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REVIEW

Cholesterol-Mediated Remodelling of the Tumour-Immune Landscape: The Role of Non-Coding RNAs

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ABSTRACT: Non-coding RNAs (ncRNAs) and cholesterol metabolism have independently been recognized as critical regulators of cancer progression. NcRNAs modulate various aspects of cancer cell behaviour, including metabolic reprogramming, proliferation, migration, and intercellular communication. Concurrently, dysregulated cholesterol metabolism has emerged as a hallmark of cancer, influencing tumour growth, immune evasion, chemoresistance, and metastasis. While numerous studies have explored the role of ncRNAs like long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in modulating cholesterol metabolism within either cancer cells or immune cells, the mechanism of their action largely depends on the involvement of microRNAs (miRNAs). However, the bidirectional metabolic crosstalk between cancer and immune cells involving miRNAs remains poorly understood. This review consolidates current knowledge on the participation of miRNAs in the dysregulation of cholesterol metabolism in both cancer and immune cells within the tumour microenvironment (TME). In particular, we focus on how intercellular communication involving miRNAs drives metabolic changes that contribute to immune cell reprogramming and the remodelling of the tumour-immune landscape. We further discuss the roles of cholesterol metabolites in facilitating such intercellular communication. By addressing this underexplored intersection, we aim to highlight potential miRNA targets and pathways that could inform future cancer immunotherapy strategies.

KEYWORDS: Cholesterol; tumour microenvironment; non-coding RNAs; tumour-associated macrophages; microRNAs; cancer; immunometabolism

1 Introduction

Cancer development occurs in constant interaction with the host immune system, which plays a critical role in recognising and eliminating transformed cells at early stages of tumorigenesis in a process described as cancer immunosurveillance. It reflects the capacity of immune cells to detect and restrain uncontrolled cell growth before clinically apparent disease emerges [1,2]. Cancer immunosurveillance consists of the cooperation between both the innate and the adaptive immunity in eliminating developing tumour cells. Various effector molecules and cells of the immune system, such as perforin, interferon-gamma (IFN-γ), Cluster of Differentiation 8^+ ($CD8^+$) T cells, and natural killer (NK) cells, work together to eliminate tumour cells before the tumour growth goes unhindered [3]. However, the surveillance role of the immune system against tumours is often compromised as cancer progresses. Tumours evolve to employ various mechanisms to hijack immune cells to work in favour of the tumour, forming an intricate immunosuppressive network

that advances the unrestricted growth of the tumour rather than suppressing it while simultaneously creating barriers to effective immune surveillance [4,5].

This intricate immunosuppressive network is maintained through the dynamic interactions between cancer cells and immune cells. Cancer-derived factors suppress immune responses, such as the recognition and elimination of cancer cells by NK cells and $CD8^+$ T cells, while immune cells release cytokines and growth factors such as interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) that promote immunosuppression and tumour growth [6–8]. The plasticity of immune cells is leveraged by cancer cells to induce nearby immune cells to adopt a pro-tumourigenic phenotype, as seen in the highly adaptable tumour-associated macrophages (TAMs). TAMs have been demonstrated to be influenced by cancer-derived factors in adopting a pro-tumourigenic role in multiple cancer types [9–11]. Cancer cells also evolve to express immune checkpoint molecules like Programmed Death-Ligand 1 (PD-L1), which inhibit T cell activation while also recruiting immunosuppressive immune cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that dampen immune responses to facilitate immune evasion [8,12].

Meanwhile, the widely elucidated mechanisms behind failed immunosurveillance in tumourigenesis also implicate the role of altered metabolic pathways in the immune-tumour cell crosstalk [13]. It is well established that cancer cells undergo metabolic reprogramming to facilitate the elevated proliferation rate necessary for tumour progression. This includes increased demand for glucose, glutamine, or lipid synthesis, upregulation of the pentose phosphate pathway (PPP), and altered mitochondrial function, as well as the dysregulation of cholesterol metabolism [14,15]. Cholesterol plays a critical role in supporting the uncontrolled growth of tumour cells, particularly by meeting the increased membrane synthesis demands associated with tumour progression [16]. Besides the plasma membrane, a high cholesterol content is needed for the synthesis of important structural components such as lipid rafts, the nuclear membrane, the Golgi apparatus, and lipid droplets. Cholesterol derivatives such as oxysterols and steroid hormones also fuel the proliferation and metastasis of tumour cells [17,18]. Besides serving as platforms for signal transduction in cancer cells, lipid rafts are also important domains of immune signalling, directly impacting immune cell function in both the innate and adaptive immunity [19].

Studies have shown that dysregulated cholesterol metabolism is pivotal to tumour progression by compromising the anti-tumourigenic activities of immune cells in the tumour microenvironment (TME), leading to the exhaustion of $CD8^+$ T cells and the polarisation of TAMs towards a pro-tumourigenic phenotype [20,21]. Perturbations in intracellular cholesterol content have also been shown to jeopardize immune effector functions of B cells and T cells, specifically by reducing their cell proliferation [22,23].

Cholesterol levels are regulated via the modulation of cholesterogenic genes at the transcriptional stage and the post-transcriptional stage through transcription factors and non-coding RNAs (ncRNAs) respectively. NcRNAs, encompassing microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), have emerged as key post-transcriptional regulators in cancer biology [24]. Beyond their established roles in oncogenic signalling and cell cycle regulation, ncRNAs are increasingly recognized for their ability to modulate cancer immunometabolism, particularly through the regulation of cholesterol homeostasis [25]. Among the diverse classes of ncRNAs, miRNAs have emerged as potent regulators of immunometabolic pathways due to their direct and often conserved interactions with target messenger RNA (mRNA) [26,27].

This review synthesizes recent advances in cancer immunometabolism, with a focus on ncRNAs mediating cholesterol metabolism perturbations in tumour-immune interactions. While current reviews have addressed the separate roles of ncRNAs and cholesterol metabolism in cancer progression and in

immune cell reprogramming, there remains a need for an integrated perspective of ncRNAs and cholesterol metabolism involved in the cancer-immune cell crosstalk. As cholesterol metabolism and signalling pathways crucial to tumourigenesis are intertwined, the interactions between the cholesterol metabolic pathway and oncogenic signal transduction pathways are also described to provide novel rationales for the development of future ncRNA-based therapeutics that target cancer cholesterol metabolism.

2 Altered Cholesterol Metabolism in Cancer

Dysregulated cholesterol metabolism is a key factor in cancer development and progression, contributing to membrane biogenesis, modulation of signalling pathways, and promotion of drug resistance in cancer cells [28]. For instance, the involvement of lipid rafts in cancer signalling and progression has been particularly emphasized in prostate cancer [29].

2.1 Enhanced Cholesterol Uptake

Owing to its primary localization in the intestine and role in intestinal cholesterol absorption, upregulation of Niemann-Pick C1 Like 1 (NPC1L1) is positively correlated with the development, pathological stage, and prognosis of colorectal cancer (CRC) [30]. Interestingly, some studies suggest that NPC1L1 might be overexpressed in certain cancer cell types outside of the intestine, such as pancreatic, breast, and ovarian cancers [31,32]. If present and functional in cancer cells, NPC1L1 could contribute to increased cholesterol uptake, potentially contributing to the effects mentioned earlier (membrane biogenesis, signalling modulation, etc.). Indeed, inhibition of NPC1L1 with ezetimibe and NPC1L1 knockdown resulted in significant perturbations in the growth of pancreatic ductal adenocarcinoma (PDAC) cells and breast cancer cells and was thus suggested as a viable therapeutic target [31,33]. In breast and ovarian cancer models, it was demonstrated that NPC1L1 plays a key role in directing the metabolic shift from cholesterol biosynthesis to cholesterol uptake in order to focus energy resources on invasion [32].

