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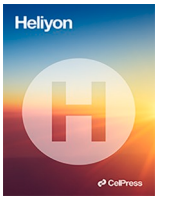

Review article

Cholesterol: The driving force behind the remodeling of tumor microenvironment in colorectal cancer

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ABSTRACT

Essential membrane components and metabolites with a wide range of biological roles are both produced by cholesterol metabolism. Cell-intrinsic and cell-extrinsic stimuli alter cholesterol metabolism in the tumor microenvironment (TME), which in turn encourages colorectal carcinogenesis. Metabolites produced from cholesterol play intricate roles in promoting the development of colorectal cancer (CRC) and stifling immunological responses. By altering the extracellular matrix of the main tumor, redesigning its immunological environment, and altering its mechanical stiffness, cholesterol can encourage the epithelial-mesenchymal transition of the primary tumor, opening up a pathway for tumor metastasis. Its functions in TME remodeling and tumor prevention have been recently identified. In this review we address the function of cholesterol in TME remodeling and therapeutic techniques designed to block cholesterol metabolism, and discuss how combining these strategies with already available anti-CRC medicines can have combined effects and open up new therapeutic avenues.

1. Introduction

In 2020 CRC accounted for 18 % of all cancer-related deaths and remained the second leading cause [1]. In 2040 there will likely be 28.4 million new instances of CRC worldwide, up 47 % from 2020 [2]. In the past few decades most research in the field of CRC has been focused on the tumor cells themselves. Bidirectional interactions between cancer cells and their surroundings, which result in remodeling of the tumor microenvironment (TME), are now understood to be essential for cancer growth and metastasis. Paracrine and juxtacrine signaling mediates and sustainably develops these linkages by secreting tumor-derived factors (TDFs) and tumor-derived exosomes [3]. Different strategies, including extracellular matrix (ECM) remodeling, metabolic reprogramming, immunosuppression, immune cell fatigue, and stromal cell activation can be used to establish TME remodeling, which facilitates the progression and

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distant colonization of tumor cells [3,4].

Cholesterol, a vital component of plasma and membrane lipids [5], supports tumor cells biomechanically and promotes their growth [6], invasion [7], metastasis [8], and drug resistance [9] by modulating TME remodeling. Although the idea of focusing on cholesterol metabolism to treat cancer has been the subject of extensive clinical research, the advantages are minimal, necessitating a thorough understanding of cholesterol metabolism in tumorigenesis and progression of CRC [10]. Emerging evidence suggests that cholesterol can modulate tumor biology by preventing tumor antigens from being identified by antigen presenting cells [11], reducing the manifestation of costimulatory and major histocompatibility complex class I components in dendritic cells [12], and impairing T cell antigen presentation. Fundamentally, cholesterol decreases the development of dendritic cells that invade tumors [13]. Cholesterol damages the T cell receptor's structure and lowers immunodetection during T cell priming and activation. Notably however, it also encourages T cell receptor clustering and relative signal transmission [14]. Lastly, cholesterol reduces granule-dependent cytotoxicity when T lymphocytes are killing cancer cells. Cholesterol and PGE2 can boost immunological checkpoint expression, increase the activity of immuneosuppressive cells, and encourage the release of immunosuppressive cytokines [15]. Erik et al. [16]reported that a reduced tumor response to endocrine treatments is a risk factor for colorectal cancers and hypercholesterolemia. More recently investigations have shown that cholesterol is one of the key regulators of TME remodeling in CRC.

In this review we summarize the most recent research on TME remodeling caused by cholesterol, with a focus on the role of several related derivatives, enzymes, and transcription factors in the initiation of CRC. We discuss potential cholesterol biomarkers for predicting metastases. Targeting cholesterol metabolism in the management and treatment of metastatic CRC is also discussed, as are potential ramifications and significant difficulties.

2. Various components involved in TME remodeling

The TME is an integral part of cancer. The concept of a complex tumor environment that supports tumor growth and metastatic dispersion has replaced the tumor cell-centered perspective of cancer development, as a result of the realization that the TME is fundamental to the evolution of cancer [17]. It is now widely acknowledged that stromal cells and the ECM, which together make up the main component of the TME, closely interact with cancer cells rather than acting independently [18]. Similarly, bone marrow-derived (stromal) cells are enlisted to create collections of purportedly normal tissue to form tumorigenic microenvironments (Table 1). There are two main ways that colorectalcancer cells can communicate with other cells and TME elements. One is through contact-dependent processes with other cells or the ECM, and the other is through contact-independent mechanisms via soluble

Table 1
Molecular and cellular components promoting TME remodeling.

