Cell Calcium 81 (2019) 38–50

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Lipid metabolism and Calcium signaling in epithelial ovarian cancer

Sana Kouba[a,c], Lobna Ouldamer[a,b], Céline Garcia[a,c], Delphine Fontaine[a,c], Aurélie Chantome[c,e], Christophe Vandier[a,c], Caroline Goupille[d,f,1], Marie Potier-Cartereau[a,c,*,1]

[a] Université de Tours, INSERM, N2C UMR 1069, Faculté de Médecine, Tours, France
[b] Université de Tours, INSERM, N2C UMR 1069, CHRU de Tours, Service de gynécologie et d'obstétrique, Tours, France
[c] Réseau Molécules Marines, Métabolisme et Cancer du Cancéropôle Grand Ouest, France
[d] Réseau CASTOR du Cancéropôle Grand Ouest, France
[e] Université de Tours, INSERM, N2C UMR 1069, Faculté de Pharmacie, Tours, France
[f] Université de Tours, INSERM, N2C UMR 1069, CHRU de Tours, Faculté de Médecine, Tours, France

A B S T R A C T

Epithelial Ovarian cancer (EOC) is the deadliest gynecologic malignancy and represents the fifth leading cause of all cancer-related deaths in women. The majority of patients are diagnosed at an advanced stage of the disease that has spread beyond the ovaries to the peritoneum or to distant organs (stage FIGO III-IV) with a 5-year overall survival of about 29%. Consequently, it is necessary to understand the pathogenesis of this disease. Among the factors that contribute to cancer development, lipids and ion channels have been described to be associated to cancerous diseases particularly in breast, colorectal and prostate cancers. Here, we reviewed the literature data to determine how lipids or lipid metabolites may influence EOC risk or progression. We also highlighted the role and the expression of the calcium (Ca^{2+}) and calcium-activated potassium (KCa) channels in EOC and how lipids might regulate them. Although lipids and some subclasses of nutritional lipids may be associated to EOC risk, lipid metabolism of LPA (lysophosphatidic acid) and AA (arachidonic acid) emerges as an important signaling network in EOC. Clinical data showed that they are found at high concentrations in EOC patients and *in vitro* and *in vivo* studies referred to them as triggers of the Ca^{2+}entry in the cancer cells inducing their proliferation, migration or drug resistance. The cross-talk between lipid mediators and Ca^{2+} and/or KCa channels needs to be elucidated in EOC in order to facilitate the understanding of its outcomes and potentially suggest novel therapeutic strategies including treatment and prevention.

1. Introduction

According to the latest estimates, ovarian cancer (OC) is the 7th most common cancer worldwide and ranks 5th as the cause of death from cancer in women leading to more deaths than any other gynecologic cancer. Most patients with OC lack disease-specific symptoms until they reach an advanced stage of the disease, increasing therefore, the risk of metastatic spread and early death; consequently, it is referred to OC as a "silent killer" [1]. Almost 90% of OC are Epithelial, which comprise several histological subtypes with different risk factors, genetic background, clinical course, sensitivity to chemotherapy, and prognosis. In the first part of this review, OC and its heterogeneities as well as its clinical care options and outcomes are explored, with a particular consideration of the high-grade serous phenotype since it is the predominant epithelial ovarian cancer (EOC).

One of the most common aspects of advanced stage EOC is the formation of carcinomatosis/ ascites in which tumor-promoting factors and molecules of lipidic nature are found. Indeed, recent clinical data of EOC patients elucidated the presence of high concentrations of cancer-promoting mediators in ascites, in particular lysophosphatidic acid (LPA) [2,3], illustrated as a mediator of cancer cell invasion and chemoresistance [4–6] and arachidonic acid (AA)-derived eicosanoids [7,8]. There is no doubt that the nutritional lipid environment has long been considered as an important contributor to cancer process, however, fat subclasses and lipids generated from phospholipid cleavage may also be involved in oncogenic mechanisms. Despite their essential roles in the tumor environment, the clinical relevance of these lipid mediators and their targets are only partially understood. In the second part of this review, we summarize the link between lipids and/or lipid metabolism and EOC.

It has been established that ion channels can act as novel and main regulators of specific pathways involved in cancer progression such as proliferation, migration or survival and were shown to be implicated in various types of cancers including breast [9–11] prostate [12–14] and colon [15–17]. Given the similarities that EOC shares with breast and prostate cancers [18], such as the involvement of the BRCA1 and BRCA2 tumor suppressor genes and in some cases, hormone sensitivity, it seems possible that ion channels expression may be modified and that environmental factors such as lipids, may affect their activity in EOC.

The emerging concept of ion channels as key regulators of cancer

* Corresponding author at: Université de Tours, INSERM, N2C UMR 1069, Faculté de Médecine, Tours, France.
E-mail address: marie.potier-cartereau@univ-tours.fr (M. Potier-Cartereau).
[1] Co-last authors.

https://doi.org/10.1016/j.ceca.2019.06.002
Received 27 March 2019; Received in revised form 3 June 2019; Accepted 4 June 2019
Available online 05 June 2019

expansion and resistance to treatment has several implications, including the perspective of their lipids and/or their lipid mediators' modulation [19–21]. The role of lipids in biological membrane processes has long been unnoticed and only recently, lipids were referred to as "the silent partner that needs more attention" [22]. There has been growing evidence of the effects of LPA, mediated by G-protein-coupled receptors (GPCRs) and of the AA on the activity of different types of ion channels, including potassium and calcium channels [23–26]. Calcium (Ca^{2+}) is involved in many fundamental physiological functions, such as cell cycle control, survival, apoptosis, migration and gene expression. Its homeostasis is highly regulated and for each cellular function, specific spatial and temporal characteristics are required. Thus, altered Ca^{2+} signaling has been suggested as an important trigger of malignant phenotypes. A way to control the cytosolic Ca^{2+} concentration is to regulate membrane Ca^{2+} channels including store-operated Ca^{2+} channels and secondary messenger-operated channels linked to GPCRs or tyrosine kinase receptors activation. The Orai channels, with or without their reticular STIM (Stromal interaction molecule) partners and Transient Receptor Potential (TRP) proteins, were considered to be the main Ca^{2+} channels involved in epithelial cells [27,28]. It is well accepted that, in response to cell stimulation, opening of these Ca^{2+} channels contributes to Ca^{2+} entry and the transient increase of the cytosolic Ca^{2+} concentration involved in intracellular signaling. To reduce energy consumption and to finely regulate the Ca^{2+}, Ca^{2+} channels can also be associated to Ca^{2+}-activated K^+ channels (KCa) as complexes and contribute to cancer-associated functions such as cell proliferation, cell migration and metastases development [29]. KCa channels, through their high Ca^{2+} sensitivity, play a role in the regulation of signaling pathways involving Ca^{2+}. Their activation in non-excitable cells, such as epithelial/endothelial cells, promotes Ca^{2+} entries through non-voltage gated Ca^{2+} channels, by increasing the Ca^{2+} driving force, leading to an elevated intracellular Ca^{2+} concentration. In the third part of this review, we discuss about studies involving Ca^{2+} and KCa channels in EOC and their potential regulation by lipids and/or lipid metabolites.

2. Epithelial ovarian cancer histotypes, therapeutics and outcomes

OC originates in the upper genital tract, a site with no direct access for cellular sampling and screening, with nonspecific symptoms, hampering early detection. OC cells arise from three potential sites (the surface of the ovary, the fallopian tube or the mesothelium lining the peritoneal cavity (hereafter referred to as tubo-ovarian cancer). More than 70% of women with OC are announced at an advanced stage of the disease (stage FIGO (*International Federation of Gynecology and Obstetrics)* III-IV: after the disease has spread beyond the reproductive organs). EOC is the most predominant histologic subtype and characterized by five major histotypes that differ in origin, pathogenesis, molecular alterations, risk factors and prognosis [30]. The five main histotypes are: high-grade serous (HGSOC; 70%, with 90% of them being hereditary BRCA1/2), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%) and low-grade serous (LGSOC; < 5%) [30].

Stage at diagnosis varies widely by histotype. Most HGSOCs are diagnosed at stage III (50%) or IV (30%), reflecting the aggressiveness of this predominant subtype. In contrast, the majority (> 60%) of ENOC, MOC, and CCOC are diagnosed at stage I. Consequently, the 5-year specific survival for HGSOC is 43%, compared with 82%, 71%, and 66% for ENOC, MOC, and CCOC, respectively.

EOC is further categorized as type I or type II based on clinicopathologic factors, with the primary distinguishing molecular factor of genetic instability in type II versus type I. Type I, with an indolent behavior in general, usually develops from extra ovarian benign lesions that embed in the ovary and subsequently undergo a series of mutations resulting in malignant transformation. Type II EOCs are high grade (primarily HGSOC) and characterized by the involvement of both ovaries, aggressive behavior, advanced stage at diagnosis and poor prognosis. Women with these cancers often turn up with extensive carcinomatosis and ascites.

Surgery is often the initial choice for treatment. Patients who are not candidates for a complete macroscopic resection should be considered for neoadjuvant chemotherapy (platinum-based) followed by interval surgery and further chemotherapy. Bevacizumab (anti-angiogenic agent) added to platinum-based chemotherapy showed an overall survival benefit in poor prognosis patients [31]. More recently, the use of maintenance therapy with olaparib (PARP inhibitor) was beneficial in terms of progression-free survival including patients with *BRCA1/2* mutations [32]. These treatments have increased the disease-free and overall survival. However, more than 70% of patients will experience relapse 2 years after the primary therapy. One of the most frequently documented predictors of response to chemotherapy in women with recurrent EOC is the platinum-free interval. However, some patients become increasingly resistant to platinum-based therapies over time, and some women respond to multiple lines of treatment [33]. The biology and the underlying cellular and molecular events that take place during the maintenance phase (variable platinum-free intervals) are far from being completely understood. Targeting the mechanisms that lead to cancer progression or tumor-initiating cells will allow EOC to be a chronic disease with less relapses.

3. Ovarian cancer and nutritional epidemiology (for summary see Table 1)

In 1986, based on international data published by the United Nations, Rose et al., showed strong associations between the total fat intake in different countries and OC mortality rates; fats of animal origin were particularly pointed out [34]. Since then, multiple nutritional epidemiologic studies, including few meta-analyses, explored the association between dietary fat, from animal or vegetal origin, or fat quality (saturated, monounsaturated or polyunsaturated fatty acids) and risk of OC. However, this led to inconsistent conclusions [35–39]. Residual confounding factors cannot be excluded as well as the limitation of self-reported assessment for food questionnaires, the failure to take into account the different subtypes of OCs, or the underestimation of the fat consumption range since high saturated fat dietary intake corresponded to 17 g/day in an European population compared to 24 g/day in North America [38]. However, the interventional randomized controlled trial of Women's Health Initiative Dietary modification may suggest that the reduction of dietary fat to 20% associated to vegetable consumption significantly decreased the EOC risk [40]. Two meta-analyses concordantly reported that total fat, fat from animal origin or saturated fat were associated to an increased OC risk [37,41]. Taking into account subtypes, serous subtype seems to be more sensitive to fat quantity and quality variations (saturated fatty acids) compared to other phenotypes [41]. This link has not been found by another study [38] or only for high saturated fat intake [35]. Associations between cholesterol intake [35,42] or serum cholesterol levels remain contradictory [43–46]. However, cholesterol could support OC development since women who have taken statins have a decreased risk of the disease [47].

Without being carcinogenic themselves, lipid or cholesterol excessiveness might clinically affect the patients by generating overweight, inflammatory factors or metabolic pathologies that may contribute to OC progression i.e. advanced FIGO stage, positive lymph node or poor tumor differentiation and shorter overall survival [48]. A recent study classified overweight and obesity as "probable" factors increasing the risk of OC [49] and the mortality of OC patients with age > 50 years [43].

Fats and cholesterol might also increase the levels of circulating estrogen and/or progesterone hormones [50,51]. It cannot be excluded that a higher exposure of the ovarian epithelium to these hormones may

Table 1
Nutritional epidemiology and ovarian cancer risk.

Nutritional Factors	Ovarian cancer Risk	Reference(s)
Total fat intake, particularly from animal origin	-Increased risk and mortality (Based on United Nations data)	[34]
Total fat intake, fat source, fat subtypes or trans fats,	-No association with ovarian cancer risk (Pooled studies published between 1983-2014 with 12,046 EOC cases and 1,105,946 non cases)	[36]
Total fat intake, fat source, fat subtypes	-No association with ovarian cancer risk except for saturated fat intake associated with increased risk (12 prospective cohorts with 523,217 women follow up, 2132 cases of EOC with histological subtype distinction)	[35]
	Increased Risk with total fat intake, saturated fat and animal-based fats (Meta-analysis 8 studies with 2529 EOC cases excluding borderline subtypes and 4160 non-cases)	[37]
	-Risk of epithelial ovarian cancer tends to be increased with higher polyunsaturated fat intake.	[38]
	No association between risk and other fat subgroups	[39]
	(European prospective cohort-EPIC, 325,007 women with 1,191 EOC including 96 borderlines, separated analysis on serous and endometrioid histologic phenotypes)	[194]
	-Positive association between high saturated fat intake and increased ovarian cancer risk -Increased risk with total and animal-based fats (European prospective cohort-EPIC, 325,007 women with 1,095 EOC excluding borderline and Netherland cohort-NLCS-2,582 women with 383 EOC)	
Total fat intake, fat source, fat subtypes, trans fat	-High Total fat, saturated fat, animal-based fat, and trans-fat associated with increased risk for serous cancer phenotype -High saturated fat associated with increased risk for endometrioid ovarian cancers (Meta-analysis of 16 case-control studies and 9 cohorts with ovarian phenotypes distinction)	[41]
Nutritional modification: Decrease of fat intake and increase vegetable consumption	-Decrease of ovarian cancer risk (American population whose three quarters were overweight or obese, 29,294 women with usual diet and 19,541 women with low fat and vegetable enriched diet	[40]
Cholesterol intake	-No association with ovarian cancer risk (12 prospective cohorts with 523,217 women follow up, 2,132 cases of EOC with histological subtype distinction) Increased risk with high cholesterol intake (Canadian population, 442 cases-2,135 controls)	[35] [42]
Serum lipids (Cholesterol triglycerides)	-No association with ovarian cancer risk (About Swedish 234,494 women including 808 ovarian cancer women)	[46]
Serum lipids (Cholesterol triglycerides)	-Increased risk with high serum cholesterol level (America, 35 cases whose 88% epithelial ovarian cancers-67 control woman) -Increased risk with high serum level of cholesterol and triglyceride (China, 573 EOC and 1,146 controls)	[44] [48]
Serum cholesterol level	-Increased risk (166 countries) -Increased risk of epithelial ovarian cancers with mucinous phenotype (Austria, Norway and Sweden, 287,230 women 644 EOC including phenotype distinction)	[45] [43]

contribute to increased risk of OC [52]. This would be in agreement with epidemiological data as early menarche, late age at menopause, number of menstrual cycle or parity are identified as potential OC risks [53]. Moreover, according to their proportion and classes (saturated versus polyunsaturated), integration of these lipids in cell membranes can regulate physical properties and alter protein activities, localization (in/out lipid raft) or the cell downstream signaling pathways [54–58].