A comprehensive review of several preclinical and clinical studies highlighted a positive correlation between low-density lipoprotein receptor (LDLR) upregulation and cancer progression due to increased cholesterol uptake from the blood in various cancers, such as colon cancer, breast cancer, prostate cancer, pancreatic adenocarcinoma, chronic lymphocytic leukaemia, and ovarian cancer [34]. For instance, breast cancer cells, particularly triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancers, showed upregulated levels of LDLRs to enhance the uptake of exogenous cholesterol in the form of low-density lipoprotein cholesterol (LDL-C) to support tumour proliferation in a mouse model of hyperlipidemia [35]. Blocking low-density lipoprotein (LDL) binding to LDLRs abrogated the effects of a high-cholesterol diet on increased intravasation observed in breast cancer [36]. Increased LDLR was also found to be correlated with decreased recurrence-free survival in the context of breast cancer [35]. Additionally, cholesterol uptake was implicated in liver metastasis of CRC through the Ephrin-B2/Ephrin type-B receptor 4 (EFNB2/EPHB4) axis, which enhances LDLR-mediated cholesterol uptake [37].

On the other hand, scavenger receptor class B type 1 (SR-B1) has been demonstrated to be upregulated in prostate cancer and glioblastoma, where it is essential for high-density lipoprotein (HDL)-mediated cell proliferation and disease progression [38,39]. Meanwhile, SR-B1 deficiency lowered LDLR expression and improved the immunity of the TME in colitis-induced CRC by reducing the levels of TAMs and MDSCs as well as the expression of PD-L1, indicating the role of SR-B1 in cancer progression and its potential as an immunotherapeutic target [40].

2.2 Dysregulated Cholesterol Efflux

Dysregulated cholesterol efflux, primarily mediated by the transporter ATP-binding cassette subfamily A member 1 (ABCA1), plays a pivotal and highly context-dependent role in the progression of various malignancies. In certain cancers, such as lung adenocarcinoma (LUAD), prostate cancer, and colon cancer, a significant decrease in ABCA1 expression functions as a driver of tumorigenesis [41–43]. In KRAS-driven LUAD, impaired cholesterol efflux in epithelial tumor progenitor cells is a hallmark that promotes cell proliferation and the creation of a pro-tumorigenic TME [41]. Similarly, in prostate cancer, the loss of ABCA1 due to promoter hypermethylation leads to the accumulation of intracellular cholesterol, which stabilizes lipid rafts and enhances protein kinase B (Akt) signaling, thereby facilitating tumor progression [42]. In colon cancer, oncogenic mutations that suppress ABCA1 allow elevated mitochondrial cholesterol levels, which inhibit the release of cell death-promoting molecules like cytochrome c, providing the cancer cells with a critical survival advantage [43].

Conversely, in other contexts, an increase in ABCA1 expression is a key contributor to cancer progression and metastasis. In TNBC and gastric adenocarcinoma (GAC), ABCA1 is frequently upregulated and serves as a marker for high histological grade and poor survival [44,45]. In endometrial cancer (EC), the nicotinamide N-methyltransferase (NNMT)-ABCA1 axis induces lipid reprogramming where increased cholesterol efflux enhances membrane fluidity, which in turn activates epithelial-mesenchymal transition (EMT) and promotes invasive capacity [46]. Furthermore, elevated ABCA1 expression in GAC and glioma is associated with a distinct immune evasion strategy, specifically by promoting the infiltration of M2 macrophages and enhancing resistance to chemotherapeutic agents like cisplatin and temozolomide [44,47]. In these scenarios, the high-level expression of ABCA1 allows tumor cells to manipulate lipid dynamics to favor survival and dissemination [41,44,47].

Dysregulated cholesterol efflux is often a survival mechanism used by cancer cells to maintain a delicate cholesterol homeostasis in lipid-rich environments. In epithelial ovarian cancer (EOC), cells frequently spread to the cholesterol-rich omentum, where excessive intracellular cholesterol can become cytotoxic [48]. High expression of ABCA1 in serous EOC acts as a vital “safety valve”, exporting excess cholesterol to prevent apoptosis while enabling rapid growth and motility [48]. A similar requirement for efflux is observed in lymphoma, where the inhibition of cholesterol export mechanisms lead to toxic free cholesterol accumulation, inducing endoplasmic reticulum (ER) stress and subsequent cell death [49]. Collectively, these findings highlight that while ABCA1 deficiency can initiate transformation by enabling oncogenic signaling and survival, ABCA1 overexpression often supports the later stages of progression, such as chemoresistance, metastasis, and immune escape, depending on the specific metabolic demands of the tumor type [43,44,48].

2.3 Enhanced Cholesterol Biosynthesis

The dysregulation in cholesterol biosynthesis preceding the accumulation of intracellular cholesterol promotes tumour metastasis and proliferation and facilitates chemoresistance [50–52]. In oestrogen receptor alpha (ERα)-positive breast cancer, upregulated cholesterol biosynthesis indirectly increased levels of 27-hydroxycholesterol (27-HC), a main metabolite of cholesterol and a ligand of ERα thereby activating oestrogen receptor signalling and promoting invasiveness [53]. Though it has been implied that cholesterol *de novo* biosynthesis requires more energy than cholesterol uptake and that cancer cells prefer the latter, there are conflicting suggestions that intracellular cholesterol derived from *de novo* biosynthesis within cancer cells plays a more substantial role in promoting cancer proliferation compared to dietary cholesterol

uptake [32,54]. This is attributed to the upregulation of cholesterol biosynthesis in cancer cells via several intrinsic cancer growth signalling pathways, such as the Akt and p53 signalling pathways [54].

Specifically, phosphoinositide 3-kinase/Akt/mammalian target of rapamycin complex 1 (PI3K/Akt/mTORC1) signalling activates SREBP, a key transcriptional regulator of cholesterol biosynthesis, leading to increased cholesterol synthesis [55]. This pathway enhances cholesterol import through upregulation of LDLR expression and simultaneously inhibits cholesterol efflux by downregulating ABCA1 expression. Consequently, this concerted action results in elevated intracellular cholesterol levels, which have been demonstrated to contribute to increased cancer aggressiveness and metastasis in prostate cancer [56,57]. In hepatocellular carcinoma (HCC), where LDLR downregulation represents a negative prognostic factor, perturbations to the supply of intracellular cholesterol were circumvented through the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) signalling pathway, which saw an increase in *de novo* cholesterol biosynthesis, ultimately contributing to HCC malignancy [58].

