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Review

Dyslipidemia in breast cancer patients increases the risk of SAR-CoV-2 infection

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ABSTRACT

Breast cancer (BC) is the most diagnosed and second leading cause of death among women worldwide. Elevated levels of lipids have been reported in BC patients. On the other hand, lipids play an important role in coronavirus infections including the newly emerged disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and designated COVID-19 by WHO. Cancer patients including BC have been reported to be at higher risk of SARS-CoV-2 infection, which is mostly attributed to the chronic immunosuppressive status of cancer patients along with the use of cytotoxic drugs. Here in this review, we highlighted the role of dyslipidemia associated with BC patients in the incidence and severity of SARS-CoV-2 infection. Elevated levels of lipids namely phospholipids, cholesterol, sphingolipids, and eicosanoids in the serum of BC patients and their re-localization to the alveolar spaces can increase susceptibility and/or severity due to SARA-CoV-2 infection. Therefore, manipulation of dyslipidemia in BC patients should be recommended as prophylactic and therapy against SARS-CoV-2 infection.

1. Introduction

Coronaviruses are a group of enveloped viruses that are having a large positive single-stranded RNA (Chan et al., 2013; Chan et al., 2012). Coronaviruses including HCoV-OC43, HCoV-229E, HCoV-HKU1, and HCoV-NL63 are reported to cause a wide range of clinical manifestations such as mild upper respiratory tract infections. On the contrary, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the recent SARS-CoV-2 cause severe life-threatening pneumonia accompanied by acute respiratory distress leading to multi-organ failure and death (Chan et al., 2015; Cheng et al., 2007; Zumla et al., 2016).

Lipids play key roles at several stages during the virus life cycle. Lipids can act as direct receptors for the attachment and cell entry of viruses (Taube et al., 2010). Furthermore, lipid synthesis plays a crucial role in the development of the viral replication complex (Nagy et al., 2016). Lipid metabolism generates the energy required for viral replication (Diamond et al., 2010). Lipids dictate the cellular distribution of proteins, besides the assembly and release of viral particles (Ono et al.,

Abbreviations: ACE-2, Angiotensin converting enzyme-2; ATP, Adenosine triphosphate; C1P, Ceramide-1-phophate; ChoK, Choline kinases; CHPT, CDP-choline diacylglycerol phosphocholinetransferase; COVID-19, Corona virus disease-19; COX, Cyclooxygenases; cPLA2α, Cytosolic phospholipase A2α enzyme; CT, CTP-choline cytidylyltransferase; DMVs, Double membrane vesicles; EETs, Epoxyeicosatrienoic acids; ERK, Extracellular signal-regulated kinases; HDL, High- density lipoproteins; HETEs, Hydroxyeicosatetraenoic acids; HMGCR, Hydroxymethylglutaryl-coenzyme A reductase; HPETEs, Hydroperoxyeicosatetraenoic acids; IDL, Intermediate-density lipoproteins; IL-1β, Interleukin-1β; LDL, Low-density lipoproteins; LOX, Lipoxygenases; LT, Leukotrienes; lysoPC, Lyso-phosphatidylcholine; lysoPE, Lyso-phosphatidylethanolamine; MAPK, Mitogen-activated protein kinases; mPGES-1, Microsomal prostaglandin E synthase-1; PC, Phosphatidylcholine; PCho, Phosphocholine; PE, Phosphatidylethanolamine; PG, Prostaglandins; PI3K, Phosphatidylinositol-3-kinase; PLA2G2D, Phospholipase A2 group IID; S1P, Sphingosine-1-phophate; S1PR1, Sphingosine kinase 1 receptor 1; SARS-CoV, Severe acute respiratory syndrome coronavirus; SK1, Sphingosine kinase 1; SR-BI, Scavenger receptor class B type I; Th, T helper cells; TNF, Tumor necrosis factor; TX, Thromboxanes; VLDL, Very-low-density lipoproteins.

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2004). Similarly, lipids have important roles in coronaviruses life cycle including receptor binding, cell entry, formation of double-membrane vesicles (DMVs), and viral replication (Knoops et al., 2008). It has been reported that lipids are used by SARS-CoV-2 in several viral processes including ACE-2 receptor binding, cellular fusion, entry and replication (Alketbi et al., 2021). Further, cellular dyslipidemia significantly affects the viral existence in the human body (Alketbi et al., 2021).

BC is the most common cancer type among women with an overall 1.7 million cases diagnosed worldwide per year (Mistry and French, 2016). Alteration in cellular and serum lipid metabolism was linked to the progression of BC (Ackerstaff et al., 2003; Patra, 2008). Lipids are elevated in BC cells and tissues (Eliyahu et al., 2007; Ting et al., 1996; Tse et al., 2007), and more importantly in the serum of BC patients (Chen et al., 2016). It has been reported that BC patients are at higher risk of contracting SARS-CoV-2 infection, which is mainly attributed to the chronic immunosuppressive state and use of cytotoxic drugs (Addeo and Friedlaender, 2020). Since host lipid metabolism plays key roles in the virus life cycle, here in this review, we hypothesized the existence of strong relationships between the lipid dysregulation in BC patients and the incidence and severity of SARS-CoV-2 infection.