TME-Remodeling Molecules		Cancer Type	Underlying Mechanisms	References
Tumor- derived	GM-CSF	PDA	Tumor cell-derived GM-CSF can orchestrate excessive Gr-1$^+$CD11b$^+$ imma ture myeloid cells	
	CCL21	melanoma	and CD8$^+$ T cells	[21]
	IL-25	melanoma	CCL21 and IL-25 can induce MDSCs to accumulate in the TME, thereby forming an in	[22]
	IL-1β	gastric cancer	flammatory microenvironment that is conducive to early tumor proliferation	[23,24]
	CCL2	gastric cancer	IL-1β, CCL2, and PGE_2 can attract adjacent peripheral fibers and neural pro genitor cells, which can guide cancer cell dissemination	[25]
	PGE_2		TGF-1 is more easily expressed when miR-142-3p and miR-506-3p are present	
	miR-142-3p	CRC		
	miR-506-3p			
Stroma- derived	Pdcd1	Melanoma	Increased protein geranylgeranylation induced by mevalonate metabolism is signaled by	[26]
	SREBP2	HCC	increased Pdcd1 expression in tumors, which is dependent on SREBP activity	[27]
	MMP8	CRC	In CD8$^+$ T cells SREBP2 signaling was more potent, resulting in more active cholesterol up	[28]
	MMP9	CRC	take that provides the building blocks for quicker proliferation	[29]
	CSF-1	lung cancer	MMP8 and MMP9 can induce VEGF production, promoting metastasis	[30]
	TLR2	LLC	CSF-1 signaling is originally used to draw macrophages to tumor locations	
	MyD88		TLR2 and MyD88 can promote cholesterol activity and an immunosuppres sive macro phage phenotype	
Lipid- derived	FABP5	Tregs	Loss of cristae structure and poor lipid metabolism are all signs of mitochon drial altera tions induced by FABP5	[31]
	XBP1	breast cancer	The endoplasmic reticulum stress sensor XBP1 can be activated by elevated cholesterol	[5]
	2B4	carcinoma	2B4 transcription can suppress CD8$^+$ T cell antitumor activity and transform the TME into an immunosuppressive phenotype	[32]
Cytokine- derived	CD36	CRC	CD36-mediated absorption of fatty acids reduces generation of cytotoxic cytokines and diminished antitumor activity	[44]
	TGF-β1	CRC	TGF-β1 expression can promote differentiation of N1 neutrophils into N2 neutrophils via the miR-142-3p/miR-506-3p-TGF-β1 axis.	[41]
	IFN	CRC	IFN-induced cholesterol 25-hydroxylase (CH25H) and type I interferon (IFN) receptor expression encourage CRC lung spread.	[38]

chemicals such as cytokines, lipid mediators, and growth factors [18,19]. This procedure encourages tumor cell invasion, survival, and growth within the TME [20].

2.1. Primary tumor-derived components

Soluble compounds released by primary tumors [33] and disseminated CTCs [34] are examples of components generated from primary tumors. TME reshaping depends on soluble chemicals called TDFs, which primary tumors secrete [35]. Numerous studies indicate that TDFs encourage TME remodeling by promoting immune evasion and cholesterol-induced macrophage induction. Cholesterol 25-hydroxylase (CH25H), a gene that controls the production of 25HC, is reportedly repressed by activating transcription factor-3 (ATF3) [36]. ATF3-CH25H axis stimulation of trogocytosis in intratumoral cytotoxic T lymphocytes reduced anti-tumor immunity, promoting tumor development. Moreover, in pancreatic ductal adenocarcinoma (PDA), tumor cell-derived granulocyte-macrophage colony-stimulating factor can induce excessive $Gr\text{-}1^{+}CD11b^{+}$ immature myeloid cells and $CD8^{+}$ T cells to assist in TME remodeling [33]. Similarly, melanoma cell secretion of CCL21 and IL-25 cause myeloid-derived suppressor cells (MDSCs) to accumulate in the TME, creating an inflammatory milieu that supports early tumor growth [37].