Farnesyl-diphosphate farnesyltransferase 1 (FDFT1), which encodes squalene synthase, is also the first committed enzyme in cholesterol biosynthesis and thus plays a pivotal role in cancer biology. In several malignancies, including colon carcinoma, HCC, and tongue squamous cell carcinoma, FDFT1 has been implicated as a tumour promoter [59–61]. In contrast, FDFT1 functions as a tumour suppressor in cancers such as gastric cancer (GC) and kidney renal clear cell carcinoma [62,63]. In ovarian cancer, FDFT1 exhibits context dependency, acting as a tumour suppressor in bulk tumour cells by restraining proliferation and invasion, while promoting tumour progression in stem-like and metastatic cell populations through sustained mevalonate pathway activity [64,65]. While it is generally upregulated in basal tumour cells of bladder cancer, FDFT1 expression is lower in cisplatin-resistant bladder cancer cells compared to cisplatin-sensitive cells, which suggests the role of this cholesterogenic gene in chemoresistance [66,67]. Metabolite profiling has evidenced the upregulation of metabolites related to FDFT1 activity, such as squalene, cholesterol, and cholesteryl esters in cisplatin-sensitive bladder cancer tissue compared to their cisplatin-resistant counterpart, making FDFT1 a valuable modulator and biomarker in determining cisplatin sensitivity in bladder cancer [68].

2.4 Enhanced Cholesterol Storage

Cholesterol storage in the form of lipid droplets for energy activates oncogenic signalling pathways and modulates the TME as well as key cholesterol homeostasis regulators, which promotes cancer progression [69,70]. A prior study demonstrated that the abnormal accumulation of esterified cholesterol in high-grade prostate cancer was mediated by the loss of phosphatase and tensin homolog (PTEN), a tumour suppressor, which leads to the activation of the PI3K/Akt/mTOR pathway. This, in turn, upregulates the expression of SREBP and LDLR, ultimately promoting ACAT1-mediated cholesterol storage within lipid droplets [71].

As free cholesterol accrued within the cytoplasm of cells is cytotoxic, strategies to inhibit the conversion of free cholesterol into cholesteryl esters (CE) for storage possess anti-tumour potential. CE-derived vacuoles are often seen in high-grade lymphomas, and inhibition of the main enzyme involved in cholesterol esterification, ACAT1, in combination with the SR-B1 inhibitor, was seen to attenuate cell proliferation in lymphoma cell lines by apoptosis induced by ER stress due to the accumulation of intracellular free cholesterol [49]. The role of dysregulated cholesterol metabolism and its contributing genes in various cancers is summarised in Table 1.

Table 1: Dysregulated cholesterol metabolism targets in various cancers.

Dysregulated Cholesterol Metabolism	Implicated Cholesterol Metabolism Gene	Cancer	Ref.
Cholesterol uptake	NPC1L1 (upregulated)	Colorectal cancer Pancreatic ductal adenocarcinoma Breast cancer Ovarian cancer	[30–32]
	LDLR (upregulated)	Breast cancer Colorectal cancer Prostate cancer	[35,37,71]
	LDLR (downregulated)	Hepatocellular carcinoma	[58]
	SR-B1 (upregulated)	Prostate cancer Glioblastoma	[38,39]
Cholesterol efflux	ABCG1 (upregulated)	Bladder cancer	[72]
	ABCA1 (upregulated)	Triple-negative breast cancer Endometrial cancer Epithelial ovarian cancer Gastric adenocarcinoma Glioma	[44–48]
	SR-B1 (upregulated)	Lymphoma	[49]
	ABCA1 (downregulated)	Lung adenocarcinoma Prostate cancer Colon cancer	[41–43]
Cholesterol biosynthesis	SREBP (upregulated)	Prostate cancer	[71]
	FDFT1 (upregulated)	Colon carcinoma Hepatocellular carcinoma Epithelial ovarian cancer Tongue squamous cell carcinoma Bladder cancer	[59–61,65–67]
	FDFT1 (downregulated)	Gastric cancer Kidney renal clear cell carcinoma Ovarian cancer Bladder cancer	[62–64,67]
Cholesterol storage	ACAT1 (upregulated)	Prostate cancer Lymphoma	[49,73]

Note: NPC1L1, Niemann-Pick C1 Like 1; LDLR, Low-density Lipoprotein Receptor; SR-B1, Scavenger Receptor Class B Type 1; ABCG1, ATP-binding Cassette Sub-family G Member 1; ABCA1, ATP-binding Cassette Subfamily A Member 1; SREBP, Sterol Regulatory Element-binding Protein; FDFT1, Farnesyl-diphosphate Farnesyltransferase 1; ACAT1, Acyl-CoA: Cholesterol Acyltransferase.

3 Altered Cholesterol Metabolism in the Immune Cells of the TME

Disruptions in the cholesterol metabolism of immune cells have been associated with impaired function, altered immune responses, and disease development. When confronted with biological threats, immune cells undergo metabolic reprogramming to optimize their function in eliminating the danger signals, including cholesterol metabolism rewiring. However, in cancer progression, immune cell metabolism

represents a vulnerability that is often hijacked by cancer cells, leading immune cells to support tumour progression instead of combating it. This can manifest as immune cell dysfunction or the acquisition of immunosuppressive phenotypes, further exacerbating tumour development. Notably, a significant body of research on immune cell metabolic reprogramming in cancer has focused on TAMs [74,75].

3.1 Cholesterol Metabolism and Immune Cells of the TME

3.1.1 TAMs

Goossens et al. [21] demonstrated that ovarian cancer cells can manipulate TAM phenotype through the induction of ABC transporters, proteins responsible for cholesterol efflux in these immune cells. This manipulation occurs via the production of hyaluronic acid (HA) by the cancer cells, which triggers cholesterol efflux from the TAM plasma membrane. Consequently, this reduction in cholesterol disrupts lipid rafts on the TAM membrane, which are crucial for signalling receptors. Depletion of these lipid rafts renders TAMs unresponsive to anti-tumour cytokines like interferon-γ (IFN-γ) and hyperresponsive to the pro-tumour signal, interleukin-4 (IL-4), suggesting the relationship between downregulation of TAMs' membrane cholesterol and tumour progression. This study further established that the genetic deletion of ABC transporters in TAMs and halting their membrane cholesterol efflux were able to reverse the tumour-promoting function of TAMs. Indeed, TAMs with reduced ABC transporters due to treatment with ABC inhibitors such as ATR101 display suppressed tumour growth [76]. This tumour suppression is attributed to the inhibition of cholesterol efflux from TAMs, leading to decreased TAM-induced angiogenesis and chemotaxis, ultimately killing tumour cells in a human lung cancer model [76].

TAMs can be categorized into two main phenotypes: the anti-tumourigenic M1 TAMs and the pro-tumourigenic M2 TAMs. M1 TAMs are typically activated by lipopolysaccharide (LPS) and IFN-γ, while M2 TAMs are activated by IL-4 or interleukin-13 (IL-13). While these phenotypic extremes are useful in well-controlled *in vitro* polarisation, *in vivo* models that treat polarisation as a spectrum of activation states are becoming the norm. The M1/M2 dichotomy is now viewed as a continuum of highly plastic states characterised by contextual cues such as cell-cell interactions, tissue-derived factors, epigenetics, and metabolic conditions [77,78]. As such, techniques employing single-cell, machine learning, spatial, and multiomics data are being increasingly employed in the distinction of TAM subsets in the tumour milieu [77–79]. Studies have shown that TAMs isolated from tumour tissues exhibit cholesterol deficiency and adopt M2-like, tumour-promoting phenotypes [76,80].

