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REVIEW ARTICLE

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27-Hydroxycholesterol in cancer development and drug resistance

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ABSTRACT

27-Hydroxycholesterol (27HC), a cholesterol metabolite, functions both as a selective oestrogen receptor (ER) modulator and a ligand for liver X receptors (LXRs). The discovery of 27HC involvement in carcinogenesis has unveiled new research avenues, yet its precise role remains controversial and context-dependent. In this review, we provide an overview of the biosynthesis and metabolism of 27HC and explore its cancer-associated signalling, with a particular focus on ER- and LXR-mediated pathways. Given the tissue-specific dual role of 27HC, we discuss its differential impact across various cancer types. Furthermore, we sort out 27HC-contributed drug resistance mechanisms from the perspectives of drug efflux, cellular proliferation, apoptosis, epithelial–mesenchymal transition (EMT), antioxidant defence, epigenetic modification, and metabolic reprogramming. Finally, we highlight the chemical inhibitors to mitigate 27HC-driven cancer progression and drug resistance. This review offers an updated role of 27HC in cancer biology, setting the stage for future research and the development of targeted therapeutics.

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Introduction

Cholesterol plays an important role in both physiological and pathological processes within the body. As a fundamental component of cell membranes, cholesterol contributes to membrane structure and fluidity, allowing for proper cellular function.[1] Moreover, it serves as a precursor for the synthesis of essential biomolecules, including steroid hormones, bile acids, and vitamin D, and plays a role in modifying proteins in the Hedgehog signalling pathway.[2–4] In physiology, cholesterol supports brain function, reproductive health, and metabolic balance. However, when cholesterol levels become dysregulated, it may cause pathological conditions such as atherosclerosis, cardiovascular disease, neurodegenerative disorders, and cancer, highlighting its dual role in both normal physiology and disease.[5–7]

Cholesterol plays a crucial role in cancer development by regulating cellular metabolism, tumour growth, and disease progression.[8] In support of this, elevated cholesterol levels have been linked to an increased risk of various cancers.[9,10] Cancer cells exhibit an increased dependency on cholesterol, often upregulating cholesterol uptake and biosynthesis to support their heightened proliferative and metabolic demands.[11,12] This dysregulation contributes to enhanced membrane synthesis, energy production, and the activation of oncogenic signalling. Given its central role in tumour biology, cholesterol metabolism has emerged as a promising therapeutic target. Strategies such as statins, which inhibit cholesterol synthesis, liver X receptor (LXR) agonists, which promote cholesterol efflux, and inhibitors of cholesterol transport and esterification are being actively explored for cancer treatment.[13]

Cholesterol metabolism involves a series of biochemical reactions related to the synthesis, uptake, efflux, breakdown, and storage of cholesterol in the body.[6,14] Cholesterol is either absorbed from dietary sources or synthesised endogenously (~70% of total body cholesterol). Cholesterol synthesis occurs primarily in the liver from acetyl-CoA through a complex multistep process involving enzymes like hydroxy-methylglutaryl-CoA reductase (HMGCR). This process involves over 20 enzymes localised in both the cytosol and the endoplasmic reticulum. Key steps include the conversion of acetyl-CoA to mevalonate, then to squalene, and finally to cholesterol.[6,14,15] Although most cells can synthesise cholesterol, the majority of them obtain it from the bloodstream by internalising low-density lipoproteins (LDL), which deliver cholesterol from the liver to tissues. This transport system ensures that cholesterol reaches peripheral tissues where it is needed for various functions, including hormone production and membrane integrity. LDL enters cells *via* the endocytic pathway using the LDL receptor (LDLR).[16] After internalisation, LDL is transported to the lysosome, where it is broken down

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into unesterified cholesterol, free fatty acids, and free amino acids. The released cholesterol is then delivered to cell membranes or, when present in excess, is either exported *via* ABC transporters to high-density lipoproteins (HDL) or stored in lipid droplets, primarily as cholesteryl esters.[17,18] Cholesterol is metabolised by conversion into bile acids, oxysterols, and steroid hormones, or it can be excreted directly in bile.[6,14,15]

Oxysterols, also known as mono-oxygenated cholesterol derivatives, are produced from cholesterol through autoxidation or the enzymatic action of specific cytochrome P450 enzymes. Enzymatic oxidation of cholesterol produces oxysterols, such as 24S-hydroxycholesterol, 25-hydroxycholesterol, and 27-hydroxycholesterol (27HC). These oxysterols serve as intermediates in bile acid synthesis or are transported from extrahepatic tissues to the liver for further metabolism.[19,20] Beyond their role as intermediates in cholesterol metabolism, oxysterols are crucial in maintaining cholesterol homeostasis by regulating intracellular cholesterol levels *via* feedback mechanisms.[21–24] Furthermore, certain oxysterols have been identified as high-affinity ligands for nuclear receptors, highlighting their significance in cellular signalling and metabolic regulation.[25–29] Among them, 27HC is the most abundant oxysterol in human bloodstream and peripheral tissues.[30,31] It is a key regulator of cholesterol metabolism, lipid homeostasis, immune response, and membrane fluidity.[32,33]

27HC is a key player in cholesterol homeostasis. It regulates cholesterol efflux by activating LXRs, particularly LXRα, which enhances the expression of cholesterol transporters such as ABCA1 and ABCG1, facilitating cholesterol removal from cells.[24,25] Additionally, 27HC inhibits *de novo* cholesterol synthesis, thereby contributing to cholesterol balance within the body.[34] Beyond its role in cholesterol homeostasis, 27HC is an endogenous selective oestrogen receptor modulator (SERM), acting as a ligand of ER signalling.[27,28,35] This ability allows 27HC to influence oestrogen-dependent physiological processes and pathological conditions. Elevated 27HC levels have been implicated in several diseases, including cancer, osteoporosis, and Alzheimer's disease.[36–38] In cancer, excessive 27HC is frequently observed, where it promotes malignancy by activating ER-mediated signalling that drives tumour progression, invasion, and metastasis.[39–41] Emerging evidence also highlights the immunomodulatory effect of 27HC, particularly in cancer progression. It interacts with myeloid immune cells, leading to T cell dysfunction and suppression of immune surveillance. By dampening anti-tumour immune responses, 27HC creates a more favourable microenvironment for cancer growth and resistance to therapy.[42,43] These diverse roles of 27HC in cholesterol metabolism, hormone signalling, and immune regulation make it a significant factor in physiological processes and disease pathology.

Chemotherapy remains a common approach for cancer treatment and can improve patient survival. The effectiveness of chemotherapy varies depending on the type and stage of cancer.[44] Modern treatment modalities, such as targeted therapy and immunotherapy, can further improve therapeutic efficiency when combined with chemotherapy.[45] However, the repetitive nature of chemotherapy treatments can lead to cancer cells developing multi-drug resistance (MDR), which limits treatment outcomes and negatively impacts patient survival.[46–48] Several mechanisms mediate MDR, including increased drug efflux, evasion of apoptosis, metabolic reprogramming, and epithelial–mesenchymal transition (EMT).[48–50] Emerging evidence suggests that 27HC is a key risk factor for tumorigenesis, promoting cancer progression and MDR through various mechanisms.[51,52]

In this review, we aim to provide a comprehensive overview of the biosynthesis and metabolism of 27HC. We also update the literature regarding 27HC-induced cancer development, with a particular focus on its contribution to drug resistance in cancer therapy. Through a detailed examination of how 27HC facilitates cancer progression and resistance to treatment, we hope to shed light on its potential as a therapeutic target in future cancer treatment strategies.

Metabolism of 27HC in physiological and neoplastic conditions

Under physiological conditions, the synthesis and degradation of 27HC are primarily regulated by two cytochrome P450 enzymes: CYP27A1 (sterol 27-hydroxylase) and CYP7B1 (oxysterol 7α-hydroxylase), respectively[53,54] (Figure 1). Both enzymes are abundantly expressed in the liver, where they convert excess cholesterol into bile acids *via* the classical (neutral) bile acid synthesis pathway. They are also present in other tissues, including the lungs, brain, and adipose tissue.[55–57] Although the liver produces most of the body's 27HC, nearly all of it is rapidly converted into bile acids and does not enter circulation.[27,58,59] In contrast, extrahepatic tissues contribute significantly to circulating 27HC through the alternative (acidic) pathway of bile acid biosynthesis.[20,58,60]

The acidic pathway of bile acid synthesis is initiated by CYP27A1, located in the inner mitochondrial membrane.[53] Therefore, cholesterol conversion to 27HC requires mitochondrial processing. The transport of cholesterol into mitochondria is tightly regulated by StAR-related lipid transfer proteins (StARD1 and StARD3).[61–64] Once inside the mitochondria, CYP27A1 catalyses the conversion of cholesterol into 27HC, initiating the subsequent acidic pathway for bile acid synthesis. Thus, the transport of cholesterol into mitochondria and the expression activity of CYP27A1 represent two critical rate-limiting steps in 27HC biosynthesis. After initial hydroxylation by CYP27A1, 27HC is further processed by CYP7B1 to produce 7α, 27-dihydroxycholesterol, which is ultimately metabolised into bile acids[65,66] (Figure 1). Alternatively, cholesterol can be converted to 7α-hydroxycholesterol in the classical (neutral) bile acid synthesis pathway by CYP7A1, i.e. a liver-specific enzyme expressed in hepatocytes.[67] This compound is then metabolised by CYP8B1 and further processed by CYP27A1 within mitochondria. CYP7B1 subsequently catalyses the resulting 27HC outside the mitochondria before being synthesised into bile acids[20] (Figure 1).

