Journal of Experimental and Basic Medical Sciences 2022;3(3):213-220

Review

Influence of Cholesterol on Cancer Progression

Tuğçe Uygur[1], Züleyha Pestil[2], Oytun Erbaş[1]

ABSTRACT

Cholesterol is a form of lipids, just as fats are and an essential component of cell membranes that are required for the synthesis of fat-soluble vitamins and steroid hormones such as estradiol, cortisol, progestins and testosterone, and bile acids. High-density lipoprotein and low-density lipoprotein (LDL), which are the most commonly known types of cholesterol, cause various diseases in the body. The LDL cholesterol raises the risk of breast, prostate, testicular, uterine, ovarian, and colorectal cancers and promotes cancer by activating several signaling pathways. This review discusses the effect of cholesterol on the progression of cancer.

Keywords: Cancer, cancer signaling pathways, cholesterol, high-density lipoprotein, low-density lipoprotein

Cancer, which originates from the Greek word karkinos, was found in mummies during the ancient Egyptian period (1600 BC). It is a disease that spreads worldwide.[1,2] According to 2017 data, a total of 180.288 cancer cases developed in Turkey.[3] Cancer, which occurs with the uncontrolled division and proliferation of cells, is a disease that occurs under the influence of genetic and environmental conditions.[4,5]

Cholesterol is an essential component of life and is maintained by a number of factors, including intracellular cholesterol levels, cholesterol synthesis, uptake, metabolism, and transport. Studies have shown that cholesterol plays a vital role in the formation and development of cancer and that high levels of cholesterol in the blood are associated with some types of cancer.[6-8]

CHOLESTEROL

Cholesterol, which is a type of fat; takes part in the production of hormones and vitamin D, cell membrane functions. Cholesterol also serves as a precursor to various steroid hormones and is involved in intracellular signal transduction. As one of its functions in cell signaling, recent evidence suggests that cholesterol plays an important role in regulating angiogenesis. It is produced by consuming milk and meat products in the body in the brain, adrenal glands, reproductive organs, intestine, and liver. In the cell, cholesterol is synthesized with the help of enzymes in the cytoplasm endoplasmic reticulum.[9-13]

Cholesterol biosynthesis occurs with the help of microsomes and peroxisomes, a mechanism called the Bloch and Kandutsch-Russell pathways, which involve a series of enzymatic reactions.[14-17] Several steps are required to convert acetyl coenzyme A (acetyl-CoA) into cholesterol, which is then involved in numerous biological roles. These steps include; acyl-CoA: cholesterol acyltransferase (ACAT), 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), sterol O-acyltransferase, oxidative squalene cyclase (OSC), acyl-coenzyme A, sterol-O-Acyl transferases and adenosine triphosphate (ATP)-binding cassette transporter A-1. In vertebrate cells, lipid homeostasis is regulated by a set of membrane-bound transcription factors, sterol-regulatory element-binding proteins (SREBPs).[18]

The enzyme HMGCR is the rate-limiting enzyme of the cholesterol synthesis pathway.[19,20] ACAT1 is

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye
[2]Pendik Veterinary Control Institute, İstanbul, Türkiye

Correspondence: Tuğçe Uygur. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: tugceuygur@gmail.com

Cite this article as: Uygur T, Pestil Z, Erbaş O. Influence of Cholesterol on Cancer Progression. JEB Med Sci 2022;3(3):213-220.

doi: 10.5606/jebms.2022.1030

Received : September 23, 2022
Accepted : October 4, 2022
Published online : January 30, 2023

a tetrameric enzyme that converts two acetyl-CoA molecules into acetyl-CoA and CoA in the ketogenesis pathway.[21,22] Cholesterol synthesis begins with the two-carbon acetate group of acetyl-CoA.[23]

Two moles of acetyl-CoA combine to form acetoacetyl-CoA, followed by 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA). In the following steps, cholesterol synthesis is completed with approximately 30 reactions that take place as a result of three stages. From the HMG-CoA formed in the first stage, mevalonate, the precursor of cholesterol, is formed by means of the HMG-CoA reductase enzyme. Here, the formation of mevalonate from HMG-CoA is the rate-limiting step, and HMG-CoA, the enzyme that catalyzes this reaction, acts as the reductase rate-limiting enzyme. In the second stage, squalene is formed from mevalonate. In the third stage, squalene follows two alternative pathways to create cholesterol, the Bloch pathway, and the Kandutsch–Russell pathway, and the cholesterol biosynthesis is completed.[23,24]

When cholesterol is in excess, it is stored as cholesterol esters (formed by the combination of fatty acids). Since it is insoluble in water, it binds to lipoproteins and circulates in the blood with the help of lipoproteins.[13] Both genetic and environmental factors affect the number of lipids and lipoproteins in the blood. Lipid concentrations increase as people age.[18]

Lipoproteins are macromolecular structures that contain a shell and nucleus consisting of phospholipids and free cholesterol. The polar part allows cholesterol to circulate in the blood as water communicates.[25]

Types of lipoproteins: low-density lipoprotein (LDL) (β mobility), very-low-density lipoprotein (VLDL;preβ mobility) and high-density lipoprotein (HDL; α mobility), chylomicrons.[26,27] High-density lipoprotein and LDL are the most widely known types of cholesterol.[27,28] Cholesterol is involved in the production of bile salts, and its overproduction causes excess fat absorption into the body.