In bladder cancer and melanoma mouse models, TAMs lacking the ABC transporter ATP-binding Cassette Sub-family G Member 1 (ABCG1) exhibit intracellular free cholesterol accumulation and shift towards the M1 phenotype. This shift activates the IκB kinase/Nuclear Factor Kappa B (IκB kinase/NF-κB pathway), directly killing tumour cells and inhibiting tumour growth [80]. The involvement of cholesterol efflux genes in the reprogramming of TAMs towards a pro-tumourigenic phenotype was demonstrated in a study involving CRC, where LXR genes were seen to be upregulated in the TAMs isolated from liver metastases of CRC, with a concomitant rise in the genes ABCA1 and ABCG1 [81]. A study using a mouse melanoma model have demonstrated that ApoA-I, a component of HDL involved in cholesterol transport, can convert TAMs from the M2 to M1 phenotype. This conversion leads to increased IFN-γ production and accumulation of $CD8^+$ T cells, ultimately enhancing anti-tumourigenic effects [82].

Besides cholesterol transport, cholesterol biosynthesis was also implicated in promoting the pro-tumourigenic function of TAMs. For instance, activation of X-box binding protein 1 (XBP1), a transcription factor, was observed in TAMs, driving CRC progression through TAM secretion of pro-tumourigenic cytokines and the inhibition of macrophage phagocytosis of tumour cells through self-recognition signals of TAMs [83].

Though an explicit connection between XBP1 and cholesterol metabolism was not made in TAMs, unspliced XBP1 was found to be involved in cholesterol biosynthesis through its role in stabilizing SREBP2 and enhancing the transcription of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in HCC [84]. Tumour-intrinsic XBP1 under ER stress has also been shown to drive cholesterol biosynthesis and shuttling to neighbouring MDSCs to fuel immunosuppression [85].

3.1.2 $CD8^+$ T cells

In a murine melanoma model, $CD8^+$ T cells were shown to be prone to exhaustion due to ER stress induced by cholesterol acquired from the TME [20]. This led to an overexpression of immune checkpoint receptors such as programmed cell death protein 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3), concomitant with the total cholesterol levels in the cells. Reduction of intracellular cholesterol through HMGCR knockdown was able to restore the anti-tumour function of $CD8^+$ T cells [20]. In line with this finding, in a model involving breast cancer, melanoma, and colon cancer cell lines, $CD8^+$ T cells sustained a hyperactivated Akt-mTORC1-SREBP1 signal axis due to the tumour-derived fibroblast growth factor 21 (FGF21), which led to overstimulation of cholesterol biosynthesis, accumulation of excess cholesterol, and eventual exhaustion of the T cells [86].

Interleukin-9 (IL-9)-secreting Tc9 cells, a subtype of $CD8^+$ T cells, were found to be more immunologically potent than the classical subtype, Tc1 cells, with intracellular cholesterol content accounting for the difference in anti-tumour responses between these subtypes in a mouse melanoma model [87,88]. IL-9 is critical for the anti-tumour functions of Tc9 cells. Mechanistically, a high cholesterol content and cholesterol derivatives like oxysterols were found to inhibit Tc9 differentiation and IL-9 secretion via cholesterol-mediated LXR sumoylation that repressed IL-9 expression, while reducing cholesterol content enhanced the persistence and anti-tumour functions of Tc9 cells *in vivo* [88]. Additionally, cholesterol biosynthesis genes and cholesterol efflux genes were found to be differentially expressed between Tc9 and Tc1, with Tc9 cells having lower cholesterol biosynthesis and higher cholesterol efflux gene expression compared to Tc1 cells, further demonstrating the role of cholesterol in regulating $CD8^+$ T cell differentiation [88]. Recently, it has been demonstrated that inhibiting cholesterol biosynthesis enzymes, SREBP and squalene epoxidase (SQLE) that drive cholesterol accumulation in the TME reduces tumour burden by reinvigorating the anti-tumour functions of the otherwise exhausted $CD8^+$ T cells while diminishing immunosuppressive tumour-infiltrating cells like MDSCs and Tregs [89,90]. Thus, reducing cholesterol availability in the TME restores the anti-tumourigenic potential of effector $CD8^+$ T cells while alleviating the effects of immunosuppressive cell populations in the TME.

Apart from cholesterol and oxysterols, high levels of esterified cholesterol were also observed to suppress the effector functions of $CD8^+$ T cells, while inhibition of stearoyl-CoA desaturase 1 (SCD1) in these cells enhanced their anti-tumour function by reducing esterified cholesterol levels in an ACAT1-dependent manner [91]. Tatsuguchi et al. [92] demonstrated another mechanism by which cancer cells evade effector T cells using another cholesterol metabolite, cholesterol sulfate, which was highly produced by cancer cells to inhibit effector T cell migration and infiltration into tumours.

3.1.3 Natural Killer (NK) Cells

Aberrant hepatic cholesterol biosynthesis was revealed to selectively disrupt NK cell function in a HCC mouse model, specifically through the SREBP2-mediated cholesterol secretion of hepatocytes, which induced lipid peroxidation and impairment of NK cell cytotoxicity [93]. In contrast, high serum cholesterol levels demonstrably increased NK cell function and enhanced suppression of HCC in mice, with a positive

correlation established between serum cholesterol levels and NK cell activation in human HCCs [94]. Specifically, elevated serum cholesterol levels led to cholesterol accumulation in NK cells, which promoted lipid raft formation for the facilitation of immune signalling pathways to enhance NK cell cytotoxicity [94]. Interestingly, elevated serum cholesterol levels reduced liver tumour growth, and depletion of NK cells nullified the inhibitory effects of high cholesterol on tumour growth, underscoring the indispensability of NK cells in cholesterol-mediated suppression of HCC [94]. Likewise, reduced cholesterol availability for uptake by NK cells due to aberrant cholesterol accumulation by immunosuppressive $CD16^+$ neutrophils disrupted NK cell lipid raft formation, impairing NK cell activation and cytotoxicity [95].

3.1.4 Neutrophils

Cholesterol metabolism has also been demonstrated to modulate cancer progression through the pro-tumourigenic activity of neutrophils [95,96]. Specifically, cholesterol uptake and tumour-derived oxysterols were implicated in the formation of neutrophil extracellular traps (NETs) and the recruitment of pro-angiogenic neutrophils, dampening anti-tumour immune responses [95,96]. Aberrant cholesterol uptake resulting in cholesterol accumulation in $CD16^+$ neutrophils reduced cholesterol availability for NK cells, disrupting NK cell anti-tumour signalling and impairing their mobility, as well as inducing NK cell apoptosis through entrapment in NETs in CRC [95].

Oxysterols have also been implicated in facilitating cancer progression by modulating the migration of neutrophils in the TME [96,97]. 27-HC, for instance, increases the number of polymorphonuclear neutrophils at metastatic sites for the facilitation of breast cancer metastasis [97]. In a pancreatic neuroendocrine tumour model, tumour-derived 24S-hydroxycholesterol (24S-HC) was found to aid in the recruitment of neutrophils to facilitate neoangiogenesis and tumour progression [96]. Correspondingly, overexpression of Cyp46a1, the enzyme responsible for the production of 24S-HC, was significantly associated with VEGF and tumour size in human pancreatic neuroendocrine tumour samples [96].