Primary tumor-derived extracellular vesicles (EVs) are crucial for TME reconstruction in CRC. For example, IFN-induced cholesterol 25-hydroxylase (CH25H) and type I interferon (IFN) receptor expression can be downregulated by CRC-secreted EVs in the TME, which encourages CRC lung spread [38]. The neurogenic switch, activated by tumor-derived EVs with a high abundance of IL-1β, CCL2, PGE_2, and other chemotactic factors, attracts adjacent peripheral fibers and neural progenitor cells that can guide cancer cell dissemination [39]. Through HMGB1/toll-like receptor (TLR) 4/NF-B signaling, EVs isolated from cancer cell cultures can activate neutrophils in a way that promotes tumor growth [40]. In colorectal cancer circPACRGL serves as a sponge for miR-142-3p/miR-506-3p, facilitating transforming growth factor (TGF) β1 expression, thus promoting colorectal cancer (CRC) cell proliferation, migration, and invasion—as well as differentiation of N1 neutrophils into N2 neutrophils via the miR-142-3p/miR-506-3p-TGF-β1 axis [41]. TME remodeling is also closely linked to the level of cholesterol in cancer cells. Abundance of cholesterol in the TME is strongly associated with tumor recurrence and metastasis. Oxysterols in the TME promote reciprocal changes in the LXR and sterol regulatory element-binding protein 2 (SREBP2) pathways, depleting T cells of cholesterol, resulting in abnormal metabolic and signaling pathways that induce T cell exhaustion and dysfunction [5]. In CRC, by encouraging the production and secretion of cholesterol, the unfolded protein response component X-box binding protein 1 (XBP1) activates myeloid-derived suppressor cells and compromises immunity [42].

2.2. Formation of an immunosuppressive microenvironment

Tumor-associated myeloid cells that have been recruited promote the development of an immunosuppressive microenvironment [43]. and reorganized host stromal cells [42]. Myeloid-derived suppressor cells can alter the expression of genes linked to lipid/cholesterol metabolism, endosomal sorting pathways, and cell cytoskeleton remodeling by activating NF-B/STAT1 and inhibiting STAT6. This promotes the colonization and growth of tumor cells as well as tumor metastasis. Regulatory T (Treg) cells are essential for immunological tolerance in melanoma and also stimulate immunosuppression in the TME [44]. Blocking SREBP or PD-1 signaling causes dysregulated PI3K activation in intratumoral Treg cells. Through a process dependent on SREBP activity, Treg cells in CRC display elevated production of programmed cell death protein 1, which further promotes protein geranylgeranylation fueled by mevalonate metabolism [45]. Yan et al. [10]reported an uneven distribution of cholesterol in intratumoral immune cells. They showed that $CD8^{+}$ T cells exhibited higher AKT-mTORC1-SREBP2 signaling, resulting in more active cholesterol uptake and more rapid proliferation of the cell's genetic material. Notably however, a low level of cholesterol may result in reduced survival and proliferation, as well as the initiation of autophagy [5,46]. Several investigations have revealed a unique, as yet uncharacterized poor-outcome immunomodulatory milieu in triplenegative breast tumors. This microenvironment includes stromal restriction of $CD8^{+}$ T cells, stromal expression of PD-L1, and enrichment for markers of cholesterol synthesis [47]. Thus, Treg cells may be key cellular components involved in TME remodeling.

An immunosuppressive TME and tumor immune escape can be caused by tumor-associated neutrophils (TANs) [48]. Activation of the catenin pathway within CRC cells has been shown to predominately exclude immune cell activation and produce a TME without neutrophil inflammation in in vivo tests, leading to the formation of an immunosuppressive microenvironment [49]. Wang and Johnson et al. [50,51] reported that TANs can alter the ECM by generating neutrophil elastase (NE), matrix metallopeptidase (MMP) 8 and MMP9, and vascular endothelial growth factor (VEGF), which promotes metastasis.

The most prevalent immune cells in the TME are tumor-associated macrophages. A number of cytokines such as C-C motif chemokine ligand 2 (CCL2), tumor necrosis factor, VEGF, C-X-C motif chemokine ligand 12 (CXCL12), and TGF [52] contribute to early recruitment of macrophages to sites of tumor formation [53]. In addition to soluble factors, a recent study found that tumor-derived exosomes (TDEs) metabolically rewire macrophages by interacting with TLR2, activating MyD88, initiating NF-B signaling, increasing cholesterol activity, producing more lactate, and polarizing them into an immunosuppressive phenotype [54].

2.3. Dysregulation of host lipid metabolism

Lipid metabolites make up the physiological host mesenchymal environment, including cholesterol, sphingolipid, phospholipid, and fatty acids, which are required for TME homeostasis. Tumor hypoxia initiates the metabolic reprogramming of fatty acid oxidation and increases free fatty acid (FFA) intake, which promotes the growth of CRC cells, thus supporting tumor invasion, antiangiogenic

drug resistance, and TME remodeling [55]. Inhibiting fatty acid binding protein 5 (FABP5) can cause mtDNA release and subsequent cGAS-STING-dependent type I IFN signaling, which increases production of the regulatory cytokine IL-10 and encourages Treg cell suppressive activity [56].