The levels of 27HC in circulation generally correlate with cholesterol levels.[68] However, the sources of circulating 27HC differ from those produced in the liver; most circulating 27HC originates from extrahepatic tissues.[60,69] In healthy individuals, peripheral blood concentrations of free 27HC typically range from 0.3 to 0.8 μM but tend to increase in older adults and those with hypercholesterolaemia.[31,68,70]

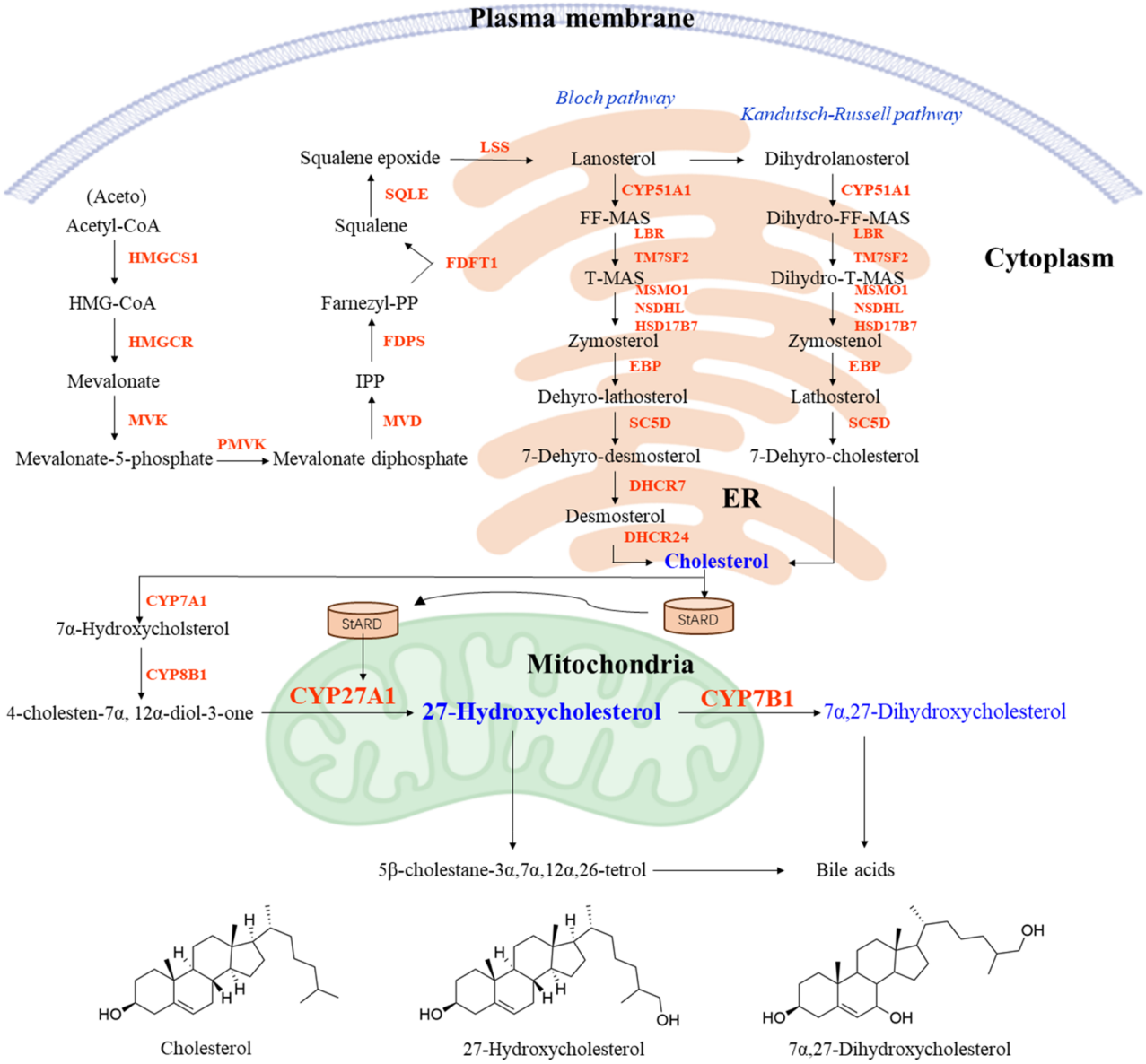


Figure 1. Overview of the intracellular metabolic pathways of 27HC. Schematic representation of the anabolic and catabolic pathways of 27HC, highlighting the organelle-specific localisation of key metabolic enzymes. Intracellular cholesterol is initially processed in the cytoplasm and endoplasmic reticulum, then transported to mitochondria *via* StARD proteins. In the mitochondria, CYP27A1 catalyses the conversion of cholesterol to 27HC. This is followed by the catabolism of 27HC by CYP7B1, ultimately resulting in the synthesis of bile acids. Diagram created using the Generic Diagramming Platform (GDP).
HMGCS1: 3-hydroxy-3-methylglutaryl-CoA synthase 1; HMGCR: 3-hydroxy-3-methyl glutaryl coenzyme A reductase; MVK: mevalonate kinase; PMVK: phosphomevalonate kinase; MVD: mevalonate diphosphate decarboxylase; FDPS: farnesyl pyrophosphate synthase; FDFT1: farnesyl-diphosphate farnesyltransferase 1; SQLE: squalene monooxygenase; LSS: lanosterol synthase; CYP51A1: cytochrome P450 Family 51 subfamily A member 1; LBR: lamin B receptor); TM7SF2: transmembrane 7 superfamily member 2; MSMO1: methylsterol monooxygenase 1; NSDHL: NAD(P)-dependent steroid dehydrogenase-like; HSD17B7: hydroxysteroid 17-beta dehydrogenase 7; EBP: EBP cholestenol delta-isomerase; SC5D: sterol-C5-desaturase; DHCR7: 7-dehydrocholesterol reductase; DHCR24: 24-dehydrocholesterol reductase; CYP27A1: cytochrome P450 family 27 subfamily A member 1; CYP7B1: cytochrome P450 family 7 subfamily B member 1;CYP7A1: cytochrome P450 family 7 subfamily A member 1; CYP8B1: cytochrome P450 Family 8 Subfamily B Member 1.

Emerging evidence suggests that elevated levels of 27HC play a pivotal role in driving tumorigenesis across various cancer types. The following section comprehensively analyses how 27HC contributes to cancer initiation, progression, and metastasis. One key factor underlying this process is the dysregulation of metabolic enzymes involved in 27HC metabolism, particularly CYP27A1 and CYP7B1 (Figure 2). CYP27A1-27HC-CYP7B1 axis is especially crucial to the development of endocrine- and metabolism-related cancers, where it alters cholesterol homeostasis and influences tumour progression. In breast cancer and endometrial cancer (EC), CYP27A1 is frequently overexpressed, while CYP7B1 is downregulated, leading to increased 27HC accumulation.[7,71–74] As an endogenous SERM and a LXR ligand, 27HC activates ER-mediated transcription and LXR-dependent signalling pathways, fuelling cancer cell proliferation, survival, and metastatic potential.[7,72,73] Elevated 27HC levels have been associated with more aggressive tumour phenotypes and poorer clinical outcomes in breast cancer and EC.[7,72,73] Conversely, prostate cancer (PCa) exhibits an opposing metabolic enzyme profile. CYP27A1 expression is significantly downregulated, while CYP7B1 is upregulated, particularly in high-grade prostatic intraepithelial neoplasia (HGPIN).[75–78] This metabolic shift leads to lower 27HC levels, potentially diminishing

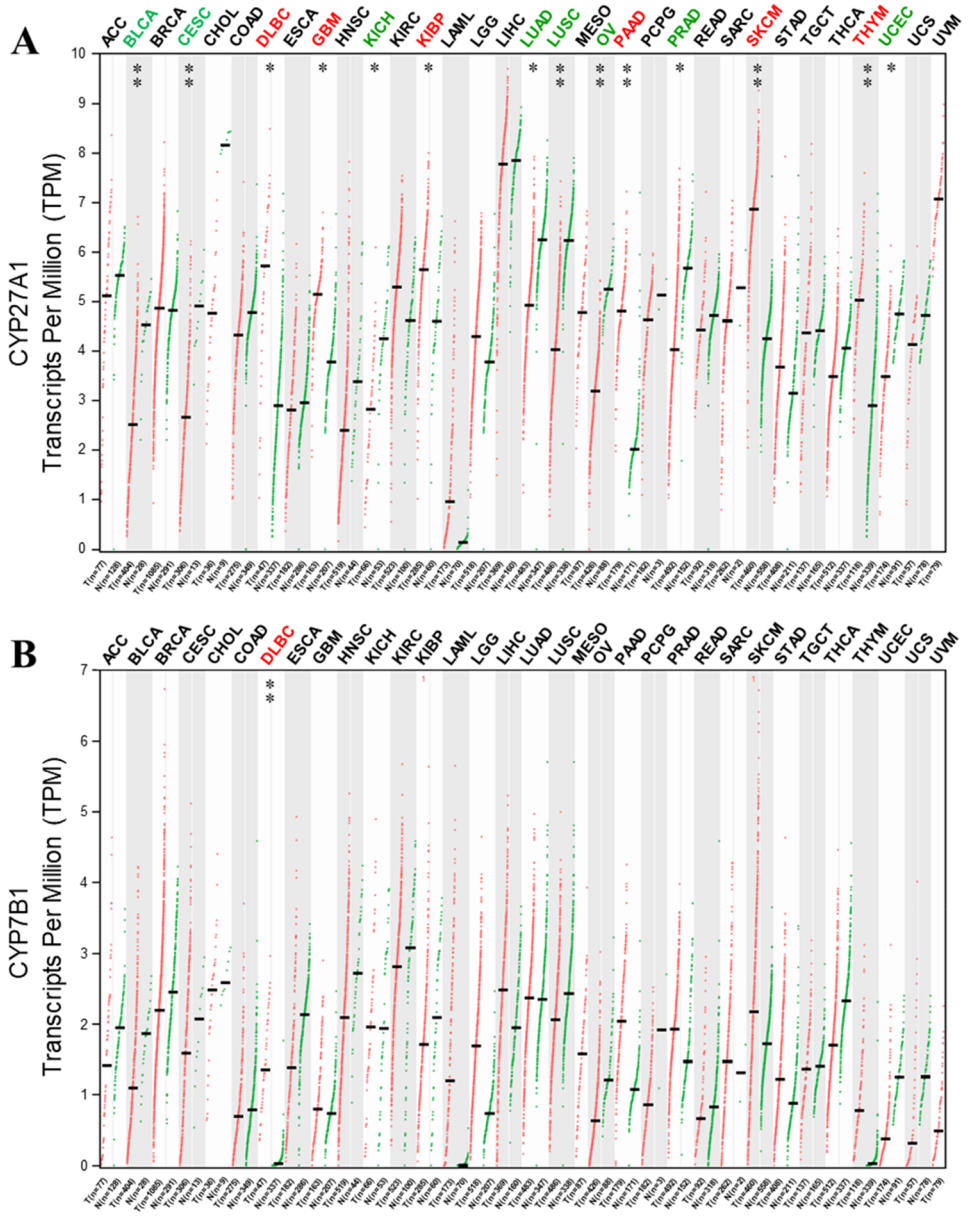


Figure 2. Expression patterns of key enzymes involved in 27HC metabolism across cancerous and normal tissues. The mRNA expression levels of enzymes involved in the synthesis (A, CYP27A1) and degradation (B, CYP7B1) of 27HC are shown. Data were obtained from the GEPIA database (http://gepia.cancer-pku.cn). Red labels indicate significantly higher gene expression in tumour tissue (T) compared to normal tissue (N), while green labels indicate significantly lower expression in tumours. Black labels denote no significant difference between tumour and normal tissues. ACC: adrenocortical carcinoma; BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: cholangio carcinoma; COAD: colon adenocarcinoma; DLBC: lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: oesophageal carcinoma; GBM: glioblastoma multiforme; HNSC: head and neck squamous cell carcinoma; KICH: kidney chromophobe; KIRC: kidney renal clear cell carcinoma; KIRP: kidney renal papillary cell carcinoma; LAML: acute myeloid leukaemia; LGG: brain lower grade glioma; LIHC: liver hepatocellular carcinoma; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; MESO: mesothelioma; OV: ovarian serous cystadenocarcinoma; PAAD: pancreatic adenocarcinoma; PCPG: pheochromocytoma and paraganglioma; PRAD; prostate adenocarcinoma; READ: rectum adenocarcinoma; SARC: sarcoma; SKCM: skin cutaneous melanoma: STAD: stomach adenocarcinoma; TGCT: testicular germ cell tumours; THCA: thyroid carcinoma; THYM: thymoma; UCEC: uterine corpus endometrial carcinoma; UCS: uterine carcinosarcoma; UVM: uveal melanoma.

LXR-mediated lipid regulation and pro-inflammatory effects, thereby altering tumour dynamics in PCa.

Although several studies have identified high CYP27A1 expression and low CYP7B1 expression as independent risk factors for poor survival of cancer patients,[71,73,74] data analysis from the GEPIA database has yielded inconsistent prognostic correlations (Figure 3). These discrepancies underscore the complexity of 27HC metabolism and highlight the need for further investigation into its precise role in tumour biology.

Role of 27HC in cancer development and progression

Breast cancer and 27HC

Breast cancer is a major global health issue, ranking among the three most common cancers worldwide.[79] Among the various risk factors for breast cancer, hypercholesterolaemia, and dyslipidaemia have gained increasing attention for their role in the development and progression of the disease.[80]

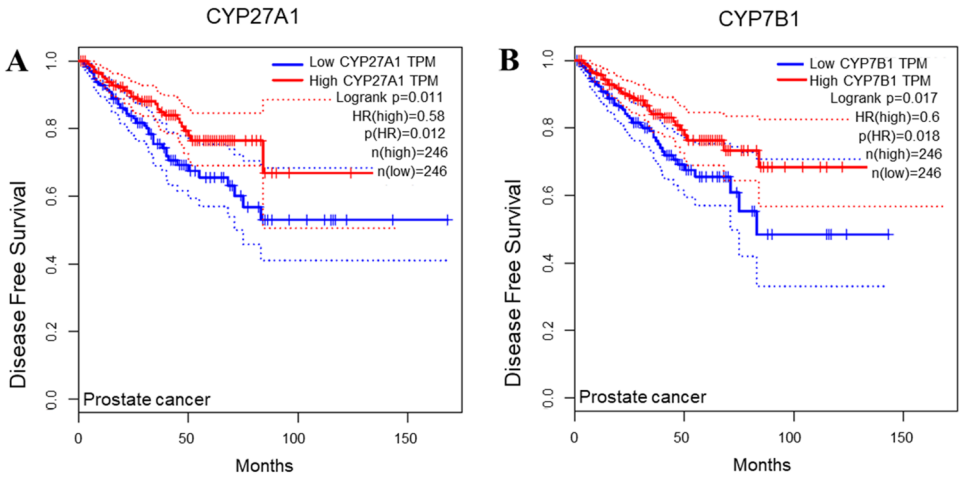


Figure 3. Association between the expression of key 27HC-metabolising enzymes and survival outcomes in PCa patients. The mRNA expression levels of enzymes involved in the synthesis (A, CYP27A1) and degradation (B, CYP7B1) of 27HC are associated with disease-free survival (DFS) in PCa patients. Survival analysis was conducted using the GEPIA database (http://gepia.cancer-pku.cn), with DFS and median expression (group cutoff) selected as statistical parameters.

Cholesterol influences several biological processes contributing to cancer growth, including inflammation, hormone regulation, and cell proliferation.[7,81] Notably, the protumorigenic effects of cholesterol are largely driven by its metabolite, 27HC.[72,73]

The protumorigenic potential of 27HC is primarily linked to chronic exposure, which is associated with increased levels of this metabolite in ER$^+$ breast cancer tissues compared to normal breast tissue. This elevation is attributed to enhanced expression of CYP27A1 and reduced expression of CYP7B1.[59,71,82–84] Nevertheless, the prospective epidemiological study examining pre-diagnostic circulating 27HC and breast cancer risk revealed an inverse relationship between blood 27HC levels and breast cancer risk in postmenopausal women. The researchers proposed that the inhibitory effect of 27HC on oestradiol-ER binding outweighed its agonistic activity in human breast cancer.[85]

Numerous studies emphasise the critical role of 27HC in breast cancer development and progression, influencing proliferation, migration, invasion, and immune modulation (Table 1). As a SERM, 27HC binds and activates ERs, promoting the growth of ER$^+$ breast cancer cells both *in vitro* and *in vivo*.[37] The intratumoral levels of 27HC in ER$^+$ breast cancer are six times higher than those found in normal breast tissue. This increase occurs because ER$^+$ breast cancer cells produce 27HC, which drives cell-autonomous proliferation through ER-dependent and glial cell-derived neurotrophic factor (GDNF)-RET-dependent mechanisms.[94] 27HC also acts on G protein-coupled oestrogen receptor (GPER), promoting ER$^-$ breast cancer progression by downregulating ERK1/2 and NF-κB signalling.[86] Beyond its role as a SERM, 27HC is also a LXR ligand.[25,37] Research has shown that 27HC drives ER-dependent tumour growth and LXR-dependent metastasis in mouse models of breast cancer. In MMTV-PyMT mice, CYP27A1 knockdown reduced tumour growth, while 27HC administration accelerated tumour progression, reinforcing its role in breast cancer pathogenesis.[73]

Several studies have explored how 27HC facilitates migration and invasion in breast cancer. 27HC promotes metastasis by increasing the expression of matrix metalloproteinase 9 (MMP9), triggering both EMT and endothelial-mesenchymal transition (EndMT), and activating the signal transducer and activator of transcription 3 (STAT3) signalling, which enhances cell proliferation and invasion.[89,115] Moreover, 27HC induces oxidative stress in human umbilical vein endothelial cells, activating p38 signalling and disrupting the 14–3-3-η/GSK-3β/β-catenin complex. This disruption leads to increased nuclear translocation of β-catenin, further promoting EndMT, invasion, and metastasis.[88] In breast cancer cells, the oxidative stress induced by 27HC elevates reactive oxygen species (ROS) levels, which activate STAT3 signalling and contribute to an aggressive tumour phenotype.[90] Research by Masha et al. demonstrated that 27HC enhances migration and invasion primarily through the activation of ERβ, which subsequently upregulates insulin-like growth factor I (IGF-I), IGF-I receptor (IGF-IR), and epidermal growth factor receptor (EGFR).[87] Together, these findings highlight the significant role of circulating and intratumoral 27HC in driving the progression of ER$^+$ breast cancer.

27HC-induced epigenetic modifications are also involved in the pathophysiology of breast cancer. Research has highlighted several ways in which 27HC contributes to breast cancer progression through its effects on gene expression and epigenetic regulation. First, 27HC promotes breast cancer progression by inducing epigenetic changes, particularly aberrant DNA methylation on the promoters of certain genes. This process is driven by the modulation of ERα and DNA methyltransferase 3 beta (DNMT3B) complexes, which cause local DNA methylation changes. These changes influence drug responses and drive the development of breast cancer.[92] Another study found that 27HC acts as a transcriptional repressor, suppressing the expression of euchromatic histone lysine methyltransferase G9a by negatively regulating ERα occupancy. This repression reduces the H3K9me2 mark on genes involved in cancer progression, proliferation, and metastasis, thus increasing their expression in breast cancer cells.[93] 27HC effect on gene expression also involves a reduction in the p53 transcriptional activity through increasing the expression of the E3 ubiquitin ligase MDM2, which targets

Table 1. Summary of 27HC functions in cancer development.