4 The Crosstalk between Cancer and Immune Cells

The crosstalk between cancer cells and immune cells can be mediated by metabolites, cytokines, extracellular vesicles, and growth factors [98,99]. For instance, exosomes, a subpopulation of extracellular vesicles, can contain nucleic acids, membrane-anchored proteins, cytosolic proteins, and lipids responsible for the cellular interaction.

The phenotypic switch between the TAMs has been demonstrated to be regulated by their cholesterogenic content, which subsequently affects cancer cell proliferation directly and indirectly. For example, 27-HC, a main metabolite of cholesterol, is produced in higher quantities in M2 TAMs compared to the M0 and M1 counterparts. 27-HC accumulation from M2 TAMs has been shown to promote the proliferation of oestrogen receptor-positive breast cancer cells and the expression of chemokines that attract monocytes to the tumour site, thereby facilitating breast cancer development [100].

While the aforementioned finding illustrates the impact of cholesterol on immune cells in relation to cancer cells, cholesterol metabolites excreted by cancer cells also play a role in the polarisation of surrounding TAMs. 27-HC derived from HCC cells, for instance, increased the lipid metabolism in surrounding macrophages and activated peroxisome proliferator-activated receptor-γ (PPARγ) signaling, thereby activating M2 macrophage polarisation and promoting HCC cell invasion and migration [101]. Additionally, Wang et al. [102] demonstrated that cholesterol secreted by glioma cells into the TME was taken up by glioma-associated macrophages (GAMs), leading to elevated intracellular and membrane-associated cholesterol levels. Interestingly, this cholesterol enrichment not only promoted M1-like polarisation of

GAMs but also concurrently suppressed their M2-like polarisation [102]. However, the precise mechanism by which increased exogenous cholesterol levels correlate with the phenotypic shift of GAMs towards the M1 phenotype remains to be known.

4.1 The Crosstalk between Cancer and Immune Cells: The Role of ncRNAs

NcRNAs are RNA molecules that do not encode proteins but play crucial regulatory roles in various cancers [103]. In the TME, ncRNAs play a pivotal role in the dynamic interactions between cancer cells and immune cells, influencing tumour progression, immune evasion, and therapy resistance [104,105]. NcRNAs are typically packaged into exosomes, which are taken up by immune cells to modulate their function [106]. Examples of these include lncRNAs, circRNAs, and miRNAs.

4.1.1 Long-Coding RNAs (lncRNAs)

LncRNAs are a broad category of ncRNAs longer than 200 nucleotides that regulate gene expression at multiple levels, i.e., epigenetic, transcriptional, and post-transcriptional levels [107]. The lncRNA CARMN was determined to regulate the hsa-miR-192-5p/LOXL2 axis in HCC progression and immune cell infiltration, specifically $CD4^+$ T Cells, macrophages, and neutrophils [108]. Similarly, the lncRNAs SNHG6 and MALAT1 modulated gene expression levels through the binding of miRNA, specifically, miR-101-3p, to influence prognosis and immune cell infiltration in HCC [109]. The myriad of lncRNAs are typically categorized according to their transcriptional location in relation to protein-coding genes, with Long Intergenic Non-Coding RNAs (lincRNAs) being a specific type of lncRNA that is located in intergenic regions [110]. The inverse relationship between lncRNAs and miRNAs in immunomodulation and cancer progression is thus further evidenced with the linc00936/miR-425-3p/monocyte chemotactic protein-induced protein 1 (ZC3H12A) axis and with the linc00511/hsa-miR-573 axis/gasdermin C (GSDMC) axis in GC and breast cancer, respectively [105,111].

4.1.2 Circular RNAs (circRNAs)

CircRNAs are a distinct class of ncRNAs consisting of covalently closed-loop RNAs without a 5′ cap or 3′ poly(A) tail [112]. Just like lncRNAs, circRNAs can act as miRNA sponges to regulate gene transcription [113]. CircRNAs are particularly effective miRNA sponges due to their circular structure, which makes them more resistant to degradation than the linear lncRNA [114]. In GC, the oncogenic circ_0136666 promotes cancer progression by upregulating the protein kinase, PRKDC, through the sponging of miR-375-3p, driving PD-L1 accumulation and immune suppression [115]. Circ_0067842 facilitated breast cancer metastasis and immune evasion by reducing peripheral blood mononuclear cells (PBMCs) and $CD8^+$ T cells and by inhibiting ubiquitination and degradation of PD-L1 [116]. Sponging of miR-328-3p and miR-3173-5p by modified circIGF2BP3 also caused immune escape in non-small cell lung cancer (NSCLC) by preventing PD-L1 degradation and $CD8^+$ T cell cytotoxicity in NSCLC [117]. The immunosuppressive effects of circRNAs extend beyond promotion of PD-L1 expression to Treg activation, where circ_0136666 was found to target the miR-497/PD-L1 axis and facilitate immune escape to advance CRC [118].

4.1.3 MicroRNAs (miRNAs)

MiRNAs are a class of small ncRNAs of roughly 23 nucleotides in length, which function to control gene expression post-transcriptionally by hybridizing to the 3′ untranslated regions (3′UTR) of target mRNAs. This binding suppresses target gene expression by destabilizing and subsequently degrading the target mRNA, inhibiting translation, or both [119]. MiRNAs are also used for cell-cell communication,

including that between cancer cells and immune cells during the latter's reprogramming in tumour advancement [120]. MiRNAs thus act as central nodes that integrate metabolic and immune signalling in cancer. Among the diverse classes of ncRNAs, miRNAs remain the most extensively characterized regulators of post-transcriptional gene expression in cancer, owing to their well-defined biogenesis, conserved mechanism of action, and broad experimental validation across tumour types [24,121].

Studies have shown the mechanism by which tumour-derived exosomal miRNAs contribute to the immunosuppressive M2 phenotype. For instance, NSCLC-derived exosomes containing miR-106a-5p were shown to contribute to M2 polarisation *in vitro* and *in vivo* by downregulating PTEN and upregulating STAT3, an essential transcription factor for M2 polarisation, which ultimately increased the proliferation, invasion, and metastasis of NSCLC cells under intermittent hypoxia conditions [122]. The same mechanism was observed through bladder cancer cell-derived exosomal miR-92b-3p and miR-1231-5p, which induced M2 polarisation via downregulation of PTEN and upregulation of STAT3 and STAT6 [123]. GC-derived exosomes promote M2 polarisation of lung macrophages by inhibiting PTEN expression via exosomal miR-92a-3p, which upregulates PD-L1 expression in M2 TAMs, thereby contributing to a pre-metastatic niche that facilitates GC lung metastasis [10]. Exosomal miR-21-5p derived from HCC cells has been shown to induce the differentiation into M2 TAMs, producing IL-10 and promoting HCC growth *in vitro* [124]. Similarly, the exosomal miR-940 released by hypoxic EOC cells could influence the polarisation of TAMs towards M2 macrophages, thereby contributing to the progression of EOC [125]. Likewise, modulation of macrophages to exhibit an M2-polarized state was achieved through the shuttling of miR-145 from DLD-1 colon cancer cells to co-cultured TAMs in the vicinity via extracellular vesicles [126].