In CRC, elevated cholesterol can activate the endoplasmic reticulum stress sensor XBP1 and regulate PD-1 and 2B4 transcription, thereby suppressing $CD8^+$ T cell antitumor activity and transforming the TME into an immunosuppressive phenotype [5]. Faulty cholesterol efflux in epithelial progenitor cells controlled their transcriptional landscape, promoting growth and producing a pro-tolerogenic TME [57]. Similarly, in hematopoietic malignancies, increased cholesterol needs enable leukemic cells to proliferate at a rapid rate and create a TME suitable for tumor growth [58].

3. Accumulation and function of cholesterol in TME remodeling

3.1. Accumulation of cholesterol in the TME

Cholesterol accumulation is the initial stage of TME remodeling in CRC. Different elements derived from primary lesions and immunosuppressive cells can activate and upregulate the cholesterol production pathway. Because the messenger RNA levels of important genes encoding cholesterol synthesis proteins and transport routes are upregulated in colon carcinoma, while those of the cholesterol efflux pathway are downregulated, cholesterol builds up in cancer cells [59]. Ma et al. [5] reported that reduced generation of cytotoxic cytokines and diminished antitumor activity were the results of CD36-mediated absorption of fatty acids by tumor-infiltrating $CD8^+$ T cells in the TME. Lipid peroxidation and ferroptosis were also brought on by this process, which finally produced a microenvironment that was tumor-tolerant [5,44,60]. Moreover, high levels of cholesterol can promote the accumulation of MDSCs in host organs through the IRE1α-XBP1 pathway [42,61]. Goossens et al. [62]found that membrane-cholesterol efflux and the depletion of lipid rafts from macrophages are encouraged by ovarian cancer cells. By enhancing cholesterol efflux and IL-4-mediated reprogramming, which involves suppressing IFN-induced gene expression, the tumor-growth-promoting effects of tumor-associated macrophages can be countered. The actions of TAMs that promote tumor growth are reversed and tumor progression is decreased by genetic deletion of ABC transporters, which facilitate cholesterol efflux. Lipid rafts, which are membrane microdomains rich in cholesterol, may prevent the destruction of the matrix caused by invadopodia in order to direct the distant colonization of cancer cells. This slows the propagation of tumors [62,63].

In addition to immune cells, transcription factors can also activate the cholesterol synthesis pathway in primary lesions [64]. Gu et al. [65] reported that in glioblastoma (GBM) tumor cores, as opposed to invasive tumor margins, cholesterol biosynthesis enzymes were expressed at higher quantities. SREBP2 enhanced CRC stem cell proliferation, self-renewal, and tumor growth, especially in starving circumstances.It's interesting to note that a different research team studying GBM came to the conclusion that the IDH mutation affects the proliferation and invasion of cancer cells by acting as a unique post-transcriptional regulator of cholesterol uptake mediated by the miR∼19a/LDLR axis [66,67]. Thus, transcription factors are crucial to TME remodeling.

TDFs and tumor-derived EVs contribute to the cholesterol synthesis pathway. For example,The ATF3 transcription factor CH25H can be activated and cholesterol 25hydroxylase can be increased by stimuli emanating from the TME. CH25H upregulation is linked to CRC progression and tumor growth in antigen-presenting cells isolated from human colorectum tumors [12,36,68]. EVs with an abundance of cholesterol can also assist in remodeling the TME. Keeping CD8 alpha-negative dendritic cells from being activated by toll-like receptors and preventing a protective Th1 type response promotes the growth of an immunosuppressive environment [69].

3.2. ECM remodeling

The ECM is a complex network of macromolecules secreted from cells, including glycoproteins, enzymes, and collagen [70]. It gives cancer cells and tissues structural and biochemical support [71]. The primary building block of the tumor matrix and an important player in ECM remodeling is cholesterol. Lipid biosynthesis and adipogenesis are regulated by the SREBP family of transcription factors, which also controls the expression of many enzymes needed for cholesterol production [65,72]. A recent study has demonstrated that in CRC,the energy sensor AMPK upregulates SREBP1 activation, promoting the production of cholesterol, evidently triggering ECM rigidity and affecting physiological and pathophysiological procedures such as tissue fibrosis and mesenchymal stem cell differentiation [73].