Systemic cholesterol or triglycerides levels could constitute biological markers to evaluate fat exposure and might help interpreting epidemiological data. But contradictory data have been reported [46,59].

Concerning OC outcomes and lipid metabolism, links between systemic lipid levels and OC outcomes remain to be clarified. Using an integrative systemic and local metabolomics analysis (taking into account tumor metabolism, ascites and blood compositions), Pils's study performed systemic glycerophospholipids and amino acids analysis. The data pointed out a systemic vLDL decrease, particularly of polyunsaturated glycerophospholipids associated with a shorter overall survival for high-grade serous patients. They identified glycerophospholipids consumption as direct source of lipids for tumors [60]. This is in accordance with Zhu's study [61] but this is at odds with Li's study [62]. Higher triglycerides levels were identified as systemic biomarkers for patients with more severe EOCs but HDL cholesterol levels were higher or lower [48,63]. Statins did not seem to improve overall survival in patients with advanced OC [64].

4. Lipid metabolism and prognosis or survival for ovarian cancer patients (for summary see Table 2)

An increased lipid synthesis is a common and important mechanism in cancer cells to supply their energetic expenditure and membrane synthesis [65]. This may be also applicable to ovarian cancer cells and majority of studies were reported in the context of EOC (see Table 2). A set of lipids associated to normal, borderline or high-grade serous carcinomas [66] has been identified and highlighted metabolic changes of membrane lipids. Moreover, functional impact of lipid metabolism changes was recently illustrated. Two studies showed increase of fatty acid transport proteins expression (CD 36 or FATP4) contributing to fatty acid influx was associated to tumor progression and metastasis [67,68]

4.1. Fatty acid synthase (FAS)

By increasing long chain fatty acid synthesis from citrate, the lipogenic enzyme FAS (Fatty acid synthase) has been associated with histologic grade and FIGO stage. Its overexpression is correlated to shorter overall survival [69–71]. In high grade serous carcinomas, FAS expression became more intense in recurrent ovarian carcinomas and was associated to shorter survival [71]. In OC cell lines, FAS expression was more likely associated to cell proliferation and the use of FAS inhibitor led to lipid profile change [72] and decreased receptor/PI3K/mTORC signaling pathway [73]. A positive cross talk has been suggested

Table 2
Lipids and enzymes of Lysophosphatidic Acid (LPA) and Arachidonic acid (AA) pathways associated with grade, stage, progression-free survival or overall survival in epithelial ovarian cancers.

Lipids or Lipid pathway	Association with grade, stage, progression-free survival or overall survival	Population	Reference(s)
Lipid metabolism	-Alteration of membrane lipids, between normal epithelium, borderline and serous tumors	- 15 normal tissues, 15 borderlines, 48 HGSC	[66]
Fatty Acid Synthesis	- High FAS expression associated with high grade and FIGO stage III/IV	−64 serous, 14 mucinous, 17 endometrioids	[69]
	- High FAS expression associated to shorter survival in high grade serous patients	- 162 HGSC	[71]
	- No association between FAS expression and histological phenotypes.	- 64 serous, 14 mucinous, 17 endometrioids	[69]
	- Positive association between FAS level and grade/ FIGO stages		
	- Overexpression of HSD17B12 strongly decrease overall survival in epithelial ovarian cancers patients	- 48 serous, 4 mucinous, 33 endometrioids, 8 clear cells	[128]
LPA pathway	- Serum LPA level as diagnostic marker of ovarian cancers	- Meta-analysis (980 cancers- 872 benign)	[82]
	- No association between LPA level in ascites and survival	- 28 HGSC	[78]
	- A molecular gene signature induced by LPA in tumor cells associated to shorter time to relapse or overall survival	- 75 patients including 65 serous, 4 endometrioids, 3 mucinous	[83]
	- Serum ATX level is not suitable diagnosis	- 121 ovarian cancer patient compared to 102 healthy subjects	[100]
	- mRNA ATX level not associated to progression-free survival or overall survival	- 146 samples HGSC with 70 effusions, 76 solid primary tumors or metastases	[101]
	- High PLA2 G7 isoform protein level in ascites - High mRNA PLA2G4B isoform in tumors reduced time before relapse	- 33 ascites from HGSC - 1638 serous tumors	[78]
	- mRNA or protein: LPAR1 not clearly different between ovarian tumors and normal epithelium, LPAR2 and LPAR3 overexpression associated to grade and FIGO stage	- 134 epithelial ovarian cancers (including 68 serous, 44 mucinous), 48 benign and 50 normal tissues	[105], [106], [108]
	- Protein : 70% EOC expressed $LPAR_1$, 40% $LPAR_2$, 17% $LPAR_3$, $LPAR_1$ associated with advanced stage and $LPAR_2$ $LPAR_3$ associated with poor differentiation	- 52 epithelial ovarian cancers (26 serous, 8 mucinous, 12 endometrioid, 6 clear cell)	
	- High mRNA LPAR1, LPAR2 and LPAR5 expressions associated to a shorter progression-free survival and overall survival	- 43 effusions pre-chemotherapy and 44 effusions post chemotherapy of HGSC	[101]
	- High LPAR3 expression reduced time before relapse in serous carcinomas	- 1638 serous tumors	[78]
	- LPAATβ protein overexpression in tumors associated to shorter survival	- 70 epithelial carcinomas (including 18 serous, 15 clear cells, 13 endometrioids, 17 mucinous)	[113]
	- LPAATβ protein overexpression in tumors associated to high grade and shorter overall survival	- 125 epithelial carcinomas (including 81 seroous, 17 endometrioids, 15 clear cells) and 33 borderlines	[112]
	- LPAATβ protein overexpression in tumors associated to high grade and shorter overall survival for < 60 years patients	- 76 carcinomas (including 39 serous, 7 mucinous, 11 endo, 4 clear cells)	[114]
AA pathway	- COX-2 overexpression in high histological grade or FIGO stages	- 442 serous carcicomas	[120]
	- COX-2 overexpression associated with worse survival rate	- 442 serous carcicomas Meta-analysis (17 studies) Meta-analysis (18 studies)	[120] [121,122]
	- HSD17B12 and COX-2 proteins increased with grade and FIGO stage in serous tumors	−48 serous, 4 mucinous, 33 endometrioids, 8 clear cells	[195]
	- High LTB4R2 protein expression in tumors with advanced stage and association with platinum resistance without impact on survival	- 245 carcinomas (150 serous, 70 endometrioids, 21 mixed, 4 mucinous	[129]
	- High AA and LTB4 levels in ascites associated to shorter progression-free survival	- 38 HGSC	[78]
	- High mRNA expressions of PTGIS, PTGES, LTB4R2 and PTGER3 in tumors associated with shorter relapse-free survival	- 1638 serous tumors	[78]

between FAS and HER-2 on breast and ovarian cancer cell lines [74] but no correlation was found between both markers on OC tissues [69]. Several studies proposed FAS inhibitors as a suitable therapeutic target [65] including for ovarian carcinomas [73,75]. First clinical trials are being proceeded for tolerance and efficiency evaluation of TVB-2640 inhibitor in breast and colon cancers.

4.2. LysoPhosphatidic acid (LPA) and LPA pathways

In the middle of 1990's, Yan Xu's team characterized LPA (lysophosphatidic acid) able to stimulate proliferation of cancer cells, increase Ca^{2+} release and activate tyrosine phosphorylation with downstream signaling [3]. While alternative pathways exist for LPA synthesis (namely from phosphatidic acid), standard metabolic pathway involves phospholipase A2 (PLA2) enzyme which releases the fatty acid chain (mostly arachidonic acid, AA) from sn-2 position from the phosphatidylcholine (PC) to form lysophosphatidylcholine (LPC). LPC is then metabolized to LPA by the Autotaxin (ATX) enzyme which has a lysophospholipase D activity to remove the choline polar head (Fig. 1). Palmitoyl, stearoyl, and oleoyl LPA (LPA with 16;0, 18;0, and 18;1 fatty acid chains linked by acyl bond, respectively) represented the major compounds but oleoyl LPA revealed a stronger activity on tumors cells [3]. It is important to notice that the fatty acid chain linkage on glycerol backbone can be chemically different as acyl- (preponderant form), alkyl- or alkenyls bonds have been described [76,77].

LPA is largely detected in ascites of patients with OC with concentrations around 2–80 μM [78] and to a lesser extent in serum [79–81]. Fifteen years ago, a meta-analysis including 19 studies concluded that serum LPA levels should be used as a biomarker for the diagnosis of OCs [82]. LPA levels in ascites did not seem to be associated to time before relapse [78]. Nevertheless, Mills's team identified a molecular gene signature regulated by LPA in tumor cells. Only in tumor serous phenotype, LPA-signature responsive cluster presented a significantly shorter median for time to progression or overall survival [83]. Linked to a very particular microenvironment for OC cells with a direct access to peritoneal cavity [84,85], several cells contribute to LPA synthesis and, consequently to tumor progression [86], like tumor associated macrophages (TAM) or T cells [78,87], mesothelial cells

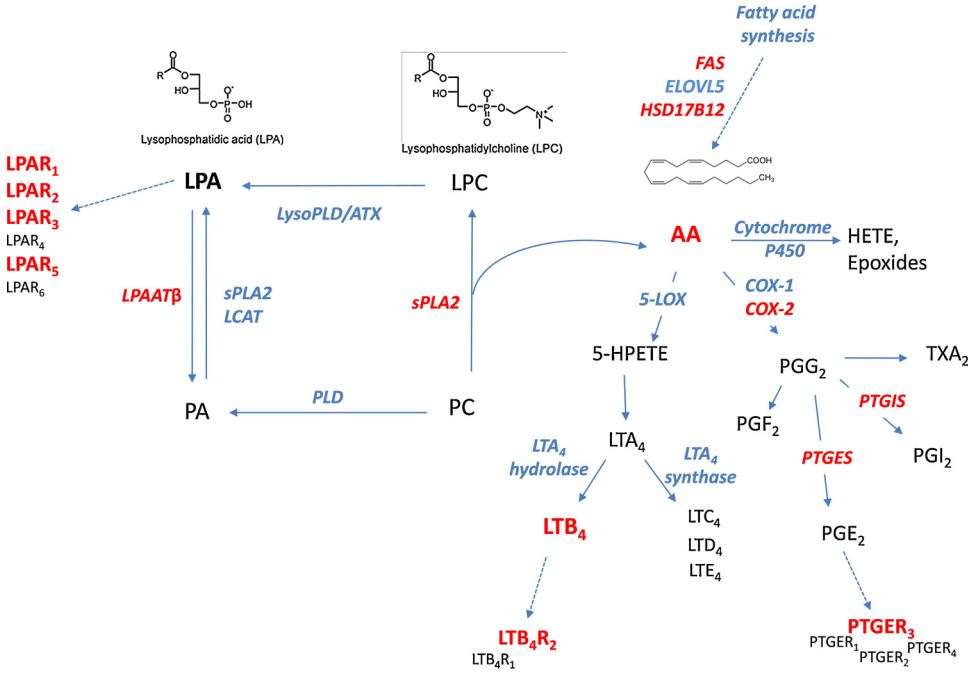

Fig. 1. Schematic summary of LPA and AA pathways including enzymes and lipids associated with the progression-free survival or overall survival of epithelial ovarian cancer (for references see Table 2). Lipids and enzymes of interest are indicated in red. The enzymes are indicated in italic. AA (Arachidonic Acid), ATX (Autotaxin), COX (1 and 2) (CycloOXygenase), 5-LOX (5-LipOXygenase), HSD17B12 (Hydroxysteroid 17-β-Deshydrogenase 12), ELOVL5 (Fatty Acid Elongase 5), CYP (Cytochrome P450), FAS (Fatty Acid Synthase), LPA (LysophosPhatidic Acid), LPC (Lysophophatidylcholine), PA (Phosphatidic Acid), PC (PhosphatidylCholine), LCAT (Lecithin-Cholesterol AcylTransferase),LPAATβ (LysoPhosphatidicAcidAcylTransferase β, PLA2 (PhosphoLipase A2), PLD PphosphoLipase D), 5-HPETE (5-hydroperoxyeicosatetraenoic acid), TXA2 (Thromboxane A2), LTX_Y (Leukotriene X_Y), PGG2 (Prostaglandin G2), PGE2 (Prostaglandin E2), PGF2 (Prostaglandin F2), PGI2 (Prostacyclin I2), HETE (Hydroxyeicosatetraenoic acids), PTGIS (ProsTaGlandin I2 Synthase), PTGES (ProsTaGlandin E Synthase), LTA4 hydrolase (Leukotriene A4 hydrolase), Leukotriene A4 hydrolase, $PTGER_X$ (prostaglandin E2 receptor x), $LPAR_X$ (LysoPhosphatidic Acid Receptor x), $LTB4R_X$ (LeukoTriene B4 Receptor x).