2. Incidence of infection and severity of SARS-CoV-2 in BC patients is augmented

Generally, cancer affects the susceptibility and prognosis of SARS-CoV-2 infection (Fillmore et al., 2020). Studies have shown that cancer patients are predisposed to higher severity of SARS-CoV-2 infection and poor prognosis especially if they are immune-compromised due to chemotherapy treatment (Zhang et al., 2020a). According to the type and site of the primary tumor, the risk of adverse events from SARS-CoV-2 infection is significantly different (Rugge et al., 2020). Among 1035 cancer patients infected with SARS-CoV-2, BC was the most prevalent type of cancer (Pathania et al., 2021). BC patients are at higher risk of hospitalization and death from SARS-CoV-2 infection (Rugge et al., 2020). BC was associated with the highest rate of COVID-19 related mortality in a study that is involved 1794 COVID-19 positive cancer patients (Fillmore et al., 2020). Studies have shown that BC patients treated with chemotherapy stay immuno-compromised for more than a year after treatment (Carreira et al., 2020). A higher prevalence rate of viral infection was reported among BC survivors compared to cancer-free people (Heo et al., 2017).

3. BC patients are at higher risk of SARS-CoV-2 infection because of elevated levels of serum lipids including

3.1. Phospholipids

A significant variation in the serum levels of phospholipids in BC patients has been reported when compared to healthy individual (Mistry and French, 2016). Several studies have reported an increase in the level of phospholipids in BC tissues particularly the main components of biological membranes, the glycerophospholipids. Similarly, the levels of phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE) and their precursors, phosphocholine (PCho) and phosphoethanolamine, are elevated in the serum of BC patients (Fig. 1) (Mistry and French, 2016). The alteration in cellular lipids affects its functions and enhances the development of cancer and its progression. For instance, changes in choline metabolism were associated with more aggressive tumors (Mistry and French, 2016). Expression and activity of choline kinases (ChoK) showed a % increase in BC patients (de Molina et al., 2002). Hammad et al., demonstrated that the major changes in lipid profiles among BC patients are attributed to PCho species, mainly ethanolamine and choline glycerophospholipids (Hammad et al., 2009). Furthermore, mutations in genes, which construct the phosphatidylinositol-3-kinase (PI3K) pathway, occur in 70% of BC.

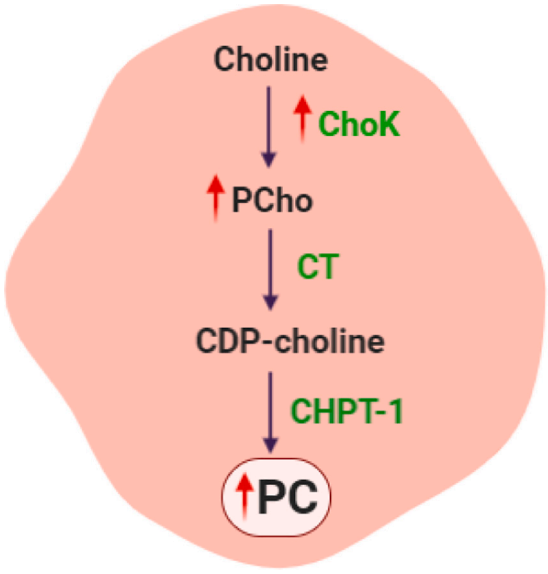

Fig. 1. Synthesis of phosphatidylcholine (PC). The red arrow represents up-regulation in the case of BC. Choline kinase (ChoK) catalyzes the phosphorylation of free choline using ATP as a phosphate donor and produces phosphocholine (PCho). CTP-choline cytidylyltransferase (CT) catalyzes the synthesis of CDP-choline from phosphocholine and CTP. CDP-choline is used by CDP-choline diacylglycerol phosphocholine transferase (CHPT) as a substrate to produce phosphatidylcholine (PC). Drawing was adapted from Hilvo and Matej Orešiè (2012).

Activation of the PI3K pathway plays an essential role in both the initiation and progression of human BC, as well as the development of resistance to several current BC therapies (Miller et al., 2011).

Replication of coronavirus is mainly associated with re-arrangement of the intracellular membrane (Yan et al., 2019) since it requires the formation of DMVs as replicative organelles. Phospholipids including in particular glycerophospholipids are the main component of DMV and the viral envelope (Xu and Nagy, 2015). Phospholipids are remarkably increased in coronavirus-infected cells. Upon infection, lysophospholipids mainly lysophosphatidylcholine (lysoPC), and lysophosphatidylethanolamine (lysoPE) are consistently upregulated in infected cells (Fig. 2) (Yan et al., 2019). The upregulation is believed to promote efficient coronavirus replication.

More interestingly, the cytosolic phospholipase A2α enzyme (cPLA2α), a crucial enzyme in the biosynthesis of lysoPC and lysoPE is significantly elevated following coronavirus infection (Fig. 2) (Müller et al., 2018). Inhibition of cPLA2α causes a significant reduction in the accumulation of viral protein and RNA together with the decrease in the production of virus progeny (Müller et al., 2018). Moreover, phospholipase A2 group IID (PLA2G2D), which is an enzyme that contributes to the expression of anti-inflammatory lipid mediator enhances the severity of SARS-CoV-infected mice by modulating the mice immune response (Vijay et al., 2015). Furthermore, coronaviruses can modulate and rearrange the host lipid profile to reach the homeostasis suitable for its replication (Yan et al., 2019).

PI3K signaling pathway plays a vital role in virus entry and trafficking, as well as modulation of post-internalization events such as virus replication and assembly (Mazzon and Mercer, 2014). Wu et al., reported that following 12 years of infection, SARS-survivors show a higher level of phosphatidylinositol and lysophosphatidylinositol when compared to uninfected individuals (Wu et al., 2017).

The aforementioned data suggest a strong correlation between the altered phospholipids profile in BC and susceptibility to coronavirus infection. Since coronaviruses are dominantly modified and re-arranged the host phospholipids to reach a sophisticated state of homeostasis optimal for their replication, the upregulation of these phospholipids in

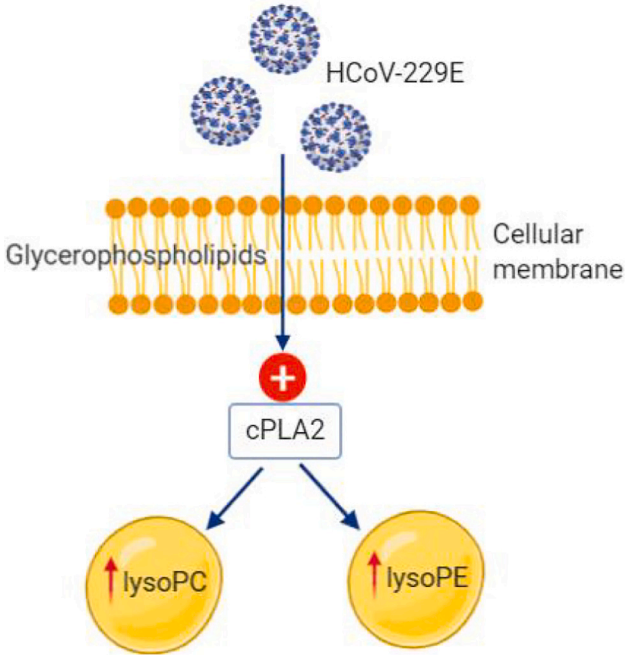

Fig. 2. Cellular lipid signaling response following HCoV-229E infection. The red arrow represents upregulation. Upon HCoV-229E infection, glycerophospholipids as main components of the cell membrane are metabolized to lysophospholipids due to cPLA2 enzyme activation. Lysophospholipids such as lysoPCs and lysoPEs are consequently increased during the infection. Drawing was adapted from Yan et al., 2019 (Yan et al., 2019).

BC can serve as an advantageous factor for viral replication and infection. For instance, glycerophospholipids are elevated in BC patients, offering a higher level of cPLA2 enzyme substrates to produce more lysoPCs and lysoPEs required for coronavirus replication, thus facilitating the progression of the infection. Similarly, the PI3K pathway is already activated in almost all BC patients, considering its vital role in virus entry, trafficking, and replication. Collectively, this can make BC patients at constant higher risk of coronavirus infection including SARS-CoV-2 infection.

3.2. Cholesterol

Cholesterol is an important constituent of the plasma membrane, the main barrier between the host cell and the external micro-environment, as it is required to maintain the integrity and fluidity of the cell membrane (Silvius, 2003). Cholesterol plays critical role in maintaining the structure and function of lipid rafts, which are discrete lipid domains enriched in glycosphingolipids (glycolipids and sphingomyelin), and glycophosphatidylinositol (GPI)-anchored proteins (Levental et al., 2010; Simons and Ikonen, 1997; Simons and Sampaio, 2011). Further, several studies have shown that rafts are implicated in the activation of AKT/protein kinase B (PKB), which is a serine/ threonine kinase that plays an important role in the stimulation of cancer cell proliferation and survival (Elhyany et al., 2004; Hill et al., 2002; Partovian and Simons, 2004).

Cancer cells modulate the metabolism and synthesis of cholesterol in order to maintain sufficient energy for their growth, proliferation and formation of lipid bilayer membranes (dos Santos et al., 2014a; Mullen et al., 2016). High levels of cholesterol and its precursor, the mevalonate, were reported in BC cells and found to promote their proliferation in vivo and induce tumor growth (Duncan et al., 2004). In BC patients, the dysregulation of cholesterol biosynthesis is associated with enhanced expression of hydroxymethylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol synthesis (Clendening et al., 2010).

Enveloped and non-enveloped viruses exploit lipid rafts to enter the host cell and initiate the viral infection (Chazal and Gerlier, 2003; Taube et al., 2010). Interestingly, lipid rafts are implicated in the early stage of SARS-CoV replication inside the host cell (Li et al., 2007). It has been demonstrated that depletion of cholesterol from Vero E6 cells by pre-treatment with methyl-β-cyclodextrin inhibits the release of SARS-CoV particles from the infected cells (Li et al., 2007). Therefore, it is postulated that SARS-CoV-2 utilizes cholesterol for its replication, the same mechanism that is used by SARS-CoV; hence a high level of cholesterol is a risk factor in SARS-CoV-2 infection (Cao et al., 2020). Thus, one can assume that BC patients may be at higher risk of coronaviruses infection, yet, further studies are of paramount importance.

Cholesterol is transported through the blood to the peripheral tissues in the form of lipoproteins (Lpa) as very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL) (Holmes and Ala-Korpela, 2019). Cholesterol and triglycerides (TG) from the liver, carried by ApoB-containing VLDL, are hydrolyzed by lipases to produce IDL and then LDL (Holmes and Ala-Korpela, 2019). LDL is either returned and degraded in the liver via binding to the hepatic LDL receptors or internalized inside the cells through receptor-mediated endocytosis (Douste-Blazy, 1987; Holmes and Ala-Korpela, 2019). Several studies reported that LDL, TG and total cholesterol present in higher levels in BC patients when compared to healthy individuals (Bhat et al., 2013; Kumar et al., 2015; Owiredu et al., 2009). Treatment of MDA-MB-231 BCE cells with LDL for 24–48 h resulted in a higher proliferation rate, an increase in the migration and a decrease in adhesion when compared to untreated cells, indicating that LDL-cholesterol is associated with the proliferation and migration of BC cells (dos Santos et al., 2014a).

High levels of LDL-cholesterol were also implicated in vasculopathy in patients with cardiovascular diseases, hypertension and diabetes (Cromwell and Otvos, 2004). Similarly, SARS-CoV-2 infection was reported to increase vascular permeability via multiple mechanisms (Fig. 3) (Teuwen et al., 2020). First, SARS-CoV-2 engages the angiotensin-converting enzyme-2 (ACE-2) receptors that are expressed by various organs such as the lung, heart, kidney, and intestine as well as by the endothelial cells (Varga et al., 2020). This binding causes impairment in the activity of ACE-2, which activates the kallikrein–-bradykinin pathway indirectly, thus increases the vascular permeability (Pober and Sessa, 2007; Teuwen et al., 2020). Second, endotheliitis, which is characterized by the lysis and death of the endothelial cells, was observed in COVID-19 patients (Varga et al., 2020). Third, the reactive oxygen species are produced by the activated neutrophils, which are recruited to the pulmonary endothelial cells following viral infection (Pober and Sessa, 2007). Fourth, endothelial contractility and opening of inter-endothelial junctions are enhanced as a result of the release of immune cells, inflammatory cytokines and vasoactive molecules (Pober and Sessa, 2007). Finally, the glycocalyx is degraded by glucuronidases, which are activated by IL-1β and tumor necrosis factor (TNF) (Pober and Sessa, 2007). All these mechanisms cause an increase in vascular permeability, which may result in the leakage of LDL into the alveoli to form an exudate with high cholesterol and protein contents (Cao et al., 2020; Heffner et al., 2002; Light et al., 1972; Teuwen et al., 2020). Exudates have been previously observed in lung autopsies from SARS-infected patients (Hwang et al., 2005; Kuiken et al., 2003; Pei et al., 2005). Remarkably, exudates from oedema, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells have been also reported following pathological examination of two COVID-19 patients, who underwent lung lobectomies because of adenocarcinoma (Tian et al., 2020).

Low levels of total cholesterol, LDL-cholesterol were observed in SARS-CoV-2 infected patients, which is correlated to the severity of the disease (Fan et al., 2020; Wei et al., 2020b). This hypolipidemia was assumed to be a result of LDL-cholesterol leakage to the lungs (Cao et al., 2020). Since BC patients have high levels of LDL, one can speculate that

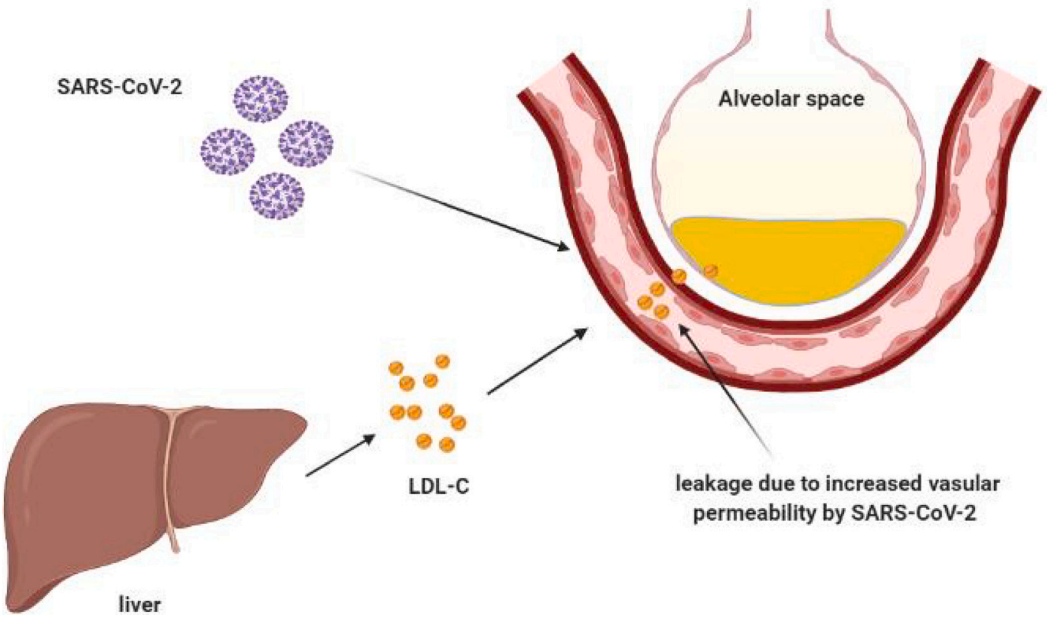

Fig. 3. Hypothetical drawing indicated the interaction of SARS-CoV-2 with LDL-cholesterol (LDL-C) in BC patients. SARS-CoV-2 increases the vascular permeability causing leakage of LDL-C into the alveolar spaces. Drawing was adapted from Cao et al., 2020 (Cao et al., 2020).

infection with SARS-CoV-2 may result in aggravated leakage of LDL to the lung, causing more severe pulmonary complications. Hence, further studies are warranted to prove this hypothesis and to determine whether LDL-cholesterol can act synergistically with SARS-CoV-2 to accelerate vasculopathy.

3.3. Sphingolipids

Sphingolipids constitute an important component in the lipid bilayer, which play important role in the structural integrity and fluidity of the cell membrane (Ogretmen, 2018). Sphingolipids such as ceramide, sphingosine-1-phosphate (S1P), and glucosylceramide act as signaling molecules that contribute to the pathogenesis of several respiratory diseases ranging from asthma, cystic fibrosis, chronic obstructive pulmonary disease, and pulmonary infections (Sharma and Prakash, 2017).

The membrane-bound sphingolipids including S1P, ceramide and ceramide-1-phosphate have been associated with host-pathogen interactions (Prakash et al., 2020). S1P is produced as a result of sphingosine kinase 1 (SK1) enzyme activation, the key enzyme in S1P biosynthesis (Seo et al., 2013). It has been reported that the production of S1P enhances viral attachment and replication through a mechanism involves activation of ERK-1/2, MAPK, and AKT dependent pathways in lipid rafts and endosomal compartment (Prakash et al., 2020). It has been suggested that upregulation of S1P receptor 1 (S1PR1) signaling is associated with the activation of the ACE-2 receptor, the official SARS-CoV-2 receptor (Prakash et al., 2020). As ACE-2 and S1PR1 were reported to cooperate and induce myopathy and fibrosis in vivo (Ohkura et al., 2017), it has been suggested that fibrosis in patients infected with SARS-CoV-2 may be a result of crosstalk between these receptors (Prakash et al., 2020). Further, S1PR1 signaling activates Ras, MAPK, PI3K/AKT, and mTOR pathways, which in turn stimulate Th2/17 responses as well as hypoxia, asthmatic reactions and anti-inflammatory response; thus promoting the replication of SARS-CoV-2, leading to the severity of disease and may be death (Prakash et al., 2020).

S1P is involved in many processes related to BC progression (Maczis et al., 2016). Upregulation of SK1 has been observed in BC patients and its expression has been associated with poor cancer prognosis (Maczis et al., 2016). Accordingly, the high levels of S1P in BC patients may increase the risk of contracting SARS-CoV-2 infection, yet further investigations are needed.

Since BC patients have high levels of S1P, which plays an important role in viral infections, attenuating S1P signaling either by improving S1P lyase activity or blocking its binding may control the pathogenesis due to SARS-CoV-2 infection (Prakash et al., 2020). Fingolimod FTY720 has been suggested as a potential drug against SARS-CoV-2, because of not only its immunomodulatory activity but also its S1P binding blocking activity (Prakash et al., 2020; Walsh et al., 2010). FTY720 is currently under Phase-2 clinical trial against SARS-CoV-2 (Prakash et al., 2020).

Cermaide-1-phosphate (C1P) is sphingolipid that is produced from ceramide by ceramide kinase enzyme (Ogretmen, 2018). C1P has been shown to enhance autophagy and activate T cell responses by increasing the antigen presentation (Prakash et al., 2020). C1P can be considered as an adjuvant immune stimulator as it activates the resting macrophages, phagocytosis and antigen presentation by dendritic cells for promoting the cytotoxic T lymphocytes responses, thus helping in mounting an adaptive response against SARS-CoV-2 (Prakash et al., 2020). The level of C1P can be increased either by the administration of L-serine essential amino acid combined with palmitoyl CoA to enhance the synthesis of ceramide or by the use of ceramide kinase enzymes (Hirabayashi and Furuya, 2008; Prakash et al., 2020; Weiss and Stoffel, 1997). Thus, maintaining high C1P and low S1P can help to mitigate SARS-CoV-2 infection in BC patients.

3.4. Eicosanoids

Eicosanoids are 20 carbon units fatty acids derived from the oxidation of arachidonic acid, which is produced in inflammatory conditions by phospholipase A2 (PLA2), or other polyunsaturated fatty acids by cyclooxygenases (COX), lipoxygenases (LOX) or P450 epoxygenases (Fig. 4) (Wang and DuBois, 2010). While COX enzymes give rise to prostanoids such as prostaglandins (PG) and thromboxanes (TX), which are pro-inflammatory lipid mediators, LOX produces the pro-inflammatory mediators such as leukotrienes (LT) along with anti-inflammatory mediators, such as lipoxins (Serhan, 2014; Wang and DuBois, 2010). Besides, LOX enzymes produce hydroperoxyl-eicosatetraenoic acids (HPETEs), epoxy-eicosatrienoic acids (EETs)

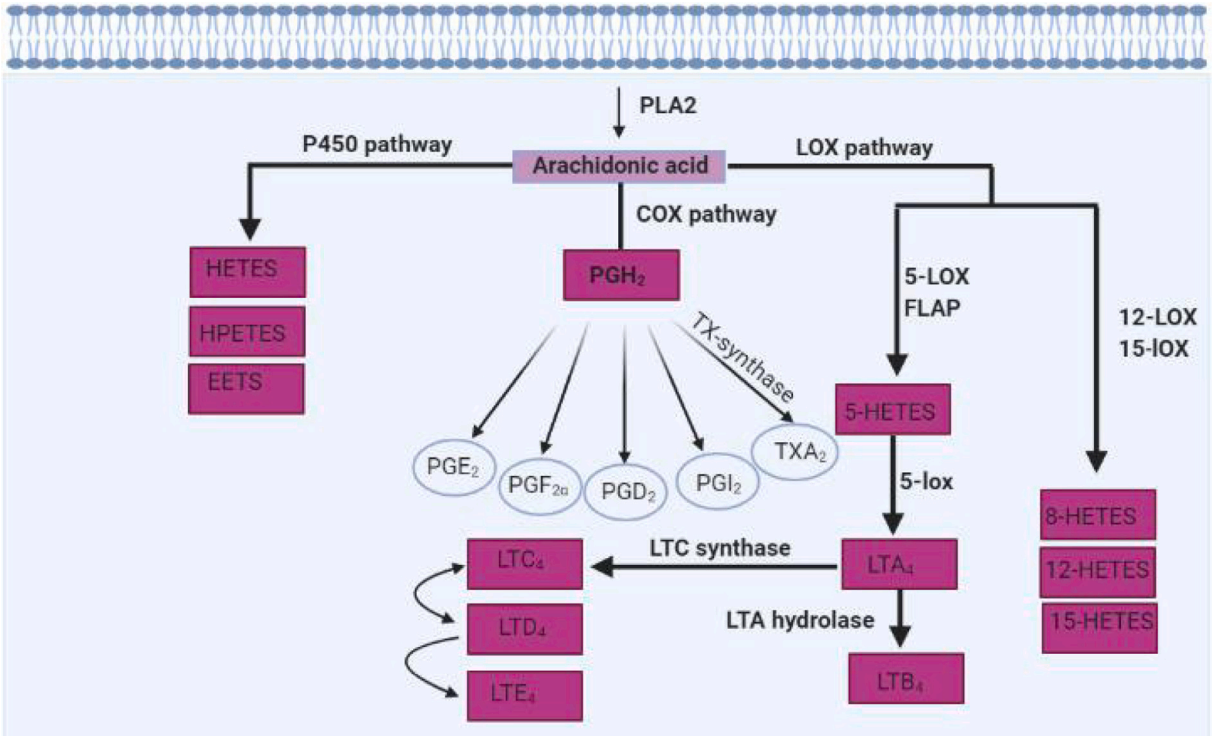

Fig. 4. Eicosanoids synthesis pathways. Arachidonic acid is produced by the cell membrane through phospholipase A_2 (PLA_2). Arachidonic acid is metabolized to eicosanoids via three major pathways: the cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 pathways. In the COX pathway, arachidonic acid is converted to the intermediate prostaglandin G_2 (PGG_2), which is further reduced to prostaglandin H_2 (PGH_2) by COX. PGH2 is then metabolized to prostanoids (prostaglandins) and thromboxanes (TX) via prostaglandin and thromboxane (TX) synthases, respectively. In the LOX pathway, arachidonic acid is converted to leukotrienenes (LT) via 5-LOX and hydroperoxyeicosatetraenoic acids (HPETEs) via 12-LOX and15-LOX, arachidonic acid is converted to 5-HPETE, which is then metabolized by 5-LOX to produce the unstable leukotriene A_4 (LTA_4). LTA4 is subsequently converted to LTB_4 via LTA hydrolase and LTC_4, LTD_4 and LTE_4 via LTC synthase. Drawing was adapted from Wang and DuBois, 2010 (Wang and DuBois, 2010).

and hydroxy-eicosatetraenoic acids (HETEs) (Wang and DuBois, 2010).

Upon activation of the endoplasmic reticulum due to stress of infection or cell debris, the inositol-requiring enzyme 1αX-box binding protein 1 (IRE 1α/XBP) enhances the biosynthesis of prostaglandins (PGE2, PGD2, and PGF2α) and thromboxane B2 from arachidonic acid and upregulates the expression of microsomal prostaglandin E synthase-1 and prostaglandin-endoperoxide synthase 2 (COX-2) (Chopra et al., 2019; Schmelzer et al., 2005). The eicosanoid storm is upstream of the cytokine storm (Gartung et al., 2019; von Moltke et al., 2012). It has been reported that cell debris produced as a result of coronavirus infection induces apoptosis and inflammation by regulating c-Jun N-terminal kinases/p38, B-cell lymphoma 2/Bcl-2 associated X-protein, inflammasome, and NF-kB pathway (Fung et al., 2014). In this regard, SARS-CoV was found to increase the production of PGs via binding to COX-2 promoter (FitzGerald, 2020). It has been hypothesized that PGE2 has a vital role in the pathogenesis of SARS-CoV-2; and hence reducing the level of PGE-2 via inhibition of human microsomal prostaglandin E synthase-1 (mPGES-1) can be a promising therapy in the prevention of severity related to SARS-CoV-2 infection (Smeitink et al., 2020). On the other hand, Müller et al. demonstrated that the downstream metabolites of arachidonic acid do not affect coronavirus itself. COX 1/2 and LOX inhibitors showed no anti-coronaviral activity, indicating that arachidonic acid metabolites may not have any effect on the replication of coronavirus in vitro (Müller et al., 2018). Further studies are needed to better understand the role of prostaglandins and other arachidonic acid metabolites in the pathogenesis of SARS-CoV-2.

Arachidonic acid inactivates enveloped viruses such as HIV and influenza virus as it has endogenous antiviral activity (Das, 2020). Accordingly, it has been suggested that immune cells and other cells release arachidonic acid upon infection with viruses including SARS-CoV-2; hence individuals with low levels of arachidonic acid may be more prone to coronavirus infection (Das, 2020). Treatment of HCoV-229E- or MERS-CoV-infected cells with exogenous arachidonic acid and linoleic acid, which is the metabolic precursor of arachidonic acid, showed a significant reduction in coronavirus replication (Yan et al., 2019). It has been speculated that coronaviruses modulate the host lipid profile to reach the optimum conditions for their replication and any change in this equilibrium interfere with viral replication (Yan et al., 2019). Therefore, high levels of arachidonic acid and linoleic acid limit the viral replication through the reversion of lysophospholipids into phospholipids through Land's cycle (Wang et al., 2012).

Several studies provide ample evidence regarding the critical role of arachidonic acid metabolites in BC growth and metastasis (Cakir et al., 2002; Paine et al., 2000; Razanamahefa et al., 2000). While the COX2 gene is normally not expressed by most cells, high expression levels have been reported during cancer progression (Dubois et al., 1998). Several studies demonstrated high levels of COX2 in both premalignant and malignant solid tumors and correlated with poor prognosis (De Groot et al., 2007). Particularly, COX-2 protein levels are elevated in 43% of invasive BC (Half et al., 2002). Similarly, 5-LOX was found to play an important role in the regulation of BC cells growth in vitro (Przylipiak et al., 1998). Moreover, elevated levels of PGs have been reported in various malignancies with PGE2 being the most abundant prostanoid (Wang and DuBois, 2004). Higher levels of PGE2, PGF2α and 15-HETEs have been reported in tumor material compared to normal mammary tissues (Kort et al., 1992). Based on these findings, it can be assumed that BC patients may be at higher risk of SARS-CoV-2 infection because of altered lipid metabolism and increased levels of PGE2, which is proposed to have a critical role in the severity of SARS-CoV-2 infection, while further studies are of paramount importance.

4. Dyslipidemia in BC patients can enhance SARS-COV-2 attachment and entry

Scavenger receptor class B type I (SR-BI) is a high-affinity HDL receptor expressed in many tissues (Calvo and Vega, 1993). HDL plays a significant role in SAR-CoV-2 infection (Wei et al., 2020a). It has been reported that the binding of SR-B1 to the spike (S) protein of SARS-CoV-2 facilitates the viral attachment and entry to the host cells (Wei et al., 2020a). Although SR-B1 cannot bind directly to SARS-CoV-2 S protein, the increase in the expression of SR-B1 enhances SARS-CoV-2 attachment and entry (Wei et al., 2020a). Further, it has been demonstrated that SR-B1 mediates the selective HDL cholesteryl ester uptake and initiates PI3K/Akt signaling pathway thereby, contributes to BC development and progression (Danilo et al., 2013). High expression levels of SR-B1were observed in 54% of BC patients and correlated with more aggressive tumor type (Yuan et al., 2016). These findings may indicate that high expression levels of SR-B1, which is associated with high serum lipid levels, in BC patients may provide more opportunity for SARS-CoV-2 attachment and entry to the host cells.

5. Proposed model of enhanced SARS-CoV-2 infection following BC-associated dyslipidemia

BC patients are accompanied with significant-high serum levels of lipoproteins including high-density (HDL) and low-density lipoproteins (LDL), phospholipids and sphingolipids (S1P). Infection with SARS-CoV-2 may result in vasculopathy causing leakage of these lipids into the lung space, thus facilitating the attachment of SARS-CoV-2 to its receptors, and hence entry and replication (Fig. 5).

6. Impact of chemotherapy on the spectrum of serum lipids in BC patients

Chemotherapy is an essential component in the treatment of BC patients to improve the disease prognosis and overall survival. However, chemotherapy can lead to long-term side effects including cardiovascular diseases (CVD) (Matyszewski et al., 2017; Truong et al., 2014), mainly because of changes in the serum lipid levels (Dos Santos et al., 2014b). A retrospective study investigated the changes in the lipid profiles during and after chemotherapy. The study reported that the overall TG, HDL-C and LDL-C levels were turned to worse levels during chemotherapy treatment, while the levels of HDL-C and LDL-C were restored after the completion of chemotherapy treatment (Tian et al., 2019). Another study indicated that serum lipids are changing following chemotherapy treatment in BC patients, where the levels of TG, LDL-C and Lpa were significantly increased, and the levels of HDL-C were decreased. Furthermore, serum lipids were varied between patients with different chemotherapy regimens (Lu et al., 2020).

7. Therapeutic strategies to manipulate the dyslipidemia associated with BC patients

Lipid-lowering medications are commonly prescribed to counter the devastating effects of impaired cholesterol metabolism in BC. Statins, HMG-CoA reductase inhibitors, are the most used lipid-lowering drugs. Statins block the rate-limiting step in the cholesterol synthesis pathway and hence reduce the systemic levels of cholesterol and its metabolites through hepatic clearance (Lv et al., 2020). Cholesterol is crucial for the biosynthesis of all steroid hormones, thereby statins are extensively studied for their potential use as anti-BC agents (Harborg et al., 2020). The use of statins resulted in a significant reduction in the risk associated with BC recurrence in a study conducted over 10 years on 14,773 post-menopausal patients diagnosed with early-stage (ER^{+}) BC and receiving adjuvant therapy of aromatase inhibitors (Harborg et al., 2020). This result was further supported by a meta-analysis involving 168,700 BCE patients in which statins were found to reduce disease-specific mortality and lower the risk of BC recurrence (Lv et al., 2020).

Statins are also prescribed for people who are contracting hypercholesterolemia, diabetes and cardiovascular diseases (Gu, 2014), who are known to be at high risk of developing serious symptoms upon infection with SARS-CoV-2 (Davies et al., 2020). A retrospective cohort study of SARS-CoV-2-hospitalized patients indicated that the use of

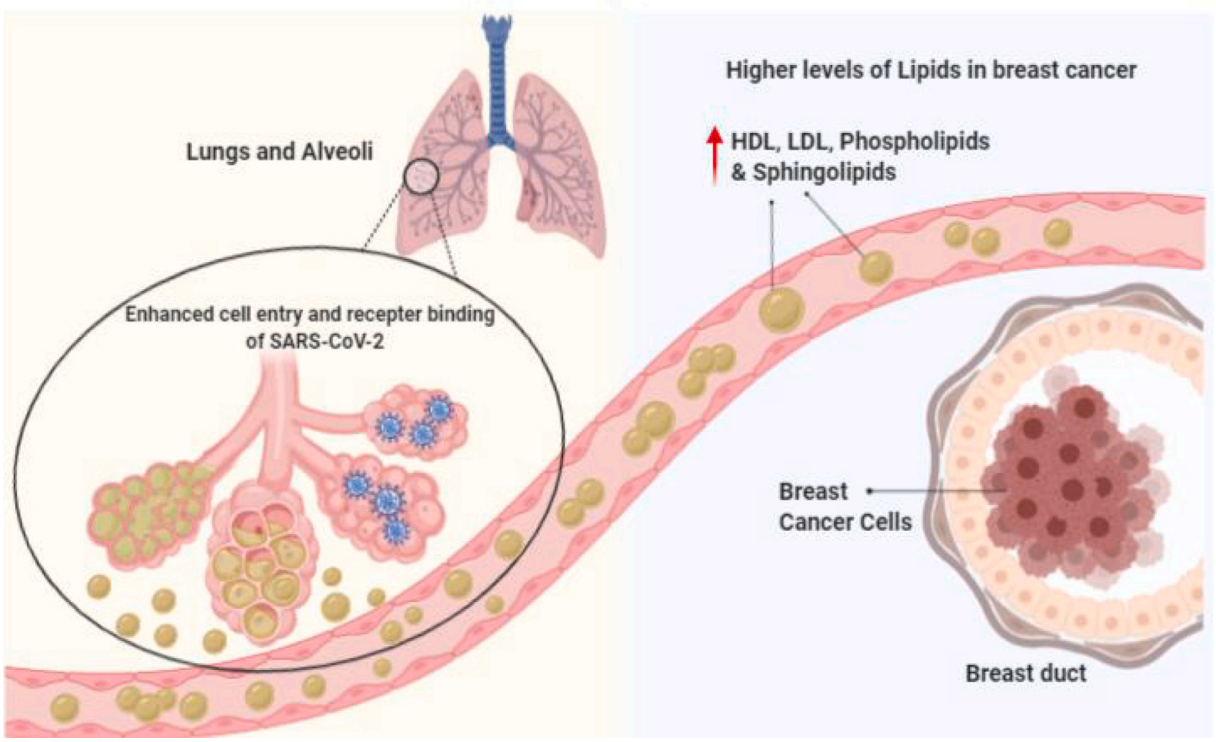

Fig. 5. Hypothetical drawing for the interaction of SARS-CoV-2 in BC patients. The red arrow represents lipids upregulation.

statins decreases the severity of infection (Tan et al., 2020). Further, two more studies of clinical data of SARS-CoV-2 hospitalized patients revealed that statins therapy is associated with an improved clinical outcome and improved reduction of SARS-CoV-2 cell entry (Moeller et al., 2020). Moreover, lower mortality rates were observed in SARS-CoV-2 patients treated with statins before hospitalization (Masana et al., 2020; Zhang et al., 2020b). This gives a piece of evidence for the current practice of using statins therapy during SARS-CoV-2 infection.

Ezetimibe is a non-statin lipid-lowering drug, which inhibits the intestinal absorption of cholesterol by selectively binding to cholesterol carrier NPC1L1, thus lowering the serum cholesterol levels (Giugliano et al., 2020). Similarly, phytosterols exert their lipid-lowering properties by decreasing the intestinal absorption of cholesterol, thus lowering LDL-C serum levels (Malhão et al., 2020). Fucosterol, a phytosterol from brown seaweeds, enhanced the doxorubicin effect in reducing cell proliferation and viability of MDA-MB-231 cells (Malhão et al., 2020). Fibrates not only control hyperlipidemia by stimulating PPARα but also inhibit the proliferation of BC cells by down-regulating the mTOR receptor (Rupitha et al., 2020).

Accordingly, lipid-lowering agents are legitimate candidates for drug repurposing as adjuvants chemotherapeutic agents in the prevention of SARS-CoV-2 infection particularly when associated with BC.

8. Conclusion

It has been reported that cancer patients are at higher risk of contracting SARS-CoV-2 infection, which is mainly attributed to the immunosuppressive status of cancer patients. Here we have described dyslipidemia associated with BC patients as a risk factor that may have a significant effect on the incidence and severity of SARS-CoV-2 infection. Coronaviruses including SARS-CoV-2 require host lipids in all their life cycle process including attachment, entry and envelop formation. For instance, the existence of high lipid profile accompanied by BC patients can increase the possibility of SARS-CoV-2 infection and severity of the disease. Therefore, management of BC-associated dyslipidemia is of an important strategy to reduce the infection due to SARS-CoV-2.

Declaration of Competing Interest

All authors declared there is no conflict of interest.

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