Bone morphogenetic protein and activin membrane bound inhibitor, a TGF pseudoreceptor, is downregulated in response to TGF-induced activation through stimulation of TLR4 [74,75]. In primary malignancies such as those of the colon [76], lung [77], and breast [78], ECM remodeling is conducive to epithelial-mesenchymal transition (EMT) or migration of tumor cells. A fluid-phase absorption mechanism mediated by the cholesterol-dependent pathway enables internalization and degradation of extracellular protein by cells expressing oncogenic RAS, which accelerates the cell cycle and/or suppresses cell death regulated by ECM, leading to uncontrolled cancer expansion [79,80]. ECM protein 1 (ECM1) expression was positively correlated with hypercholesterolemia of triple-negative breast cancer cells, enhancing ECM stiffness in the TME [81]. It is interesting that various studies have emphasized how MMPs affect control of the ECM and cholesterol homeostasis [82]. For example, by degrading cholesterol, MMP2 and MMP9 can facilitate the invasion of CRC cells into the basement membrane, leading to tumor spread and diffusion [83].

3.3. Immunosuppression and angiogenesis

When it comes to the establishment of an immunosuppressive TME in CRC, cholesterol is essential. Depending on the circumstance,

cholesterol can help tumor cells avoid immune surveillance by interacting with different kinds of immune cells [84]. For example, in a mouse CRC model,cholesterol caused $CD8^+$ T cell "exhaustion" [5,10]. Furthermore, by inhibiting TCR phosphorylation and restricting TCR allosteric transitions in human $CD4^+$ Jurkat T cells, cholesterol and its metabolites can adversely affect TCR signaling [85], thus suppressing T cell infiltration into the TME. MHC class I chain-related protein A expression on human CRC cell lines can be reduced by cholesterol in NK cells, shielding them from being targeted by NK cells, thus providing an immunosuppressive microenvironment for melanoma cells [86]. Furthermore, mTORC1-induced cholesterol accumulation through SREBP activation encourages myeloid cell differentiation into MDSC [87].

Cholesterol encourages angiogenesis [88], which facilitates colorectal tumor growth. Local cholesterol is important for promoting angiogenesis in the TME. Researchers reported that apoA-I binding protein affects VEGFR2 dimerization and accelerates cholesterol efflux from endothelial cells to high-density lipoprotein (HDL), thereby promoting VEGF-induced angiogenesis [89]. Older macrophages have a polarized phenotype that is abnormally alternately activated and promotes pathologic vascular development when intracellular cholesterol is increased, indicating that it could be an effective therapeutic target [90]. Activated cholesterol synthesis induced by tumor-derived C-X-C motif chemokines is also involved in angiogenesis and TME reconstruction [91].

3.4. *Metabolism reprogramming*

Cholesterol homeostatic imbalance is responsible for TME remodeling. Enzymes [92], derivatives [93], and transcription factors [72,94] involved in cholesterol metabolic pathways all regulate metabolic TME [95] reprogramming in CRC. Squalene monooxygenase, or squalene epoxidase (SQLE), is an enzyme that controls the rate at which cholesterol is produced [96,97]. Several studies have reported that the N-terminal 100 amino acids of SQLE can be ubiquitinated by MARCHF6, causing proteasomal degradation. This enables tumor cells to proliferate through the production of migratory cancer stem cells, senescence bypass, anoikis resistance, and EMT [98,99]. Additionally, cholesterol accumulation that reduces SQLE promotes p53 breakdown and catenin activation, which ultimately speeds up TME remodeling and tumor progression in colorectal cancer (CRC) by inhibiting GSK3, which in turn leads p53 to dissociate from it and upregulate MDM2 [99]. Similar findings were made by another team, which stated that SQLE encourages the conversion of squalene to 2,3oxidosqualene in the cholesterol synthesis pathway and that its absence results in an accumulation of the upstream metabolite squalene. This process modifies the cellular lipid profile and prevents ferroptotic cell death in cancer cells, giving them an advantage during oxidative stress and in tumor xenografts [100].

As well as enzymes, related derivatives are involved in TME remodeling. In breast cancer, ER and the liver X receptor (LXR) ligand 27-hydroxycholesterol, a major metabolite of cholesterol, promotes ER-dependent proliferation and LXR-dependent metastasis [8]. Recent studies suggest that 27-hydroxycholesterol may play a pro-metastatic role by inducing immune reprogramming [101]. Baek and his colleagues showed that this oxysterol promotes an immunologically suppressive milieu by increasing the number of polymorphonuclear-neutrophils and γδ T cells at distal metastatic sites. Myeloid immune cell activity is required for the potent