Chylomicrons transport cholesterol from the small intestine to the liver. The majority of this transported cholesterol is taken in through food. When the amount decreases, it is produced in the liver. In order for the produced cholesterol and other lipids to be delivered to other tissues in the body, it is secreted into the blood in very VLDL (since it does not dissolve in water). As the cholesterol in the VLDL in the blood decreases and is transferred to the cells, the structure and density of VLDL change, first it turns into intermediate-density lipoprotein (IDL) and then into LDL. A high amount of LDL in the blood leads to the accumulation of these lipoproteins on the walls of arterial vessels, which causes clots, heart disease, and stroke.[29,30]

Blood cholesterol levels are affected by obesity, dietary habits, blood pressure imbalances, heredity, lipid metabolism disorder, diabetes, smoking and alcohol consumption, advanced age, lack of physical activity, estrogen deficiency, elevated fibrinogen, significant brain, heart, kidney, thyroid or vascular disease.[31-35]

THE RELATIONSHIP BETWEEN CHOLESTEROL AND CANCER

Dietary fat intake causes death in humans. High-fat consumption causes many chronic diseases such as obesity, cardiovascular diseases, some types of cancer, and type 2 diabetes.[36-40]

The most important features of cancer cells are the activation of oncogenes and the loss of tumor suppressors.[41] In the research, it is understood that cholesterol affects tumor development.[42] All types of fat, especially LDL, increase the risk of breast, testicular, uterine ovarian, and colorectal cancers.[36] Tumors must meet membrane biogenesis and biofunctional requirements in order to multiply. Cholesterol is also necessary for the membrane.[43]

An excess of lipids in the body increases the levels of reactive oxygen species (ROS), which causes the oxidation of intracellular LDL to oxidized low-density lipoproteins (ox-LDL). In addition, oxidative stress causes deoxyribonucleic acid (DNA) damage to carcinogenesis in cancers.[44,45] Low-density lipoprotein contains polyunsaturated fatty acids that can be oxidized by ROS (reactive oxygen species) and reactive nitrogen species (RNS) to produce lipid peroxides such as ox-LDL. Ox-LDL stimulates ROS production. Apolipoprotein B-100 (ApoB-100) is the protein component of LDL and is the best ligand for LDL receptor (LDLR). The residues of histidine, cysteine, tyrosine, and lysine in ApoB-100 are also oxidation targets of ROS and RNS, and oxidative modification of ApoB-100 can eliminate its function as an LDLR ligand. When ox-LDL are no longer recognized by LDLR, they can be identified and combined with scavenger receptors such as lectin-like oxidized LDL receptor-1 (LOX-1), scavenger receptor A, and the cluster of differentiation 36 (CD36). Ox-LDL is a well-known biomarker for cardiovascular disease and increases

endothelial cell adhesion by activating oxidative stress and stimulating the expression of pro-inflammatory factors and adhesion molecules, as well as chemokines in vascular endothelial cells, leading to endothelial dysfunction. In recent years, more and more studies have focused on ox-LDL and cancers, and high levels of ox-LDL, as well as LOX-1, and CD36 have been found to be associated with increased risk of various cancers. Ox-LDL promotes epithelial-mesenchymal growth, and cytoplasmic transformation induces protective autophagy, activates inflammatories, and promotes the release of growth factors, cytokines, and other pro-inflammatory markers to stimulate oncogenic signals, resulting in cell mutations and chemotherapy resistance. Low-density lipoprotein may cause cancer by activating numerous signaling pathways; phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), extracellular signal-regulated protein kinases (ERKs), Signal transducer and activator of transcription (STAT)-3, etc.[2,46-52]