Studies have also shown that miRNAs from TAMs can influence tumourigenesis by modulating key signaling pathways involved in angiogenesis, invasion, and drug resistance. For instance, TAM-derived miR-21-5p promoted tumour angiogenesis in head and neck squamous cell carcinoma (HNSCC) via the miR-21-5p/YAP1/HIF-1α axis, highlighting the role of TAM-derived miRNAs in supporting the formation of a pro-tumourigenic microenvironment [127]. Similarly, in PDAC, the exosomal transfer of miRNAs from TAMs to tumour cells not only enhanced their invasive and migratory capacities but also contributed to drug resistance, particularly through miR-202-5p, miR-142-5p, and miR-365 [128,129]. These findings underscore the functional diversity of TAM-derived miRNAs in shaping tumour progression and highlight their potential as therapeutic targets. Interestingly, not all TAM-derived miRNAs promote tumour progression. M1-derived exosomal miR-29c-3p demonstrated an opposing role by suppressing melanoma cell migration and invasion through the downregulation of ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), which subsequently impaired extracellular matrix (ECM) remodeling and reduced cell membrane fluidity, thereby limiting cellular motility [130]. This suggests that the polarisation state of macrophages plays a crucial role in determining the functional output of miRNA transfer, with M2 macrophages typically fostering a tumour-supportive environment, while M1 macrophages may exert tumour-suppressive effects.

Recent work evidences miRNAs directly fine-tuning cholesterol flux by targeting key regulatory nodes across uptake, biosynthesis, and efflux. For example, miR-33a has been shown to suppress ABCA1, thereby attenuating ABCA1-dependent cholesterol efflux and reinforcing cholesterol retention in cholesterol-loaded, macrophage-like vascular cells [131]. In the uptake axis, miR-148a decreases cellular LDL uptake by repressing the (pro)renin receptor ((P)RR), which in turn reduces LDLR protein abundance and LDL internalization in human hepatic cell models [132]. Complementarily, miR-99a-5p has been reported to directly bind the proprotein convertase subtilisin/kexin type 9 (PCSK9) 3′UTR, downregulating PCSK9 and consequently increasing LDLR levels and functional LDL-C uptake in human hepatocytes [133]. Beyond uptake, miRNAs also regulate biosynthesis. MiR-7 was demonstrated to block late steps of the cholesterol

biosynthetic pathway by post-transcriptionally targeting the enzyme 24-dehydrocholesterol reductase (DHCR24), which catalyses the terminal step of the Bloch pathway of cholesterol biosynthesis by reducing desmosterol to cholesterol, thereby regulating the final yield of endogenous cholesterol production [134,135].

MiR-146b-5p was found to contribute to bladder cancer chemoresistance by targeting a key cholesterol biosynthesis enzyme, FDFT1, to reduce cisplatin sensitivity [67]. Notably, miR-146b-5p was also positively correlated with M2 TAM infiltration and was upregulated in high-grade bladder tumours [136]. Preliminary bioinformatics analysis conducted in our lab found several common target genes regulated by miR-146b-5p in bladder cancer and macrophages. Of these, tumor necrosis factor receptor-associated factor 6 (TRAF6) was found to be a negative prognostic indicator in bladder cancer and an inducer of IL-4-mediated M2 macrophage activation [137,138]. CC motif chemokine ligand 5 (CCL5), another predicted target of miR-146b-5p, promoted the growth and migration of bladder cancer through JAK2/STAT3 signalling and was found to be highly expressed in co-cultures involving bladder cancer cells and TAMs [139]. Moreover, sortilin 1 (SORT1), a miR-146b-5p putative target gene and modulator of cholesterol metabolism, was observed to regulate macrophage function by influencing LDL uptake and is highly expressed in primary bladder carcinoma tissues [140,141].

4.2 Cancer Cells-Derived miRNAs Affecting Cholesterol Metabolism in Macrophages

Cancer cells can influence their surrounding environment by engaging in a crosstalk with immune cells using miRNAs as immune modulators. miR-375 derived from apoptotic breast cancer cells was demonstrated to be responsible for the recruitment and infiltration of TAMs into the TME [142]. This miRNA exerts a positive feedback loop between breast cancer cells and TAMs by directly targeting lactate dehydrogenase B (LDHB), one of the key glycolytic enzymes. Consequently, production of lactate increased, adapting TAMs to become tumour-supportive and conferring apoptosis resistance to breast cancer cells [120,143]. The increase in lactate had created an acidic intracellular environment in TAMs, stimulating the nuclear translocation of SREBP2 and subsequent increase in cholesterol biosynthesis, making the TAMs take up a pro-tumourigenic function [120]. The miR-375/LDHB axis could thus be exploited for anti-tumour strategies. Frank et al. [120] also proposed and validated a combinatorial treatment consisting of miR-375 decoy and simvastatin to reduce cancer proliferation in a pre-clinical setting.

Gerloff et al. [144] also showed that miR-125b-5p from cutaneous melanoma-derived exosomes induces a tumour-promoting phenotype in TAMs, by directly targeting the lysosomal acid lipase A (LIPA) gene in macrophages. As LIPA encodes for lysosomal acid lipase (LAL), which hydrolyses cholesteryl esters to generate free cholesterol in the cell, this could mean that miR-125b-5p causes a depletion in the free cholesterol pool of melanoma-associated macrophages, mirroring the effects of intracellular cholesterol efflux that eventually promotes the pro-tumourigenic phenotype of TAMs [21]. However, the tumour-promoting phenotype identified by Gerloff et al. [144] was associated with both M1 and M2 markers, showing an enrichment of genes associated with inflammation, angiogenesis, and macrophage recruitment. This hybrid phenotypic characterization is postulated to align with the plasticity of TAMs observed *in vivo* [77,144].

4.3 Macrophage-Derived miRNAs Affecting Cholesterol Metabolism in Cancer Cells

M1-derived exosomal miR-29c-3p has been shown to suppress the migration and invasion of melanoma cells by targeting ENPP2, a key enzyme involved in ECM remodelling [130]. The downregulation of ENPP2 subsequently impairs ECM dynamics, which are crucial for cancer cell motility. Furthermore, miR-29c-3p reduces cholesterol efflux in melanoma cells through the suppression of ABCA1, resulting in the intracellular

accumulation of cholesterol, which diminishes membrane fluidity, a critical factor for cancer cell migration and invasion. By altering cholesterol metabolism, immune cell-derived miRNAs such as miR-29c-3p may serve as regulatory molecules in the TME, potentially offering novel therapeutic strategies to limit cancer metastasis [130].

In an *in vitro* breast cancer model, Yang et al. [145] demonstrated that miR-223 released by macrophages was taken up by SKBR3 and MDA-MB-231 breast cancer cells, inducing invasion of the recipient cells via the miR-223/Mef2c/β-catenin axis. While the observation was not directly related to the cholesterol pathway, Wnt-β-catenin is critical for the transcription of mevalonate pathway-related genes, especially those related to the LXR/RXR pathway genes that are associated with cholesterol efflux and reverse cholesterol transport [146,147]. It would thus be interesting to investigate if miR-223 released by M2 and taken up by the breast cancer cells could dysregulate their cholesterol homeostasis in favour of tumour progression.