[88], adipose tissue [89–91]. Autocrine production by ovarian tumor cells was only reported under LPA or EGF stimulation [92,93]. Cancer stem cells of EOC also produce LPA which increased their resistance to chemotherapy and ATX invalidation reserved chemoresistance and slowed down tumor progression in mice [94].

In addition, with venous thromboembolism phenomenon, activated platelets also contribute to LPA rates [95] and were correlated to tumor progression and poor survival [96–99]. The management of this ancillary pathology offers an interesting opportunity for future OC researches.

ATX enzyme is closely linked to OC development but serum ATX levels remained similar between OC patients and healthy controls excluding this enzyme as a suitable biomarker for OC diagnosis, to follow cancer progression [100] or for prognosis [78]. ATX expression in ovarian carcinomas and solid metastasis was not associated to patient survival [101]. High levels of PLA2 enzyme's activity were reported in EOC [102] and a significant part of PLA2 synthesis would come from macrophages [76]. High PLA2G7 isoform protein levels in ascites and high mRNA of PLA2G4B isoform in tumors reduced time before relapse [78].

LPA activities have been extensively described and shown to mediate Ca^{2+} signaling, migration, proliferation and tumor aggressiveness [103,104] (for details see lipid metabolites and calcium signaling section). LPAR1 (LPA receptor 1) was not clearly different between tumors and normal epithelial cells [105–107]. It was expressed in about 70% of EOC and was strongly associated with advanced stage [108]. The mRNA or protein levels of LPAR2 and LPAR3 were upregulated and their expression status is positively associated to the histological grade and/or clinical FIGO stage [105–109]. In high-grade serous carcinoma patients, high mRNA expression of LPAR1, LPAR2 and LPAR5 in post-chemotherapy effusions were associated to a shorter progression-free survival and overall survival (OS) [101]. On a thousand serous carcinoma patients, whose chemotherapy status was not specified, Reinartz's team showed that high LPAR3 expression significantly reduced time before relapse [78]. A part of the LPA activity could be mediated through nuclear peroxisome proliferator-activated receptor gamma ($PPAR\gamma$) [103,104].

LPA accumulation in ovarian carcinomas may be due to lipid phosphate phosphatases failure [110,111]. Moreover, LPA can be converted by lysophosphatidic acid acyltransferaseβ (LPAATβ) to PA (phosphatidic acid). In 70 epithelial carcinomas, high mRNA or protein amounts of LPAATβ were reported in high grade tumors and associated to shorter survival [112–114]. These results are in accordance with the fact that PA should not be considered as a simple LPA degradation metabolite or a synthesis intermediate but also as a bioactive phospholipid able to generate intracellular signaling pathway [115].

Several strategies are currently under development to control LPA synthesis or to antagonize LPA effects via its receptors [116]. All lipid products or enzymes, involved in LPA metabolism and showing expression associated with OC relapse or outcome were summarized in Fig. 1 in red.

4.3. Cyclooxygenase 2 (COX-2) and Arachidonic Acid (AA) metabolism

The dysregulation of the arachidonic acid (AA) metabolism has long been known for its implication in chronic inflammation process and carcinogenesis [117]. OC does not seem to escape from this rule. Considered as a major substrate for three enzyme classes, cyclooxygenases (COXs), lipoxygenases (LOXs) and cytochromes P450 (CYPs), AA generates eicosanoids distributed into three families with prostanoids (prostaglandins, prostacyclins, thromboxanes etc) formed via the COX pathway, leukotrienes, lipoxins and hepoxins formed via the LOX pathway and epoxyeicosatrienoic acid and hydroxy fatty acids (EETs, HETEs, HPETEs) formed via the CYP pathway [118] (Fig. 1).

Five compounds metabolized from AA or linoleic acid via LOX and P450 cytochrome have been identified and associated with the increased risk of developing OC in the ensuing decade [119].

In the largest immunohistological study (more than 400 serous carcinomas), COX-2 in tumor cells was overexpressed in high histological grade, positively associated with HER-2 expression, but not clearly associated with stage [120]. However, COX-2 overexpression was associated to FIGO stage in two meta-analyses and was significantly associated to a reduced survival in serous OC [120–122]. With the potential beneficial effects of a COX-2 inhibitor in preclinical models

[123,124], clinical trials have been initiated with promising activity [125]. However, toxicity of a COX-2 specific inhibitor, Celecoxib, cannot be eluded and efficiency trials targeting COX remain to be established for human OC [126,127]. Several trials were going on with substitution inhibitors (acetylsalicylic acid, indomethacin or ketorolac) in OC including in prevention setting.

Reductive estrogenic enzyme HSD17B12 may participate in the accumulation of AA since it seems to catalyze the elongation of fatty acid chain. High protein expression of HSD17B12 strongly reduced the overall survival in EOCs [128] (Fig. 1).

In 2008, Rocconi et al., reported altered LOX pathway with higher LTB4R2 (leukotriene B4 receptor 2) expression in tumors with advanced stage and an association to platinum resistance without having an impact on patient survival [129]. High levels of AA and LTB4 (leukotriene B4) in ascites are associated to a shorter relapse-free survival [78]. Among enzymes and receptors involved in eicosanoids metabolism and expressed by OC tumors, high mRNA amounts of PTGIS (Prostaglandin I2 synthase), PTGES (prostaglandin E synthase), LTB4R2 (leukotriene B4 receptor 2) and PTGER3 (prostaglandin E2 receptor 3) (Fig. 1) led to adverse clinical outcome with shorter relapse-free survival [78].

5. Ovarian cancer and calcium channels (for summary see Table 3)

In normal ovarian cell physiology, results obtained by several groups suggested that the rapid elevation of intracellular Ca^{2+} after acute stimulation by various locally produced ovarian signaling molecules (e.g. acetylcholine, oxytocin, prostaglandins, ATP) mainly arises from release of Ca^{2+} from intracellular stores [130–132]. However, no studies focused on plasma membrane Ca^{2+} channels in ovarian epithelial cells and few studies focused on human ovarian endocrine cells. A study conducted by Agoston et al., showed that Ca^{2+} influx from T and L-types Voltage Gated Calcium Channels (VGCCs) in human ovarian endocrine cells is necessary for steroidogenesis [133]. It has been also demonstrated by Lee et al., that ATP elicits changes in intracellular Ca^{2+} concentration in human ovarian cells through P2-purinoreceptor activation and that these events are initiated by the release of Ca^{2+} from cytosolic stores, and sustained by extracellular calcium influx [134]. Another work suggested that the plurality and co-expression of different Ca^{2+}-activated K^+ channels (KCa) might allow differentiated responses to Ca^{2+} signals over a wide range caused by various intra-ovarian signaling molecules (e.g. acetylcholine, ATP, dopamine) [135]. However, nature, regulation, and functional roles of ion channels of human ovarian endocrine cells are not very well known.

In pathology, membrane ion channels have been proposed to play a significant role in cancer process: from initial tumor development to metastasis and are considered as promising functional biomarkers and pharmacological targets for human cancers and may even correlate with the main hallmarks of the cancer process [136–139]. Among these ion channels, Ca^{2+} channels have been widely studied in cancer research. Cytosolic Ca^{2+} is highly regulated by a wide variety of Ca^{2+} channels, pumps and exchangers [140]. However, in cancer, Ca^{2+} homeostasis is disrupted leading to cancer growth and progression [141]. It is well known that Ca^{2+} signaling is necessary for signaling cascades of tumorigenesis and neoplastic progression by controlling gene expression, DNA synthesis, cell cycle progression, apoptosis, proliferation, migration and survival [142–146].

5.1. Store operated calcium channels

In non-excitable cells, some of the mechanisms contributing to the regulation of cytosolic Ca^{2+} concentration include Ca^{2+} release from intracellular stores and subsequent activation of Store Operated Ca^{2+} Entry (SOCE) [147]. The Ca^{2+} enters the cells via the Ca^{2+} Release-Activated Ca^{2+} Channels (CRAC) formed by the Orai1, Orai2 and/or Orai3 channels as well as their regulators STIM1 and/or STIM2 [148]. The Orais and STIMs proteins were shown to be implicated in many cancer types such as prostate, colon and breast cancer [149,150]. Few studies focused on the roles of these channels in OC. One work from Schmidt et al., showed that Orai1 and STIM1 are highly regulated in the A2780 cisplatin-resistant ovary carcinoma cells compared to A2780 non-resistant cells, leading to elevated SOCE [151]. In their work, they coupled 2-APB (2-aminoethoxydiphenyl borate) treatment (50 μM) to cisplatin in resistant cells and observed an increase of number of these cells in late apoptosis. This finding underlines a possible role of Orai channels in resistance to treatment but the authors did not carry on with functional assays in their study. One way to try to understand the implication of SOCE in resistance to apoptosis is to look at some actors that are calcium-dependent and involved in the cell cycle progression. Indeed, SOCE triggers oscillations that are required for cell cycle progression mostly during the S, M or G2/ M phases as shown in several types of cancers [152,153]. This could help to better understand these channels' functions in OC cell survival and resistance to treatment. Most recently, Abdelazeem et al., showed in ovary carcinoma cells that the expression of both Orai1 and STIM1 is upregulated by placental growth factor enhancing SOCE as well as the expression of the Hypoxia Inducible Factor HIF1α [154]. The transcription factor HIF1α is known for its role in carcinogenesis. Its overexpression in human cancers causes genetic alterations such as gain of function mutations in

Table 3
Summary of *in vitro* function of calcium channels expressed in ovarian cancer cells lines.

Ion channel	Model(s)	Effect(s)	Mechanism	Reference(s)
Orai1/STIM1	A2780cis cisplatin-resistant ovary carcinoma cells	Therapy resistance	Elevated SOCE/AKT activity	[151]
TRPC1	Ovarian cancer tissues	Lower expression in undifferentiated OC	–	[161]
TRPC3	SKOV-3 ovarian	Increased proliferation		
TRPC4	cancer cell line			
TRPC6				
TRPC3	Ovarian cancer specimens	Increased proliferation	EGF-induced Ca^{2+} entry Dephosphorylation of CDC2 and CAMKII Progression through the M phase of the cell cycle	[166]
	SKOV-3 and ES2 cells	Tumor Growth		
	Nude Mice			
TRPC1	Ovarian cancer tissues and microarrays	Downregulation correlated with drug resistance and high histological grade	–	[162]
TRPV6	OD/SCID xenograft mice with tumor-derived from SKOV-3	Tumor Growth	–	[81]
T-Type Voltage-Gated Calcium Channels	HO8910 and A2780 ovarian cancer cells	Increased Proliferation	Block in G0/G1 phase of the cell cycle	[168]
	OV207 and OVCAR-3 ovarian cancer cells	Increased migration	Activation of the MAPK signaling cascade as well as the ERK signaling pathway	[169]

oncogenes and loss of function mutations in tumor-suppressor genes. In addition, pharmacological inhibition of its activity reduces tumor growth by impacting the angiogenesis, glucose metabolism and cell survival [155]. Some studies focused on the direct link between SOCE and HIF1α of which, the work from Li *et al.* in hepatocarcinogenesis [156]. Very interestingly, they found that the hypoxia-induced Ca^{2+} transient was store operated and that HIF1α directly controls the transcription of STIM1, by binding to its promoter, and contributes to SOCE. On the other hand, STIM1-mediated SOCE is also required for HIF1α accumulation in hypoxic HCC cancer cells via activation of Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) and p300. This direct link between STIM1 and HIF1α in hepatocarcinogenesis could give insights into what is happening in OC when expression and activity of ORAI1/STIM1 and HIF1α are elevated.

5.2. Transient receptor potential channels (TRP)

The concentration of cytosolic Ca^{2+} is also controlled by other ion channels such as the TRP channels. TRPs channels are novel class of Ca^{2+}-permeable cationic channels [157] including seven subfamilies: the canonical (TRPC), the vanilloid (TRPV), the melastatin (TRPM), the ankyrin (TRPA), the "No mechanoreceptor potential (TRPN), the polycystin (TRPP) and the mucolipin (TRPML).

