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Review Article

Dysregulated Cholesterol Metabolism Including Oxysterols in the Pathophysiology of Breast Cancer: Therapeutic Implications - A Narrative Review

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Abstract

Breast Cancer (BC) represents one of the commonest cancer in case of women. During 2018 it was calculated that mortality of 627, 800 women occurred due to BC. BC has multiple factors contributing to its etiology besides is a chronic disease. Earlier we updated the pathophysiology and treatment of BC. Despite significant advancements have been made regarding its treatment, numerous queries remain regarding carcinogenesis**.** At the time of carcinogenesis cells illustrate decontrolled cholesterol homeostasis. Subsequent to this intracellular cholesterol accrual takes place which is the requirement for sustenance of greater growth rate. Both cholesterol efflux along with influx represent 2 metabolic pathways which is essential for avoidance of intracellular cholesterol accrual. Liver X receptor (LXRs) reflect nuclear receptors which following activation result in the expression of ABC transporters implicated in facilitating cholesterol efflux besides causing Induction of IDOL (inducible degrader of low density lipoprotein receptor (LDLR) implicated in cholesterol influx reduction. Oxysterols are oxygenated cholesterol products that get generated via various pathways have been invented in the form of LXR particular ligands. Certain Oxysterols are implicated in tumor generation, whereas others are believed to work as anti tumor substances. Thus here we conducted a narrative review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like Breast Cancer; cholesterol homeostasis; LXRs; Oxysterols; 27OHC; pro-protein convertase subtilisn/kexin type9 (PCSK9) in BC generation, from 1983 till date 2022. We found over 2000 articles where we used 50 articles due to journal specification for this review. Here we detail regarding the implication of cholesterol, Oxysterols along with LXRs in the pathophysiology of BC, highlighting the biological actions of LXRs ligands. Further the part of PCSK9 regarding the breast cancer robustness along with cholesterogenic gene signatures might aid in anticipating prognosis of young breast cancer patients.

Keywords: BC; Cholesterol; LXRs; Oxysterols

Introduction

Breast Cancer (BC) represents a chronic disease that takes place secondary to numerous factors. It has been acknowledged that obesity along with Metabolic Syndrome (MetS) are associated with risk of generation of BC. It was further illustrated that circulating estrogen receptor (ER) were correlated with adiposity as well as BC. Escalated blood cholesterol is frequently observed in obesity along with MetS [1], with its involvement in the form of risk factor remains contradictory. These variations can be reasoned out by the blood cholesterol placement amongst various classes of lipoproteins (very low density lipoprotein (VLDL), low density lipoprotein (LDL), in addition to high density lipoprotein (HDL)) besides it getting modulated by lifestyle along with menopausal status [2].

Animal as well as human studies have illustrated that circulating quantities of cholesterol **i**ntricately reflect that of the primary cholesterol metabolite, the oxysterol 27OHC, with hypercholesterolemia causing greater quantities of 27OHC [3]. Numerous studies have illustrated that this oxysterol possesses mitogen function in case of ER positive tumor besides in the form of nuclear receptors, Liver X receptor (LXR) expression of crucial genes LXRα (alias NR1H3), LXRα as well as LXR β (alias NR1H2) transcription factors which control the expression of genes implicated in lipid along with cholesterol metabolism.

This corroboration made researchers evaluate LXRs besides their ligands (oxysterols as well as their synthetic ligands) in association with direct implications in breast tumor formation. The outcomes of numerous studies have illustrated that full range of oxysterols obtained from cholesterol do not work in akin manner like27OHC. Actually, synthetic as well as natural ligands of LXRs, like T0901317 along with 22 (R) hydroxy cholesterol (22(R)- OHC) resulted in repression of proliferation, in addition to apoptosis induction in a Breast Cancer- model cell line (ER+) [4]. Furthermore, activation of LXR by T0901317 resulted in reduction of the expression of Flotillin-2, which represents a biomarker of lipid rafts which possess a significant part regarding Cancer propagation along with Akt signaling pathway in the MCF-7 cell line [5]. Both 22(R)-OHC as well as 24 (S) hydroxy cholesterol caused repression of proliferation of prostate lipid along with pathway of Breast Cancer-cells [6]. Cancer-cell lines possessing a greater LXRα mRNA expression possessed a greater sensitivity towards 22 (R)-OHC hampering [7].