Cancer type	Mechanism	Phenotype/effect	References
Breast cancer	27HC activates GPER, and downstream NF-κB signalling together with ERK1/2 phosphorylation	Promotes cancer cell growth and proliferation	[86]
	Long-term 27HC exposure inhibits ferroptosis by maintaining GPX4 expression	Promotes cancer cell survival, migration growth and metastasis	[72]
	27HC increases the expression level of IGF-I and EGFR by activating ER-β	Promotes cancer cell invasion and migration	[87]
	27HC induces oxidative stress and activates p38 signalling. This disturbs the complex formation of 14-3-3-η/GSK-3β/β-catenin, and increases free β-catenin and its nuclear translocation	Promotes cancer cell EMT, invasion, and migration	[88]
	27HC upregulates the transcriptional expression of MMP9 by activating STAT3 signalling	Enhances cancer cell invasion, migration, and EMT	[89]
	27HC downregulates the expression of reversion-inducing cysteine-rich protein with Kazal motifs (RECK) through ROS-induced DNA methylation, thereby activating STAT3 signalling	Enhances cancer cell invasion and migration	[90]
	27HC reduces the microRNA content in neutrophils-released small extracellular vesicles (sEVs). These sEVs activate WNT/beta-catenin signalling in recipient cells	Promotes cancer cell EMT	[91]
	27HC induces DNA hypermethylation of *PTDSS2, MIR613, IDO1, THRA, DTYN,* and *MIER* by weakening the DNMT3B bound to ERα	Enhances cancer cell development	[92]
	27HC acts as ER and LXR agonist to increase ER-dependent growth and LXR-dependent metastasis	Enhances cancer cell invasion and migration	[73]
	27HC inhibits G9a expression *via* acting on ERα, further reduces H3K9 dimethylation in genes related to the development and invasion of cancer cells	Enhance tumorigenesis and invasion of breast cancer	[93]
	27HC stimulates ER-dependent cell-autonomous and GDNF-RET-dependent cell proliferation	Promotes tumour growth	[94]
	As a master transcriptional regulator of 27HC metabolism, ZMYND8 increases cholesterol biosynthesis and oxidation, but blocks cholesterol efflux and 27HC catabolism, leading to 27HC accumulation in cancer stem cells. 27HC promotes EMT by activating LXR signalling	Promotes tumorigenesis	[95]
	27HC increases the number of polymorphonuclear neutrophils and γδT cells in metastatic tumour. 27HC decreases the number of cytotoxic $CD8^+$T cells and promotes the immunosuppressive environment.	Enhances cancer cell metastasis	[43]
	27HC reduces the transcriptional expression of p53 and destroys p53 signalling in ER^+ cells. 27HC enhances the E3 ubiquitin protein ligase MDM2 bound with p53 in MDM2-dependent manner	Promotes cancer cell proliferation and progression	[96]
Prostate cancer	27HC inhibits SREBP activation and downregulates LDLR expression, reducing cholesterol level in cancer cells	Inhibits cancer cell growth	[97]
	27HC activates both ERα and ERβ	Increases cancer cell proliferation, but reduces invasion	[98]
	27HC disrupts lipid rafts in cell membrane, prevents IL6-JAK-STAT signal axis	Inhibits cancer cell growth	[77]
	27HC downregulates the DNA damage repair signalling, and decreases the expression of FEN1 and RAD51. 27HC induces "BRCAness" by down-regulating gene expression involved in homologous recombination repair	Inhibits cancer cell growth	[76]
Liver cancer	27HC upregulates GRP75 expression by enhancing ROS level. GRP75 controls Nrf2-mediated antioxidant signalling by modulating redox balance	Resistance to doxorubicin, sorafenib, 5-Fu, oxaliplatin	[51]
	27HC activates NF-κB signalling and enhances Twist1 expression	Enhances EMT and cancer cell metastasis	[99]
	27HC upregulates GPX4 expression, increases ferroptosis resistance. 27HC increases lipid metabolism, activates PPAR-γ signalling, activates macrophage polarisation	Enhances cancer cell proliferation, invasion, and migration	[100]
	Increased 27HC promotes cell proliferation and anti-apoptosis through targeting HNF4A/CYP27A1/cholesterol axis	Promotes cancer cell proliferation and tumour growth	[101]
Ovarian cancer	27HC inhibits cell growth in LXR-dependent manner	Inhibits cancer cell proliferation	[102]
Gastric cancer	27HC inhibits cell proliferation *via* activating LXR-β, and inhibits cell migration by combined activating on LXR-α and LXR-β	Inhibits cancer cell proliferation and migration	[103]
	Decreased 27HC level maintains gastric epithelial function *via* modulating PI3K/Akt signalling. SULT2B1 knockdown induces the malignant transition of gastric epithelial cells	Promotes epithelial cell dysfunction	[104]
Thyroid cancer	27HC accumulation promotes cellular aggressiveness	Enhances invasion and migration of cancer cells	[105]
Endometrial cancer	27HC selectively targets LXR and increases the target gene transcription *via* LXR- or ER-dependent manner	Promotes cancer cell proliferation	[106]
Lung cancer	27HC induces the phosphorylation of Akt and NF-κB/p65, and promotes PPIB expression. 27HC induces FGF2 and IL-6 secretion, thus promoting the expression of Snail and Vimentin	Promotes cancer cell proliferation and invasion	[107]
	27HC promotes cell proliferation by activating ERβ-dependent PI3K-Akt signalling	Promotes cancer cell proliferation	[108]
	27HC promotes osteoclastogenesis and bone metastasis *via* inhibiting miR-139 expression and activating STAT3/c-Fos/NFATc1 signalling	Enhances bone metastases of cancer cells	[109]
Colorectal cancer	27HC increases the expression of IL6, IL8, MCP1, VEGF, MM2, and MM9 by activating Akt signalling, thus facilitating cancer progression	Promotes tumorigenesis	[110]
	27HC inhibits cell proliferation by deactivating Akt signalling	Inhibits cancer cell proliferation	[111]
Melanoma	27HC activates ERα and increases the phosphorylation of AKT, ERK and JNK	Promotes cancer cell proliferation	[112]
	27HC upregulates the expression of Rap1A, Rap1B and increases the phosphorylation of AKT	Promotes cancer cell growth and drug resistance	[113]
	Excess cholesterol or 27HC promotes cellular invasion *via* activating AP-1 that is associated with metastasis	Promotes cancer cell invasion	[114]

p53 for degradation. Additionally, 27HC enhances the physical interaction between p53 and MDM2, further suppressing p53 activity.[96] Finally, Luo et al. identified the histone reader ZMYND8 as a key transcriptional regulator of 27HC metabolism. ZMYND8 is selectively expressed in breast cancer stem cells, where it promotes cholesterol biosynthesis and oxidation while blocking cholesterol efflux and 27HC catabolism, leading to 27HC accumulation. This buildup of 27HC triggers EMT, oncogenic transformation, and tumour initiation through activation of LXR.[95]

27HC also reshapes the immune microenvironment and alters extracellular vesicle (EV)-mediated signalling in breast cancer pathways. It was reported that CYP27A1 is also highly expressed in monocytes and monocyte-derived macrophages besides breast cancer cells. Meanwhile, CYP7B1 is hypermethylated in breast cancer tumour cells, leading to 27HC accumulation in the breast cancer microenvironment. Additionally, M2 macrophages produce large amounts of 27HC, which, beyond stimulating ER^+ breast cancer cell proliferation, also enhances monocyte recruitment by inducing macrophages to express chemokines CCL2, CCL3, and CCL4.[82] Apart from recruiting monocytes to the tumour microenvironment, 27HC further promotes an immunosuppressive microenvironment that supports breast cancer growth by decreasing cytotoxic $CD8^+$ T lymphocyte population and facilitating the recruitment of polymorphonuclear neutrophils (PMNs) and γδ-T cells. Finally, emerging evidence highlights the role of 27HC in modulating the composition of EVs, which are key regulators of cell–cell communication within the tumour microenvironment.[116] Recent studies have shown that 27HC specifically alters the composition of small EVs released from neutrophils, notably by reducing their microRNA (miR) content. This reduction of miRs within EVs triggers the activation of WNT/β-catenin signalling in recipient breast cancer cells, promoting their proliferation, invasion, and metastasis.[91] 27HC-triggered changes within the tumour microenvironment create a pro-tumorigenic landscape, enhancing the metastatic potential and accelerating breast cancer progression.

Overall, these findings highlight the importance of lipid metabolism in breast cancer biology and suggest that targeting 27HC could be a valuable strategy in the fight against breast cancer.

Prostate cancer and 27HC

Advanced PCa is an aggressive cancer with high mortality rates.[117] While its exact aetiology remains unclear, epidemiological studies suggest that elevated circulating cholesterol levels are linked to an increased incidence of high-grade PCa.[118–120] Additionally, higher levels of total serum cholesterol are associated with an increased risk of recurrence in men diagnosed with PCa, suggesting a correlation between elevated cholesterol levels and prostate malignancy.[121] There is no direct evidence linking 27HC levels to prostate PCa risk. However, it is well established that 27HC levels increase with age, particularly in males, and are elevated in individuals with hypercholesterolaemia – both of which are risk factors for PCa.[31,118]

Current research indicates that 27HC exhibits both pro-tumorigenic and anti-tumorigenic effects in PCa, with its influence varying based on cellular context and specific signalling pathways. The protumorigenic effect of 27HC in PCa is primarily linked to its ability to stimulate cell proliferation. This occurs through the activation of ERβ, as demonstrated by studies showing that specific ERβ inhibitors, such as PHTPP, significantly reduce 27HC-induced proliferation.[98] Conversely, certain studies suggest that 27HC might reduce the proliferation and invasion of PCa cells. Notably, lower expression levels of CYP27A1 have been linked to shorter disease-free survival and higher tumour grades in PCa. Restoring CYP27A1 expression or administering 27HC has demonstrated the ability to suppress PCa growth both *in vitro* and *in vivo*. Mechanistically, 27HC lowers cholesterol levels in PCa cells by inhibiting the activation of sterol regulatory element-binding protein (SREBP) and downregulating LDLR expression.[97] Additionally, 27HC disrupts lipid rafts on the cell membrane, which are essential for IL6-JAK-STAT signalling. This disruption prevents STAT3 activation, thereby inhibiting PCa cell growth.[77] Furthermore, 27HC can induce a "BRCAness" phenotype in PCa cells, characterised by impaired DNA damage repair due to the downregulation of key genes such as *FEN1* and *RAD51*. This induction not only inhibits PCa growth but also increases the susceptibility of these cells to DNA-damaging agents and therapies, such as PARP inhibitors, leading to more significant DNA damage in castration-sensitive PCa.[76]

These findings underscore the complex role of 27HC in PCa, revealing evidence for both tumour-promoting and inhibiting effects. Further research is needed to fully elucidate the context-dependent actions of 27HC in PCa (Table 1).

Liver cancer and 27HC

Liver cancer encompasses malignant tumours originating in or spreading to the liver. The most prevalent primary liver cancer is hepatocellular carcinoma (HCC), accounting for approximately 90% of cases. HCC is a significant global health concern, ranking as the fourth leading cause of cancer-related deaths worldwide.[122] It is linked to several risk factors, including chronic hepatitis B (HBV) and hepatitis C (HCV) infections, excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD), aflatoxin exposure, and certain genetic disorders.[123] Ongoing research aims to understand liver cancer pathogenesis and develop more effective treatments to improve patient outcomes.

27HC has been implicated in the progression of HCC. The levels of 27HC are significantly elevated in advanced HCC,[124,125] and its increased presence may actively drive HCC development through multiple mechanisms. It has been reported that increased expression of tubulin beta class I genes (TUBBs) is an independent prognostic factor for shorter overall survival of HCC patients and a driver for HCC cell proliferation and survival. From a mechanistic perspective, TUBB2B upregulates CYP27A1 expression *via* suppressing HNF4A, leading to increased 27HC levels and facilitating HCC progression. These findings suggest that targeting the TUBB2B/HNF4A/CYP27A1 axis may be a potential therapeutic strategy for HCC.[101] While the mechanism of 27HC-mediated anti-apoptotic activity has not been identified in HCC cells, it's reported that 27HC-induced ROS-generation triggers Nrf2-mediated

antioxidant responses and ERK and PI3K/Akt signalling activation, thus promoting cell survival in human promonocytic cells.[126,127]

Ferroptosis is a distinct form of regulated cell death characterised by iron-dependent lipid peroxidation and oxidative membrane damage.[128] Interestingly, emerging evidence suggests that 27HC may play a role in modulating this process. Studies indicate that chronic exposure to 27HC can lead to resistance to ferroptosis in cancer cells, thereby enhancing tumorigenicity and metastatic potential. This resistance is associated with increased expression of glutathione peroxidase 4 (GPX4), an enzyme that inhibits lipid peroxidation and protects against ferroptosis.[72] Consistent with this observation, liver cancer exhibits high expression of transmembrane protein 147 (TMEM147), which interacts with 7-dehydrocholesterol reductase (DHCR7) to regulate cellular cholesterol homeostasis and elevates extracellular 27HC levels. As a result, increased 27HC exposure upregulates GPX4 expression, thus enhancing resistance to ferroptosis and further driving HCC cell proliferation.[100] Additionally, elevated 27HC levels enhance lipid metabolism in macrophages and activate peroxisome proliferator-activated receptor-γ (PPAR-γ) signalling, which induces M2 macrophage polarisation and contributes to HCC cell invasion and migration.[100] He et al. also reported the prometastatic activity of 27HC, demonstrating that it drives metastasis by activating SULT2A1-dependent NF-κB signalling. This activation enhances Twist1 expression and promotes EMT in HCC.[99]

Another important function of 27HC in HCC progression is its involvement in MDR. Prolonged exposure to 27HC induces adaptive resistance in HCC cells, diminishing its cytotoxic effect and facilitating the development of MDR.[51] Mechanistically, 27HC upregulates glucose-regulated protein 75 (GRP75), a key regulator of redox signalling and homeostasis, by mediating ROS production and activating antioxidant defence mechanisms.[129–131] Elevated GRP75 expression also drives metabolic reprogramming, enabling HCC cell proliferation in a hostile microenvironment.[51]

Overall, these studies highlight that 27HC plays a key role in promoting liver cancer cell survival, proliferation, metastasis, and drug resistance (Table 1).

Ovarian cancer and 27HC

Ovarian cancer is a significant cause of cancer-related mortality among women. Its early detection is challenging due to subtle and often overlooked symptoms, leading to diagnoses at advanced stages when treatment becomes more difficult.[132] Several risk factors, including age, family history, and specific genetic mutations, such as *BRCA1* and *BRCA2*, influence ovarian cancer. Treatment typically involves surgery and chemotherapy; however, the prognosis remains poor for many women, especially those diagnosed at advanced stages.[133]

The relationship between obesity and ovarian cancer is complex. Elevated plasma LDL level is positively associated with shorter progression-free survival (PFS) and shorter disease-specific survival (DSS) in ovarian cancer patients.[134,135] Conversely, longer PFS and DSS are generally observed in patients treated with cholesterol-lowering drugs.[136–138] These findings suggest that high cholesterol levels contribute to ovarian cancer progression and poor prognosis. 27HC has been shown to modulate the activity of ERs and LXRs, potentially linking cholesterol metabolism to ovarian cancer progression. Studies reported that high expression of CYP27A1 correlates with decreased PFS, while high expression of CYP7B1 is associated with increased PFS.[102] Interestingly, while 27HC inhibits the proliferation of ovarian cancer cell lines in a LXR-dependent manner *in vitro*, *in vivo* studies revealed a contrasting effect: ovarian cancer cells failed to grow in CYP27A1$^{-/-}$ mice, suggesting a tumour-promoting role for 27HC in the host microenvironment. Further analysis revealed that exposing mice to increasing dietary cholesterol or exogenous 27HC accelerated ovarian cancer growth by altering immune cell populations within tumours, particularly increasing CD11B^{+} myeloid cells. Combining CYP27A1 inhibition with immune checkpoint blockade significantly reduced tumour size compared to single-agent treatments, highlighting the therapeutic potential of targeting this pathway.[102] These studies highlight the role of 27HC in promoting ovarian cancer development and progression (Table 1).

Gastric cancer and 27HC

Gastric cancer ranks as the fifth most common cancer worldwide and is the third leading cause of cancer-related deaths globally.[139] Oxysterols have a complex role in gastrointestinal cancers, exhibiting both pro-apoptotic/cytotoxic and pro-cancerous effects. They induce metabolic disturbances, generate ROS, and trigger lipid peroxidation, ultimately causing DNA damage, impairing repair mechanisms, and leading to genetic alterations that may drive gastric cancer progression.[140]

Although 27HC is known to drive tumorigenesis and metastasis in several cancers, its specific role in gastric cancer remains largely unclear. Research shows that 27HC levels are significantly elevated in gastric cancer tissues and cancerous gastric juice compared to healthy gastric mucosa.[103] Furthermore, 27HC contributes to gastric cancer development by modulating cell proliferation and migration through complex interaction with LXRs, indicating its potential as a therapeutic target in gastric cancer treatment.[103]

Gastric epithelial cell dysfunction is a crucial factor in gastric cancer development. Oxysterols in gastric epithelium can undergo further sulphation by hydroxysteroid sulfotransferase 2B1 (SULT2B1). Hong et al. reported that SULT2B1 overexpression in normal gastric epithelial cells reduces oxysterol accumulation, particularly 27HC levels. Moreover, SULT2B1 overexpression activates PI3K/Akt signalling, maintaining epithelial integrity and suppressing carcinogen-induced tumorigenesis in gastric cancer.[104] These findings suggest that elevated 27HC levels play a role in the initiation and progression of gastric cancer (Table 1).

In summary, initial findings suggest that 27HC has tumour-promoting effects in gastric cancer. Further studies

are needed to clarify the exact mechanisms underlying its role in gastric cancer progression.

Thyroid cancer and 27HC

Thyroid cancer is the most common endocrine malignancy, with its incidence rising globally.[141] While most thyroid cancers have a favourable prognosis, aggressive forms can be challenging to treat.[142] Recent studies indicate that a high proportion of fat mass, elevated cholesterol levels, and obesity are all linked to an increased risk of thyroid cancer,[143,144] highlighting the potential role of cholesterol metabolism and its byproducts, such as 27HC, in tumour progression. In support of this notion, a study by Revilla et al. has shown the link between lipoprotein profiles, intratumoral cholesterol, and thyroid cancer aggressiveness. They found that patients with advanced thyroid cancers exhibited lower blood levels of LDL cholesterol and apolipoprotein B (ApoB), alongside increased expression of LDLR in thyroid tissues. These changes are associated with elevated intratumoral levels of 27HC and downregulation of genes involved in cholesterol metabolism, such as HMGCR and CYP7B1. *In vitro* experiments demonstrated that LDL cholesterol promoted proliferation in normal and anaplastic thyroid cell lines but enhanced migration only in anaplastic cells[105] (Table 1). Together, these findings show that the accumulation of cholesterol and 27HC in tumours contributes to the aggressiveness of papillary thyroid cancer, implying that targeting cholesterol metabolism could be a potential therapeutic strategy for thyroid cancer with poor prognosis.

Endometrial cancer and 27HC

EC is one of the most prevalent gynaecological malignancies, with its incidence rising in parallel with increasing rates of obesity and overweight.[145] A recent meta-analysis highlights the significant association between dietary cholesterol intake and an increased risk of developing EC.[146] Obesity is a well-established risk factor for EC, contributing to elevated cholesterol levels and increased production of cholesterol metabolites, such as 27HC. Although 27HC has been shown to promote tumorigenesis and metastasis in various cancers, its role in EC remains poorly understood. A recent study by Gibson et al. explored the role of cholesterol metabolites in EC by analysing tissue samples from postmenopausal women with stage I EC who underwent hysterectomy. Their results showed that expression of enzymes that regulate bioavailability of 27HC (CYP27A1 and CYP7B1) and its cognate receptor LXRs (LXRα and LXRβ) is changed in EC consistent with increased 27HC exposure as EC progresses from well to poorly differentiated. Notably, 27HC activates LXR- and ER-dependent transcription in EC cells and alters proliferation of EC cells. Targeting LXRs with an agonist (GW3965) activates LXR-dependent transcription and alters cell proliferation in a cell-specific manner.[106] Interestingly, 27HC selectively activates ER-dependent transcription and promotes the proliferation of well- and moderately-differentiated EC cells, similar to the effect triggered by the LXRs agonist GW3965.[106] This study highlights that 27HC functions as both a SERM and an endogenous agonist for LXR, driving EC cell proliferation and tumour progression (Table 1). Decreasing 27HC levels by lifestyle changes, lipid-lowering drugs (e.g. statins), or novel therapeutics that target 27HC synthesis (e.g. CYP27A1 inhibitors) may be effective approaches to disrupt 27HC-mediated EC development.

Lung cancer and 27HC

Emerging evidence supports that elevated cholesterol levels play a significant role in the development and progression of lung cancer.[147,148] Notably, 27HC has gained recognition as a key mediator linking cholesterol metabolism to lung cancer growth, invasion, and metastasis.

Recent findings indicate that CYP27A1 is highly expressed in lung cancer cells compared to normal lung tissue. 27HC promotes the proliferation of ERβ-positive lung cancer cells by activating the ERβ-dependent PI3K/Akt signalling, while it does not affect ERα-positive or ER-negative cells.[108] Additionally, 27HC is linked to the proliferation and invasion of cholesterol-driven lung adenocarcinoma (LAC). Knockdown of CYP27A1 reduces these effects, whereas knockdown of CYP7B1 enhances them, suggesting a regulatory role of cholesterol metabolism in lung cancer progression.[107] Mechanistic studies revealed that 27HC exposure activates Akt and NF-κB/p65 phosphorylation while upregulating peptidylprolyl isomerase B (PPIB) expression, particularly in the presence of THP-1-derived macrophages.[107] These findings suggest that 27HC is a crucial link between high cholesterol levels and lung cancer progression by activating NF-κB/PPIB signalling (Table 1). These effects are particularly pronounced when lung cancer cells are co-cultured with macrophages, highlighting the role of the tumour microenvironment in 27HC-driven metastasis.

Advanced lung cancer frequently metastasises to the bone, leading to osteolytic lesions.[149] Metastatic lung cancer cells influence bone remodelling through complex interactions between osteoclasts and osteoblasts.[150] Additionally, cancer cells alter immune cell function, driving the production of mediators that accelerate osteoclast formation.[151] 27HC plays a role in this process by inducing macrophages to secrete pro-osteoclastogenic cytokines, such as interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α),[152] both of which promote osteoclast differentiation.[153,154] Additionally, lung cancer-derived conditioned media containing 27HC decreases miR-139 expression while activating the STAT3/cFos/NFATc1 signalling, further enhancing osteoclastogenesis and bone degradation.[109]

Taken together, 27HC serves as a critical link between high cholesterol levels and lung cancer progression. Moreover, its role in osteoclast differentiation contributes to bone metastases, a severe complication of advanced lung cancer. Targeting 27HC and its associated signalling may offer promising therapeutic strategies for treating lung cancer and its metastasis.