The TRP channels have been identified as protein Tyrosine Kinase or G protein-coupled Receptor Operated Ca^{2+}channels (ROCs) or internal Ca^{2+} Store Operated Channels (SOCs). TRP channels are expressed almost ubiquitously and contribute to a wide range of cellular functions [158]. Altered expression of some TRP channels (TRPV1, TRPV2, TRPV6, TRPM1, TRPM8, TRPC1 and TRPC6) has been implicated in various cancers [159,160]. In a study aiming to investigate whether the TRPs can act as potential therapeutic targets for OC, it has been shown that the mRNA levels of TRPCs were detected in human EOC [161]. They showed lower levels of TRPC1, TRPC3, TRPC4 and TRPC6 in undifferentiated ovarian cancer tissues (grade3) compared to well differentiated tissues (grade 1–2). In the same way, Liu et al., showed that the downregulation of TRPC1 is associated to drug resistance and high histological grade in OC [162]. In this study, they performed experiments on OC tissues using real-time quantitative polymerase chain reaction assays where they found that the expression of TRPC1 differs significantly between grades 2 and 3 tumors. Liu et al., also confirmed these results using bioinformatical techniques and microarrays databases. The analysis of the mRNA-microRNA interactions showed that 8 out of 11 major pathways enriched from 38 predominant microRNAs targeting TRPC1 were involved in the regulation of drug resistance in OC, and 8 out of these top 10 microRNAs were implicated in the drug resistance in ovarian and other cancers. Among the genetic interactions which were analyzed by the authors, and involving TRPC1, strong interactions between this channel and PIK3C3 and SPARKL1 were particularly interesting. The PIK3C3 protein was shown to play a critical role in the regulation of autophagy *in vitro* and *in vivo* [163] and SPARCL1 protein was shown to be involved in the regulation of drug resistance via several pathways, including autophagy [164]. Autophagy contributes to drug resistance in OC as proved when the induction of ERK-mediated autophagy conferred cisplatin resistance to ovarian cancer cells [165]. These results suggest that autophagy is a possible mechanism underlying TRPC1 in drug resistance suggesting that the lower expression of TRPCs could be considered as a negative prognostic biomarker for certain types of cancers, such as the undifferentiated type of OC. *in vitro*, Zeng B. et al., showed in SKOV3 EOC cell line that when TRPC channels were blocked using the non-selective 2-ABP and SKF-96365 compounds, the proliferation of EOC cell was decreased and these data were confirmed using siRNA sequences directed against TRPC1, TRPC3, TRPC4 and TRPC6; while the overexpression of TRPC1/3/4 and 6 increased the cancer cell colony growth [161]. However, these results have been obtained just on a single EOC cell line. We do not know about the expression level of TRPC between normal ovarian epithelial cell lines and other EOC cell lines. TRPC3 expression was also studied in human EOC [166]. EOC specimens contained more TRPC3 protein levels compared to normal tissues. Knocking-down TRPC3 expression in the SKOV3 and ES2 cell lines (respectively from serous cystadenocarcinoma and clear cell adenocarcinoma), reduced the proliferation and the Epidermal Growth Factor (EGF)-induced Ca^{2+} entry, dephosphorylation of cdc2 and CAMKII and prolonged the progression of cells through the M phase of the cell cycle. In addition, size and weight of tumors formed by RNAi-transfected SKOV3 EOC cells in nude mice were significantly reduced indicating that TRPC3 would promote proliferation also *in vivo*. There is also evidence that TRPV6 mRNA and protein levels were elevated in biopsies of EOCs compared to normal tissues and inhibition of TRPV6 activity significantly reduces ovarian tumor growth [81]. The mechanism for TRPV6 involvement in the progression and proliferation of OC is still unclear. A reasonable starting point to further investigate the involvement of TRPV6 is to check the status of anti-apoptotic events that could be active in OC like the NFAT/calcineurin pathway, as reported for prostate cancer [167]. If the proliferative and anti-apoptotic roles of this ion channel are proved in OC, the data from pre-clinical and clinical studies could support the potential therapeutic utility of targeting TRPV6 ion channels.

5.3. Voltage gated calcium channels

Other Ca^{2+} channels that have been proved to promote ovarian cancer progression are the T-Type VGCCs. Li et al., observed a decrease in the proliferation of HO8910 and A2780 (respectively from ovarian serous cystadenocarcinoma and endometrioid adenocarcinoma) cancer cells when the T-Type VGCC was blocked using NNC55-0396 and mibefradil [168]. The decrease of proliferation resulted from the arrest of cells at the G0/G1 phase of the cell cycle. It was also shown that the expression of the T-type VGCC was higher in OC tissues compared to normal tissues. This Ca^{2+} channel was not only implicated in OC cell proliferation, but also in OC cell migration. In OV207 and OVCAR-3 cancer cells (respectively from ovarian clear cell adenocarcinoma and serous epithelial ovarian cancer), the Ca^{2+} entry via the VGCC was responsible for the activation of the MAPK signaling cascade as well as the ERK signaling pathway which increased cell migration [169] suggesting that targeting these pathways and their second messenger may offer new therapeutic options for the treatment of EOC.

6. Ovarian cancer and Ca^{2+}-activated K^+ channels (KCa)

KCa channels can be divided into three subfamilies: big conductance (BKCa), intermediate conductance (IKCa) and small conductance (SKCa). SKCa, included SK1, SK2 and SK3 (KCNN1, 2, 3, KCa2.1, 2.2, 2.3 SK1, 2, 3), BKCa included KCa1.1 (KCNMA1) and IKCa is also named KCa3.1 or SK4 or IK1.

Studies focusing on KCa channels in OC are few but some of them showed that KCa channels could be potential markers of OC. Oeggerli *et al.,* showed that the amplification of KCNMA1, analyzed by fluorescence-*in-situ*-hybridization, was restricted to a small but distinct fraction of OC with the highest prevalence in ovarian serous carcinoma (˜7%) and in malignant müllerian mixed tumors (˜25%) [170]. However, the authors did not test if this enhanced expression of *KCNMA1* may be correlated with the grade, stage, progression-free survival or overall survival of OC. Zhao *et al.,* identified that high expression of KCNN4 was associated to a high incidence of recurrence in optimally debulked serous ovarian carcinoma patients on both the mRNA and protein levels [171]. More recently, report showed that mRNA and protein expression of *KCNN3* was considerably lower in OC tissues compared to normal tissues, and in drug-resistant OC tissues compared to sensitive OC tissues. Low *KCNN3* expression consistently predicted shorter disease-free and overall survival [172].

Since Ca^{2+} enters the cells through Ca^{2+} channels and activates KCa channels, their association as complexes seems to be efficient for

their mutual fine regulation. There is now evidence that KCa and Ca^{2+} channels, alone or associated in complexes, play important roles in the proliferation and migration of cancer cells and metastatic development [29]. As for OC, only one study showed an association between KCa and ATP-gated cationic channels. In 2017, Robles-Martínez *et al.,* provided evidence that both KCa3.1 channel and $P2Y_2$ (purinergic receptor) are expressed in SKOV-3 cells and in neoplastic cells of human ovarian tumor biopsies. They showed that $K_{ca}3.1$ activation via $P2Y_2$ receptors which mediate Ca^{2+} entry, promotes human OC cell migration [173]. The formation of ion channel complexes between KCa and Ca^{2+} channels, as found in breast and colon cancers [29], must be highlighted in order to evaluate their potential role as cancer-specific targets and aim to develop targeted therapies.

7. Ovarian cancer chemoresistance and Ca^{2+}/KCa channels

The standard treatment of advanced OC involves surgery followed by chemotherapy usually involving the use of a platinum-based drug (such as carboplatin) especially for high grade serous OC, associated to taxan such as paclitaxel. Although 40–60% of patients with advanced disease respond to treatment, most of them relapse after 18 months due to the appearance of drug-resistant tumors [174,175]. Drug resistance was responsible for treatment failure and death in more than 90% of OC patients with advanced disease [176,177].

A recent study showed that the inhibition of T-type Ca^{2+} channels with a Ca^{2+} channel blocker, mibefradil, increased the sensitivity to carboplatin of platinum-resistant tumors in a mouse model of peritoneal metastasis [178]. In 2016, Samuel *et al.,* demonstrated that the upregulation of miR-31 increased resistance, as did the knockdown or inhibition of BKCa channels suggesting that these genes directly modulate cisplatin response in ovarian carcinoma cells. Comparing the levels of miR-31 and BKCa to cisplatin resistance in the NCI60 panel or chemoresistance in cohorts of OC tumors, reveals correlations that support a role for partners *in vitro* and *in vivo* [179]. The anti-apoptotic proteins Bcl-x_L and Mcl-1 have been identified to play a pivotal role in apoptosis resistance in OC. Ca^{2+} signaling was reported to activate the signaling pathway controlling Mcl-1 expression. In this context, Bonnefond *et al.,* showed that the carboxyamidotriazole, a Ca^{2+} channel inhibitor used in clinical trials, inhibits SOCE and Mcl-1 translation through mTORC1 deactivation in OC cell lines (IGROV1-R10, OVCAR3 and SKOV3). Moreover, it sensitized ovarian carcinoma cells to Bcl-x_L inhibitors as their combination elicited massive apoptosis. Its effect was mimicked by the SOCE inhibitor, YM58483, which also triggered apoptosis when combined with anti-Bcl-x_L [180]. Schmidt et al., showed that Orai1 and STIM1 are highly regulated in cisplatin-resistant ovary carcinoma cells comparing to non-resistant cells, leading to elevated SOCE and an enhanced Akt activity which contributes to therapy resistance in those cells [151]. According to previous observations, enhanced SOCE contributed to therapy resistance of OC cells. Pelzl *et al.,* demonstrated that several isoforms of the Na^+/Ca^{2+} exchanger (NCX), responsible for Ca^{2+} extrusion, are higher in therapy resistant than in therapy sensitive OC cells and pharmacological inhibition of NCX sensitizes resistant ovary carcinoma cells to cisplatin [181].

Taken together, these data strongly suggest that Ca^{2+} and KCa channels could contribute to ovarian tumorigenesis, progression and could participate to resistance to treatment and might become potential drug targets or new prognostic markers for OC. However, further studies would be worthwhile extending to other components of Ca^{2+} signaling including intracellular mechanisms.

8. Lipid metabolites and Calcium signaling (For summary see Graphical abstract)

Lipid molecules are able to selectively interact with specific sites on integral membrane proteins, and modulate their structure and/or function. LPA stimulates proliferation, migration and invasion of OC cells through regulation of vascular endothelial growth factor, matrix metalloproteinases, urokinase plasminogen activator, interleukin-6, interleukin-8, COX2, cyclin D, etc. As mentioned before (in section LPA and LPA pathways) LPA acts mainly *via* GPCRs from endothelial differentiation gene (Edg) family located in the cell membrane. The most studied in OC cell lines are LPAR1 (Edg-2), LPAR2 (Edg-4) and LPAR3 (Edg-7) receptors. LPA receptors differ in expression according to cell type, affinity to various LPA molecular species and their activation effects. LPAR1 and LPAR2 are coupled with Gi, Gq or G12/13 protein alpha subunits, whereas LPAR3 binds to Gi or Gq [182]. Activation of GPCRs by LPA initiates variety of signaling pathways [183]. Thus, the Gq protein activation by LPA can increase the cytosolic Ca^{2+} concentration through the classic phospholipase C (PLC)-dependent pathway. The expression of LPAR2 and LPAR3 receptors is significantly higher in OC cell lines comparing to benign tumors and/or normal ovarian tissues [105,109], whereas LPAR1 expression seems to be lower [105–107]. In OC cells, LPA is a prominent growth factor that contributes to tumor survival and proliferation. It has been reported that LPA induces proliferation and a transient increase of intracellular Ca^{2+} concentration in HEY, OCC1 and OCC2 OC cell lines [3]. Recently Yu *et al.,* showed that LPA induces OC cell migration *in vitro* and metastases development *in vivo* through LPAR1 [108] but no experiment was performed on intracellular Ca^{2+} variations. The ability of LPA to increase cellular Ca^{2+} would reside in the structure, linkage and location of the fatty acyl chain of LPA. For example, LPA with saturated fatty acids at the sn-1 position would be more active to induce Ca^{2+} mobilization than LPA with unsaturated fatty acids or fatty acids at the sn-2 position [183]. In the same way, in the SKOV-3 OC cell line, LPA-dependent Ca^{2+} mobilization responsible for cancer cell migration was attenuated by pre-treatment with carboxyl group-containing polyunsaturated fatty acids (PUFAs) omega-3 and omega-6 such as linoleic acid (LA), arachidonic acid (AA), α-linolenic acid (LNA) and eicosapentaenoic acid (EPA). However, ethyl linoleate (ELA), AA ethyl ester, α-ethyl linolenate (ELN) and eicosapentaenoic acid (EPA) ethyl ester which have the ethyl ester structure were not effective [184]. Furthermore, in the same study, the authors demonstrated that the blocking of Ca^{2+} mobilization by the L-type Ca^{2+} channel blocker, nifedipine, significantly blocked LPA-induced SKOV-3 cell migration and adhesion [184]. Today, the molecular characterization of ion channels involved in this LPA-induced Ca^{2+} mobilization remains to be elucidated in OC. We can hypothesize that in ovarian cancers cells, LPA could i) modulate directly Ca^{2+} channels through a binding site or ii) indirectly through the PLC/InsP3 pathway leading to a release of Ca^{2+} from intracellular stores and thereby trigger SOCE through ORAI and/or TRP channels.

As for the G-protein-mediated PLC, the other product of PIP_2 hydrolysis is diacylglycerol (DAG). DAG stays in the plasma membrane where it can activate protein kinase C (PKC), or be metabolized further. Both PKC and DAG have been demonstrated to cause Ca^{2+} influx distinct from SOCE in different cell types [185,186]. Furthermore, other messengers resulting from DAG metabolism, including AA and leukotrienes, activate non-store-operated Ca^{2+} influx (for review [187]). AA resting concentration can be varied dynamically by either increases, via activation of G-protein coupled receptors and phospholipase A2, or decreases via AA degenerative pathways mediated principally by COX and LOX. A critical role for AA in the regulation of Ca^{2+} entry during agonist activation of Ca^{2+} signals has become increasingly apparent in numerous studies over the past 10 years. AA has been shown to induce Ca^{2+} entry in a store-independent manner through a direct activation of Arachidonate Regulated Ca^{2+} (ARC) channels composed by Orai1/Orai3 subunits. Zhang et al., demonstrated that AA directly inhibits TRPC3 in mammary MCF-7 cells and is a potent mechanism for regulating Ca^{2+} entry and cytosolic Ca^{2+} concentration leading to a decrease of breast cancer cell migration/invasion [188]. TRPV4 has a critical role in the migration of tumor-derived but not 'normal' epithelial cells migration; and AA induces actin remodeling in endothelial

cells derived from human breast carcinomas, resulting in a corresponding increase of TRPV4 expression in the plasma membrane [189]. Nevertheless, the authors did not show a direct activation of TRPV4 by AA. A recent study showed that AA treatment enhanced the migration of a gastro-enteropancreatic neuroendocrine tumor model and this migration could be abrogated by selective inhibition of the AA-induced Orai3-dependent Ca^{2+} entry [190]. Dubois *et al.,* showed in prostate cancer cells the Orai1/Orai3 protein redistribution as an oncogenic switch mechanism favoring the formation of store-independent Ca^{2+} channels activated by AA leading to a more aggressive pro-proliferative phenotype [191]. Taken together, LPA, AA (and/or their metabolites) which are found at high concentrations in the ascites fluid of ovarian carcinomas could modify the expression and/or the activity of Ca^{2+} channels promoting an aggressive behavior of ovarian carcinoma cells.