Having reviewed in detail the management of Breast Cancer earlier, besides that of triple negative Breast Cancer [8,9], here our concentration was on association amongst cholesterol, oxysterols, LXRs along with Breast Cancer (Figure 1) [10].

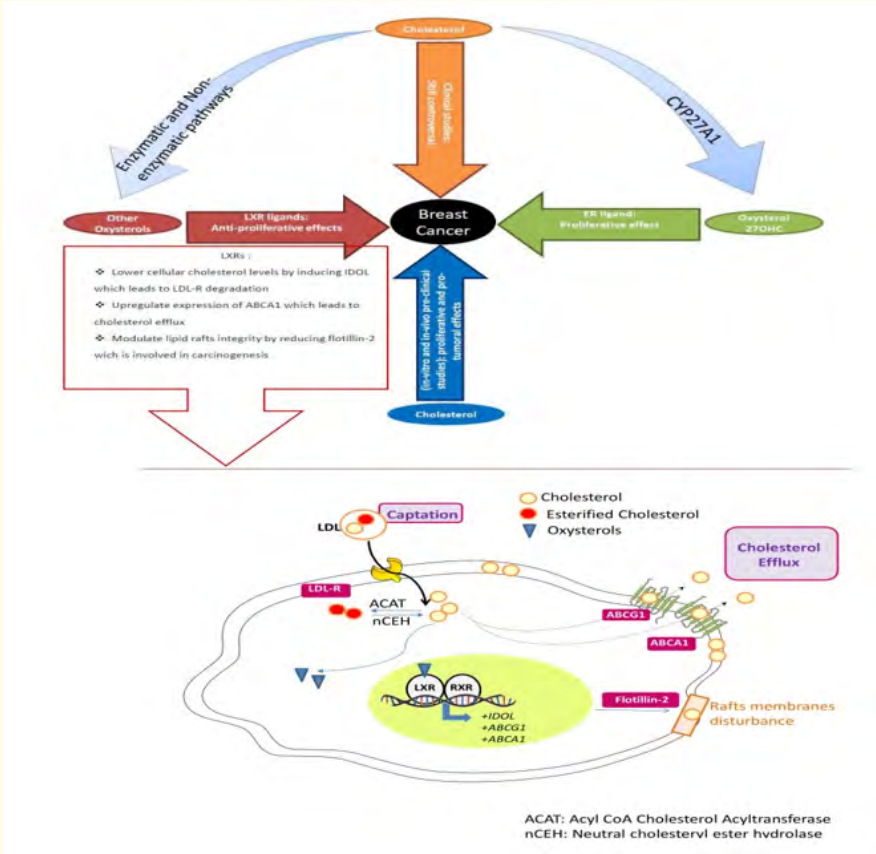

Figure 1: Influence of cholesterol, oxysterols and liver X receptors (LXRs) on breast cancer pathophysiology.

Cholesterol, oxysterols, LXRs along with breast cancer

Every cell inclusive of the mammary cell possesses the capacity of formation of cholesterol with utilization of the mevalonate pathway by an enzymatic stepwise event where 3 hydroxy, 3 methyl glutaryl-coenzyme reductase (HMGCR)is implicated. Acquisition of cholesterol can take place by cells via lipoproteins as well. Actually, lipoproteins modulate the cholesterol administration (from di*et al*ong with biogeneration) to cells from the blood.

Besides cholesterol being a significant constituent of cell membrane, it works in the form of a precursor regarding steroid hormone, Bile Acid, Vitamin D along with oxysterols generation, represents a key molecule regarding cell growth along with function [11].