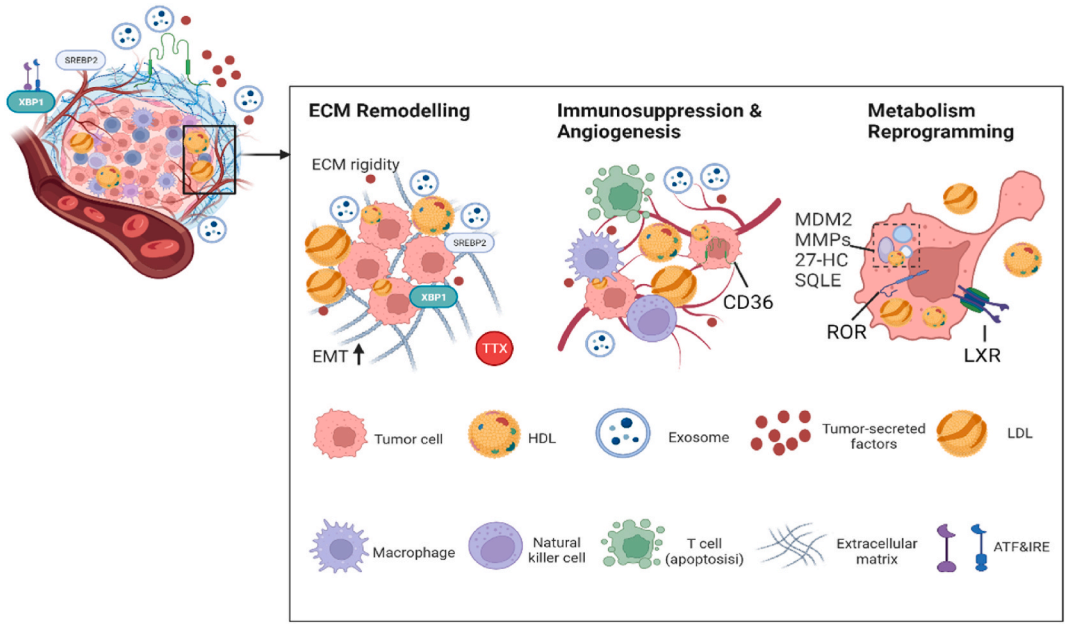

Fig. 1. Function of cholesterol in tumor microenvironment remodeling.Cholesterol derived from tumor cells or ingested externally can help tumor cells escape immune surveillance. In primary lesions cholesterol interacts with other cells such as T cells and NK cells, remodeling the tumor microenvironment (TME), increasing the survival of cancer cells. Cholesterol reshapes the TME through extracellular matrix remodeling, immunosuppression, angiogenesis, and metabolism reprogramming.ECM, extracellular matrix; EMT, epithelial-mesenchymal transition.

anti-metastatic effects of 27-hydroxycholesterol [7].

In recent years growing numbers of researchers have focused on transcription factors and related receptors involved in the cholesterol metabolic pathway. For example, via the downregulation of LXR and HIVEP2, YTHDF2 promotes carcinogenesis in GBM cells and prevents LXR-dependent cholesterol homeostasis in GBM cells by activating the EGFR/SRC/ERK pathway [102]. Another team investigating CRC reported that with promotion of cholesterol manufacture in the tumor core and absorption in the margin, the transcription factor SREBP2 exhibited context-specific regulation of cholesterol biology based on its availability in the microenvironment [65]. In triple-negative breast cancer and CRC, nuclear receptor RORγ increases the tumor cholesterol synthesis rate and total tumor cholesterol content, while disrupting host cholesterol homeostasis. Cai et al. [103] demonstrated that RORγ interacts with SREBP2 and promotes chromatin acetylation at the locations of the genes responsible for cholesterol production, which advances tumors. p53, a well-known tumor suppressor gene, exerts anti-tumor effects by inhibiting cholesterol synthesis. Moon et al. [104] reported that p53 inhibits the mevalonate pathway and prevents SREBP-2 activation by transcriptionally activating the ABCA1 cholesterol transporter gene.

Recent research indicates that cholesterol influences EMT/mesenchymal transition, which in turn increases TME remodeling (MMT). In CRC cancer stem cells (CSCs), ZMYND8, a master transcriptional regulator of 27-HC metabolism, promotes EMT, oncogenic transformation, and tumor initiation by activating liver X receptor while decreasing 27-HC catabolism. This results in an accumulation of 27-HC in CSCs, and increases cholesterol biosynthesis and oxidation while decreasing 27-HC efflux [105]. Moreover, statins and NAD (P) dependent steroid dehydrogenase-like gene loss activate SREBP1, which promotes TGF-β1 expression and facilitates epithelial-mesenchymal transition [106]. Cholesterol has significant functions in TME remodeling, promotion of tumor incidence, and growth of the main lesion. It is necessary to conduct more research on the functions of cholesterol in ECM, metabolic reprogramming, immunosuppression, and angiogenesis in TME reshaping (Fig. 1).