9. Conclusion

Ovarian cancer has the highest mortality rate among cancers in women. This is due to late-appearing and nonspecific symptoms as well as a lack of diagnostic, prognostic, and predictive markers. Therefore, additional investigations and establishment of specific nutritional recommendations may provide an opportunity to build a primary prevention strategy for OC. In this review, we listed the roles of lipids mediators and of some Ca^{2+} channels and Ca^{2+}-activated potassium channels in OC but unfortunately, the expression evaluation of these channels and their involvement in OC is still at its start and much work remains to be done in the field.

The literature about the role of lipids LPA and AA in the ovarian cancer progression becomes substantial but the link between LPA and/or AA and ion channels needs to be further investigated and characterized. Indeed, patients suffering from OC endure ascites formation which are enriched in tumor promoting factors including LPA and AA. These two agents were shown to activate specific and convenient pathways for cancer cells to progress in a Ca^{2+} -dependent manner involving Ca^{2+} channels and their potential KCa partners. Despite the research progress in the field of ion channels in cancer, many questions remain unanswered: since channels proteins are hijacked from their normal physiological function, could they form complexes in transformed malignant cells? Are these complexes different from those formed in a physiological context? Are they linked to particular membrane structures specifically associated to malignant transformation (e.g. nanodomains)? Or to the tumor microenvironment (e.g. lipids and other soluble molecules)? The possibility of the ion channel complex formation between lipid-sensitive KCa and Ca^{2+} channels, as found in breast and colon cancers [29], could provide significant advantages in order to develop targeted therapies.

Today, no study has stated a clear or a direct link between lipid intake, OC outcome and ion channels. In addition, the development of approaches for cancer-specific targeting of tumor promoting lipids would also be another good starting point. Some approaches consisting of blocking the synthesis of these lipids, their receptors or their metabolization are under development and some of them are currently being evaluated in clinical trials for ovarian cancer. For example, LPA degradation by the introduction of lipid phosphate phosphohydrolase-3 appears to be effective for the control of tumor growth in OC [192] and pharmacological targeting of LPA receptor LPA1 by the antagonist Ki16425, efficiently controls the migration and invasion of cancer cells [193].

Finally, characterizing the expression of ion channels in human EOC tissues associated with the lipid microenvironment of tumors or serum LPA levels is essential to carry out in order to place *in vitro* and *in vivo* studies in a clinical context. If the implication of these channels is confirmed in EOC, as it has been found in breast, colon or prostate cancers, they could be considered as functional biomarkers and could be novel therapeutic targets for EOC to control cell proliferation, migration, survival or chemotherapy resistance.

Funding

This work was supported by “University of Tours”, “Région Centre Val de Loire”, “INSERM”, “Ligue Contre le Cancer” (Comities 37, 41, 85, 18, 17, 44, 45, 29), “Cancéropôle Grand Ouest”, CHRU de Tours, Tours' Hospital oncology association ACORT and CANCEN. Sana Kouba held her fellowship from the “Ministère de l’enseignement supérieur et de la recherche”.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

References

[1] N. Colombo, M. Peiretti, G. Parma, M. Lapresa, R. Mancari, S. Carinelli, C. Sessa, M. Castiglione, Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 21 (Suppl. 5) (2018) v23–30.
[2] A.M. Westermann, E. Havik, F.R. Postma, J.H. Beijnen, O. Dalesio, W.H. Moolenaar, S. Rodenhuis, Malignant effusions contain lysophosphatidic acid (LPA)-like activity, Ann. Oncol. 9 (1998) 437–442.
[3] Y. Xu, D.C. Gaudette, J.D. Boynton, A. Frankel, X.J. Fang, A. Sharma, J. Hurteau, G. Casey, A. Goodbody, A. Mellors, et al., Characterization of an ovarian cancer activating factor in ascites from ovarian cancer patients, Clin. Cancer Res. 1 (1995) 1223–1232.
[4] D.N. Brindley, F.T. Lin, G.J. Tigyi, Role of the autotaxin-lysophosphatidate axis in cancer resistance to chemotherapy and radiotherapy, Biochim. Biophys. Acta 1831 (2013) 74–85.
[5] G.B. Mills, W.H. Moolenaar, The emerging role of lysophosphatidic acid in cancer, Nat. Rev. Cancer 3 (2003) 582–591.
[6] T. Tsujiuchi, M. Araki, M. Hirane, Y. Dong, N. Fukushima, Lysophosphatidic acid receptors in cancer pathobiology, Histol. Histopathol. 29 (2014) 313–321.
[7] N. Obermajer, R. Muthuswamy, K. Odunsi, R.P. Edwards, P. Kalinski, PGE(2)-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment, Cancer Res. 71 (2011) 7463–7470.
[8] R. Punnonen, E. Seppala, K. Punnonen, P.K. Heinonen, Fatty acid composition and arachidonic acid metabolites in ascitic fluid of patients with ovarian cancer, Prostaglandins Leukot. Med. 22 (1986) 153–158.
[9] A. Chantome, M. Potier-Cartereau, L. Clarysse, G. Fromont, S. Marionneau-Lambot, M. Gueguinou, J.C. Pages, C. Collin, T. Oullier, A. Girault, F. Arbion, J.P. Haelters, P.A. Jaffres, M. Pinault, P. Besson, V. Joulin, P. Bougnoux, C. Vandier, Pivotal role of the lipid Raft SK3-Orai1 complex in human cancer cell migration and bone metastases, Cancer Res. 73 (2006) 4852–4861.
[10] N. Deliot, B. Constantin, Plasma membrane calcium channels in cancer: alterations and consequences for cell proliferation and migration, Biochim. Biophys. Acta 1848 (2015) 2512–2522.
[11] L. Zhang, W. Zou, S.S. Zhou, D.D. Chen, Potassium channels and proliferation and migration of breast cancer cells, Sheng Li Xue Bao 61 (2009) 15–20.
[12] S. Kappel, I.J. Marques, E. Zoni, P. Stoklosa, C. Peinelt, N. Mercader, M. Kruithof-de Julio, A. Borgstrom, Store-operated Ca(2+) entry as a prostate Cancer biomarker - a riddle with perspectives, Curr. Mol. Biol. Rep. 3 (2017) 208–217.
[13] N. Prevarskaya, R. Skryma, G. Bidaux, M. Flourakis, Y. Shuba, Ion channels in death and differentiation of prostate cancer cells, Cell Death Differ. 14 (2007) 1295–1304.
[14] G. Shapovalov, R. Skryma, N. Prevarskaya, Calcium channels and prostate cancer, Recent Pat. Anticancer Drug Discov. 8 (2013) 18–26.
[15] Y. Fourbon, M. Gueguinou, R. Felix, B. Constantin, A. Uguen, G. Fromont, L. Lajoie, C. Magaud, T. Lecomte, E. Chamorey, A. Chatelier, O. Mignen, M. Potier-Cartereau, A. Chantome, P. Bois, C. Vandier, Ca(2+) protein alpha 1D of CaV1.3 regulates intracellular calcium concentration and migration of colon cancer cells through a non-canonical activity, Sci. Rep. 7 (2017) 14199.
[16] M. Gueguinou, T. Harnois, D. Crottes, A. Uguen, N. Deliot, A. Gambade, A. Chantome, J.P. Haelters, P.A. Jaffres, M.L. Jourdan, G. Weber, O. Soriani, P. Bougnoux, O. Mignen, N. Bourmeyster, B. Constantin, T. Lecomte, C. Vandier, M. Potier-Cartereau, SK3/TRPC1/Orai1 complex regulates SOCE-dependent colon cancer cell migration: a novel opportunity to modulate anti-EGFR mAb action by the alkyl-lipid Ohmline, Oncotarget 7 (2016) 36168–36184.
[17] C. Villalobos, D. Sobradillo, M. Hernandez-Morales, L. Nunez, Calcium remodeling in colorectal cancer, Biochim. Biophys. Acta Mol. Cell Res. 1864 (2017) 843–849.
[18] K.H. Tung, M.T. Goodman, A.H. Wu, K. McDuffie, L.R. Wilkens, A.M. Nomura, L.N. Kolonel, Aggregation of ovarian cancer with breast, ovarian, colorectal, and prostate cancer in first-degree relatives, Am. J. Epidemiol. 159 (2004) 750–758.
[19] P.A. Jaffres, C. Gajate, A.M. Bouchet, H. Couthon-Gourves, A. Chantome, M. Potier-Cartereau, P. Besson, P. Bougnoux, F. Mollinedo, C. Vandier, Alkyl ether lipids, ion channels and lipid raft reorganization in cancer therapy, Pharmacol. Ther. 165 (2016) 114–131.