Fine controlling of intracellular cholesterol of takes place by various complicated modes. Numerous experimental studies illustrated that Cancer cells show decontrolled transcription of various genes implicated in cholesterol control as well as metabolism like low density lipoprotein receptor (LDLR), HMGCR along with sterol regulatory element binding protein (SREBPs) [12]. Actually, numerous cancer cells illustrate escalated quantities of LDLR besides enhanced LDL uptake [13]. In a Breast cancer-model acknowledged for its exaggerated cell behavior (MDA-MB-231). Upregulation of LDLR has been illustrated, along with LDL induces cell hamper migration [14]. Scavenger receptor class B member 1 (SR-B1)is frequently overexpressed in tumors along with is believed to aid in escalating HDL cholesterol uptake in cancer cells [13,15]. Regarding MDA-MB-231 cells knockout of SR-B1 hampers migration *in vitro* along with tumor growth *in vivo* [16]. Furthermore, assessment of cancer cells illustrated that cholesterol bio generation modulated by HMGCR is escalated in view of enhanced transcriptional control (modulated bySREBP2) [17]. The action of statins, hypercholesterolemic drugs which selectively hamper HMGCR was of inspiration to researchers. They have been illustrated to display anti-proliferative anti-apop**t**otic actions in various experimental studies) [18]. Different modes have been regarding the mode of action of statins, inclusive of hampering of isoprenoids, that are deemed to be essential for the prenylation, directing along with placement of Ras proteins. Ras superfamily of GTPases possesses well acknowledged part regarding cell proliferation, cell survival migration, with as well as invasion. Besides this action regarding cholesterol bio generation, another mode has been recently illustrated.

The outcomes of Bai., *et al*. [19], illustrated that simvastatin escalated miR-140-5p in a dose based fashion through activation of transcription factor NRF1, that decreased BC (ER+ as well as ER-) cell proliferation besides resulted in apoptosis induction [19]. Different experimental studies with utilization of statins or genetic modulation corroborate that dyscontrolled cholesterol homeostasis result in intracellular cholesterol accrual, that is the need regarding sustenance of greater growth rate along with function of cancer cells seen in prior studies [20]. Besides these genes in detail below, the transcription factor LXRs are further implicated in sustenance of intracellular cholesterol homeostasis by regulating its efflux along with/or influx.

Certain studies documented that escalated cholesterol efflux along with/or influx are correlated with reduction in cancer cells proliferation besides tumor generation. Actually, ElRoz., *et al*. [4], illustrated that LXR activation by T0901317 or 22(R)-OHC in MCF-7 cell line eliminates cholesterol by stimulating cholesterol efflux via the expression of ATP binding cassette transporter G1 (ABCG1). This causes hampering of cell proliferation as well as stimulate apoptosis [4]. Regarding mode of cholesterol influx decrease, LXR hampers the expression of LDLR via the induction of an E3 ligase which ubiquitinates LDLR known as IDOL (inducible degrader of LDLR) [21].

Cholesterol along with breast cancer in animal studies

A study conducted by Llaverias., *et al*. [12], evaluated the part of plasma cholesterol in the generation of mammary tumors in a MMTV-PYMT mouse model of mammary cancer. Their outcomes obtained illustrated that escalated dietary consumption of lone cholesterol (via a diet with abundance of cholesterol)led to a significant reduction of tumor latency along with enhanced tumor growth which validated the concept regarding cholesterol by itself possessed the capacity of impacting tumor pathophysiology. Llaverias., *et al*. [12], further revealed that in case of mammary tumors enhanced expression of cyclinD1, a biomarker of tumor generation was correlated with cholesterol plasma quantities. Furthermore, escalated expression of SR-B1 as well as LDLRs in tumors were illustrated [12]. Regarding assessment of mode implicated in LDL facilitating Breast Cancer growth as well as invasiveness dos Santos., *et al*. [22], assessed the actions of LDL on various Breast Cancer-models. The observation was that LDL (however not HDL) facilitated cell proliferation, migration,

elimination of adhesion. With the utilization of *in vivo* models (in receipt of diet with greater cholesterol plasma quantities) they further demonstrated that breast tumors were persistently greater in size, possessed the greater proliferation capacity in case of hypercholesterolemic mice, with these mice possessing lung metastasis. They documented that overexpression of the survival pathways Akt along with ERK, besides reduction of adhesion molecules existed in breast cancer cells that received exposure to LDL [22]. Hampering of pro-protein convertase subtilisn/kexin type9 (PCSK9) represents a great approach regarding reduction of cholesterol along with LDL-cholesterol [23]. A study conducted by Momtazi-Borojeni., *et al*. [24], anti PCSK9-antibody induction was done through a vaccine inoculation in mice with breast cancer cells. They documented a reduction of tumor growth by 21% in the vaccine group in contrast to control group. Moreover escalation of life span by 4.2% in the vaccine group in contrast to control group was observed [24].

Cholesterol along with breast cancer in human studies

Studies conducted in humans regarding correlation amongst serum cholesterol along with its carriers like lipoprotein besides cancer resulted in contradictory outcomes. Certain researchers observed a protective action, whereas others found that cholesterol was a risk factor, while others observed no action. Actually, Chang., *et al*. [25], illustrated that greater quantities of VLDL-C along with lesser quantities of ApoA1, a constituent of HDL possessed a significant correlation with breast cancer [25]. Another study pointed that greater quantities of HDL-C might decrease the risk of breast cancer in case of pre menopausal women [26]. The outcomes of the ARIC cohort pointed that lesser quantities of HDL-C cancer in case of pre menopausal women might be a marker of escalated breast cancer risk [27].

In a recent assessment it was illustrated that breast cancer risk escalated by 1. 6 times in patients with hyperlipidaemia [28]. In a different study it was illustrated that patients having well developed breast cancer, a greater LDL-C along with VLDL-C was observed without a correlation amongst HDL-C or total cholesterol was prominent [29]. In a meta-analysis conducted by Touvier., *et al*. [30], corroborated a modest, however statistically significant inverse correlation amongst total cholesterol, with in particular HDL-C along with breast cancer risk [30].

In the British study ACAIM (Algorithm for Co-morbidities, Associations, Length of Stay, and Mortality) illustrated that women≥40 years who possessed greater quantities of cholesterol had 45% lesser likelihood of breast cancer generation. The mortality risk in patients with established breast cancer decreased by 40% in patients possessing greater quantities of cholesterol [31].

In view of serum cholesterol gets impacted by diet, in particular lipid ingestion along with hypocholesterolaemia drugs, the actions of dietary cholesterol along with statins regarding the incidence of breast cancer has further attracted researchers. Hu., *et al*. [32], in a population dependent study observed a positive correlation with risk of breast cancer, in particular in postmenopausal women [32]. Li., *et al*. [33], conducted a meta-analysis regarding the correlation amongst dietary cholesterol as well as breast cancer, they observed that the correlation acquired significance on ingestion of cholesterol greater than 0. 37g daily [33].

The observation of certain meta-analysis do not corroborate the posit regarding the protection conferring action against breast cancer [3,34]. Nevertheless, in a separate meta-analysis, utilization of statins correlated with breast cancer recrudescence reduction [35].

Clarification is not there with these studies regarding cholesterol acting in the form of best risk biomarker. Following these it was pointed that 27OH would make a more appropriate biomarker.

Role of 27OHC, oxysterols, LXRs along with breast cancer

Oxysterols represent metabolites of cholesterol. Certain of these are oxygenated enzymatically (like 25-hydroxy cholesterol (25OHC), 27-hydroxy cholesterol (27OHC) as well as 24S-hydroxy cholesterol (24OHC), whereas certain do not get generated enzymatically (like 7 alpha/beta hydroperoxy cholesterol (7OOHC), 7keto cholesterol (7KC) [36].

Maximum oxysterols are detailed in the form of LXR ligands. Activation of ligands of LXR result in enrolment of particular coactivator**s** (like steroid receptorcoactivator-1 (SRC-1), Peroxisome Proliferator Activated Receptor **γ-**coactivator-1 alpha (PGC-1 alpha) along with activating signal-co integrator-2 (ASC2) which causes transcription of genes [10].

The oxysterol 27OHC reflects a primary metabolite of cholesterol developed by CYP27A, that circulates at marginally greater quantities in contrast to other oxysterols [10]. Dependent on numerous studies 27OHC is believed to be a LXR ligand which gets generated endogenously in the form of SERM [37]. Thus it is feasible that 27OHC possesses various actions regarding cell growth, based on ER status. Actually, it has been illustrated that 27OHC stimulated proliferation in ER positive breast cancer cell models [10]. Furthermore, it has been illustrated that the exogenous co-delivery of ER antagonists along with 27OHC reverts the breast tumors growth in a xenografted animal model in contrast to lone 27OHC [10]. Utilization of LXR -/- in another study in breast cancer cells 27OHC escalated the target gene induction. Conversely27OHC caused upregulationof LXR target genes in case of ER knockout cells [38].

Furthermore, finding escalated quantities of CYP27B1, a cytochrome p450 enzyme implicated in the catabolism of 27OHC have a greater advantageous correlation regarding survival resultsin mice pointed to the implications of oxysterols in breast cancer pathophysiology [10]. However, this action might differ as per the ER status of the tumor.

Taking into account the part of 27OHC in breast tumors, various researchers performed studies in case of humans. The study performed by Wu., *et al*. [39], illustrated that intratumor quantities of 27OHC are 6 times greater in case of ER positive breast tumors in contrast to normal tissue nearby [39]. Solheim., *et al*. [40], performed side chain oxysterols assessment in breast cancer tumors (ER+ as well as ER -). Their finding was an association amongst esterified along with free 27-hydroxy cholesterol in both tumors. Nevertheless, no significant variation in quantities of other endogenous oxysterols were seen amongst ER+ as well as ER - tumors [40].

Exosomes obtained from cancer cells possess abundance of biomarkers along with might be of utility regarding the diagnosis of these cancers. Roberg-Larsen., *et al*. [41], observed an enhanced quantity of exosomes from the MCF-7 (ER+) breast cancer cell line in contrast to those obtained from an ER - breast cancer cell (MDA-MB-231) in addition to other control exosomes (obtained from a non cancerous cell line (HEK293) besides human plasma [41].

Utilizing this European Prospective investigation into Cancer and Nutrition (EPIC) Heidelberg cohort, Lu., *et al*. [42], evaluated the correlation amongst serum 27OHC along with breast cancer risk. Their study illustrated that the correlation amongst serum 27OHC along with breast cancer risk varied as per menopausal status, however not as per age at the time of diagnosis. Absence of correlation amongst premenopausal women at blood collection was seen. Nevertheless, amongst post menopausal women greater serum 27OHC quantities had a correlation with lesser breast cancer risk [42].

25-hydroxy cholesterol (25OHC), another oxysterol observed to be escalated in the circulation of patients with breast cancer who have recurred in contrast to the ones with primary disease [43].

In view of the LXR agonist 25OHC is believed to impact towards breast cancer cells proliferation, studies have been performed regarding the expression of LXR by itself along with oxysterol estimation in human tumors as well as cell lines. Hutchison., *et al*. [44], performed assessment of variations regarding oxysterols along with LXR signaling amongst ER+ as well as ER - breast cancers along with cell lines. Their findings regarding the ER - breast cancers possessed greater responsiveness to LXR agonists in contrast to ER+ breast cancers to LXR agonists. They further queried if the transcriptional action of LXR observed in cellular models (ER -) could be observed in primary breast tumors. For validation, they evaluated if the expression of LXRα along with LXR βwere associated with the classical LXR target genes (ABCA1 as well as ApoE) in primary tumors with various ER statuses (ER+ as well as ER -). They illustrated that ABCA1 was associated with LXRα in ER -, however not in ER+ tumors. ApoE was associated with LXRα in both subkinds, however there was considerably weaker association with ER+ in contrast to ER - tumors. Assessment of ABCA1 as well as ApoE was performed regarding their association with LXR β. A weak association of LXR β in ER+ tumors was observed, however not associated with it in ER – tumors. From their findings it was concluded that an inverse correlation existed with the capacity of LXR regarding induction of classical target genes expression [44].