4. Cholesterol-related CRC biomarkers and therapeutic strategies

4.1. Finding cholesterol-related biomarkers to predict metastasis

Studies investigating the influences of particular cholesterol subtypes on tumor progression have become more prevalent as metabolomics techniques have advanced [107]. Modern studies are no longer limited to the conventional cholesterol classifications "HDL" and "LDL." Various malignancies, organs, and even different regions of the same organ have different cholesterol characteristics. Cholesterol and associated indicators can be used as therapeutic targets or biomarkers.

A range of cholesterol-related indicators in the initial tumor are reportedly strongly associated with tumor growth and metastasis by metabolomics and other multi-omics studies. According to Mihajlovic et al. [108], colorectal cancer incidence is affected by the activity of PON1 and lactonase (LACT), two of cholesterol's primary antioxidant components. This in turn causes a drop in HDL cholesterol concentration. In CRC, increased cholesterol inhibits expression of the scavenger receptor class B type 1 (SR-B1) in mitochondria, which prevents the mitochondria from inducing apoptosis [109]. In her2-positive heterogeneous gastric cancer, levels of CAV1 tumoral protein, a significant protein of cholesterol-rich membrane domains, were reportedly negatively correlated with TDM1 tumor uptake, causing limited trastuzumab benefit and poor patient survival [110]. Similarly recombinant HDL, a drug delivery nanoparticle that is currently being used to deliver small-molecule drugs, siRNAs, therapeutic proteins, and vaccine antigens, can be created from HDL via a processing step. Recent years have seen a significant increase in studies investigating the use of recombinant HDL and SR-B1 for the treatment of CRC [111].

In addition to HDL, recent studies have also revealed that some derivatives and receptors that maintain cholesterol homeostasis may help to improve CRC prevention and treatment [7]. For example, Noguchi et al. [112] discovered that inducing an adaptive response by activating the liver X receptor signaling system, 24S-OHC reportedly protects neuronal cells from malignant growth at sublethal dosages. Furthermore, the primary protein of HDL, apolipoprotein A-I, is a versatile protein that regulates inflammation and the immune system as well as cholesterol traffic. It might be a valuable biomarker that aids earlier CRC diagnosis, follow-up, and prognostic stratification in cancer patients as well as improved estimation of cancer risk [113]. Zeng et al. [114]found that the sigma-2 receptor TMEM97 has already been created and validated as a PET imaging biomarker of tumor proliferative status, and as a predictor of the effectiveness of cancer therapy. Sterol depletion and SREBP expression levels, among other cholesterol-regulating cues, control the expression of TMEM97. Understanding the several types of cholesterol-related indicators found in CRC and their properties and effects on TME remodeling will be crucial for developing new therapeutic approaches for the prevention of CRC.

TDFs and EVs with high cholesterol abundances have drawn a lot of interest. Potential biomarkers for primary and metastatic CRC include TDFs and EVs with elevated cholesterol concentrations in the TME or metastatic locations. For example, in CRC TEV reduced expression of the IFN-inducible cholesterol 25-hydroxylase and type I interferon (IFN) receptor (CH25H). A worse prognosis was associated with low CH25H levels in leukocytes from CRC patients [115]. In CRC, early-onset mammalian immune surveillance mechanisms can become "blind" to a growing cancer and lose their capacity to recognize and launch measures to eradicate a tumor due to the formation of cholesterol-enriched pmEV [34].

4.2. Targeting cholesterol for CRC therapy

Cholesterol is a prospective therapeutic target for CRC therapies due to its protumor activities. Cholesterol tumors are challenging to target due to the absence of distinct tumor markers. The following list describes the alternatives for current anti-cholesterol therapy in main tumor locations and metastases.

The mechanical tension in the membranes of cancer cells is changed. A novel approach to controlling cell membrane tension offers a possible course of action for cancer treatment. One study describes how cholesterol oxidase (COD) increases cell membrane tension in vitro by depleting cholesterol and how Hf-TBP/COD, a COD-functionalized nanoscale metal-organic framework, is designed to deplete cholesterol and regulate tumor mechanogenesis in vivo. It has been discovered that COD reduces cholesterol and modifies the mechanical characteristics of lipid bilayers, which inhibits cell motility, proliferation, and oxidative stress tolerance. Hf-TBP/COD increases mechanical tension of plasma membranes and osmotic fragility of cancer cells, which induces influx of zinc ions, inhibits cell migration, increases rupturing propensity for effective caspase-1 mediated pyroptosis, and decreases tolerance to oxidative stress. In a subcutaneous colon cancer model, Hf-TBP/COD increases anti-tumor immune response and tumor growth inhibition from 79.8 % to 95 % when compared to Hf-TBP alone [115,116].