In experiments involving renal cell carcinoma (RCC) cell lines treated with the exosomes of M2 polarized macrophages, the RCC cells showed enhanced migration, invasion, and EMT markers upon internalization of the M2 macrophage-derived exosomes [148]. The most abundant miRNA found encapsulated within those M2-derived exosomes was miR-21-5p, which was demonstrated to regulate the PTEN/Akt signalling pathway [148]. Although a direct link between the PTEN/Akt signalling pathway and the cholesterol pathway was not elucidated, this pathway has been suggested to inhibit ABCA1-mediated cholesterol efflux, leading to an overall accumulation of intracellular cholesterol, simultaneously facilitating ACAT1-mediated conversion of cholesterol into CE in cancer cells [28]. CE forms one of the main components of lipid droplets, which have been linked with chemotherapeutic resistance [149].

Existing studies underscore the important roles of miRNAs in manipulating vital signalling pathways in the context of cancer progression, particularly in the immune-cancer crosstalk. Further studies are needed to elucidate the modulation of cholesterol metabolism in cancer cells by immune cells from the TME, specifically with the utilization of miRNAs as potent mediators in cell-cell communication. Fig. 1 illustrates the bidirectional communication between cancer cells and TAMs, mediated by multiple oncogenic or tumour-suppressor miRNAs targeting cholesterol metabolism genes. A summary of miRNAs associated with TAM polarisation in the cancer-immune cell crosstalk and their cholesterol metabolism target genes is listed in Table 2.

Table 2: Summary of miRNAs involved in the cancer-macrophage crosstalk and their cholesterol metabolism target genes.

miRNA	Macrophage Phenotype Promoted	Cancer Type	miRNA Variation	Cholesterol Target	Corresponding Cholesterol Metabolism Pathway
miR-125b [144]	M2	melanoma	hsa-miR-125b-5p	LIPA	storage
miR-106a-5p [122]	M2	NSCLC	hsa-miR-106a-5p	ABCG8* MYLIP* MSMO1*	efflux uptake biosynthesis
miR-92b-3p [123]	M2	bladder cancer	mmu-miR-92b-3p	LDLR* MYLIP* HMGCR*	uptake uptake biosynthesis
miR-92a-3p [10]	M2	gastric cancer	mmu-miR-92a-3p	SR-B1* LDLRAP1* HMGCS1* SREBF2*	uptake/efflux uptake biosynthesis biosynthesis

Table 2: *Cont.*

miRNA	Macrophage Phenotype Promoted	Cancer Type	miRNA Variation	Cholesterol Target	Corresponding Cholesterol Metabolism Pathway
miR-29c-3p [130]	-	melanoma	hsa-miR-29c-3p	ABCA1	efflux
miR-223 [145]	-	breast cancer	hsa-miR-223-3p	SR-B1*	uptake/efflux

Note: *Predicted cholesterol target genes of miRNAs in the crosstalk between TAMs and cancer cells. These gene targets are included to show that miRNAs may facilitate intercellular communication whilst influencing TAM polarisation by potentially altering their cholesterol metabolism; -, Unspecified TAM phenotype; LIPA, Lipase A; ABCG8, ATP-binding cassette sub-family G member 8; MYLIP, Myosin Regulatory Light Chain Interacting Protein; MSMO1, Methylsterol Monooxygenase 1; LDLR, Low-Density Lipoprotein Receptor; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; SR-B1, Scavenger Receptor Class B Type 1; LDLRAP1, Low Density Lipoprotein Receptor Adaptor Protein 1; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; SREBF2, Sterol Regulatory Element-Binding Transcription Factor 2; ABCA1, ATP-Binding Cassette Subfamily A Member 1.

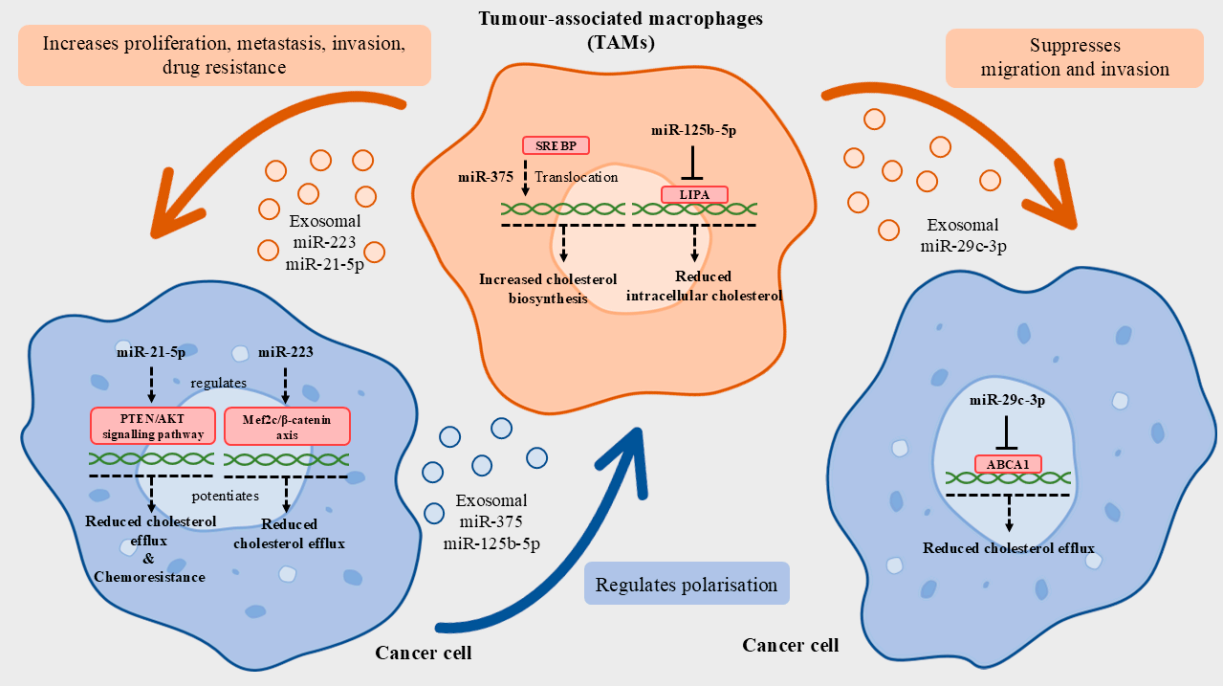

Figure 1: Crosstalk between cancer cells and TAMs involving miRNAs targeting cholesterol metabolism genes.

5 Conclusion and Future Perspectives

Cholesterol metabolism is crucial for cancer and immune cell survival as well as the latter's activation. It plays important roles in cancer cells' proliferation and membrane biosynthesis. It is also pivotal in signal transduction in both cancer and immune cells, as cholesterol is a crucial component of lipid rafts. NcRNAs, specifically miRNAs, lncRNAs, and circRNAs, facilitate cholesterol metabolism regulation in cancer and immune cells. These ncRNAs modulate key processes such as cholesterol biosynthesis, efflux, and intracellular accumulation, thereby influencing oncogenic signaling pathways and immune cell activation [150–152].