The transcriptional actions of LXR (alpha along with beta) gets controlled by the co-repressors NCOR1, NCOR2 as well as LCOR [45]. It has been acknowledged that LXR alpha possesses 100

times greater binding capacity in contrast to LXR beta for the co-repressors NCOR1, along with NCOR2 [46]. Dependent on these findings apparently single determination of LXR agonists is not enough; with it is apparently essential to estimate the quantities of both the ligands quantities along with transcriptional actions. The study by Hutchison., *et al*. [44], illustrated that MDA-MB-468 breast cancer cells (ER -) expressed considerably lesser NCOR1, NCOR2 as well as LCOR transcripts in contrast to MCF-7 (ER+) breast cancer cell line. They further documented that the knockdown of these co-repressors resulted in equalization of sensitivity to ligands amongst ER sub kinds [44]. Pan., *et al*. [46], in another study evaluated the expression quantities of ABCA1, ABCG1 as well as LXR beta in triple negative breast cancer (TNBC) tissues along with non cancerous mammary tissues. Their observation was that just ABCA1 in TNBC tissues was greater in contrast to non cancerous mammary tissues. A greater expression of ABCA1 in TNBC tissues possessed significant **c**orrelation with histological grade. Nevertheless, no significant variations were observed amongst the expression quantities of as LXR beta as well as ABCG1 in both the mammary tissues [46]. A mass spectrometry dependent label free quantification with subsequent functional elucidation was conducted for evaluation of the maximum decontrolled proteins amongst different tissues from the patients having a diagnosis of invasive ductal carcinoma; the primary breast tumor, axillary metastatic lymph node in addition to the analogous opposite as well as adjoining non tumor tissues. This study tissues revealed that the differential expression of proteins amongst malignant besides non tumor breast tissues possessed maximum correlation with LXR/RXR pathway [47].

Regarding reasoning out why TNBC possessed greater aggressiveness in case of African besides African American women, Torres-Luquis., *et al*. [48], contrasted the proteomic profiles of TNBC with luminal A (LA) cancer, besides in African American (AA), along with European American (EA) patients. They revealed that **e**nhancement of representation regarding LXR/RXR signaling pathway existed in LA samples from AA women along with changes in this pathway were observed in AA women. Moreover, they illustrated that Cyp7B1, the enzyme implicated in breakdown of 27OHC possessed robust immunoreactivity in the tumor cells of LA patients along with lesser in case of TNBC tissues [48].

Furthermore, Chong,., *et al*. [49], attempted to study the part of circulating quantities of PCSK9, ANGPTL3 along with Lp (a) in case of Stage III breast cancers. Their findings pointed that in their small cohort comprising of 46 women, PCSK9 possessed a tendency to escalate with the escalating robustness of breast disease. With the knowledge regarding the **s**ignificant part played by PCSK9 in sustenance of cholesterolemia along with probable part regarding tumor evasion, requirement for greater studies in future exist in a larger cohort for corroborating the correlation amongst PCSK9 along with breast cancer robustness [49].

Li., *et al*. [50], established a risk score cell regarding 5 cholesterogenic gene signatures for anticipating the prognosis of young breast cancer patients. Their observation was that these 5 cholesterogenic gene signatures possessed independent prognostic **s**ignificance in case of young breast cancer patients. They further illustrated that NFKBIA possessed a protective part, whereas INHBA had a pro cancer generating role [50].

Conclusions

Thus the impact of cholesterol regarding the breast cancer incidence continues to be an attractive**,** yet a contradictory issue.

Whereas 27OHC is a primary oxysterol metabolite, acknowledged to be a LXR ligand in addition to a SERM, it has been illustrated that it works in disease in the form of a mitogen along with is escalating believed to be a probable biomarker for risk. Nevertheless, other oxysterols are believed to be anti tumor substances. Additionally, the LXR/RXR signaling pathway as well as Cyp7B1, the enzyme implicated in breakdown of 27OHC are significantly escalated in case of women presenting with luminal A (LA) cancer in contrast to TNBC. Moreover LXR alpha along with LXR beta, along with their co-repressors, get differentially expressed in case of tumors possessing variable ER statuses. These findings further highlight the significance of assessment of oxysterols along with nuclear LXRs in breast cancer. Thus innovative approaches might get planned regarding future therapeutics for breast cancer. Additionally, cholesterogenic gene signatures might aid in anticipating prognosis of young breast cancer patients, besides

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