Cholesterol primarily aids CRC cell survival and proliferation, and the development of medication resistance in primary tumors. In CRC patients, overexpression of transcriptional coactivator with PDZ-binding motif (TAZ) is closely associated with poor survival. However, it was demonstrated that cholesterol synthesis restricted TAZ expression in CRC by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, farnesyl pyrophosphate synthase, farnesyl-diphosphate farnesyltransferase 1, or sterol regulatory element-binding protein 2. The mevalonate-cholesterol-TAZ-TEAD2-Anln/Kif23 pathway has been identified as a novel tumor-specific target for CRC treatment in the past investigation. A combination of statins and immune checkpoint inhibitors greatly reduced tumor development, despite statins' moderate therapeutic effects on this pathway's blockage [116]. Additionally, discoveries made by Yan et al. [10]have intriguing therapeutic ramifications. It may be possible to develop methods that successfully stop cancer cells from synthesizing cholesterol while maintaining the availability of cholesterol in lymphocytes. Conversely newly created LXR-inverse agonists, which have previously been demonstrated to improve $CD8^+$ T cell activity in preclinical models, may offer therapeutic promise in the future [117]. Given these encouraging findings, a more thorough analysis of regulating cholesterol metabolism to enhance chimeric antigen receptor T-Cell immunotherapy is unquestionably required.

In metastases, high cholesterol levels are more likely to promote immunosuppressive cells, stimulate angiogenesis, and create favorable ECM conditions and immunosuppressive environments for the colonization and proliferation of CRC cells. There may be a "tipping point" whereby metastases starts with cholesterol buildup. In a subcutaneous inoculation mouse model, Uchida et al. [118] used polyplex nanomicelles with a cholesterol moiety to treat metastatic CRC via the delivery of mRNA encoding an anti-angiogenic protein (sFlt-1). PEG-PAsp(TEP)-Chol nanomicelles, as opposed to those without Chol, effectively synthesized protein from that mRNA in tumor tissue, leading to a detectable decrease in tumor growth [119]. Further research is needed to identify more precise molecular targets that affect cholesterol signals and effectors in CRC. Moreover, traditional regimens' combinatorial methods with anti-cholesterol treatments need to be investigated.

5. Conclusions and perspective

The rate at which CRC develops is mostly determined by how invasive the tumor cells are, as well as by a number of other factors. The intricate molecular mechanisms enabling TME reconfiguration have recently been the subject of increased study. Developments have improved CRC diagnosis techniques and our understanding of the mechanisms underlying tumor spread, laying the groundwork for viable treatment plans. In order for tumor cells to attach, live, and multiply at primary and metastatic sites, as well as to drive tumor spread, the TME must interact with host stromal cells and cholesterol. With an emphasis on TDFs and EVs, more study has been done in recent years on cholesterol in primary lesions and at metastatic sites. Notably however, a number of questions about the origin, purpose, dynamics, and importance of the TME remain unanswered. For the prevention and treatment of metastatic CRC, a deeper comprehension of the mechanisms underpinning cholesterol driving TME remodeling, and the discovery of its effects on CRC metastasis will be extremely beneficial.

CRediT authorship contribution statement

Ke Wang: Writing – original draft. **Yuanyuan Zhang:** Writing – review & editing, Writing – original draft. **Chengshuai Si:** Supervision. **Yuepeng Cao:** Supervision, Funding acquisition. **Peng Shao:** Validation. **Pei Zhang:** Validation, Supervision. **Nannan Wang:** Visualization, Validation. **Guoqing Su:** Writing – original draft. **Jinghang Qian:** Writing – original draft. **Liu Yang:** Validation, Supervision.

Ethics approval and consent to participate

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CRC	colorectal cancer
TME	tumor microenvironment
TDFs	tumor-derived factors
ECM	extracellular matrix
GM-CSF	granulocyte-macrophage colony-stimulating factor
CCL	chemotactic ligand
PGE2	prostaglandin E2
Pdcd1	programmed cell death protein 1
SREBP2	Sterol Regulatory Element-Binding Protein 2
FABP5	fatty acid-binding protein 5
XBP1	X-box binding protein-1
HCC	hepatocellular carcinoma
PDA	Pancreatic Ductal Adenocarcinoma
EMT	epithelial-mesenchymal transition
CH25H	cholesterol 25-hydroxylase

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