NcRNAs are also indispensable in the tumour-immune crosstalk, influencing immune cell differentiation and tumour survival. Mounting evidence suggests that miR-146a/b limits excessive inflammation by targeting TRAF6 and IRAK1, suppressing M1 TAM polarisation in the TME [153–155]. Tumour-derived exosomal miRNAs can induce M2 macrophage phenotype, subsequently promoting the invasiveness of laryngeal squamous cell carcinoma and metastasis of CRC [156–158]. LncRNAs can regulate

immune checkpoint pathways by modulating PD-L1 expression, thereby facilitating immune escape in glioblastoma [159]. To summarize, ncRNAs modulate both cholesterol metabolism and immune responses, positioning them as metabolic checkpoints in cancer.

Despite rapid advances in cancer biology, current research examining ncRNAs and cholesterol metabolism largely remains compartmentalized. Most studies focus either on the tumour-intrinsic roles of ncRNAs in cancer progression or immune cell reprogramming, or independently on how cholesterol metabolism supports tumour growth and immune suppression. As a result, the mechanistic integration of ncRNA regulation with cholesterol metabolic rewiring across tumour and immune compartments is still poorly defined. This represents a critical gap, as cancer progression is increasingly recognised as an immunometabolic process shaped by the dynamic, bidirectional crosstalk between cancer and immune cells. Emerging spatial multiomics approaches offer a powerful opportunity to overcome these limitations by simultaneously resolving ncRNA expression, metabolic programs, and immune states within their native tissue context [160]. Integrating spatial transcriptomics, metabolomics, and functional perturbation studies will be essential to delineate how ncRNA-driven cholesterol metabolism orchestrates localized immunosuppressive niches and to identify context-specific vulnerabilities that may be exploited therapeutically [161,162]. Development of exosome-based delivery systems is a rapidly evolving frontier in ncRNA research, particularly in the context of cancer-immune-metabolism crosstalk [163]. For example, exosomes containing miRNAs derived from NK cells induced anti-tumour immunity in pancreatic cancer cells [164]. Exosomes are interesting therapeutic targets due to their potential for engineering to express specific ligands for targeted delivery to target tumour or immune cells. Internalized-arginylglycylaspartic acid cyclic peptide (iRGD)-modified exosomes loaded with anti-miR-221, for instance, targeted Neuropilin-1(NRP-1) receptor-positive CRC to exert an anti-tumour effect [165]. Studies into ncRNAs are timely and central to investigating cancer vulnerabilities in both tumour-immune communications and metabolic regulation.

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Abbreviations

27-HC	27-Hydroxycholesterol
3′UTR	3′ Untranslated Regions
ABCA1	ATP-binding Cassette Subfamily A Member 1
ABCG1	ATP-binding Cassette Sub-Family G Member 1
ABCG8	ATP-binding Cassette Sub-Family G Member 8
ACAT1	Acetyl-coA Acetyltransferase 1

ADAM9	A Disintegrin and Metalloprotease Domain 9
ApoA-I	Apolipoprotein A-I
ApoM	Apolipoprotein M
CCDC25	Coiled-coil Domain Containing Protein 25
CCL5	CC Motif Chemokine Ligand 5
$CD8^+$	Cluster of Differentiation 8+
CE	Cholesteryl Esters
CircRNAs	Circular RNAs
CRC	Colorectal Cancer
DC	Dendritic Cell
DHCR24	24-Dehydrocholesterol Reductase
EC	Endometrial Cancer
ECM	Extracellular Matrix
EFNB2	Ephrin-B2
EGF	Epidermal Growth Factor
EMT	Epithelial-Mesenchymal Transition
ENPP2	Ectonucleotide Pyrophosphatase/Phosphodiesterase 2
EOC	Epithelial Ovarian Cancer
EPHB4	Ephrin Type-B Receptor 4
ER	Endoplasmic Reticulum
ERα	Oestrogen Receptor Alpha
ERK	Extracellular Signal-Regulated Kinase
FDFT1	Farnesyl-Diphosphate Farnesyltransferase 1
FGF21	Fibroblast Growth Factor 21
GAMs	Glioma-associated Macrophages
GC	Gastric Cancer
GSDMC	Gasdermin C
HA	Hyaluronic Acid
HCC	Hepatocellular Carcinoma
HDL	High-Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HMGCR	3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase
HMGCS1	3-Hydroxy-3-Methylglutaryl-Coa Synthase 1
HNSCC	Head and Neck Squamous Cell Carcinoma
IFN-γ	Interferon-Gamma
IL-10	Interleukin-10
IL-13	Interleukin-13
IL-4	Interleukin-4
IL-9	Interleukin-9
iRGD	Internalized-arginylglycylaspartic acid cyclic peptide
LAG-3	Lymphocyte-Activation Gene 3
LAL	Lysosomal Acid Lipase
LDHB	Lactate Dehydrogenase B
LDL-C	Low-Density Lipoprotein Cholesterol
LDLR	Low-Density Lipoprotein Receptor
LDLRAP1	Low Density Lipoprotein Receptor Adaptor Protein 1
lincRNAs	Long Intergenic Non-coding RNAs
LIPA	Lipase A, Lysosomal Acid Type
LLC	Lewis Lung Carcinoma
lncRNAs	Long Non-Coding RNAs
LPS	Lipopolysaccharide
LXRs	Liver X Receptors
MDSCs	Myeloid-Derived Suppressor Cells
MEK	Mitogen-Activated Protein Kinase

mRNA	Messenger RNA
miRNA	microRNA
MSMO1	Methylsterol Monooxygenase 1
mTORC1	Mammalian Target of Rapamycin Complex 1
MYLIP	Myosin Regulatory Light Chain Interacting Protein
ncRNAs	Non-coding RNAs
NF-κB	Nuclear Factor Kappa B
NK cells	Natural Killer Cells
NNMT	Nicotinamide N-Methyltransferase
NPC1L1	Niemann-Pick C1 Like 1
NSCLC	Non-Small Cell Lung Cancer
PBMCs	Peripheral Blood Mononuclear Cells
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PD-1	Programmed Cell Death Protein 1
PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Death-Ligand 1
PI3K	Phosphoinositide 3-Kinase
PKB	Protein Kinase B
PPARγ	Peroxisome Proliferator-Activated Receptor-Γ
PPP	Pentose Phosphate Pathway
(P)RR	(Pro)Renin Receptor
PTEN	Phosphatase and Tensin Homolog
RCC	Renal Cell Carcinoma
RCT	Reverse Cholesterol Transport
RIPK3	Receptor-Interacting Protein Kinase 3
RNA	Ribonucleic Acid
RXRs	Retinoid X Receptors
SCAP	Sterol Regulatory Element-Binding Protein Cleavage-Activating Protein
SCD1	Stearoyl-Coa Desaturase 1
SORT1	Sortilin 1
SQLE	Squalene Epoxidase
SR-B1	Scavenger Receptor Class B Type 1
SREBF2	Sterol Regulatory Element-Binding Transcription Factor 2
SREBP2	Sterol Regulatory Element-Binding Protein 2
SREs	Sterol-Regulatory Elements
TAMs	Tumour-associated Macrophages
TGF-β	Transforming Growth Factor-Beta
TNBC	Triple-Negative Breast Cancer
TRAF6	Tumor Necrosis Factor Receptor-Associated Factor 6
Tregs	Regulatory T cells
VEGF	Vascular Endothelial Growth Factor
XBP1	X-Box Binding Protein 1

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