The PI3K/Akt activation; PI3K family is divided into four classes: Three of the PI3K family phosphorylate lipids and one phosphorylates proteins. Class I of PI3K is divided into two subunits, p85 and p110. PI3K activation occurs by binding to the growth factor receptor (ERBB or epidermal growth factor (EGF). When PI3K is activated, the effect of p85 on p110 is reduced and it converts phosphatidylinositol-4,5-diphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). The increase in PIP3 (phosphatidyl inositol 1-4-5-triphosphate) causes an increase in AKT/AKT and ERK. phosphoinositide-dependent kinase 1 (PDK1) is activated by the binding of PIP3 to the pleckstrin homology (PH) domain at the C terminus of PDK1. Activated PDK1 phosphorylates AKT at thr/ser T308. Phosphorylation of T308 allows PDK2 to phosphorylate S473. Double phosphorylation of AKT at T308 and S473 activates AKT and stimulates cell cycle progression, survival, metabolism, and migration. AKT has three family members, AKT1, AKT2, and AKT3. Inactivation of AKT destroys Class I PI3K-induced survival. The most common PI3K mutations are E542K, E545K, and H104R.[53,54] PI3K/AKT regulates cancer cell growth by activating the mammalian target of rapamycin (mTOR), which can promote cholesterol synthesis and uptake by activating SREBPs. The mitogen-activated protein kinase (MAPK) pathway, consisting of the Ras-Raf-MEK-ERK signaling cascade is activated by the activation of ERBB2. Growth factor receptor-bound protein 2 (Grb2) contains the Src homology 2 (SH2) domain, which recognizes phosphorylated tyrosine sites in the active receptor. Grb2 binds to the guanine nucleotide exchange factor son of sevenless (SOS) through the SH3 domain. When the Grb2/SOS complex approaches the active receptor, SOS is activated and removes guanosine 5'-diphosphate (GDP) from the inactive Ras. The released Ras becomes active by binding to guanosine triphosphate (GTP). Ras/GTP) binds to Raf-1 and activates it. It also activates MEK-1 and MEK-2. For Ras proteins to become active, they must be localized to the membrane after post-translational regulation. In resting cells, Ras proteins are inactive (Ras-GDP) and act as nodes for signaling pathways. They activate MEK, ERK-1, and ERK-2 by phosphorylating them. ERK activation causes changes in cell physiology, cell cycle control, differentiation, migration, apoptosis, and angiogenesis.[54,55]

STAT3 activation causes the differentiation of cells and the proliferation of tumor cells. Activation of STAT3 leads to increased levels of anti-apoptotic proteins such as Bcl-xL, Bcl-2, and myeloid leukemia cell differentiation protein 1 in cancer cells and cell proliferation. STAT3 phosphorylates and activates survivin, vascular endothelial growth factor (VEGF), c-myc, cyclin D1, and matrix metalloproteinase (MMP) and enables cell proliferation.[56-61]

High blood cholesterol is a common comorbidity in obesity. Its impact as a risk factor for breast cancer is contradictory and it is unclear whether total, LDL, or HDL cholesterol contributes to the disease.[62,63]

In experimental studies, cancer cells have been shown to have an LDLR, They showed that HMG-CoA reductase HMGCR and sterol regulatory element-binding protein SREBPs exhibit deregulated transcriptional levels of several genes involved in cholesterol regulation and metabolism.[64-66]

Many cancer cells show high LDL receptor levels and increased LDL uptake.[67,68] In a breast cancer cell model known for its aggressive cell behavior (MDA-MB-231), the LDL receptor has been shown to be up-regulated and LDL stimulates cell migration.[69] Scavenger receptor-BI is also frequently overexpressed in tumors and is thought to contribute to increased HDL-cholesterol uptake in cancer cells.[67,70] In MDA-MB-231 cells, scavenger receptor-BI deficiency inhibits migration *in vitro* and tumor growth *in vivo*.[71] Liver X receptor (LXR) activation induced by 27-hydroxycholesterol accumulation promotes the development of highly aggressive basal breast carcinoma characterized by mesenchymal features.[72]

Excess fat accumulates in the liver and the liver enlarges due to fat accumulation and then inflammation begins in the fatty liver. If this situation

continues for a long time, scar tissue forms in the liver, and eventually, cirrhosis occurs. If the cirrhosis problem progresses, it can cause cancer.[73,74] In a study, it was observed that serum cholesterol in the blood can cause increased expression of VEGF, MMP-2, and MMP-9 by activating the nuclear factor kappa B signaling pathway in hepatocellular carcinoma cells and cholesterol can cause inflammation.[6,75]

Studies have shown that the development of colorectal cancer is closely related to high fat intake in the diet and especially to cholesterol levels. It has been understood that high cholesterol levels cause colorectal cancer formation by the HMG-CoA mechanism.[76-79] It has been shown that LDL cholesterol is associated with colorectal cancer progression[79,80], HDL cholesterol is inversely associated with colorectal cancer risk[79,81], and total cholesterol and triglyceride levels are positively associated with increased colorectal cancer risk.[82-84]