[20] J.A. Poveda, A. Marcela Giudici, M. Lourdes Renart, A. Morales, J.M. Gonzalez-Ros, Towards understanding the molecular basis of ion channel modulation by lipids: mechanistic models and current paradigms, Biochim. Biophys. Acta Biomembr. 1859 (2017) 1507–1516.
[21] F.J. Taberner, G. Fernandez-Ballester, A. Fernandez-Carvajal, A. Ferrer-Montiel, TRP channels interaction with lipids and its implications in disease, Biochim. Biophys. Acta 1848 (2015) 1818–1827.
[22] J.H. Naismith, I.R. Booth, Bacterial mechanosensitive channels–MscS: evolution's solution to creating sensitivity in function, Annu. Rev. Biophys. 41 (2012) 157–177.
[23] I. Hernandez-Araiza, S.L. Morales-Lazaro, J.A. Canul-Sanchez, L.D. Islas, T. Rosenbaum, Role of lysophosphatidic acid in ion channel function and disease, J. Neurophysiol. 120 (2018) 1198–1211.
[24] R. Jans, L. Mottram, D.L. Johnson, A.M. Brown, S. Sikkink, K. Ross, N.J. Reynolds, Lysophosphatidic acid promotes cell migration through STIM1- and Orai1-mediated Ca2+(i) mobilization and NFAT2 activation, J. Invest. Dermatol. 133 (2013) 793–802.
[25] P. Martin, M. Moncada, N. Enrique, A. Asuaje, J.M. Valdez Capuccino, C. Gonzalez, V. Milesi, Arachidonic acid activation of BKCa (Slo1) channels associated to the beta1-subunit in human vascular smooth muscle cells, Pflugers Arch. 466 (2014) 1779–1792.
[26] T.J. Shuttleworth, Arachidonic acid, ARC channels, and Orai proteins, Cell Calcium 45 (2009) 602–610.
[27] D. Bodnar, W.Y. Chung, D. Yang, J.H. Hong, A. Jha, S. Muallem, STIM-TRP pathways and microdomain organization: Ca(2+) influx channels: the Orai-STIM1-TRPC complexes, Adv. Exp. Med. Biol. 993 (2017) 139–157.
[28] O. Mignen, B. Constantin, M. Potier-Cartereau, A. Penna, M. Gautier, M. Gueguinou, Y. Renaudineau, K.F. Shoji, R. Felix, E. Bayet, P. Buscaglia, M. Debant, A. Chantome, C. Vandier, Constitutive calcium entry and cancer: updated views and insights, Eur. Biophys. J. 46 (2017) 395–413.
[29] M. Gueguinou, A. Chantome, G. Fromont, P. Bougnoux, C. Vandier, M. Potier-Cartereau, KCa and Ca(2+) channels: the complex thought, Biochim. Biophys. Acta 1843 (2014) 2322–2333.
[30] R.J. Kurman, M. Shih Ie, The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory, Am. J. Surg. Pathol. 34 (2010) 433–443.
[31] T.J. Perren, A.M. Swart, J. Pfisterer, J.A. Ledermann, E. Pujade-Lauraine, G. Kristensen, M.S. Carey, P. Beale, A. Cervantes, C. Kurzeder, A. du Bois, J. Sehouli, R. Kimmig, A. Stahle, F. Collinson, S. Essapen, C. Gourley, A. Lortholary, F. Selle, M.R. Mirza, A. Leminen, M. Plante, D. Stark, W. Qian, M.K. Parmar, A.M. Oza, A phase 3 trial of bevacizumab in ovarian cancer, N. Engl. J. Med. 365 (2011) 2484–2496.
[32] K. Moore, N. Colombo, G. Scambia, B.G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. Gonzalez-Martin, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, P. DiSilvestro, Maintenance olaparib in patients with newly diagnosed advanced ovarian Cancer, N. Engl. J. Med. 379 (2018) 2495–2505.
[33] J. Francis, N. Coakley, L. Elit, H. Mackay, Systemic therapy for recurrent epithelial ovarian cancer: a clinical practice guideline, Curr. Oncol. 24 (2017) e540–e546.
[34] D.P. Rose, A.P. Boyar, E.L. Wynder, International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption, Cancer 58 (1986) 2363–2371.
[35] J.M. Genkinger, D.J. Hunter, D. Spiegelman, K.E. Anderson, W.L. Beeson, J.E. Buring, G.A. Colditz, G.E. Fraser, J.L. Freudenheim, R.A. Goldbohm, S.E. Hankinson, K.L. Koenig, S.C. Larsson, M. Leitzmann, M.L. McCullough, A.B. Miller, C. Rodriguez, T.E. Rohan, J.A. Ross, A. Schatzkin, L.J. Schouten, E. Smit, W.C. Willett, A. Wolk, A. Zeleniuch-Jacquotte, S.M. Zhang, S.A. Smith-Warner, A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer, Cancer Causes Control 17 (2006) 273–285.
[36] R. Hou, Q.J. Wu, T.T. Gong, L. Jiang, Dietary fat and fatty acid intake and epithelial ovarian cancer risk: evidence from epidemiological studies, Oncotarget 6 (2015) 43099–43119.
[37] M. Huncharek, B. Kupelnick, Dietary fat intake and risk of epithelial ovarian cancer: a meta-analysis of 6,689 subjects from 8 observational studies, Nutr. Cancer 40 (2001) 87–91.
[38] M.A. Merritt, E. Riboli, E. Weiderpass, K.K. Tsilidis, K. Overvad, A. Tjonneland, L. Hansen, L. Dossus, G. Fagherazzi, L. Baglietto, R.T. Fortner, J. Ose, A. Steffen, H. Boeing, A. Trichopoulou, D. Trichopoulos, P. Lagiou, G. Masala, S. Sieri, A. Mattiello, R. Tumino, C. Sacerdote, H.B. Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, A. Hjartaker, I.T. Gram, J.R. Quiros, M. Obon-Santacana, E. Molina-Montes, J.M. Huerta Castano, E. Ardanaz, S. Chamosa, E. Sonestedt, A. Idahl, E. Lundin, K.T. Khaw, N. Wareham, R.C. Travis, S. Rinaldi, I. Romieu, V. Chajes, M.J. Gunter, Dietary fat intake and risk of epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition, Cancer Epidemiol. 38 (2014) 528–537.
[39] M.A. Merritt, I. Tzoulaki, P.A. van den Brandt, L.J. Schouten, K.K. Tsilidis, E. Weiderpass, C.J. Patel, A. Tjonneland, L. Hansen, K. Overvad, M. His, L. Dartois, M.C. Boutron-Ruault, R.T. Fortner, R. Kaaks, K. Aleksandrova, H. Boeing, A. Trichopoulou, P. Lagiou, C. Bamia, D. Palli, V. Krogh, R. Tumino, F. Ricceri, A. Mattiello, H.B. Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, G. Skeie, M. Jareid, J.R. Quiros, M. Obon-Santacana, M.J. Sanchez, S. Chamosa, J.M. Huerta, A. Barricarte, J.A. Dias, E. Sonestedt, A. Idahl, E. Lundin, N.J. Wareham, K.T. Khaw, R.C. Travis, P. Ferrari, E. Riboli, M.J. Gunter, Nutrient-wide association study of 57 foods/nutrients and epithelial ovarian cancer in the European Prospective Investigation into Cancer and Nutrition study and the Netherlands Cohort Study, Am. J. Clin. Nutr. 103 (2016) 161–167.
[40] R.L. Prentice, C.A. Thomson, B. Caan, F.A. Hubbell, G.L. Anderson, S.A. Beresford, M. Pettinger, D.S. Lane, L. Lessin, S. Yasmeen, B. Singh, J. Khandekar, J.M. Shikany, S. Satterfield, R.T. Chlebowski, Low-fat dietary pattern and cancer incidence in the women's health initiative dietary modification randomized controlled trial, J. Natl. Cancer Inst. 99 (2007) 1534–1543.
[41] W. Qiu, H. Lu, Y. Qi, X. Wang, Dietary fat intake and ovarian cancer risk: a meta-analysis of epidemiological studies, Oncotarget 7 (2016) 37390–37406.
[42] S.Y. Pan, A.M. Ugnat, Y. Mao, S.W. Wen, K.C. Johnson, A case-control study of diet and the risk of ovarian cancer, Cancer Epidemiol. Biomarkers Prev. 13 (2004) 1521–1527.
[43] T. Bjorge, A. Lukanova, S. Tretli, J. Manjer, H. Ulmer, T. Stocks, R. Selmer, G. Nagel, M. Almquist, H. Concin, G. Hallmans, H. Jonsson, C. Haggstrom, P. Stattin, A. Engeland, Metabolic risk factors and ovarian cancer in the Metabolic Syndrome and Cancer project, Int. J. Epidemiol. 40 (2011) 1667–1677.
[44] K.J. Helzlsouer, A.J. Alberg, E.P. Norkus, J.S. Morris, S.C. Hoffman, G.W. Comstock, Prospective study of serum micronutrients and ovarian cancer, J. Natl. Cancer Inst. 88 (1996) 32–37.
[45] C.C. Mandal, A. Sharma, M.S. Panwar, J.A. Radosevich, Is cholesterol a mediator of cold-induced cancer? Tumour Biol. 37 (2016) 9635–9648.
[46] J.C. Melvin, D. Seth, L. Holmberg, H. Garmo, N. Hammar, I. Jungner, G. Walldius, M. Lambe, A. Wigertz, M. Van Hemelrijck, Lipid profiles and risk of breast and ovarian cancer in the Swedish AMORIS study, Cancer Epidemiol. Biomarkers Prev. 21 (2012) 1381–1384.
[47] B. Akinwunmi, A.F. Vitonis, L. Titus, K.L. Terry, D.W. Cramer, Statin therapy and association with ovarian cancer risk in the New England Case Control (NEC) study, Int. J. Cancer 144 (2019) 991–1000.
[48] Y. Chen, L. Zhang, W. Liu, K. Wang, Case-control study of metabolic syndrome and ovarian cancer in Chinese population, Nutr. Metab. (Lond.) 14 (2017) 21.
[49] P. Latino-Martel, V. Cottet, N. Druesne-Pecollo, F.H. Pierre, M. Touillaud, M. Touvier, M.P. Vasson, M. Deschasaux, J. Le Merdy, E. Barrandon, R. Ancellin, Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence, Crit. Rev. Oncol. Hematol. 99 (2016) 308–323.
[50] B.K. Armstrong, J.B. Brown, H.T. Clarke, D.K. Crooke, R. Hahnel, J.R. Masarei, T. Ratajczak, Diet and reproductive hormones: a study of vegetarian and non-vegetarian postmenopausal women, J. Natl. Cancer Inst. 67 (1981) 761–767.
[51] B.R. Goldin, H. Adlercreutz, S.L. Gorbach, J.H. Warram, J.T. Dwyer, L. Swenson, M.N. Woods, Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women, N. Engl. J. Med. 307 (1982) 1542–1547.
[52] R.T. Fortner, J. Ose, M.A. Merritt, H. Schock, A. Tjonneland, L. Hansen, K. Overvad, L. Dossus, F. Clavel-Chapelon, L. Baglietto, H. Boeing, A. Trichopoulou, V. Benetou, P. Lagiou, C. Agnoli, A. Mattiello, G. Masala, R. Tumino, C. Sacerdote, H.B. Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, E. Weiderpass, I. Torhild Gram, E.J. Duell, N. Larranaga, E. Ardanaz, M.J. Sanchez, M.D. Chirlaque, J. Brandstedt, A. Idahl, E. Lundin, K.T. Khaw, N. Wareham, R.C. Travis, S. Rinaldi, I. Romieu, M.J. Gunter, E. Riboli, R. Kaaks, Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: results from the EPIC cohort, Int. J. Cancer 137 (2015) 1196–1208.
[53] C. La Vecchia, Ovarian cancer: epidemiology and risk factors, Eur. J. Cancer Prev. 26 (2017) 55–62.
[54] L. Chauvin, C. Goupille, C. Blanc, M. Pinault, I. Domingo, C. Guimaraes, P. Bougnoux, S. Chevalier, K. Maheo, Long chain n-3 polyunsaturated fatty acids increase the efficacy of docetaxel in mammary cancer cells by downregulating Akt and PKCepsilon/delta-induced ERK pathways, Biochim. Biophys. Acta 1861 (2016) 380–390.
[55] J. Chemin, A.J. Patel, P. Delmas, F. Sachs, M. Lazdunski, E. Honore, Regulation of the mechano-gated K2P channel TREK-1 by membrane phospholipids, Curr. Top. Membr. 59 (2007) 155–170.
[56] F.E. Herrera, C.M. Sevrain, P.A. Jaffres, H. Couthon, A. Grelard, E.J. Dufourc, A. Chantome, M. Potier-Cartereau, C. Vandier, A.M. Bouchet, Singular interaction between an antimetastatic agent and the lipid bilayer: the ohmline case, ACS Omega 2 (2017) 6361–6370.
[57] A.J. Patel, M. Lazdunski, E. Honore, Lipid and mechano-gated 2P domain K(+) channels, Curr. Opin. Cell Biol. 13 (2001) 422–428.
[58] S. Serini, G. Calviello, Modulation of Ras/ERK and phosphoinositide signaling by long-chain n-3 PUFA in breast cancer and their potential complementary role in combination with targeted drugs, Nutrients (2017) 9.
[59] I. Delimaris, E. Faviou, G. Antonakos, E. Stathopoulou, A. Zachari, A. Dionyssiou-Asteriou, Oxidized LDL, serum oxidizability and serum lipid levels in patients with breast or ovarian cancer, Clin. Biochem. 40 (2007) 1129–1134.
[60] A. Bachmayr-Heyda, S. Aust, K. Auer, S.M. Meier, K.G. Schmetterer, S. Dekan, C. Gerner, D. Pils, Integrative systemic and local metabolomics with impact on survival in high-grade serous ovarian Cancer, Clin. Cancer Res. 23 (2017) 2081–2092.
[61] F. Zhu, X. Xu, B. Shi, L. Zeng, L. Wang, X. Wu, H. Zhu, The positive predictive value of low-density lipoprotein for recurrence-free survival in ovarian cancer, Int. J. Gynaecol. Obstet. 143 (2018) 232–238.
[62] A.J. Li, R.G. Elmore, I.Y. Chen, B.Y. Karlan, Serum low-density lipoprotein levels correlate with survival in advanced stage epithelial ovarian cancers, Gynecol. Oncol. 116 (2010) 78–81.
[63] Y. Zhang, J. Wu, J.Y. Liang, X. Huang, L. Xia, D.W. Ma, X.Y. Xu, P.P. Wu, Association of serum lipids and severity of epithelial ovarian cancer: an observational cohort study of 349 Chinese patients, J. Biomed. Res. 32 (2018) 336–342.
[64] H.Y. Chen, Q. Wang, Q.H. Xu, L. Yan, X.F. Gao, Y.H. Lu, L. Wang, Statin as a combined therapy for advanced-stage ovarian Cancer: a propensity score matched analysis, Biomed Res. Int. (2016) 91252382016.