Colorectal cancer and 27HC

Colorectal cancer (CRC) ranks as the third most prevalent malignancy worldwide.[155,156] While oxidative sterol-mediated signalling contributes to tumorigenesis, research specifically investigating the role of 27HC in CRC remains limited.

Emerging evidence highlights the complex and context-dependent role of 27HC in CRC progression. The assessment of circulating 27HC levels in CRC patients using liquid chromatography-mass spectrometry (LC/MS) demonstrated a correlation between elevated plasma 27HC and an increased risk of developing CRC precursor lesions, excluding serrated polyps.[157] Additionally, a significant rise in 27HC levels was observed exclusively in advanced-stage CRC (TNM stage III). Elevated 27HC levels promoted the release of multiple pro-inflammatory and tumour-promoting factors, including IL-6, IL-8, monocyte chemotactic protein-1 (MCP-1), vascular endothelial growth factor (VEGF), MMP2, and MMP9. These factors contribute to CRC progression by activating Akt signalling, which is triggered by supra-physiological levels of 27HC.[110] In contrast, Warns et al. presented opposing findings from *in vitro* experiments exploring the impact of 27HC on CRC cell proliferation. This study demonstrated that 27HC treatment at varying concentrations inhibited CRC cell proliferation. This anti-proliferative effect was independent of cytotoxicity, apoptotic cell death, and LXR- or ER-activation pathways. Instead, the suppression of proliferation was attributed to a reduction in Akt activation, a key regulator of cell cycle progression, protein synthesis, and survival of cancer cells[111] (Table 1).

Together, these findings underscore the dual role of 27HC in CRC progression, with context-dependent effects on tumour growth and signalling pathways. Further research is warranted to clarify these contradictory effects and to explore the potential of 27HC as a biomarker or therapeutic target in CRC management.

Melanoma and 27HC

Melanoma is the deadliest form of skin cancer, particularly prevalent in the United States and Europe.[158] Obesity increases the risk of melanoma through the secretion of adipokines that promote tumour growth.[159] Melanoma has also been studied in relation to cholesterol metabolism. One key molecule in this context is 27HC. Tian et al. reported that high levels of 27HC are associated with melanoma development, particularly in obese or hypercholesterolaemic individuals. 27HC promotes the growth of melanoma cells by activating ERα and downstream AKT and MAPK signalling.[112] However, conflicting evidence exists regarding ER expression in melanoma. Some studies have shown that ERβ, rather than ERα, is predominantly expressed in less invasive primary melanoma tissues without sentinel lymph node involvement. ERβ expression is downregulated in aggressive melanomas with sentinel node metastasis, and ERβ agonists differentially regulate the proliferation of distinct melanoma cell lines.[160,161] This suggests that ER isoforms may have differential roles depending on the melanoma stage.

BRAF inhibitors, including vemurafenib, dabrafenib, and encorafenib, are pivotal in the treatment of BRAF-mutant melanoma. These agents selectively target BRAF kinase, disrupting the mitogen-activated protein kinase (MAPK) signalling, which is crucial for melanoma cell proliferation and survival.[162] Interestingly, it has been shown that administration of 24-dehydrocholesterol reductase (DHCR24) or cholesterol induces resistance to a BRAF inhibitor, vemurafenib, and promotes melanoma growth in xenografted mice. Further studies revealed that 27HC administration activates the Rap1-PI3K/AKT signalling, which promotes melanocyte proliferation and vemurafenib-resistance, reproducing the DHCR24- or cholesterol-induced phenotypes. Moreover, CYP27A1 is highly expressed in melanoma patients and upregulated by DHCR24 induction.[113] In addition, excess 27HC promotes melanoma aggressiveness by activating AP-1 transcriptional program, which is associated with increased melanoma cell invasion and metastasis[114] (Table 1).

Collectively, these findings suggest that 27HC contributes to melanoma progression through complex mechanisms involving ER signalling, PI3K/AKT signalling, and AP-1 transcriptional programme. Targeting 27HC or its associated pathways may provide novel therapeutic opportunities for melanoma treatment.

Mechanisms of 27HC-mediated multi-drug resistance

27HC and drug efflux

In human tissues, ATP-binding cassette (ABC) transporters play a crucial role in drug resistance.[163,164] Among these, P-glycoprotein (Pgp), multidrug-resistant associated protein 1 (MRP1/ABCC1), ABC subfamily G member 1 (ABCG1), G member 2 (ABCG2/BCRP), and member A1 (ABCA1) are key contributors to the efflux of chemotherapeutic agents from cancer cells. These transporters are highly expressed in drug-resistant cancers and can be targeted to reverse efflux-mediated resistance.[165]

Cholesterol homeostasis is essential for cellular proliferation and is primarily regulated by two transcription factors: LXRs and SREBPs. LXRs modulate intracellular cholesterol efflux by upregulating ABCG1 and ABCA1.[166] Conversely, SREBPs regulate intracellular cholesterol biosynthesis and extracellular uptake through LDLR expression.[167] Recent studies have shown that 27HC acts as an agonist for LXRs. In bladder cancer cells with downregulated CYP27A1 expression, exogenous administration of this oxysterol increases the expression of ABCG1 and ABCA1 while decreasing LDLR levels. This results in reduced intracellular cholesterol concentrations, thus inhibiting cancer cell proliferation.[168] Moreover, both 7-ketocholesterol (7KC) and 27HC elicit oestrogenic effects that contribute to Pgp induction in breast cancer cells. Treatment with subtoxic concentrations of 27HC decreases doxorubicin accumulation within cells cultured under conditions mimicking low oestrogen levels. This effect may be attributed to the induction of ER target genes like Trefoil factor 1 (TFF1) by 27HC, suggesting a mechanism through which

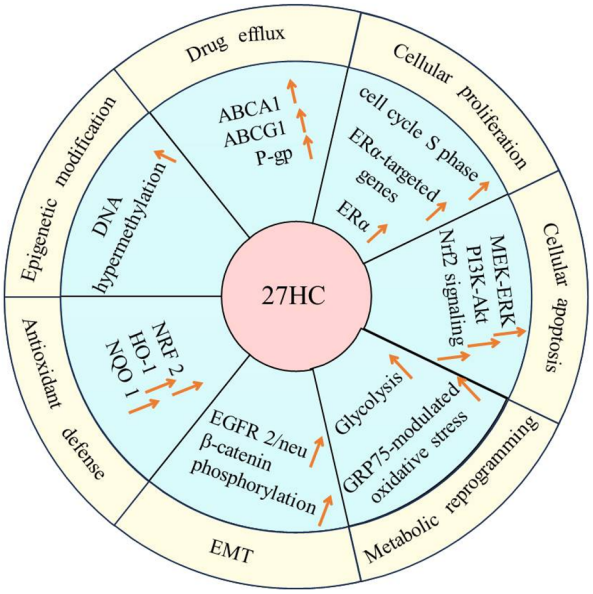


Figure 4. Proposed mechanisms of 27HC-mediated cancer drug resistance. Illustration of potential cellular pathways (blue) and associated phenotypic outcomes (yellow) that contribute to drug resistance induced by 27HC. The diagram is drawn by the authors.

it enhances drug resistance *via* modulation of ABC transporters.[169] These findings collectively suggest that 27HC promotes cancer drug resistance by influencing the expression of ABC transporters involved in chemotherapeutic agent efflux (Figure 4).

27HC and cellular apoptosis

Most cancer therapies, including chemotherapy, exert their effects by inducing apoptosis – a tightly regulated process essential for eliminating damaged or unnecessary cells. However, dysregulation of apoptosis is a common mechanism contributing to drug resistance in cancer cells.[170] For instance, docetaxel, a pro-apoptotic agent used to treat advanced PCa, relies on apoptosis induction for its therapeutic efficacy.[171,172]

27HC exposure has been shown to stimulate the proliferation of prostate epithelial cells by increasing the transcriptional activity of androgen receptor (AR) and enhancing AR binding to androgen response elements. This effect is accompanied by increased expression of prostate-specific antigen (PSA). Silencing AR expression using siRNA significantly reduces the 27HC-induced proliferative effect, highlighting the role of AR in mediating these changes. When co-treating prostate epithelial cells with docetaxel and 27HC, it was observed that 27HC blocks docetaxel-induced apoptosis. Such an inhibitory effect becomes more pronounced with increasing concentrations of 27HC.[173] In aggressive PCa, 27HC treatment leads to a rapid and significant reduction in plasma membrane cholesterol levels, disrupting lipid raft structure and function. This disruption impairs the IL6-JAK-STAT3 signalling by reducing STAT3 activation, as evidenced by decreased phosphorylation, dimerisation, nuclear translocation, and DNA binding of STAT3. Consequently, the expression of STAT3 target genes associated with proliferation, migration, and survival is diminished, resulting in decreased cancer cell growth and survival *in vitro* and *in vivo*. Additionally, combining 27HC with STAT3 inhibitors results in synergistic effects, further suppressing cancer cell proliferation and migration.[77] This study highlights how modulation of intracellular cholesterol by 27HC can inhibit oncogenic signalling critical for tumour progression and supports novel approaches to targeting these pathways (Figure 4).

27HC and cellular proliferation

SERMs activate ERα and ERβ, leading to the upregulated transcription of pro-survival genes and promoting breast cancer cell proliferation.[174] Generally, obesity increases breast cancer risk due to elevated aromatase expression in adipose and tumour tissues, which converts androgens into oestrogens. To counteract this, aromatase inhibitors (AIs) are commonly used in breast cancer treatment. However, AIs do not eliminate other oestrogen-like molecules, including 27HC, allowing their proliferative effects to persist.[175,176] Oestradiol is a steroid hormone with well-documented roles in promoting cell growth.[177] 27HC exhibits similar effects to oestradiol by acting as an endogenous SERM that activates ERα. In AI-resistant cells, enhancers of cholesterol biosynthesis genes are epigenetically activated, leading to increased CYP27A1 expression and higher levels of 27HC. This metabolic shift contributes to constitutive activation of ERα in AI-resistant cancers by enhancing 27HC biosynthesis.[178] Tamoxifen, a widely used nonsteroidal SERM, inhibits ER-mediated proliferation by competitively binding ERs, thereby reducing cancer cell growth.[179,180] However, its efficacy diminishes over time, likely due to complex crosstalk between SERM-modulated ER signalling and mitogenic signalling pathways.[181,182]

Some studies have demonstrated that 27HC reduces the anti-proliferative effect of fulvestrant, i.e. a selective ER degrader, in long-term oestrogen-deprived (LTED) ER$^+$ breast cancer cells by functioning as an ER agonist. This leads to enhanced transcriptional activation of the oestrogen-responsive gene *TFF1*. Additionally, 27HC increases the recruitment of ER and CREB-binding proteins (CBP) to *TFF1* and *GREB1* promoters, further amplifying oestrogenic signalling.[183] Moreover, 27HC stimulates cell cycle progression, significantly increasing the proportion of ER$^+$ breast cancer cells in S-phase, thereby promoting proliferation. This mechanism enables certain ER$^+$ breast cancer cells to develop resistance to anti-oestrogens or local oestradiol production inhibitors.[184] These findings suggest that 27HC enhances breast cancer drug resistance by promoting S-phase enrichment and upregulating ER-driven cell proliferation, highlighting its role as a key factor in therapy resistance (Figure 4).

27HC and epithelial-mesenchymal transition

EMT is a reversible biological process that confers epithelial cells with migratory and invasive properties, transforming them into a fibroblast-like phenotype. During EMT, there is a characteristic downregulation of epithelial markers such as E-cadherin and ZO-1, while mesenchymal markers like Vimentin and N-cadherin are upregulated.[185,186] Dysregulated

EMT often leads to cancer drug resistance by imparting cancer cells with characteristics similar to those of cancer stem cells, including enhanced drug efflux capability and resistance to apoptosis.[187,188]

Recent studies have shown that small EVs released from neutrophils treated with 27HC can enhance EMT and stem-like properties in breast cancer cells. These EVs lead to loss of cell adhesion, increased migratory capacity, and increased resistance to cytotoxic chemotherapy. Notably, decreased miR s within these EVs activate the WNT/β-catenin signalling in recipient breast cancer cells – a key mechanism potentially driving both stem-like phenotype and EMT.[91] Furthermore, 27HC exposure has been demonstrated to induce EMT in ERα^{+} breast cancer cells by reducing the expression of critical adhesion molecules such as E-cadherin, β-catenin, and adhesion junction complexes. This shift to mesenchymal phenotype is associated with EGFR2/neu activation on the surface of these cancer cells.[52] Given that EGFR-triggered β-catenin activation promotes the mesenchymal phenotype in tamoxifen-resistant (Tam^{R}) breast cancer cells, this observation supports this pathway in drug resistance.[189] Thus, 27HC promotes cancer drug resistance by upregulating EGFR-mediated β-catenin activation (Figure 4). Overall, these findings suggest that targeting 27HC-associated EMT process may provide innovative strategies for overcoming cancer drug resistance.

27HC and metabolic reprogramming

Metabolic reprogramming is a hallmark of drug-resistant cancer cells, characterised by altered enzyme activity and dysregulated metabolic products.[190] Long-term exposure of 27HC to liver cancer cells triggers oxidative stress signalling, leading to the upregulation of GRP75. GRP75 overexpression changes the redox balance by reducing ROS levels and enhancing the antioxidant defence system, thereby protecting cancer cells from oxidative damage.[51,130] Beyond redox regulation, overexpressed GRP75 also drives metabolic reprogramming by increasing glycolysis, supplying energy and biosynthetic precursors essential for cancer cell survival.[51,129–131] This metabolic shift enables liver cancer cells to develop adaptive mechanisms, allowing them to thrive in hostile microenvironments. Ultimately, these changes reduce 27HC-induced cytotoxicity and contribute to the MDR phenotype.[51] These findings suggest that 27HC can promote cancer drug resistance by enhancing glycolysis and GRP75-mediated oxidative stress adaptation, highlighting a potential metabolic vulnerability for therapeutic targeting (Figure 4).

27HC and Nrf2-dependent antioxidant defence

The Kelch-like ECH-associated protein 1-NF-E2-related factor 2 (KEAP1-NRF2) signalling pathway is a crucial cellular defence mechanism against oxidative stress, playing a pivotal role in maintaining redox balance and promoting cell survival under adverse conditions.[191,192] NRF2 is a redox-sensitive transcription factor that is typically sequestered by KEAP1 in the cytoplasm. Under oxidative stress conditions, NRF2 dissociates from KEAP1 and translocates to the nucleus, where it binds to antioxidant response elements (AREs) within gene promoters. Such a binding upregulates the transcription of antioxidant enzymes essential for mitigating oxidative damage.[193] Additionally, p62/SQSTM1 can interact with KEAP1 at its NRF2-binding site, competitively releasing NRF2 and further enhancing its transcriptional activity.[194]

Studies suggest that 27HC influences the NRF2 pathway and promotes cellular resistance mechanisms. Vurusaner et al. reported that low concentrations of 27HC activate NRF2, leading to resistance against 27HC-induced apoptosis in human promonocytic cells. This activation results in increased expression of antioxidant enzymes, such as haem oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase-1 (NQO-1), which are dependent on ERK and Akt signalling. These changes effectively reduce intracellular ROS levels and initiate adaptive pro-survival response that protects cells from oxidative insults.[126] In advanced atherosclerotic lesions, 27HC has been shown to activate the ERK- and PI3K/Akt-dependent pro-survival autophagic response, which further enhances antioxidant defences. This process is accompanied by p62 accumulation and activation of NRF2-dependent antioxidant reactions.[195] In liver cancer, long-term exposure to 27HC has been linked to MDR development in cancer cells. During prolonged exposure, liver cancer cells exhibit increased ROS production due to activation of NADPH oxidase-2 and develop mechanisms for tolerating this cytotoxicity through upregulating GRP75 expression. GRP75 plays an indispensable role by activating antioxidant factors like NRF2, HO-1, and NQO-1, thereby contributing significantly to MDR acquisition through its protective effects against ROS-induced damage.[51] Collectively, these findings suggest that 27HC enhances cancer drug resistance through NRF2-mediated antioxidant activation. By modulating oxidative stress response, promoting pro-survival signalling, and driving MDR phenotype, 27HC contributes to the persistence and progression of cancer cells (Figure 4).

27HC and epigenetic modifications

Epigenetic modifications, such as DNA methylation and histone modifications, are crucial to tumour progression and drug resistance. One of the most prominent epigenetic alterations observed in cancer is genome-wide hypomethylation coupled with site-specific hypermethylation, particularly at the promoters of tumour suppressor genes.[196,197] This hypermethylation disrupts normal gene expression patterns and facilitates progression by affecting processes like DNA repair, apoptosis, cell cycle, angiogenesis, and drug resistance.[198,199]

A growing body of evidence suggests that 27HC influences epigenetic regulation in breast cancer cells through multiple mechanisms. In ER^{+} breast cancer cells, resistance to AIs has been linked to widespread upregulated cholesterol biosynthesis pathways, including genes involved in 27HC biosynthesis. This metabolic shift promotes ERα activation and enhances cellular invasion. The use of cholesterol biosynthesis blockers like statins can reduce ERα binding and abrogate cell invasion, suggesting potential therapeutic strategies for managing AI resistance.[178] Moreover, it was reported that 27HC downregulates the expression of histone lysine

methyltransferase G9a *via* ERα, leading to a reduced H3K9 di-methylation in a subset of genes, including *BRIP1*, *BCAS1*, *TBX4,* and *CYP24A1*. Such a modification enhances the expression of these genes, promoting breast cancer development and invasion.[93] Additionally, 27HC disrupts the interaction between DNMT3B and ERα, resulting in aberrant DNA hypermethylation at key tumour-associated genes such as *phosphatidylserine synthase 2 (PTDSS2), MIR613, indoleamine 2,3-dioxygenase 1 (IDO1), thyroid hormone receptor alpha (THRA), dystrotelin (DTYN),* and *mesoderm induction early response 1, family member 3 (MIER)*. The hypermethylation of these genes has been correlated with enhanced breast cancer progression.[92] Taken together, these findings indicate that 27HC plays a crucial role in promoting cancer progression and drug resistance by modulating the epigenetic landscapes (Figure 4).

Conclusion and future outlook

The discovery of 27HC as a critical player in carcinogenesis has opened new research frontiers in endocrine- and metabolism-related cancers. Acting as both a SERM and LXR ligand, 27HC exerts complex regulatory effects on tumour growth, metastasis, and drug resistance. While this review provides a comprehensive overview of 27HC biosynthesis and metabolism, its intricate signalling mechanisms in cancer remain incompletely understood.

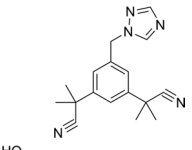
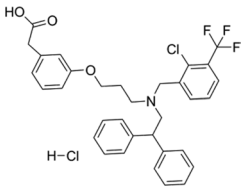
Given its pathological role in tumour development and progression, we focus extensively on 27HC-modulated ER and LXR signalling and their effects on cancer cell survival, proliferation, invasion, migration, EMT, and metastasis. However, the interplay between 27HC-triggered SERM effects and LXR-dependent signalling is highly tissue-specific, leading to both pro-tumorigenic and tumour-suppressive outcomes across different cancers. Beyond its direct role in tumour progression, 27HC has been implicated in cancer drug resistance through multiple mechanisms, including drug efflux modulation, enhanced cellular proliferation, evasion of apoptosis, induction of EMT, upregulation of antioxidant defence, epigenetic modifications, and metabolic reprogramming. The integration of these mechanisms provides a more comprehensive understanding of 27HC-driven resistance to cancer therapies, updating its role in cancer progression and treatment failure.

Despite growing evidence that 27HC acts as a metabolic link between cholesterol homeostasis and tumorigenesis, its precise role in cancer biology remains complex. Several key factors contribute to this complexity. As a SERM, 27HC exhibits its tissue-dependent effects on ER signalling, either stimulating or repressing ER activity. In endocrine-related cancers, particularly breast cancer, 27HC promotes tumorigenesis through ER-dependent signalling. However, ER activation is not involved in 27HC-driven lung metastases.[73] In certain cancers, 27HC plays a dual role, acting as both an ER agonist, stimulating tumour growth, and a cholesterol regulator, restricting tumour progression. For example, in ovarian cancer and PCa, 27HC has been shown to promote cell proliferation *via* ERβ activation while simultaneously lowering intracellular cholesterol levels, which can limit tumour growth.[97] This suggests that the role of 27HC on cancer progression is context-dependent, balancing pro- and anti-tumorigenic effects.

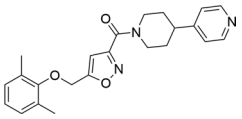
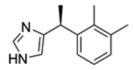
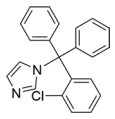
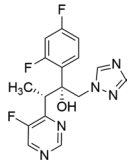
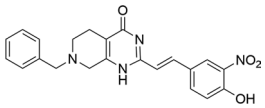
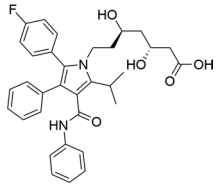
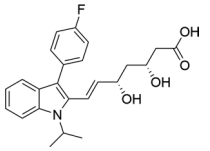
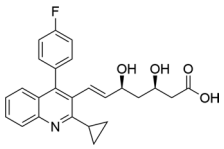
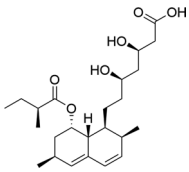
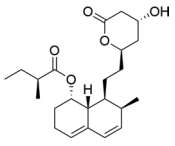
The expression profile of 27HC-metabolising enzymes varies widely across different cancer types. CYP27A1 is upregulated in many cancers. However, CYP7B1 is not consistently downregulated in most cancers (Figure 2). Additionally, the expression of upstream cholesterol metabolism enzymes (CYP51A1, CYP7A1, and CYP8B1) is rarely elevated in cancer tissues. This heterogeneous expression pattern suggests that 27HC levels differ among cancers, contributing to its context-dependent pro- and anti-tumour effects. Besides binding ERs and LXRs, 27HC also interacts with other molecular targets, leading to diverse oncogenic signalling across different tissue types. This multifaceted signalling may contribute to tumour progression, inflammation, and immune evasion. Moreover, the concentration of 27HC within specific tumour microenvironments influences its pro-inflammatory or pro-survival roles, further complicating its role in cancer progression.[38,40]

While evidence of 27HC-mediated MDR in cancer therapy is growing, the precise mechanisms underlying 27HC-driven drug resistance remain unclear. Some studies have reported

Table 2. Inhibitors of 27HC-metabolising enzymes and their chemical structures.

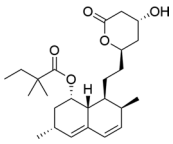
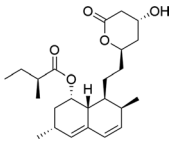
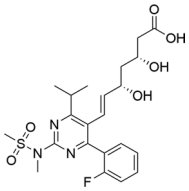
Name	Chemical structure	Cancer type	Mechanisms of action and effect	References
CYP27A1 inhibitors				
Anastrozole		Breast cancer	As an aromatase inhibitor, anastrozole unexpectedly inhibits CYP27A1, leading to its repurposing for breast cancer treatment. Additionally, anastrozole reverses 27HC-induced memory impairment by decreasing glucose uptake in the brain.	[200] [201] [202]
GW3965		Breast cancer	27HC increases ER-dependent growth and LXR-dependent metastasis in mice model of breast cancer. GW3975 mitigates this effect by inhibiting 27HC production.	[73]

(*Continued*)

Name	Chemical structure	Cancer type	Mechanisms of action and effect	References
Dafadine-A		Melanoma	Dafadine-A inhibits 27HC-induced upregulation of Rap1A/Rap1B expression and AKT phosphorylation, thereby suppressing melanoma growth and reducing vemurafenib resistance.	[113]
Dexmedetomidine		Breast cancer, lung cancer, colorectal cancer	Dexmedetomidine inhibits the activity of CYP27A1 and may target PARP1 to promote necroptosis, affecting non-small cell lung cancer. It also promotes colorectal cancer progression by activating the α2-adrenoceptor-dependent Nrf2/Piwil2/Siah2 pathway and the EMT. Its therapeutic benefits may be mediated through the upregulation of adaptive anti-tumour immune responses.	[203] [200] [204] [205]
CYP7B1 inhibitors				
Clotrimazole		Breast cancer, melanoma	Clotrimazole inhibits mitochondrial-bound glycolytic enzymes and calmodulin, depriving cancer cells of energy. It also reduces cancer cell proliferation, induces G1-phase cell cycle arrest, and enhances pro-apoptotic factors, ultimately leading to cancer cell death.	[206] [207] [208]
Voriconazole		Skin cancer	As an antifungal drug, voriconazole induces DNA damage-dependent chromatin remodelling, leading to skin cancer development. It is associated with an increased risk of cutaneous squamous cell carcinoma in solid organ transplant recipients.	[209] [210] [211]
StARD3 inhibitor				
VS1		Breast cancer, colon cancer	VS1 targets and induces the degradation of STARD3, thus reducing cancer cell proliferation.	[212]
HMGCR inhibitors				
Atorvastatin		Breast cancer, prostate cancer, lung cancer	As an HMG-CoA reductase inhibitor, atorvastatin inhibits proliferation, migration, and survival, while inducing necrosis and caspase-dependent apoptosis in breast cancer cells. It also blocks Cav1-controlled GLUT3-mediated glucose uptake and overcomes EGFR-TKI resistance in non-small cell lung cancer (NSCLC). However, while it does not reduce prostate cancer proliferation, it provides therapeutic benefit by lowering PSA levels.	[213] [214] [215] [216]
Fluvastatin		Breast cancer, lung cancer, renal cancer	Fluvastatin upregulates RhoB through the AKT-mTOR signalling pathway and induces autophagy, thereby inhibiting breast cancer metastasis. It also suppresses lung cancer progression by downregulating SATB1 *via* the Wnt/β-catenin signalling pathway. Additionally, fluvastatin inhibits renal cancer cell growth, invasion, angiogenesis, and metastasis *in vitro*.	[217] [218] [219]
Pitavastatin		Pancreatic cancer, colorectal cancer, cervical cancer, lung cancer, oral cancer	Itavastatin inhibits the membrane recruitment and activation of TBK1 through the mevalonate pathway, thereby reducing IL-33 expression and preventing pancreatic cancer. It induces apoptosis and reduces cervical cancer cell migration by modulating the PI3K/AKT and MAPK signalling pathways. Pitavastatin also alleviates EGFR-TKI resistance in lung cancer by regulating the YAP pathway and inhibiting the downstream AKT/BAD-BCL-2 signalling. Additionally, it blocks autophagic flux, promotes FOXO3a accumulation, activates pERK signalling, and triggers CHOP-mediated apoptosis in cancer cells. In combination with atorvastatin, pitavastatin synergistically induces apoptosis and enhances 5-FU-mediated cytotoxicity by activating autophagy and pERK/ATF4/CHOP signalling. Moreover, pitavastatin and atorvastatin overcome chemoresistance in metastatic colorectal cancer under high glucose conditions.	[220] [221] [222] [223] [224]
Pravastatin		Colon cancer, lung cancer	Pravastatin was incorporated into first-line standard chemotherapy for small-cell lung cancer. However, it is associated with an increased risk of cancer as age advances.	[225] [226] [227]
Mevastatin		colon cancer, Prostate cancer, breast cancer	Mevastatin enhances the antiproliferative effect of butyrate in cancer cells by inducing apoptosis and causing G0/G1 cell cycle arrest. However, the cell cycle arrest is cell-type dependent. It also inhibits autolysosome maturation and promotes LBH589-induced cancer cell death.	[228] [229] [230]

(*Continued*)

Table 2. Continued.

Name	Chemical structure	Cancer type	Mechanisms of action and effect	References
Simvastatin		Lung cancer, liver cancer, prostate cancer, breast cancer, skin cancer, colon cancer	As an HMGCR inhibitor, simvastatin suppresses the proliferation, migration, and survival of cancer cells in both *in vitro* and *in vivo* models. It downregulates ROS production and induces protein aggregation through the Caspase-1/GSDMD pathway, triggering heat shock and inhibiting cancer cell proliferation.	[231] [232] [233]
Lovastatin		Breast cancer, liver cancer, cervical cancer, lung cancer, colon cancer	Lovastatin inhibits cell proliferation, induces apoptosis, and causes cell cycle arrest. It modulates p53 activity through the p38/MAPK and LKB1-AMPK signalling pathways. By increasing p21 levels and reducing cyclin D and Survivin, it promotes cancer cell apoptosis. Additionally, it disrupts the mevalonate pathway intermediates, affecting oncogenic signalling linked to cancer stem cells.	[234] [235] [236]
Rosuvastatin		Prostate cancer, pancreatic cancer, lung cancer	Rusvastatin inhibits cancer cell proliferation, spheroid formation and EMT. It reduces cancer cell proliferation and metastasis by inhibiting Ca^{2+}/CaM/CaMKII/ERK and Ca^{2+}-mediated ERS signalling. It reduces RAS protein, MMP2/9, and NF-κB-p65 level in cancer tissues.	[237] [238] [239]

contradictory findings, highlighting the need for further research into how 27HC interacts with key signalling pathways to drive drug-resistant phenotypes. A deeper understanding of these mechanisms is essential for overcoming MDR in cancer treatment.

Although the role of 27HC in cancer biology is not yet fully elucidated, targeting 27HC metabolism offers promising therapeutic strategies for reducing tumour growth and overcoming drug resistance (Table 2). Several studies suggest that inhibiting CYP27A1 can suppress tumour growth and enhance the efficacy of cancer therapies.[42,43] Anastrozole, an aromatase inhibitor, has been found to have an off-target effect on CYP27A1, reducing 27HC production and improving treatment outcomes in hormone-sensitive cancers.[136] Lowering cholesterol levels through statins, PCSK9 inhibitors, or direct cholesterol reduction may help counteract 27HC-driven tumour progression.[240,241] However, since these approaches also affect systemic cholesterol homeostasis, comprehensive preclinical studies are needed to assess their safety and therapeutic potential. From a clinical perspective, the development of pharmacologically optimised inhibitors targeting 27HC-relevant metabolic enzymes is critical. Future translational clinical trials are needed to evaluate their effectiveness and feasibility as cancer therapies.

In conclusion, the involvement of 27HC in cancer progression and drug resistance is highly complex and tissue-specific. Thus, future research should focus on elucidating the intricate signalling networks influenced by 27HC and evaluating novel treatment strategies in both preclinical models and clinical trials. This will help clarify how manipulating these pathways might improve the outcomes for cancers influenced by similar mechanisms involving cholesterol derivatives.

Author contributions

Yaxin Hou, Zhiguang Fu, Chenhui Wang, Yuan Guo, and Paulina Kucharzewska acquired and analysed the data for this work, drafted the manuscript, and created tables and figures. Sihe Zhang initiated the conception, designed the outline, and revised the manuscript. All the authors have carefully checked the accuracy and integrity of this work, reviewed, approved, and agreed the final version of this manuscript for submission.

Disclosure statement

The authors declare that they have no competing interests.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and can be obtained from public databases or websites as noted in the figure ligands.

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