The possible link between the incidence of pancreatic ductal adenocarcinoma (PDAC) and cholesterol metabolism has been demonstrated by epidemiologic studies showing high serum cholesterol and obesity as risk factors.[84,85] Rapid uptake and endogenous biosynthesis of cholesterol and phospholipids are a feature of oncogene-transformed cells.[85,86] PDAC causes increased expression of cholesterol synthesis genes, although this is not certain.[87] Cholesterol, its precursors, and/or metabolites may modulate the oncogenic functions of tumor cells to alter the disease course in early PDAC stages. For this reason, metabolites of cholesterol and other components of the cholesterol biosynthetic pathway are known to influence progression in some types of cancer.[72,88] A study examining the causal relationship between endogenous cholesterol metabolism and PDAC development and differentiation revealed that a metabolically determined PDAC differentiation duality is mediated by cholesterol-sensitive SREBP1-dependent transforming growth factor beta (TGFβ) expression, TGFβ receptor activation, and induction of a canonical Smad2/3 signaling pathway.[89]

Membrane rafts are heterogeneous and dynamic domains characterized by tight packing of lipids.[90] Signals critical for the survival and proliferation of prostate cancer (PCa) cells are transmitted through lipid rafts.[90,91] Studies have shown that some proteins critical for PCa growth and survival are regulated by lipid rafts and that changes in membrane cholesterol measurably affect the signals generated by these molecules.[92-94] Epidermal growth factor receptor (EGFR) in the lipid rafts of PCa cells is much more active and much more highly phosphorylated than the cohort of receptors in non-raft membranes, and cholesterol targeting by EGFR also disrupts downstream effectors.[95,96] The study also showed that a subpopulation of Akt present in rafts exhibits very different substrate specificity than non-raft Akt. This raft-localized Akt is inhibited by decreased cholesterol levels.[97] Signaling by LXRs down-regulates the level of phosphorylated Akt present in rafts, leading to PCa cell apoptosis, a process precipitated by LXR-stimulated cholesterol efflux and reversed by exogenous cholesterol addition. Collective data suggest that cholesterol regulates lipid dynamics, which in turn affects vital signaling pathways and acts to protect cells from apoptosis through the effects of increased cholesterol on lipids.[98,99]

Fatty acids and cholesterol are the two main types of lipids. Multiple fatty acids and enzymes involved in fatty acid metabolisms, such as fatty acid-binding protein 4, CD36, and stearoyl-CoA desaturase 1, significantly increase ovarian cancer proliferation, survival, drug resistance, and metastasis.[100-104] Proteins and enzymes highly expressed in cholesterol metabolism induce ovarian cancer progression; cholesterol and its derivatives also cause proliferation and chemo-resistance in ovarian cancer.[105-110]

In conclusion, the effect of LDL on the body causes various diseases. Excess LDL can cause heart disease, stroke, and cancer. It activates various signaling pathways and increases the risk of breast, prostate, testicular, uterine ovarian, and colorectal cancers.In addition, HDL eliminates cholesterol and tumor cells, which inhibits the growth and spread of tumors.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Sevinç S, Erbaş O. Effects of DNA Methylation on Cancer and Aging. JEB Med Sci 2020;1:126-30.
2. Sudhakar A. History of Cancer, Ancient and Modern Treatment Methods. J Cancer Sci Ther. 2009 Dec 1;1:1-4.
3. T. C. Halk Sağlığı Genel Müdürlüğü. 2017 Yılı Türkiye Kanser İstatistikleri. 2017. Available from:

https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Turkiye_Kanser_Istatistikleri_2017.pdf
4. Hausman DM. What Is Cancer? Perspect Biol Med. 2019;62:778-84.
5. Wang JJ, Lei KF, Han F. Tumor microenvironment: recent advances in various cancer treatments. Eur Rev Med Pharmacol Sci. 2018 Jun;22:3855-64.
6. Deng CF, Zhu N, Zhao TJ, Li HF, Gu J, Liao DF, et al. Involvement of LDL and ox-LDL in Cancer Development and Its Therapeutical Potential. Front Oncol. 2022 Feb 16;12:803473.
7. Lyu J, Yang EJ, Shim JS. Cholesterol Trafficking: An Emerging Therapeutic Target for Angiogenesis and Cancer. Cells. 2019 Apr 28;8:389.
8. King RJ, Singh PK, Mehla K. The cholesterol pathway: impact on immunity and cancer. Trends Immunol. 2022 Jan;43:78-92.
9. Luo J, Yang H, Song BL. Mechanisms and regulation of cholesterol homeostasis. Nat Rev Mol Cell Biol. 2020 Apr;21:225-45.
10. Schade DS, Shey L, Eaton RP. Cholesterol Review: A Metabolically Important Molecule. Endocr Pract. 2020 Dec;26:1514-23.
11. Hagita S, Rogers MA, Pham T, Wen JR, Mlynarchik AK, Aikawa M, et al. Transcriptional control of intestinal cholesterol absorption, adipose energy expenditure and lipid handling by Sortilin. Sci Rep. 2018 Jun 13;8:9006.
12. Levy E, Spahis S, Sinnett D, Peretti N, Maupas-Schwalm F, Delvin E, et al. Intestinal cholesterol transport proteins: an update and beyond. Curr Opin Lipidol. 2007 Jun;18:310-8.
13. Vance DE, Van den Bosch H. Cholesterol in the year 2000. Biochim Biophys Acta. 2000 Dec 15;1529(1-3):1-8.
14. Bloch K. The biological synthesis of cholesterol. Science. 1965 Oct 1;150:19-28.
15. Kandutsch AA, Russell AE. Preputial gland tumor sterols. 3. A metabolic pathway from lanosterol to cholesterol. J Biol Chem. 1960;235:2256-61.
16. Genaro-Mattos TC, Anderson A, Allen LB, Korade Z, Mirnics K. Cholesterol Biosynthesis and Uptake in Developing Neurons. ACS Chem Neurosci. 2019 Aug 21;10:3671-81.
17. Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: sometimes determinant and frequently implicated. EMBO Rep. 2014 Oct;15:1036-52.
18. Yang J, Wang L, Jia R. Role of de novo cholesterol synthesis enzymes in cancer. J Cancer. 2020 Jan 17;11:1761-67.
19. Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest. 2002 May;109:1125-31.
20. Allenbach Y, Keraen J, Bouvier AM, Jooste V, Champtiaux N, Hervier B, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain. 2016 Aug;139:2131-5.
21. Saraon P, Trudel D, Kron K, Dmitromanolakis A, Trachtenberg J, Bapat B, et al. Evaluation and prognostic significance of ACAT1 as a marker of prostate cancer progression. Prostate. 2014 Apr;74:372-80.
22. Balasse EO, Féry F. Ketone body production and disposal: effects of fasting, diabetes, and exercise. Diabetes Metab Rev. 1989 May;5:247-70.
23. Haapalainen AM, Meriläinen G, Pirilä PL, Kondo N, Fukao T, Wierenga RK. Crystallographic and kinetic studies of human mitochondrial acetoacetyl-CoA thiolase: the importance of potassium and chloride ions for its structure and function. Biochemistry. 2007 Apr 10;46:4305-21.
24. Porter FD, Herman GE. Malformation syndromes caused by disorders of cholesterol synthesis. J Lipid Res. 2011 Jan;52:6-34.
25. Lehmann R, Bhargava AS, Günzel P. Serum lipoprotein pattern in rats, dogs and monkeys, including method comparison and influence of menstrual cycle in monkeys. Eur J Clin Chem Clin Biochem. 1993 Oct;31:633-7.
26. Ye SQ, Kwiterovich PO Jr. Influence of genetic polymorphisms on responsiveness to dietary fat and cholesterol. Am J Clin Nutr. 2000 Nov;72:1275S-84S.
27. Rigotti A, Miettinen HE, Krieger M. The role of the high-density lipoprotein receptor SR-BI in the lipid metabolism of endocrine and other tissues. Endocr Rev. 2003 Jun;24:357-87.
28. Wilson PW. High-density lipoprotein, low-density lipoprotein and coronary artery disease. Am J Cardiol. 1990 Sep 4;66:7A-10A.
29. Nakajima K, Nakano T, Tokita Y, Nagamine T, Inazu A, Kobayashi J, et al. Postprandial lipoprotein metabolism: VLDL vs chylomicrons. Clin Chim Acta. 2011 Jul 15;412:1306-18.
30. Chait A, Ginsberg HN, Vaisar T, Heinecke JW, Goldberg IJ, Bornfeldt KE. Remnants of the Triglyceride-Rich Lipoproteins, Diabetes, and Cardiovascular Disease. Diabetes. 2020 Apr;69:508-16.
31. Millar CL, Duclos Q, Blesso CN. Effects of Dietary Flavonoids on Reverse Cholesterol Transport, HDL Metabolism, and HDL Function. Adv Nutr. 2017 Mar 15;8:226-39.
32. Zhong VW. Eggs, dietary cholesterol, and cardiovascular disease: the debate continues. J Thorac Dis. 2019 Sep;11:E148-50.
33. Gluba-Brzozka A, Franczyk B, Rysz J. Cholesterol Disturbances and the Role of Proper Nutrition in CKD Patients. Nutrients. 2019 Nov 18;11:2820.
34. Ellington AA, Berhow M, Singletary KW. Induction of macroautophagy in human colon cancer cells by soybean B-group triterpenoid saponins. Carcinogenesis. 2005 Jan;26:159-67.
35. Erbaş O, Solmaz V, Aksoy D, Yavaşoğlu A, Sağcan M, Taşkıran D. Cholecalciferol (vitamin D 3) improves cognitive dysfunction and reduces inflammation in a rat fatty liver model of metabolic syndrome. Life Sci. 2014 May 17;103:68-72.
36. Huang B, Song BL, Xu C. Cholesterol metabolism in cancer: mechanisms and therapeutic opportunities. Nat Metab. 2020 Feb;2:132-41.
37. Topal E, Aydemir K, Çağlar Ö, Arda B, Kayabaşı O, Yıldız M,