[65] D. Buckley, G. Duke, T.S. Heuer, M. O'Farrell, A.S. Wagman, W. McCulloch, G. Kemble, Fatty acid synthase - Modern tumor cell biology insights into a classical oncology target, Pharmacol. Ther. 177 (2017) 23–31.
[66] M. Sans, K. Gharpure, R. Tibshirani, J. Zhang, L. Liang, J. Liu, J.H. Young, R.L. Dood, A.K. Sood, L.S. Eberlin, Metabolic markers and statistical prediction of serous ovarian Cancer aggressiveness by ambient ionization mass spectrometry imaging, Cancer Res. 77 (2017) 2903–2913.
[67] Y.S. Kim, J. Jung, H. Jeong, J.H. Lee, H.E. Oh, E.S. Lee, J.W. Choi, High membranous expression of fatty acid transport protein 4 is associated with tumorigenesis and tumor progression in clear cell renal cell carcinoma, Dis. Markers (2019) 57020262019.
[68] A. Ladanyi, A. Mukherjee, H.A. Kenny, A. Johnson, A.K. Mitra, S. Sundaresan, K.M. Nieman, G. Pascual, S.A. Benitah, A. Montag, S.D. Yamada, N.A. Abumrad, E. Lengyel, Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis, Oncogene 37 (2018) 2285–2301.
[69] Y. Cai, J. Wang, L. Zhang, D. Wu, D. Yu, X. Tian, J. Liu, X. Jiang, Y. Shen, L. Zhang, M. Ren, P. Huang, Expressions of fatty acid synthase and HER2 are correlated with poor prognosis of ovarian cancer, Med. Oncol. 32 (2015) 391.
[70] T.S. Gansler, W. Hardman 3rd, D.A. Hunt, S. Schaffel, R.A. Hennigar, Increased expression of fatty acid synthase (OA-519) in ovarian neoplasms predicts shorter survival, Hum. Pathol. 28 (1997) 686–692.
[71] S.M. Ueda, K.L. Yap, B. Davidson, Y. Tian, V. Murthy, T.L. Wang, K. Visvanathan, F.P. Kuhajda, R.E. Bristow, H. Zhang, M. Shih Ie, Expression of fatty acid synthase depends on NAC1 and is associated with recurrent ovarian serous carcinomas, J. Oncol. (2010) 2851912010.
[72] D. Veigel, R. Wagner, G. Stubiger, M. Wuczkowski, M. Filipits, R. Horvat, B. Benhamu, M.L. Lopez-Rodriguez, A. Leisser, P. Valent, M. Grusch, F.G. Hegardt, J. Garcia, D. Serra, N. Auersperg, R. Colomer, T.W. Grunt, Fatty acid synthase is a metabolic marker of cell proliferation rather than malignancy in ovarian cancer and its precursor cells, Int. J. Cancer 136 (2015) 2078–2090.
[73] R. Wagner, G. Stubiger, D. Veigel, M. Wuczkowski, P. Lanzerstorfer, J. Weghuber, E. Karteris, K. Nowikovsky, N. Wilfinger-Lutz, C.F. Singer, R. Colomer, B. Benhamu, M.L. Lopez-Rodriguez, P. Valent, T.W. Grunt, Multi-level suppression of receptor-PI3K-mTORC1 by fatty acid synthase inhibitors is crucial for their efficacy against ovarian cancer cells, Oncotarget 8 (2017) 11600–11613.
[74] J.A. Menendez, L. Vellon, I. Mehmi, B.P. Oza, S. Ropero, R. Colomer, R. Lupu, Inhibition of fatty acid synthase (FAS) suppresses HER2/neu (erbB-2) oncogene overexpression in cancer cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 10715–10720.
[75] M.T. Rahman, K. Nakayama, M. Rahman, H. Katagiri, A. Katagiri, T. Ishibashi, M. Ishikawa, K. Iida, N. Nakayama, Y. Otsuki, S. Nakayama, K. Miyazaki, Fatty acid synthase expression associated with NAC1 is a potential therapeutic target in ovarian clear cell carcinomas, Br. J. Cancer 107 (2012) 300–307.
[76] S. Reinartz, S. Lieber, J. Pesek, D.T. Brandt, A. Asafova, F. Finkernagel, B. Watzer, W.A. Nockher, A. Nist, T. Stiewe, J.M. Jansen, U. Wagner, A. Konzer, J. Graumann, R. Grosse, T. Worzfeld, S. Muller-Brusselbach, R. Muller, Cell type-selective pathways and clinical associations of lysophosphatidic acid biosynthesis and signaling in the ovarian cancer microenvironment, Mol. Oncol. 13 (2019) 185–201.
[77] Y.J. Xiao, B. Schwartz, M. Washington, A. Kennedy, K. Webster, J. Belinson, Y. Xu, Electrospray ionization mass spectrometry analysis of lysophospholipids in human ascitic fluids: comparison of the lysophospholipid contents in malignant vs nonmalignant ascitic fluids, Anal. Biochem. 290 (2001) 302–313.
[78] S. Reinartz, F. Finkernagel, T. Adhikary, V. Rohnalter, T. Schumann, Y. Schober, W.A. Nockher, A. Nist, T. Stiewe, J.M. Jansen, U. Wagner, S. Muller-Brusselbach, R. Muller, A transcriptome-based global map of signaling pathways in the ovarian cancer microenvironment associated with clinical outcome, Genome Biol. 17 (2016) 108.
[79] I. Sedlakova, J. Vavrova, J. Tosner, L. Hanousek, Lysophosphatidic acid (LPA)-a perspective marker in ovarian cancer, Tumour Biol. 32 (2011) 311–316.
[80] Y. Xu, Z. Shen, D.W. Wiper, M. Wu, R.E. Morton, P. Elson, A.W. Kennedy, J. Belinson, M. Markman, G. Casey, Lysophosphatidic acid as a potential biomarker for ovarian and other gynecologic cancers, Jama 280 (1998) 719–723.
[81] H. Xue, Y. Wang, T.J. MacCormack, T. Lutes, C. Rice, M. Davey, D. Dugourd, T.T. Ilenchuk, J.M. Stewart, Inhibition of Transient Receptor Potential Vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model, J. Cancer 9 (2018) 3196–3207.
[82] Y.Y. Li, W.C. Zhang, J.L. Zhang, C.J. Zheng, H. Zhu, Fan L.M. Yu HM, Plasma levels of lysophosphatidic acid in ovarian cancer versus controls: a meta-analysis, Lipids Health Dis. 14 (2015) 72.
[83] M.M. Murph, W. Liu, S. Yu, Y. Lu, H. Hall, B.T. Hennessy, J. Lahad, M. Schaner, A. Helland, G. Kristensen, A.L. Borresen-Dale, G.B. Mills, Lysophosphatidic acid-induced transcriptional profile represents serous epithelial ovarian carcinoma and worsened prognosis, PLoS One 4 (2009) e5583.
[84] M.V. Barbolina, Molecular mechanisms regulating organ-specific metastases in epithelial ovarian carcinoma, Cancers (Basel) (2017) 10.
[85] D.S. Tan, R. Agarwal, S.B. Kaye, Mechanisms of transcoelomic metastasis in ovarian cancer, Lancet Oncol. 7 (2006) 925–934.
[86] M.G.K. Benesch, Z. Yang, X. Tang, G. Meng, D.N. Brindley, Lysophosphatidate signaling: the tumor microenvironment's new Nemesis, Trends Cancer 3 (2017) 748–752.
[87] T. Worzfeld, E. Pogge von Strandmann, M. Huber, T. Adhikary, U. Wagner, S. Reinartz, R. Muller, The unique molecular and cellular microenvironment of ovarian Cancer, Front. Oncol. 7 (2017) 24.
[88] J. Ren, Y.J. Xiao, L.S. Singh, X. Zhao, Z. Zhao, L. Feng, T.M. Rose, G.D. Prestwich, Y. Xu, Lysophosphatidic acid is constitutively produced by human peritoneal mesothelial cells and enhances adhesion, migration, and invasion of ovarian cancer cells, Cancer Res. 66 (2006) 3006–3014.
[89] R. Dusaulcy, C. Rancoule, S. Gres, E. Wanecq, A. Colom, C. Guigne, L.A. van Meeteren, W.H. Moolenaar, P. Valet, J.S. Saulnier-Blache, Adipose-specific disruption of autotaxin enhances nutritional fattening and reduces plasma lysophosphatidic acid, J. Lipid Res. 52 (2011) 1247–1255.
[90] P.E. Feist, E.A. Loughran, M.S. Stack, A.B. Hummon, Quantitative proteomic analysis of murine white adipose tissue for peritoneal cancer metastasis, Anal. Bioanal. Chem. 410 (2018) 1583–1594.
[91] K.M. Nieman, H.A. Kenny, C.V. Penicka, A. Ladanyi, R. Buell-Gutbrod, M.R. Zillhardt, I.L. Romero, M.S. Carey, G.B. Mills, G.S. Hotamisligil, S.D. Yamada, M.E. Peter, K. Gwin, E. Lengyel, Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth, Nat. Med. 17 (2011) 1498–1503.
[92] A.M. Eder, T. Sasagawa, M. Mao, J. Aoki, G.B. Mills, Constitutive and lysophosphatidic acid (LPA)-induced LPA production: role of phospholipase D and phospholipase A2, Clin. Cancer Res. 6 (2000) 2482–2491.
[93] A.J. Snider, Z. Zhang, Y. Xie, K.E. Meier, Epidermal growth factor increases lysophosphatidic acid production in human ovarian cancer cells: roles for phospholipase D2 and receptor transactivation, Am. J. Physiol. Cell Physiol. 298 (2010) C163–70.
[94] E.J. Seo, Y.W. Kwon, I.H. Jang, D.K. Kim, S.I. Lee, E.J. Choi, K.H. Kim, D.S. Suh, J.H. Lee, K.U. Choi, J.W. Lee, H.J. Mok, K.P. Kim, H. Matsumoto, J. Aoki, J.H. Kim, Autotaxin regulates maintenance of ovarian cancer stem cells through lysophosphatidic acid-mediated autocrine mechanism, Stem Cells 34 (2016) 551–564.
[95] F. Gaits, O. Fourcade, F. Le Balle, G. Gueguen, B. Gaige, A. Gassama-Diagne, J. Fauvel, J.P. Salles, G. Mauco, M.F. Simon, H. Chap, Lysophosphatidic acid as a phospholipid mediator: pathways of synthesis, FEBS Lett. 410 (1997) 54–58.
[96] R.J. Lin, V. Afshar-Kharghan, A.I. Schafer, Paraneoplastic thrombocytosis: the secrets of tumor self-promotion, Blood 124 (2014) 184–187.
[97] J. Menczer, Preoperative elevated platelet count and thrombocytosis in gynecologic malignancies, Arch. Gynecol. Obstet. 295 (2017) 9–15.
[98] N. Swier, H.H. Versteeg, Reciprocal links between venous thromboembolism, coagulation factors and ovarian cancer progression, Thromb. Res. 150 (2017) 8–18.
[99] Q. Zhou, F. Huang, Z. He, M.Z. Zuo, Clinicopathological and prognostic significance of platelet count in patients with ovarian cancer, Climacteric 21 (2018) 60–68.
[100] K. Nakamura, K. Igarashi, R. Ohkawa, H. Yokota, A. Masuda, S. Nakagawa, T. Yano, H. Ikeda, J. Aoki, Y. Yatomi, Serum autotaxin is not a useful biomarker for ovarian cancer, Lipids 47 (2012) 927–930.
[101] H. Onallah, L.J. Catane, C.G. Trope, T.E. Hetland Falkenthal, R. Reich, B. Davidson, Activity and clinical relevance of autotaxin and lysophosphatidic acid pathways in high-grade serous carcinoma, Virchows Arch. 473 (2018) 463–470.
[102] Q. Cai, Z. Zhao, C. Antalis, L. Yan, G. Del Priore, A.H. Hamed, F.B. Stehman, J.M. Schilder, Y. Xu, Elevated and secreted phospholipase A(2) activities as new potential therapeutic targets in human epithelial ovarian cancer, FASEB J. 26 (2012) 3306–3320.
[103] A. Jesionowska, E. Cecerska-Heryc, N. Matoszka, B. Dolegowska, Lysophosphatidic acid signaling in ovarian cancer, J. Recept. Signal Transduct. Res. 35 (2015) 578–584.
[104] Y. Xu, Lysophospholipid signaling in the epithelial ovarian Cancer tumor microenvironment, Cancers (Basel) (2018) 10.
[105] J. Si, Y. Su, Y. Wang, Y.L. Yan, Y.L. Tang, Expressions of lysophosphatidic acid receptors in the development of human ovarian carcinoma, Int. J. Clin. Exp. Med. 8 (2015) 17880–17890.
[106] P. Wang, X. Wu, W. Chen, J. Liu, X. Wang, The lysophosphatidic acid (LPA) receptors their expression and significance in epithelial ovarian neoplasms, Gynecol. Oncol. 104 (2007) 714–720.
[107] T. Wasniewski, I. Woclawek-Potocka, D. Boruszewska, I. Kowalczyk-Zieba, E. Sinderewicz, K. Grycmacher, The significance of the altered expression of lysophosphatidic acid receptors, autotaxin and phospholipase A2 as the potential biomarkers in type 1 endometrial cancer biology, Oncol. Rep. 34 (2015) 2760–2767.
[108] X. Yu, Y. Zhang, H. Chen, LPA receptor 1 mediates LPA-induced ovarian cancer metastasis: an in vitro and in vivo study, BMC Cancer 16 (2016) 846.
[109] E.J. Goetzl, H. Dolezalova, Y. Kong, Y.L. Hu, R.B. Jaffe, K.R. Kalli, C.A. Conover, Distinctive expression and functions of the type 4 endothelial differentiation gene-encoded G protein-coupled receptor for lysophosphatidic acid in ovarian cancer, Cancer Res. 59 (1999) 5370–5375.
[110] J. Nakayama, T.A. Raines, K.R. Lynch, J.K. Slack-Davis, Decreased peritoneal ovarian cancer growth in mice lacking expression of lipid phosphate phosphohydrolase 1, PLoS One 10 (2015) e0120071.
[111] J.L. Tanyi, Y. Hasegawa, R. Lapushin, A.J. Morris, J.K. Wolf, A. Berchuck, K. Lu, D.I. Smith, K. Kalli, L.C. Hartmann, K. McCune, D. Fishman, R. Broaddus, K.W. Cheng, E.N. Atkinson, J.M. Yamal, R.C. Bast, E.A. Felix, R.A. Newman, G.B. Mills, Role of decreased levels of lipid phosphate phosphatase-1 in accumulation of lysophosphatidic acid in ovarian cancer, Clin. Cancer Res. 9 (2003) 3534–3545.
[112] C.S. Diefenbach, R.A. Soslow, A. Iasonos, I. Linkov, C. Hedvat, L. Bonham, J. Singer, R.R. Barakat, C. Aghajanian, J. Dupont, Lysophosphatidic acid acyltransferase-beta (LPAAT-beta) is highly expressed in advanced ovarian cancer and is associated with aggressive histology and poor survival, Cancer 107 (2006) 1511–1519.
[113] G.M. Springett, L. Bonham, A. Hummer, I. Linkov, D. Misra, C. Ma, G. Pezzoni, S. Di Giovine, J. Singer, H. Kawasaki, D. Spriggs, R. Soslow, J. Dupont, Lysophosphatidic acid acyltransferase-beta is a prognostic marker and therapeutic target in gynecologic malignancies, Cancer Res. 65 (2005) 9415–9425.

[114] S. Niesporek, C. Denkert, W. Weichert, M. Kobel, A. Noske, J. Sehouli, J.W. Singer, M. Dietel, S. Hauptmann, Expression of lysophosphatidic acid acyltransferase beta (LPAAT-beta) in ovarian carcinoma: correlation with tumour grading and prognosis, Br. J. Cancer 92 (2005) 1729–1736.
[115] R.C. Bruntz, C.W. Lindsley, H.A. Brown, Phospholipase D signaling pathways and phosphatidic acid as therapeutic targets in cancer, Pharmacol. Rev. 66 (2014) 1033–1079.
[116] N.C. Stoddard, J. Chun, Promising pharmacological directions in the world of lysophosphatidic Acid signaling, Biomol. Ther. (Seoul) 23 (2015) 1–11.
[117] D. Wang, R.N. Dubois, Eicosanoids and cancer, Nat. Rev. Cancer 10 (2010) 181–193.
[118] R.N. Gomes, S. Felipe da Costa, A. Colquhoun, Eicosanoids and cancer, Clinics (Sao Paulo) 73 (2018) e530s.
[119] M. Hada, M.L. Edin, P. Hartge, F.B. Lih, N. Wentzensen, D.C. Zeldin, B. Trabert, Prediagnostic serum levels of fatty acid metabolites and risk of ovarian Cancer in the prostate, lung, colorectal, and ovarian (PLCO) Cancer screening trial, Cancer Epidemiol. Biomarkers Prev. 28 (2018) 189–197.
[120] T.L. Erkinheimo, H. Lassus, P. Finne, B.P. van Rees, A. Leminen, O. Ylikorkala, C. Haglund, R. Butzow, A. Ristimaki, Elevated cyclooxygenase-2 expression is associated with altered expression of p53 and SMAD4, amplification of HER-2/neu, and poor outcome in serous ovarian carcinoma, Clin. Cancer Res. 10 (2004) 538–545.
[121] J.Y. Lee, S.K. Myung, Y.S. Song, Prognostic role of cyclooxygenase-2 in epithelial ovarian cancer: a meta-analysis of observational studies, Gynecol. Oncol. 129 (2013) 613–619.
[122] H. Sun, X. Zhang, D. Sun, X. Jia, L. Xu, Y. Qiao, Y. Jin, COX-2 expression in ovarian cancer: an updated meta-analysis, Oncotarget 8 (2017) 88152–88162.
[123] A. Gartung, J. Yang, V.P. Sukhatme, D.R. Bielenberg, D. Fernandes, J. Chang, B.A. Schmidt, S.H. Hwang, D. Zurakowski, S. Huang, M.W. Kieran, B.D. Hammock, D. Panigrahy, Suppression of chemotherapy-induced cytokine/lipid mediator surge and ovarian cancer by a dual COX-2/sEH inhibitor, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 1698–1703.
[124] A. Suri, X. Sheng, K.M. Schuler, Y. Zhong, X. Han, H.M. Jones, P.A. Gehrig, C. Zhou, V.L. Bae-Jump, The effect of celecoxib on tumor growth in ovarian cancer cells and a genetically engineered mouse model of serous ovarian cancer, Oncotarget 7 (2016) 39582–39594.
[125] F. Legge, A. Paglia, M. D'Asta, G. Fuoco, G. Scambia, G. Ferrandina, Phase II study of the combination carboplatin plus celecoxib in heavily pre-treated recurrent ovarian cancer patients, BMC Cancer 11 (2011) 214.
[126] J. Chen, P. Shen, X.C. Zhang, M.D. Zhao, X.G. Zhang, L. Yang, Efficacy and safety profile of celecoxib for treating advanced cancers: a meta-analysis of 11 randomized clinical trials, Clin. Ther. 36 (2014) 1253–1263.
[127] A.K. Reyners, L. de Munck, F.L. Erdkamp, W.M. Smit, K. Hoekman, R.I. Lalisang, H. de Graaf, A.N. Wymenga, M. Polee, H. Hollema, M.A. van Vugt, M. Schaapveld, P.H. Willemse, A randomized phase II study investigating the addition of the specific COX-2 inhibitor celecoxib to docetaxel plus carboplatin as first-line chemotherapy for stage IC to IV epithelial ovarian cancer, Fallopian tube or primary peritoneal carcinomas: the DoCaCel study, Ann. Oncol. 23 (2012) 2896–2902.
[128] M. Szajnik, M.J. Szczepanski, E. Elishaev, C. Visus, D. Lenzner, M. Zabel, M. Glura, A.B. DeLeo, T.L. Whiteside, 17beta Hydroxysteroid dehydrogenase type 12 (HSD17B12) is a marker of poor prognosis in ovarian carcinoma, Gynecol. Oncol. 127 (2012) 587–594.
[129] R.P. Rocconi, T.O. Kirby, R.S. Seitz, R. Beck, J.M. Straughn Jr., R.D. Alvarez, W.K. Huh, Lipoxygenase pathway receptor expression in ovarian cancer, Reprod. Sci. 15 (2008) 321–326.
[130] T.E. Harris, P.E. Squires, A.E. Michael, A.L. Bernal, D.R. Abayasekara, Human granulosa-lutein cells express functional EP1 and EP2 prostaglandin receptors, Biochem. Biophys. Res. Commun. 285 (2001) 1089–1094.
[131] A. Mayerhofer, K.J. Fohr, K. Sterzik, M. Gratzl, Carbachol increases intracellular free calcium concentrations in human granulosa-lutein cells, J. Endocrinol. 135 (1992) 153–159.
[132] A. Mayerhofer, K. Sterzik, H. Link, M. Wiemann, M. Gratzl, Effect of oxytocin on free intracellular Ca2+ levels and progesterone release by human granulosa-lutein cells, J. Clin. Endocrinol. Metab. 77 (1993) 1209–1214.
[133] A. Agoston, L. Kunz, A. Krieger, A. Mayerhofer, Two types of calcium channels in human ovarian endocrine cells: involvement in steroidogenesis, J. Clin. Endocrinol. Metab. 89 (2004) 4503–4512.
[134] P.S. Lee, P.E. Squires, A.M. Buchan, B.H. Yuen, P.C. Leung, P2-purinoreceptor evoked changes in intracellular calcium oscillations in single isolated human granulosa-lutein cells, Endocrinology 137 (1996) 3756–3761.
[135] M.H. Traut, D. Berg, U. Berg, A. Mayerhofer, L. Kunz, Identification and characterization of Ca2+-activated K+ channels in granulosa cells of the human ovary, Reprod. Biol. Endocrinol. 7 (2009) 28.
[136] S.B. Chalmers, G.R. Monteith, ORAI channels and cancer, Cell Calcium 74 (2018) 160–167.
[137] E. Lastraioli, J. Iorio, A. Arcangeli, Ion channel expression as promising cancer biomarker, Biochim. Biophys. Acta 1848 (2015) 2685–2702.
[138] N. Prevarskaya, R. Skryma, Y. Shuba, Ion Channels in Cancer: Are Cancer Hallmarks Oncochannelopathies? Physiol. Rev. 98 (2018) 559–621.
[139] A. Vashisht, M. Trebak, R.K. Motiani, STIM and Orai proteins as novel targets for cancer therapy. a review in the theme: cell and molecular processes in cancer metastasis, Am. J. Physiol. Cell Physiol. 309 (2015) C457–69.
[140] M.F. Franzoni, M. Canonaco, A. Frova, R. Tavolaro, Brain natriuretic peptide (BNP)-like immunoreactivity in the central nervous system of the crested newt, Eur. J. Histochem. 36 (1992) 455–466.
[141] T.A. Stewart, K.T. Yapa, G.R. Monteith, Altered calcium signaling in cancer cells, Biochim. Biophys. Acta 1848 (2015) 2502–2511.
[142] A. Becchetti, A. Arcangeli, Integrins and ion channels in cell migration: implications for neuronal development, wound healing and metastatic spread, Adv. Exp. Med. Biol. 674 (2010) 107–123.
[143] R.D. Burgoyne, Neuronal calcium sensor proteins: generating diversity in neuronal Ca2+ signalling, Nat. Rev. Neurosci. 8 (2007) 182–193.
[144] T. Capiod, The need for calcium channels in cell proliferation, Recent Pat. Anticancer Drug Discov. 8 (2013) 4–17.
[145] S. Orrenius, B. Zhivotovsky, P. Nicotera, Regulation of cell death: the calcium-apoptosis link, Nat. Rev. Mol. Cell Biol. 4 (2003) 552–565.
[146] H.L. Roderick, S.J. Cook, Ca2+ signalling checkpoints in cancer: remodelling Ca2+ for cancer cell proliferation and survival, Nat. Rev. Cancer 8 (2008) 361–375.
[147] J.W. Putney Jr., L.M. Broad, F.J. Braun, J.P. Lievremont, G.S. Bird, Mechanisms of capacitative calcium entry, J. Cell. Sci. 114 (2001) 2223–2229.
[148] M. Vig, C. Peinelt, A. Beck, D.L. Koomoa, D. Rabah, M. Koblan-Huberson, S. Kraft, H. Turner, A. Fleig, R. Penner, J.P. Kinet, CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry, Science 312 (2006) 1220–1223.
[149] G.R. Monteith, N. Prevarskaya, S.J. Roberts-Thomson, The calcium-cancer signalling nexus, Nat. Rev. Cancer 17 (2017) 367–380.
[150] N. Prevarskaya, R. Skryma, Y. Shuba, Calcium in tumour metastasis: new roles for known actors, Nat. Rev. Cancer 11 (2011) 609–618.
[151] S. Schmidt, G. Liu, G. Liu, W. Yang, S. Honisch, S. Pantelakos, C. Stournaras, A. Honig, F. Lang, Enhanced Orai1 and STIM1 expression as well as store operated Ca2+ entry in therapy resistant ovary carcinoma cells, Oncotarget 5 (2014) 4799–4810.
[152] N. Heise, D. Palme, M. Misovic, S. Koka, J. Rudner, F. Lang, H.R. Salih, S.M. Huber, G. Henke, Non-selective cation channel-mediated Ca2+-entry and activation of Ca2+/calmodulin-dependent kinase II contribute to G2/M cell cycle arrest and survival of irradiated leukemia cells, Cell. Physiol. Biochem. 26 (2010) 597–608.
[153] J.T. Taylor, X.B. Zeng, J.E. Pottle, K. Lee, A.R. Wang, S.G. Yi, J.A. Scruggs, S.S. Sikka, M. Li, Calcium signaling and T-type calcium channels in cancer cell cycling, World J. Gastroenterol. 14 (2008) 4984–4991.
[154] K.N.M. Abdelazeem, B. Droppova, B. Sukkar, T. Al-Maghout, L. Pelzl, N. Zacharopoulou, N.H. Ali Hassan, K.I. Abdel-Fattah, C. Stournaras, F. Lang, Upregulation of Orai1 and STIM1 expression as well as store-operated Ca(2+) entry in ovary carcinoma cells by placental growth factor, Biochem. Biophys. Res. Commun. (2019).
[155] G.L. Semenza, Targeting HIF-1 for cancer therapy, Nat. Rev. Cancer 3 (2003) 721–732.
[156] Y. Li, B. Guo, Q. Xie, D. Ye, D. Zhang, Y. Zhu, H. Chen, B. Zhu, STIM1 mediates hypoxia-driven hepatocarcinogenesis via interaction with HIF-1, Cell Rep. 12 (2015) 388–395.
[157] D.E. Clapham, L.W. Runnels, C. Strubing, The TRP ion channel family, Nat. Rev. Neurosci. 2 (2001) 387–396.
[158] D.E. Clapham, TRP channels as cellular sensors, Nature 426 (2003) 517–524.
[159] N. Nielsen, O. Lindemann, A. Schwab, TRP channels and STIM/ORAI proteins: sensors and effectors of cancer and stroma cell migration, Br. J. Pharmacol. 171 (2014) 5524–5540.
[160] N. Prevarskaya, L. Zhang, G. Barritt, TRP channels in cancer, Biochim. Biophys. Acta 1772 (2007) 937–946.
[161] B. Zeng, C. Yuan, X. Yang, S.L. Atkin, S.Z. Xu, TRPC channels and their splice variants are essential for promoting human ovarian cancer cell proliferation and tumorigenesis, Curr. Cancer Drug Targets 13 (2013) 103–116.
[162] X. Liu, J. Zou, J. Su, Y. Lu, J. Zhang, L. Li, F. Yin, Downregulation of transient receptor potential cation channel, subfamily C, member 1 contributes to drug resistance and high histological grade in ovarian cancer, Int. J. Oncol. 48 (2016) 243–252.
[163] N. Jaber, Z. Dou, R.Z. Lin, J. Zhang, W.X. Zong, Mammalian PIK3C3/VPS34: the key to autophagic processing in liver and heart, Autophagy 8 (2012) 707–708.
[164] F. Yin, X. Liu, D. Li, Q. Wang, W. Zhang, L. Li, Bioinformatic analysis of chemokine (C-C motif) ligand 21 and SPARC-like protein 1 revealing their associations with drug resistance in ovarian cancer, Int. J. Oncol. 42 (2013) 1305–1316.
[165] J. Wang, G.S. Wu, Role of autophagy in cisplatin resistance in ovarian cancer cells, J. Biol. Chem. 289 (2014) 17163–17173.
[166] S.L. Yang, Q. Cao, K.C. Zhou, Y.J. Feng, Y.Z. Wang, Transient receptor potential channel C3 contributes to the progression of human ovarian cancer, Oncogene 28 (2009) 1320–1328.
[167] V. Lehen'kyi, M. Flourakis, R. Skryma, N. Prevarskaya, TRPV6 channel controls prostate cancer cell proliferation via Ca(2+)/NFAT-dependent pathways, Oncogene 26 (2007) 7380–7385.
[168] W. Li, S.L. Zhang, N. Wang, B.B. Zhang, M. Li, Blockade of T-type Ca(2+) channels inhibits human ovarian cancer cell proliferation, Cancer Invest. 29 (2011) 339–346.
[169] I. Mertens-Walker, C. Bolitho, R.C. Baxter, D.J. Marsh, Gonadotropin-induced ovarian cancer cell migration and proliferation require extracellular signal-regulated kinase 1/2 activation regulated by calcium and protein kinase C{delta}, Endocr. Relat. Cancer 17 (2010) 335–349.
[170] M. Oeggerli, Y. Tian, C. Ruiz, B. Wijker, G. Sauter, E. Obermann, U. Guth, I. Zlobec, M. Sausbier, K. Kunzelmann, L. Bubendorf, Role of KCNMA1 in breast cancer, PLoS One 7 (2012) e41664.
[171] H. Zhao, E. Guo, T. Hu, Q. Sun, J. Wu, X. Lin, D. Luo, C. Sun, C. Wang, B. Zhou, N. Li, M. Xia, H. Lu, L. Meng, X. Xu, J. Hu, D. Ma, G. Chen, T. Zhu, KCNN4 and S100A14 act as predictors of recurrence in optimally debulked patients with serous ovarian cancer, Oncotarget 7 (2016) 43924–43938.

[172] X. Liu, L. Wei, B. Zhao, X. Cai, C. Dong, F. Yin, Low expression of KCNN3 may affect drug resistance in ovarian cancer, Mol. Med. Rep. 18 (2018) 1377–1386.
[173] L. Robles-Martinez, E. Garay, M.G. Martel-Gallegos, A. Cisneros-Mejorado, D. Perez-Montiel, A. Lara, R.O. Arellano, Kca3.1 activation via P2y2 purinergic receptors promotes human ovarian Cancer cell (Skov-3) migration, Sci. Rep. 7 (2017) 4340.
[174] E.L. Christie, D.D.L. Bowtell, Acquired chemotherapy resistance in ovarian cancer, Ann. Oncol. 28 (2017) viii13–viii15.
[175] G. Corrado, V. Salutari, E. Palluzzi, M.G. Distefano, G. Scambia, G. Ferrandina, Optimizing treatment in recurrent epithelial ovarian cancer, Expert Rev. Anticancer Ther. 17 (2017) 1147–1158.
[176] I.U. Khan, R.U. Khan, H. Asif, Khalid S.H. Alamgeer, S. Asghar, M. Saleem, K.U. