases (ADAMs) are transmembrane glycoproteins of the metalloproteinase family, and ADAM12 is expressed at high levels in colorectal cancer tissues, and low expression is associated with a better prognosis of life expectancy. ADAM12 expression was influenced by age, stage, TP53 mutation status, and several other factors. ADAM12 is associated with the EGFR signaling pathway and regulates tumor progression through interactions with other factors, also inducing the formation of new blood vessels in tumors. ADAM12 expression was significantly positively associated with CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells but no significant relationship with B cells. ADAM12 is closely related to immune cells in colorectal cancer and requires further research on colorectal cancer immunotherapy [29].

Another component that influences the tumorigenesis process is low-density lipoprotein receptor-related protein-1 (LRP-1). LRP-1 is a large endocytic receptor that is ubiquitous and mediates the clearance of various molecules from the extracellular matrix. LRP-1 induces the endocytosis of discoidin domain receptors (DDRs) in colorectal cancer cells, thereby reducing the ability to inhibit tumor cell proliferation. DDRs are type I collagen receptors with tyrosine kinase activity [23].

Thrombospondin-4 (THBS4) is an extracellular matrix protein. In colorectal cancer, together with platelet-derived growth factor receptor (PDGFR), it initiates cell migration, invasion, proliferation, and metastasis. Both of these proteins are associated with transforming growth factor-β (TGFβ). TGFβ increases PDGF-D mRNA levels, but PDGF-D does not increase THBS4 mRNA levels; TGFβ and PDGFRβ are involved in stabilization via post-translational modification of THBS4 [6]. TGF-β2 induces transdifferentiation of mesenchymal human microvascular endothelial cells (HMEC-1 cells) into CAF-like cells associated with elongation of cell morphology, high levels of -SMA protein and activation of the RhoA and Rac-1 pathways. Integrin-linked kinase (ILK) is a multifunctional serine/threonine protein kinase in focal adhesions. Upregulation of ILK also increases myocardin-related transcription factor (MRTF) activation via RhoA and Rac-1-MMP9 via inner-outer integrin activation and could be a target for cancer therapy [8]. MMP-2 and MMP-9, as a family of MMPs, play an important role in the destruction and removal of the extracellular matrix, whereas tissue inhibitors of metalloproteinase-3 (TIMP-3), which is only present in the extracellular matrix, can bind to MMPs and render them inactive. Research has shown that the expression of MMP-2 and MMP-9 is higher in colorectal cancer tissue than in normal tissue. MMP-2 expression will increase in line with the increase in tumor stage, and MMP-9 expression will be highest at stage III [5].

The integrin protein, beta-like 1 (ITGBL1), is located in the extracellular matrix and is involved in the development and metastasis of several tumors. β-catenin interacts with many extracellular Wnt signals and can bind to ITGBL1. High expression of ITGBL1 in colorectal cancer is associated with shorter life expectancy of colorectal cancer patients [20]. Loss of SMAD4 in colorectal cancer leads to the recruitment of the CCR1 motif chemokine receptor (C-C motif chemokine receptor 1) to initiate colorectal cancer invasion and metastasis. CCR1 is expressed on monocytes, neutrophils, and peripheral blood macrophages, leading to the initiation of tumor progression through tumor angiogenesis and immune suppression (decreased CD8+ T cells and increased Foxp3+ Treg cells) [21].

Invasive progression of cancer cells into the stroma is also affected by Vascular Endothelial Cadherin (VE-cadherin), where lower expression is found in highly invasive colorectal cancers. Highly invasive cancers require higher oxygen levels, which irritates the blood vessels more [15]. The interactions between tumor cells and the surrounding extracellular matrix, including E-cadherin and β-catenin, play a role in colon cancer invasion. Changes in the extracellular matrix also give different results in the resistance and sensitivity of chemotherapy, so research on the extracellular matrix will provide an understanding to understand the treatment mechanism more precisely [26].

The process of cancer development is influenced by hypoxia tumor microenvironment conditions where various non-cellular components that exist affect the progression of colorectal cancer to good or bad outcomes. Components that influence aggressiveness and poor outcome are SPARC, LRP-1, THBS4, PDGFR, MMP, ITGBL1, CCR1, VE-cadherin, whereas the component associated with a better prognosis is ADAMs.

Cellular components

Tumor microenvironmental factors that play a role in tumor development are fibroblasts, stromal cells involved in many biological processes. Based on data from The Cancer Genome Atlas (TCGA), they were divided into high and low groups. Overall survival (OS) in the high-fibroblast group was shorter than in the low-fibroblast group. Fibroblasts increased significantly at an advanced stage and in cases of lymph node

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metastases. Immune cell lineages, including B-cell, T-cell, and NK cell-derived, were inversely associated with the risk value. In contrast, endothelial cells and monocyte-derived were positively associated with the risk value. So, it is concluded that fibroblast-associated markers can predict the patient's prognosis, which might explain the CRC treatment [30].

Fibroblasts isolated from tubulovillous adenomas and having a high risk for malignant transformation were used to study the interaction between benign tumor stroma and the circadian biological clock. The interaction between colon cancer cells and tumor-associated fibroblasts (TAFs) affects the molecular clockwork and exacerbates the malignant cell phenotype. Colon cancer cells exhibit changes in circadian and metabolic parameters, with decreased apoptosis, increased colon cancer cell viability, and increased resistance to chemotherapy [16].

WNT signaling is important in gut development and homeostasis, with Wingless-type MMTV integration site family member 2 (WNT2) being a pro-angiogenic factor in placental vasculature and increasing angiogenesis in endothelial cells. In a study conducted by Unterleuthner et al. [18], it was proven that WNT2, which is selectively increased in cancer-associated fibroblasts (CAFs), affects the migration and invasion of endothelial cells through the process of angiogenesis in colorectal cancer. CAFs secrete the cytokine Interleukin (IL)-33, which increases its number in patients with lymphatic metastases. Increased IL-33 and decreased stromal ST2 (IL-33 receptor) were associated with greater desmoplasia in left-sided colonic tumors [14]. IL-36, which is a family of IL-1 cytokines, has an effect on the colonic mucosa. Yang et al. [4] proved that IL-36γ does not regulate gene expression in the Wnt pathway but synergizes with Wnt3a to induce Wnt target genes in a protein synthesis-dependent manner. IL-36γ levels were positively correlated with extracellular matrix levels and -catenin levels in human colorectal tumor biopsies. This suggests an important role of IL-36γ and IL-36Ra in intestinal inflammation and tumorigenesis.

Another tumor microenvironment that plays a role in colorectal cancer is dendritic cells, which express chemokine ligand 1 (CXCL1). CXCL1 is a proinflammatory mediator of inflammatory and infectious diseases, widely initiating and causing exacerbation of tumor growth and progression of some cancers. Elevated CXCL1 was positively associated with cancer stage, metastasis, and poor life expectancy. CXCL1 not only affects cancer progression but is also responsible for resistance to some chemotherapy drugs [11]. Neutrophil infiltration coupled with TGFβ activation indicates T cell suppression in colorectal cancer through matrix metalloproteinases (MMPs). High T-cell infiltration in colorectal cancer is associated with better disease outcomes and immunotherapy response [19].

Cellular components that affect the tumor microenvironment are immune cells that secrete cytokines and ultimately affect invasion, progression, metastasis, and response to therapy. Micrometastases in colorectal cancer are often inoperable and resistant to chemotherapy. Targeted photothermal nanoparticles that can ablate micrometastases offer promise for detecting and treating small nodules [27].

CONCLUSIONS

The many components in the tumor microenvironment prove that colorectal cancer is a heterogeneous disease with many pathways from tumor development to metastasis. Research with 3D culture systems is beneficial to understand the various mechanisms of interaction between components of the tumor microenvironment to understand the process of colorectal cancer treatment. However, the search for articles obtained did not discuss much about the components of immune cells that also affect the treatment response and patient prognosis. Further studies need to be carried out to better understand the relationship between components in the tumor microenvironment, both in vitro and in vivo.

DECLARATIONS

Competing interest

The author(s) declare no competing interest in this study.

Ethics approval

There is no ethics approval for this study.

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