et al. Fatty Liver Disease: Diagnosis and Treatment. JEB Med Sci 2021;2:343-57.
38. Akdemir A, Sahin C, Erbas O, Yeniel AO, Sendag F. Is ursodeoxycholic acid crucial for ischemia/reperfusion-induced ovarian injury in rat ovary? Arch Gynecol Obstet. 2015 Aug;292:445-50.
39. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015 Mar;31:196-201.
40. Erbaş O, Akseki HS, Aktuğ H, Taşkıran D. Low-grade chronic inflammation induces behavioral stereotypy in rats. Metab Brain Dis. 2015;30:739-46.
41. Xu H, Zhou S, Tang Q, Xia H, Bi F. Cholesterol metabolism: New functions and therapeutic approaches in cancer. Biochim Biophys Acta Rev Cancer. 2020 Aug;1874:188394.
42. Çelik S, Çini N, Atasoy Ö, Erbaş O. Stress and Cancer. JEB Med Sci 2021;2:76-9.
43. Negre-Salvayre A, Coatrieux C, Ingueneau C, Salvayre R. Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. Br J Pharmacol. 2008 Jan;153:6-20.
44. Balzan S, Lubrano V. LOX-1 receptor: A potential link in atherosclerosis and cancer. Life Sci. 2018 Apr 1;198:79-86.
45. Ortiz N, Díaz C. Mevalonate pathway as a novel target for the treatment of metastatic gastric cancer. Oncol Lett. 2020 Dec;20:320.
46. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144:646-74.
47. Naito S, Makhov P, Astsaturov I, Golovine K, Tulin A, Kutikov A, et al. LDL cholesterol counteracts the antitumour effect of tyrosine kinase inhibitors against renal cell carcinoma. Br J Cancer. 2017 Apr 25;116:1203-1207.
48. Carnero A. The PKB/AKT pathway in cancer. Curr Pharm Des. 2010 Jan;16:34-44.
49. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. Hypertension. 2005 Jun;45:1042-9.
50. Morita SY. Metabolism and Modification of Apolipoprotein B-Containing Lipoproteins Involved in Dyslipidemia and Atherosclerosis. Biol Pharm Bull. 2016;39:1-24.
51. Sukhbold E, Sekimoto S, Watanabe E, Yamazaki A, Yang L, Takasugi M, et al. Effects of oolonghomobisflavan A on oxidation of low-density lipoprotein. Biosci Biotechnol Biochem. 2017 Aug;81:1569-75.
52. Bitorina AV, Oligschlaeger Y, Shiri-Sverdlov R, Theys J. Low profile high value target: The role of OxLDL in cancer. Biochim Biophys Acta Mol Cell Biol Lipids. 2019 Dec;1864:158518.
53. Baselga J. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer. Oncologist. 2011;16 Suppl 1:12-9.
54. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature. 2006 May 25;441:424-30.
55. Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer. 2002 Jul;2:489-501.
56. Bromberg J, Darnell JE Jr. The role of STATs in transcriptional control and their impact on cellular function. Oncogene. 2000 May 15;19:2468-73.
57. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer. 2009 Nov;9:798-809.
58. Rébé C, Végran F, Berger H, Ghiringhelli F. STAT3 activation: A key factor in tumor immunoescape. JAKSTAT. 2013 Jan 1;2:e23010.
59. Loh CY, Arya A, Naema AF, Wong WF, Sethi G, Looi CY. Signal Transducer and Activator of Transcription (STATs) Proteins in Cancer and Inflammation: Functions and Therapeutic Implication. Front Oncol. 2019 Feb 21;9:48.
60. Sato T, Neilson LM, Peck AR, Liu C, Tran TH, Witkiewicz A, et al. Signal transducer and activator of transcription-3 and breast cancer prognosis. Am J Cancer Res. 2011;1:347-55.
61. Zhang X, Yue P, Fletcher S, Zhao W, Gunning PT, Turkson J. A novel small-molecule disrupts Stat3 SH2 domain-phosphotyrosine interactions and Stat3-dependent tumor processes. Biochem Pharmacol. 2010 May 15;79:1398-409.
62. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999 Oct 27;282:1523-9.
63. Nelson ER, Chang CY, McDonnell DP. Cholesterol and breast cancer pathophysiology. Trends Endocrinol Metab. 2014 Dec;25:649-55.
64. Nazih H, Bard JM. Cholesterol, Oxysterols and LXRs in Breast Cancer Pathophysiology. Int J Mol Sci. 2020 Feb 17;21:1356.
65. Llaverias G, Danilo C, Mercier I, Daumer K, Capozza F, Williams TM, et al. Role of cholesterol in the development and progression of breast cancer. Am J Pathol. 2011 Jan;178:402-12.
66. Scheinman EJ, Rostoker R, Leroith D. Cholesterol affects gene expression of the Jun family in colon carcinoma cells using different signaling pathways. Mol Cell Endocrinol. 2013 Jul 15;374:101-7.
67. Hoque M, Rentero C, Conway JR, Murray RZ, Timpson P, Enrich C, et al. The cross-talk of LDL-cholesterol with cell motility: insights from the Niemann Pick Type C1 mutation and altered integrin trafficking. Cell Adh Migr. 2015;9:384-91.
68. Tatidis L, Masquelier M, Vitols S. Elevated uptake of low density lipoprotein by drug resistant human leukemic cell lines. Biochem Pharmacol. 2002 Jun 15;63:2169-80.
69. Antalis CJ, Uchida A, Buhman KK, Siddiqui RA. Migration of MDA-MB-231 breast cancer cells depends on the availability of exogenous lipids and cholesterol esterification. Clin Exp Metastasis. 2011 Dec;28:733-41.
70. Cruz PM, Mo H, McConathy WJ, Sabnis N, Lacko AG. The role of cholesterol metabolism and cholesterol transport in carcinogenesis: a review of scientific findings, relevant to future cancer therapeutics. Front Pharmacol. 2013 Sep 25;4:119.

