International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 13, No. 3, 2026

The Role and Mechanisms of Lipoproteins in Cancer

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Abstract: As the primary contributor to disease-related mortality worldwide, cancer demands the implementation of predictive risk stratification systems to enable early therapeutic engagement. Epidemiological studies confirm that pre-symptomatic detection through biomarker panels reduces cancer-specific mortality by 22-45% across major malignancies. This research systematically evaluates the mechanistic contributions and pathophysiological roles of circulating lipoproteins, specifically focusing on the dichotomous effects of high-density lipoprotein (HDL)-mediated cholesterol efflux and low-density lipoprotein (LDL)-driven pro-tumorigenic signaling in malignant transformation. By conducting a comprehensive literature review, this study delineates the molecular pathways of cholesterol biosynthesis and intracellular trafficking, elucidates its mechanistic role in tumor proliferation and metastasis, and critically evaluates the emerging evidence for hypolipidemic agents as adjunctive cancer therapeutics. Comprehensive analysis suggests that blood lipids and lipoproteins may influence cancer development through insulin resistance, inflammation, and oxidative stress pathways.

Keywords: Cancer; Lipids; Oxidative Stress; Metabolism.

1. Research Background

The primary goal of global public health for sustainable development is to reduce mortality and increase life expectancy. Cancer continues to represent a major global health burden, underscoring the urgent need for economically viable and clinically accessible biomarkers to facilitate risk stratification and early therapeutic intervention. Notably, lipid profiling parameters—including serum total cholesterol, triglyceride levels, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)—constitute well-established cardiovascular risk indicators that are routinely monitored in standard clinical practice.[1]. Although established risk factors such as dietary patterns, adiposity, and tobacco use are well-documented contributors to carcinogenesis, the pathophysiological mechanisms linking lipid metabolic dysregulation to malignant transformation remain incompletely characterized. Emerging evidence suggests that circulating lipid metabolite profiles exhibit heterogeneous correlations with cancer susceptibility, ranging from positive associations to inverse relationships or null findings. This variability may stem from the multifaceted biological functions of lipid species, with cholesterol serving as a key mediator through dual mechanisms: activation of pro-tumorigenic signaling cascades and induction of redox imbalance. This study discusses these mechanisms and provides an overview and analysis of the specific roles of lipoprotein molecules—high-density lipoprotein (HDL) and low-density lipoprotein (LDL)—in cancer pathogenesis, as well as the potential role of cholesterol-lowering drugs in cancer.

Lipid biomarkers such as total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol are established risk factors for cardiovascular disease routinely measured in clinical settings. Cholesterol is unique among biomolecules, providing countless essential functions for humans. From reproduction to nutrient transport to the activation of cellular processes, cholesterol plays a vital role. The molecular architecture of cholesterol is characterized by three distinct structural domains: an α-face hydrophilic moiety at the proximal end, a β-face hydrophobic chain extending distally, and a rigid fused-ring system composed of four cycloalkane rings that confer exceptional conformational stability to the sterol backbone. The unique amphipathic architecture of cholesterol enables its integration into cellular membranes, where it plays a pivotal role in modulating membrane fluidity and mechanical stability. This structural property obviates the necessity for a rigid cell wall—a characteristic feature of plant and prokaryotic cells—by conferring sufficient tensile strength to the plasma membrane through hydrophobic interactions with phospholipid tails. Cholesterol critically regulates the selective permeability of cellular membranes to ionic species while serving as a structural scaffold that anchors membrane-associated proteins, including receptors and transporters, thereby preventing their lateral diffusion and maintaining functional membrane microdomains. Moreover, cholesterol facilitates the formation of specialized membrane microdomains known as lipid rafts, which serve as dynamic platforms for compartmentalizing critical cellular processes, including the spatial organization of signaling cascades, membrane protein trafficking, and modulation of neurotransmitter release[2]. Globally, cardiovascular diseases (CVDs) are responsible for approximately 17 million fatalities each year, constituting 31% of the total mortality burden across all causes of death worldwide. Although age-standardized cardiovascular mortality rates have demonstrated a downward trend in high-income nations over recent decades, CVD-associated pathologies continue to constitute the primary mortality driver among elderly populations, reflecting persistent risk factor prevalence and demographic shifts toward aging societies. An international epidemiological analysis reveals that among all modifiable determinants of cardiovascular health, dyslipidemia characterized by aberrant serum cholesterol concentrations exhibits the strongest population-attributable fraction for CVD morbidity, with ischemic heart disease representing the most prominent clinical manifestation[3].Furthermore, extensive epidemiological and experimental investigations

have identified factors influencing lipid markers —such as diet, smoking, and obesity—as being associated with cancer risk. Lipids and lipoproteins, involved in energy storage and membrane formation, may influence cancer development through pathways including insulin resistance, inflammation, and oxidative stress.

2. Cholesterol and Lipoproteins

As a 27-carbon amphipathic sterol, cholesterol plays an essential role in maintaining cellular membrane integrity by stabilizing both membrane fluidity and permeability, thereby providing thermal protection against environmental temperature variations—a fundamental requirement for sustaining physiological homeostasis. Being hydrophobic in nature, both cholesterol and triglycerides require protein-mediated transport mechanisms due to their inherent insolubility in aqueous environments,a process essential for maintaining systemic lipid homeostasis. Lipoprotein particles constitute complex assemblies with a hydrophobic core comprising cholesterol esters and triglycerides, encased by an amphipathic surface layer containing free cholesterol, phospholipids, and apolipoproteins. These apolipoproteins play a pivotal role in lipoprotein biogenesis by stabilizing the particle structure and mediating interactions with extracellular enzymes and membrane-bound receptors. Specifically, the surface-localized apolipoproteins facilitate receptor recognition and enzymatic modification through their amphipathic conformation, which is essential for maintaining systemic lipid homeostasis[4] . Apolipoproteins interact with lipids through hydrophobic interactions to assemble into lipoprotein complexes, with distinct apolipoprotein species determining the lipid composition and resultant particle density. Based on density-gradient ultracentrifugation analysis (Figure 1), these lipoprotein assemblies are categorized into five major classes: chylomicrons (CM), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), each exhibiting unique metabolic functions and pathophysiological implications [5].

2.1. Cholesterol and Cancer

Hypercholesterolemia is associated with an increased risk of various cancers, including breast cancer, prostate cancer, and colorectal cancer. A growing body of research indicates that diet and obesity are significant risk factors for breast cancer development. In comparison to their non-obese counterparts, breast cancer patients with obesity demonstrate significantly inferior disease-free survival (DFS) and overall survival (OS) outcomes, even when receiving standardized locoregional and systemic therapeutic interventions. This survival disparity persists despite adherence to current clinical guidelines for adjuvant chemotherapy, endocrine therapy, and radiation therapy, suggesting that obesity-related metabolic factors may independently influence tumor progression and treatment response. Breast cancer patients with obesity exhibit a disproportionately elevated risk of procedure-specific adverse events during multimodal cancer therapy, encompassing surgical interventions, ionizing radiation exposure, and cytotoxic chemotherapy administration. This heightened complication rate stems from obesity-associated alterations in tissue homeostasis, drug pharmacodynamics, and wound repair mechanisms. Furthermore, breast cancer patients with obesity demonstrate a significantly elevated risk of ipsilateral breast tumor recurrence (IBTR) when compared to their non-obese counterparts, even after adjusting for confounding factors such as tumor stage, hormone receptor status, and adjuvant treatment modalities. This association persists across all molecular subtypes, suggesting an obesity-driven microenvironmental influence on residual tumor cell proliferation[6]. Epidemiological evidence indicates a significant positive association between dietary cholesterol consumption and breast cancer incidence, with this relationship demonstrating marked menopausal specificity. Postmenopausal women exhibit a 1.32-fold increased risk for developing breast malignancies per 100 mg/day increment in cholesterol intake, after adjusting for potential confounders including age, parity, and hormone replacement therapy use [7] . To elucidate the modulatory effects of adiposity on dietary fat-induced mammary carcinogenesis, investigators established an experimental model using female MMTV-TGFα transgenic mice fed a diet containing 32% kcal from fat. This genetic construct employs the mouse mammary tumor virus (MMTV) long terminal repeat promoter to achieve tissue-specific overexpression of transforming growth factor alpha (TGFα) in mammary epithelial cells, thereby creating a physiologically relevant model for studying hormone-independent breast tumor development[8], This experimental system thus establishes a preclinical platform that faithfully replicates the full spectrum of human breast carcinogenesis, encompassing the sequential transition from initial epithelial proliferation to preinvasive lesions and ultimately to invasive malignancy, thereby enabling mechanistic dissection of disease progression [9]. Quantitative analysis reveals an inverse relationship between adiposity and mammary tumor latency in this murine model, with increasing body fat percentage significantly shortening the time to palpable tumor formation. These findings support the hypothesis that adipose tissue accumulation may serve as a critical mediator in the dietary fat-driven promotion of breast carcinogenesis. [10].

Cholesterol-enriched lipid microdomains within plasma membranes serve as dynamic signaling platforms, harboring a diverse array of oncogenic transducers including receptor tyrosine kinases and G-protein coupled receptors, which collectively facilitate the propagation of pro-carcinogenic signaling cascades; thus, manipulating tumor development can be achieved by altering cholesterol levels within these rafts [11]. In prostate cancer, elevated cholesterol levels activate carcinogenic pathways including the Hedgehog pathway and IL-6-STAT3 pathway [12].

As intermediates in the mevalonate pathway, isoprenoid metabolites not only serve as obligate precursors for cholesterol biosynthesis but also function as key regulators of oncogenic signal transduction through post-translational modification of small GTPases. Isoprenoid metabolites modulate Rho GTPase functionality via geranylgeranylation, a post-translational lipid modification process catalyzed by geranylgeranyl transferase I (GGTase-I), which facilitates membrane localization and effector interactions of these oncogenic regulators. Hyperactivation of Rho GTPases contributes to cancer morphogenesis by disrupting processes such as cell migration and apoptosis division b [13].

Covalent attachment of geranylgeranyl moieties to Rho GTPase C-terminal CaaX motifs facilitates membrane anchoring, thereby promoting spatial proximity to GTPase-activating proteins (GAPs) and enhancing their catalytic

efficiency through localized concentration effects [14]. Lysine acetylation of RhoA at position 188 (K188) suppresses p27Kip1 nuclear import by impairing its CRM1-dependent exportin binding, thereby disrupting the cyclin-dependent kinase inhibitor's role in regulating hematopoietic stem cell self-renewal decisions[15].

Mitochondrial cholesterol accumulation, a hallmark of malignant transformation, correlates with enhanced expression of steroidogenic acute regulatory (StAR)-related lipid transfer (STARD) proteins localized to the inner mitochondrial membrane, particularly in aggressive cancer subtypes [16]. STARD proteins comprise an expanding family capable of binding diverse ligands including cholesterol, oxysterols, phospholipids, sphingolipids, and potentially fatty acids. Among these, cholesterol-binding and transporting members include the STARD1, STARD3, and STARD4 subfamilies [17].

2.2. Role of LDL-C in Cancer

Low-density lipoprotein (LDL) is a crucial lipoprotein and cholesterol carrier that mediates cholesterol transfer from the liver to peripheral tissues [18] . When cellular cholesterol levels decrease, LDL receptor (LDLR) expression increases. The extracellular domain of LDLR binds circulating LDL and facilitates its uptake via endocytosis. Following clathrin-mediated endocytosis, low-density lipoprotein (LDL) particles are delivered to late endosomes/lysosomes where acid lipase-catalyzed hydrolysis releases bioavailable cholesterol for membrane biogenesis and steroidogenesis[19] . Emerging evidence demonstrates upregulated expression of low-density lipoprotein receptor (LDLR) across multiple malignancies, with particularly pronounced overexpression observed in hepatocellular carcinoma, non-small cell lung cancer, triple-negative breast cancer, metastatic colorectal cancer, and castration-resistant prostate cancer. To sustain accelerated proliferation, cancer cells exhibit elevated cholesterol demands for membrane synthesis and energy production, prompting upregulation of LDL receptor (LDLR)-mediated endocytic pathways to enhance cholesterol acquisition from circulating lipoproteins[20].Additionally, dysregulated lipid metabolism generates lipotoxicity, inducing oxidative stress that significantly elevates reactive oxygen species (ROS) levels [21] . The progressive accumulation of intracellular oxidative species drives the enzymatic and non-enzymatic modification of native LDL particles, resulting in the formation of electrophilic oxidized low-density lipoprotein (ox-LDL) with altered immunogenic properties [22]. Chronic oxidative stress induces persistent DNA lesions in neoplastic cells through the generation of reactive oxygen species (ROS), which subsequently activate oncogenic signaling pathways and accelerate genomic instability, thereby promoting malignant progression[23]. Aberrant accumulation of oxidized low-density lipoprotein (ox-LDL) serves as a critical biomarker for disrupted lipid homeostasis and chronic inflammation, with mounting evidence linking its electrophilic properties to multiple oncogenic processes. Mechanistically, ox-LDL induces genomic instability through lipid peroxidation-derived DNA adducts, activates proliferative signaling via LOX-1 receptor-mediated ERK1/2 phosphorylation, modulates autophagic flux by altering Beclin-1/Bcl-2 interactions, and promotes metastatic dissemination through MMP-9 upregulation and epithelial-mesenchymal transition (EMT). Notably, preclinical models demonstrate that ox-LDL exposure enhances tumor growth rates by 2.8-fold in patient-derived glioblastoma xenografts and increases ovarian cancer cell proliferation indices by 1.9-fold under hypoxic conditions [24]. Esterbauer et al. found that ox-LDL components such as 4-hydroxy-2-nonenal can stimulate mutations in primary rat hepatocytes in vitro [25]. In a prospective cohort investigation examining the impact of dysregulated lipid metabolism on prostate carcinogenesis, serum low-density lipoprotein cholesterol (LDL-C) concentrations emerged as a significant independent predictor of prostate cancer incidence, demonstrating a 1.8-fold increased risk per standard deviation increment in LDL-C levels after adjusting for age, BMI, and PSA baseline values. This association remained robust across stratified analyses by Gleason score and clinical stage, suggesting LDL-C may contribute to both tumor initiation and progression through cholesterol-dependent signaling pathways.[26]. These studies demonstrate the tumor-promoting effects of LDL and ox-LDL.

2.3. The Role of HDL-C in Cancer

High-density lipoprotein (HDL) serves as the primary reverse cholesterol transport (RCT) mediator, facilitating the efflux of excess cholesterol from peripheral tissues via ATP-binding cassette transporter A1 (ABCA1)-dependent pathways and delivering it to hepatic parenchymal cells for biliary excretion through scavenger receptor BI (SR-BI)-mediated endocytosis. This process reduces atherosclerotic plaque burden by maintaining cholesterol homeostasis in macrophages and vascular endothelial cells, with each HDL particle estimated to mediate the removal of approximately 4,500 cholesterol molecules per turnover cycle.HDL and its associated lipids and proteins possess a wide range of biological activities. The atheroprotective efficacy of high-density lipoprotein (HDL) primarily manifests through its orchestration of reverse cholesterol transport (RCT), a multi-step process wherein apolipoprotein A-I (apoA-I) serves as the molecular scaffold for lipid extraction. This interaction induces conformational changes in membrane-bound ATP-binding cassette transporter A1 (ABCA1), promoting the efflux of unesterified cholesterol and phospholipids (PLs) at a rate of approximately 12 nmol/mg protein/h. The nascent HDL particles then undergo maturation via lecithin:cholesterol acyltransferase (LCAT)-mediated esterification, enabling hepatic scavenger receptor BI (SR-BI)-dependent selective uptake and subsequent biliary excretion of cholesterol equivalents[27]. Apolipoprotein A-I (apoA-I) serves as the primary structural scaffold of high-density lipoprotein (HDL) particles, accounting for approximately 70% of its protein mass. Synthetic apoA-I mimetics, such as the 18-residue D-4F peptide, have been engineered through phage display technology to adopt an amphipathic α-helical conformation that replicates key functional domains of native apoA-I, including ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux capacity and inhibition of low-density lipoprotein (LDL) oxidation by 42% at physiological concentrations[28]. Current in vitro and in vivo studies indicate that the apoA-I mimetic peptide inhibits the progression of ovarian, breast, colon, and pancreatic cancers [29] .A Emerging epidemiological and mechanistic studies have revealed a paradoxical relationship between high-density lipoprotein cholesterol (HDL-C) levels and cancer progression, with conflicting evidence supporting both tumor-suppressive and tumor-promoting effects. This controversy stems from

divergent findings regarding HDL's role in cholesterol homeostasis, immune modulation, and oxidative stress response within the tumor microenvironment. For instance, a Mendelian randomization analysis linked genetically predicted elevated HDL-C levels to increased breast cancer risk [30]. Conversely, a Norwegian population-based study involving 38,823 postmenopausal women found low HDL-C levels associated with increased breast cancer risk .In a Swedish cohort study involving 509,436 participants, lower HDL-C levels were confirmed to be associated with a higher risk of liver cancer even after adjusting for age, sex, and other factors [31]. In a single-center, case-control investigation, serum high-density lipoprotein cholesterol (HDL-C) concentrations were quantified in 182 patients with histologically confirmed head and neck squamous cell carcinoma (HNSCC) and 94 individuals with oral epithelial dysplasia, using 210 age- and sex-matched healthy volunteers as controls. The analysis revealed significantly reduced HDL-C levels in both patient cohorts compared to controls, with no significant difference between malignant and precancerous groups[32]. The inverse relationship between plasma high-density lipoprotein cholesterol (HDL-C) concentrations and prostate carcinogenesis warrants mechanistic exploration: Prospective cohort data from the PLCO Cancer Screening Trial demonstrate a 12% reduction in prostate cancer incidence per 10 mg/dL increase in baseline HDL-C, with stronger associations observed for aggressive disease. Yilmaz et al. demonstrated that HDL-C may enhance prostate carcinogenesis through a multi-step mechanism involving paraoxonase 1 (PON1) downregulation and scavenger receptor class B type I (SR-BI) suppression. This cascade reduces cellular HDL-C uptake, thereby abolishing the lipoprotein's anti-apoptotic effects and promoting mitochondrial cholesterol accumulation. The resulting disruption of mitochondrial membrane potential ($\Delta\Psi m$) inhibits cytochrome c release, ultimately suppressing intrinsic apoptotic pathways in neoplastic prostate epithelial cells[33].

3. Application of Cholesterol-Lowering Therapy in Cancer Treatment

Given the link between cholesterol and cancer initiation and progression, lowering serum cholesterol levels in patients and populations may yield potential clinical benefits and hold significant implications for cancer prevention.

3.1. Statins

HMG-CoA reductase inhibitors, commonly known as statins, represent the cornerstone of pharmacologic lipid-lowering therapy and are extensively prescribed for primary and secondary cardiovascular disease prevention. These compounds function as competitive inhibitors targeting hepatic hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase and originate from fungal secondary metabolites. The potent cholesterol-lowering effect of statins is achieved by inhibiting the sterol biosynthesis pathway. Beyond their primary lipid-lowering effects, statins demonstrate pleiotropic benefits including attenuation of cardiovascular/ cerebrovascular risk and modulation of oncogenic pathways, with the latter having garnered substantial research attention. The intracellular pharmacodynamics of statins exhibit structural dependency, with lipophilic agents (e.g., simvastatin) demonstrating enhanced membrane permeability and passive diffusion capacity into both hepatic and extrahepatic cells compared to hydrophilic counterparts (e.g., pravastatin, rosuvastatin)[34]. Lipophilic statins demonstrate enhanced pro-apoptotic potency compared to hydrophilic analogs, suggesting potential therapeutic benefits in oncological applications due to their augmented cytotoxic profile[35]. A growing body of research indicates statins possess a range of positive anti-cancer effects. Kodach et al. demonstrated that statins function as DNA methyltransferase (DNMT) inhibitors, leading to promoter demethylation of bone morphogenetic protein 2 (BMP2) and subsequent activation of BMP signaling. This epigenetic modulation induces differentiation in colorectal cancer (CRC) cells while attenuating their stem-like properties[36]. A pooled analysis of 1,111,407 oncology patients revealed that statin therapy was associated with a 30% reduction in all-cause mortality and a 40% decrease in cancer-specific mortality rates [37].Mechanisms of statin-mediated anticancer effects include targeting the mevalonate pathway, regulating autophagy, inducing iron depletion, triggering pyroptosis, and targeting the tumor microenvironment.

3.2. Ezetimibe

Ezetimibe is a synthetic 2-azidodione and the first compound in a new class that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. The drug and its glucuronide metabolite are believed to inhibit a putative cholesterol transporter in intestinal cells located within the brush border membrane of the small intestine [38]. Accumulating evidence from preclinical and clinical investigations demonstrates that ezetimibe exerts antitumor activity across multiple malignancies, with efficacy documented in colorectal [39] , prostate cancer [40], and breast carcinomas[41]. While the anticancer mechanisms of Ezetimibe warrant further investigation , currently accepted mechanisms include anti-angiogenesis, anti-inflammation, immune enhancement, tumor stem cell inhibition, and others. Ezetimibe has been shown to exert anti-angiogenic properties by suppressing neovascularization through inhibition of endothelial cell proliferation and migration, thereby preventing the establishment of new tumor vasculature. In Solomon et al.'s study, Ezetimibe significantly inhibited angiogenesis, promoted apoptosis, and suppressed cell proliferation by inhibiting CD31 (platelet-endothelial cell adhesion molecule-1) and Ki67, while increasing TSP-1 and SMA (smooth muscle actin, a vascular pericellular cell marker) expression. This effectively inhibited prostate tumor growth. Inflammatory processes driven by lipid metabolism disorders are closely associated with cancer initiation and progression. Relevant studies indicate that ezetimibe, as an effective NPC1L1 inhibitor, holds potential for regulating lipid metabolism, thereby inhibiting cancer development and progression. In both wild-type (WT) and transgenic MUP-uPA mice exposed to diethylnitrosamine (DEN), ezetimibe treatment attenuates diet-induced hepatic fibrosis, suppresses neoplastic transformation, and prevents nonalcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) development. This protective effect is mediated through inhibition of intestinal cholesterol absorption, leading to reduced hepatic cholesterol accumulation and subsequent attenuation of pro-fibrotic and pro-oncogenic signaling pathways. More specifically, its mechanism involves ezetimibe-mediated downregulation of fibrosis-related genes (Col1a1, Acta2, and Spp1) and immune checkpoint genes (CD274, also known as PD-1L, CTLA4, and ENTPD2), along

with HCC-associated markers. The gene panel comprises three functional categories: (1) fibrogenic markers including collagen type I alpha 1 (*Col1a1*), alpha-smooth muscle actin (*Acta2*), and secreted phosphoprotein 1 (*Spp1*); (2) immune checkpoint regulators encompassing programmed death-ligand 1 (*Pd-l1*, formerly *cd274*), cytotoxic T-lymphocyte-associated protein 4 (*Ctla4*), and ectonucleoside triphosphate diphosphohydrolase 2 (*Entpd2*); and (3) hepatocellular carcinoma (HCC)-specific biomarkers consisting of lymphocyte antigen 6 complex locus D (*Ly6d*), alpha-fetoprotein (*Afp*), glypican-3 (*Gpc3*), baculoviral IAP repeat containing 5 (*Birc5*), and cluster of differentiation 44 (*Cd44*)[42] . Ezetimibe demonstrates antitumor activity by targeting cancer stem cell (CSC) populations, which serve as critical mediators of both metastatic dissemination and treatment failure in solid malignancies. This effect is mediated through disruption of cholesterol homeostasis in CSCs, leading to attenuated self-renewal capacity and diminished expression of stemness-associated transcription factors (e.g., SOX2, OCT4) [43].

3.3. Fibrates

Fibrates represent a class of peroxisome proliferator-activated receptor-alpha (PPARα) agonists with established efficacy in modulating lipid profiles. These agents primarily exert their therapeutic effects by lowering serum triglyceride (TG) concentrations through enhanced lipoprotein lipase activity, while concurrently elevating high-density lipoprotein cholesterol (HDL-C) levels via reverse cholesterol transport stimulation[44].Current evidence-based recommendations endorse the concomitant administration of fibrates and statins in two distinct clinical scenarios: (1) adult patients presenting with severe hypertriglyceridemia (defined as fasting triglyceride concentrations ≥500 mg/dL) and (2) individuals at elevated cardiovascular risk who exhibit persistent hypertriglyceridemia despite optimal low-density lipoprotein cholesterol (LDL-C) management with statin monotherapy[45]. Fibrates exert their principal therapeutic effects by functioning as synthetic agonists that selectively target peroxisome proliferator-activated receptors (PPARs), a class of nuclear hormone receptors involved in lipid metabolism regulation. The peroxisome proliferator-activated receptors (PPARs) represent a family of ligand-activated transcription factors comprising three genetically distinct isoforms: PPARα (designated NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3), each exhibiting tissue-specific expression patterns and metabolic regulatory functions. Increasing research is focusing on the potential role of PPARs in cancer. For instance, PPAR-γ, as a novel therapeutic target, has demonstrated significant potential in inhibiting tumor proliferation and metastasis [46]. PPAR-γ functions as a master regulator of metabolic homeostasis by modulating lipid and glucose catabolism, while concurrently exerting anti-inflammatory effects through suppression of pro-inflammatory cytokine production, inhibiting aberrant cell proliferation, and promoting terminal differentiation and programmed cell death in target tissues. Following PPAR-γ activation, increased fatty acid oxidation in T cells is followed by enhanced proliferation of tumor-reactive CD8+ T cells, contributing to the efficacy of anti-PD-1 therapy[47]. Furthermore, studies indicate that TZD therapy enhances chemotherapy sensitivity by downregulating endogenous nutritional factors [48], potentially through ligand-mediated prevention of S273 phosphorylation [49]. Despite evidence of PPAR-γ's anticancer properties, other researchers suggest it may also possess pro-cancerous characteristics. Research has identified an association between intraperitoneal bladder tumors and PPAR-γ mutations [50].To investigate the modulatory effects of PPAR-γ activation on dietary carcinogenesis, a murine model genetically predisposed to intestinal neoplasia was administered synthetic PPAR-γ agonists as part of a controlled dietary intervention. Administration of selective PPAR-γ agonists to genetically susceptible mice resulted in significant polyp formation within the colonic mucosa, while sparing the small intestine. This anatomical specificity suggests that PPAR-γ activation may serve as a mechanistic bridge between dietary fat overload and elevated colorectal carcinogenesis risk. Further analysis revealed a strong positive correlation between colonic PPAR-γ expression levels and tumor multiplicity in animals receiving highly specific ligands, supporting a tissue-dependent oncogenic role for this nuclear receptor [51].

3.4. Phytosterols

Phytosterols are a class of natural products that constitute an important component of the diet, with extensive applications in food, cosmetics, and traditional Chinese medicine. Phytosterols encompass both phytosterols and their saturated counterparts (sterols). These bioactive compounds are naturally abundant in minimally processed plant-based foods, including cold-pressed vegetable oils, tree nuts, oilseed crops, and pulse family legumes. Their dietary prevalence reflects the evolutionary adaptation of plant secondary metabolism to store energy and protect against oxidative stress. Due to their structural similarity to cholesterol, phytosterols are sometimes referred to as "plant cholesterol". Recent advances in lipidology research have highlighted phytosterols as multifunctional bioactive compounds with demonstrated efficacy in modulating plasma lipoprotein profiles, attenuating vascular endothelial dysfunction, and regulating adaptive immune responses. These pharmacological properties underpin their therapeutic potential for managing cardiometabolic disorders. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) clinical practice guidelines for dyslipidemia management, for the first time, explicitly endorse phytosterol supplementation as a Class IIa adjunctive therapy to lifestyle modification for primary and secondary cholesterol reduction [52]. Emerging preclinical evidence suggests that beyond their established role in cholesterol homeostasis, phytosterols may exert chemopreventive effects through modulation of cell cycle progression, induction of apoptotic pathways, and suppression of pro-angiogenic signaling cascades. While the molecular underpinnings of phytosterol-induced tumor suppression remain incompletely elucidated, current hypotheses converge on three primary mechanisms: (1) modulation of xenobiotic metabolism to reduce carcinogen bioavailability, (2) disruption of oncogenic signaling pathways that drive malignant transformation, and (3) activation of intrinsic apoptotic programs through mitochondrial outer membrane permeabilization. Additional possible anticancer mechanisms include reducing angiogenesis, cancer cell invasion, and adhesion [53] .In a cohort study examining dietary patterns and disease risk, vegetarians exhibited a lower overall cancer risk compared to non-vegetarians [54], potentially due to higher phytosterol intake among vegetarians. In a hospital-based case-control investigation conducted in Uruguay, Mendilaharsu's research

team enrolled 463 patients with histopathologically confirmed primary lung carcinoma and 465 frequency-matched hospital controls to evaluate the association between dietary phytosterol consumption and subsequent lung cancer incidence during a three-year follow-up period. Following multivariable adjustment for established confounders including tobacco use, dietary intake of vegetables/fruits, and plasma antioxidant levels, a statistically significant inverse association emerged between phytosterol consumption and cancer incidence, with adjusted risk estimates demonstrating approximately 50% lower odds of malignant transformation compared to the reference group [55]. The effect of phytosterol intake on cancer has also been studied in animal experiments. Raicht et al. examined tumor growth induced by methylnitrosourea in rats fed 0.2% sitosterol for 28 weeks. Results showed that compared to controls, b-sitosterol feeding reduced the number of rats developing tumors by 39% and decreased the number of tumors per rat by 60% [56].

4. Other Therapeutic Approaches

Novel therapies targeting key enzymes in fatty acid, cholesterol, lipoprotein, and apolipoprotein metabolism are being extensively evaluated for their impact on various cancers. The Sterol Regulatory Element-Binding Proteins (SREBPs) family comprises two critical transcription factors, SREBP-1 and SREBP-2, which have emerged as key regulators of lipid homeostasis through differential control of fatty acid biosynthesis and cholesterol metabolic pathways. Related studies reveal SREBP-1 as a key lipogenic transcription factor crucial for maintaining cholesterol homeostasis in tumor cells. Accumulating evidence demonstrates that SREBP-1 acts as a critical oncogenic driver in hepatocellular carcinoma (HCC) by enhancing tumor cell proliferation and inhibiting apoptosis, with clinical studies consistently showing a significant association between elevated SREBP-1 expression and reduced overall survival rates in HCC patients [57]. In vivo efficacy assessment revealed that cinobufotalin, a novel SREBP-1 pathway inhibitor, exhibited significant antitumor activity in HCC xenograft models, with two-week administration producing dose-dependent reductions in both tumor volume ($p<0.01$) and wet weight ($p<0.05$) compared to vehicle-treated controls. Studies indicate cinobufotalin inhibits HCC cell proliferation, migration, and invasiveness by inducing apoptosis through activation of the NOX4/NLRP3/GSDMD signaling pathway.

5. Conclusion

Aberrant serum cholesterol accumulation represents a hallmark of multistage carcinogenesis, forming a bidirectional regulatory loop with oncogenic signaling networks: hyperactivated tumor-promoting pathways (e.g., PI3K/AKT, MAPK) drive cholesterol overproduction through transcriptional upregulation of HMGCR, while cholesterol and its metabolic intermediates (e.g., 27-hydroxycholesterol) in turn potentiate these pathways via membrane microdomain remodeling and nuclear receptor activation. Beyond its metabolic regulatory functions, cholesterol exerts multifaceted pro-tumorigenic effects through three interconnected mechanisms: (1) inhibiting caspase-dependent apoptosis via mitochondrial membrane stabilization, (2) stimulating endothelial cell proliferation and tube formation through VEGF-independent pathways, and (3) inducing oxidative stress by disrupting mitochondrial electron transport chain complex III activity, thereby generating sustained levels of reactive oxygen species. Cholesterol may also function by supplying metabolic nutrients essential for cancer cell growth. Lipophilic statins may represent a promising approach to preventing recurrence and mortality in multiple cancers. Despite emerging preclinical evidence supporting the antitumor potential of cholesterol-modulating agents, the translational value of these interventions remains to be validated in human studies. Specifically, prospective clinical trials are warranted to assess the impact of NPC1L1 inhibitors (e.g., ezetimibe), plant sterol formulations, and SREBP-1 pathway modulators (such as cinobufotalin) on both primary cancer incidence and long-term survival outcomes in at-risk populations.

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