71. Danilo C, Gutierrez-Pajares JL, Mainieri MA, Mercier I, Lisanti MP, Frank PG. Scavenger receptor class B type I regulates cellular cholesterol metabolism and cell signaling associated with breast cancer development. Breast Cancer Res. 2013;15:R87.
72. Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, et al. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science. 2013 Nov 29;342:1094-8.
73. Liu CY, Chen KF, Chen PJ. Treatment of Liver Cancer. Cold Spring Harb Perspect Med. 2015 Jul 17;5:a021535.
74. Tanaka K, Tsuji I, Tamakoshi A, Matsuo K, Ito H, Wakai K, et al.; Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan. Obesity and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol. 2012 Mar;42:212-21.
75. He M, Zhang W, Dong Y, Wang L, Fang T, Tang W, et al. Pro-inflammation NF-κB signaling triggers a positive feedback via enhancing cholesterol accumulation in liver cancer cells. J Exp Clin Cancer Res. 2017 Jan 18;36:15.
76. Herbey II, Ivankova NV, Katkoori VR, Mamaeva OA. Colorectal cancer and hypercholesterolemia: review of current research. Exp Oncol. 2005 Sep;27:166-78.
77. Gray RT, Loughrey MB, Bankhead P, Cardwell CR, McQuaid S, O'Neill RF, et al. Statin use, candidate mevalonate pathway biomarkers, and colon cancer survival in a population-based cohort study. Br J Cancer. 2017 Jun 6;116:1652-59.
78. Murai T. Cholesterol lowering: role in cancer prevention and treatment. Biol Chem. 2015 Jan;396:1-11.
79. Jacobs RJ, Voorneveld PW, Kodach LL, Hardwick JC. Cholesterol metabolism and colorectal cancers. Curr Opin Pharmacol. 2012 Dec;12:690-5.
80. Wang Y, Liu C, Hu L. Cholesterol regulates cell proliferation and apoptosis of colorectal cancer by modulating miR-33a-PIM3 pathway. Biochem Biophys Res Commun. 2019 Apr 9;511:685-92.
81. Ghahremanfard F, Mirmohammadkhani M, Shahnazari B, Gholami G, Mehdizadeh J. The Valuable Role of Measuring Serum Lipid Profile in Cancer Progression. Oman Med J. 2015 Sep;30:353-7.
82. Van Duijnhoven FJ, Bueno-De-Mesquita HB, Calligaro M, Jenab M, Pischon T, Jansen EH, et al. Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. Gut. 2011 Aug;60:1094-102.
83. Yao X, Tian Z. Dyslipidemia and colorectal cancer risk: a meta-analysis of prospective studies. Cancer Causes Control. 2015 Feb;26:257-68.
84. Han KT, Kim S. Do cholesterol levels and continuity of statin use affect colorectal cancer incidence in older adults under 75 years of age? PLoS One. 2021 Apr 23;16:e0250716.
85. Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena JW, et al. Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. Ann Oncol. 2015 Nov;26:2257-66.
86. Pitroda SP, Khodarev NN, Beckett MA, Kufe DW, Weichselbaum RR. MUC1-induced alterations in a lipid metabolic gene network predict response of human breast cancers to tamoxifen treatment. Proc Natl Acad Sci U S A. 2009 Apr 7;106:5837-41.
87. Silvente-Poirot S, Poirot M. Cancer. Cholesterol and cancer, in the balance. Science. 2014 Mar 28;343:1445-6.
88. Karasinska JM, Topham JT, Kalloger SE, Jang GH, Denroche RE, Culibrk L, et al. Altered Gene Expression along the Glycolysis-Cholesterol Synthesis Axis Is Associated with Outcome in Pancreatic Cancer. Clin Cancer Res. 2020 Jan 1;26:135-46.
89. Gabitova L, Restifo D, Gorin A, Manocha K, Handorf E, Yang DH, et al. Endogenous Sterol Metabolites Regulate Growth of EGFR/KRAS-Dependent Tumors via LXR. Cell Rep. 2015 Sep 22;12:1927-38.
90. Brown D. Structure and function of membrane rafts. Int J Med Microbiol. 2002 Feb;291:433-7.
91. Atasoy Ö, Erbaş O. Up to date of prostate cancer. D J Med Sci 2020;6:92-102.
92. Hryniewicz-Jankowska A, Augoff K, Sikorski AF. The role of cholesterol and cholesterol-driven membrane raft domains in prostate cancer. Exp Biol Med (Maywood). 2019 Oct;244:1053-61.
93. Adam RM, Mukhopadhyay NK, Kim J, Di Vizio D, Cinar B, Boucher K, et al. Cholesterol sensitivity of endogenous and myristoylated Akt. Cancer Res. 2007 Jul 1;67:6238-46.
94. Freeman MR, Cinar B, Kim J, Mukhopadhyay NK, Di Vizio D, Adam RM, et al. Transit of hormonal and EGF receptor-dependent signals through cholesterol-rich membranes. Steroids. 2007 Feb;72:210-7.
95. Zhuang L, Lin J, Lu ML, Solomon KR, Freeman MR. Cholesterol-rich lipid rafts mediate akt-regulated survival in prostate cancer cells. Cancer Res. 2002 Apr 15;62:2227-31.
96. Freeman MR, Solomon KR. Cholesterol and prostate cancer. J Cell Biochem. 2004 Jan 1;91:54-69.
97. Hager MH, Solomon KR, Freeman MR. The role of cholesterol in prostate cancer. Curr Opin Clin Nutr Metab Care. 2006 Jul;9:379-85.
98. Krycer JR, Brown AJ. Cholesterol accumulation in prostate cancer: a classic observation from a modern perspective. Biochim Biophys Acta. 2013 Apr;1835:219-29.
99. Pommier AJ, Alves G, Viennois E, Bernard S, Communal Y, Sion B, et al. Liver X Receptor activation downregulates AKT survival signaling in lipid rafts and induces apoptosis of prostate cancer cells. Oncogene. 2010 May 6;29:2712-23.
100. Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. Curr Opin Pharmacol. 2012 Dec;12:751-9.
101. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Gutbrod R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med. 2011 Oct 30;17:1498-503.
102. Ji Z, Shen Y, Feng X, Kong Y, Shao Y, Meng J, et al. Deregulation of Lipid Metabolism: The Critical Factors in Ovarian Cancer. Front Oncol. 2020 Oct 19;10:593017.

103. Ladanyi A, Mukherjee A, Kenny HA, Johnson A, Mitra AK, Sundaresan S, et al. Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. Oncogene. 2018 Apr;37:2285-301.
104. Tesfay L, Paul BT, Konstorum A, Deng Z, Cox AO, Lee J, et al. Stearoyl-CoA Desaturase 1 Protects Ovarian Cancer Cells from Ferroptotic Cell Death. Cancer Res. 2019 Oct 15;79:5355-66.
105. Li J, Condello S, Thomes-Pepin J, Ma X, Xia Y, Hurley TD, et al. Lipid Desaturation Is a Metabolic Marker and Therapeutic Target of Ovarian Cancer Stem Cells. Cell Stem Cell. 2017 Mar 2;20:303-314.e5.
106. Criscuolo D, Avolio R, Calice G, Laezza C, Paladino S, Navarra G, et al. Cholesterol Homeostasis Modulates Platinum Sensitivity in Human Ovarian Cancer. Cells. 2020 Mar 30;9:828.
107. Zheng L, Li L, Lu Y, Jiang F, Yang XA. SREBP2 contributes to cisplatin resistance in ovarian cancer cells. Exp Biol Med (Maywood). 2018 Apr;243:655-62.
108. He S, Ma L, Baek AE, Vardanyan A, Vembar V, Chen JJ, et al. Host CYP27A1 expression is essential for ovarian cancer progression. Endocr Relat Cancer. 2019 Jul;26:659-75.
109. Chang SS, O'Keefe DS, Bacich DJ, Reuter VE, Heston WD, Gaudin PB. Prostate-specific membrane antigen is produced in tumor-associated neovasculature. Clin Cancer Res. 1999 Oct;5:2674-81.
110. He J, Siu MKY, Ngan HYS, Chan KKL. Aberrant Cholesterol Metabolism in Ovarian Cancer: Identification of Novel Therapeutic Targets. Front Oncol. 2021 Nov 8;11:738177.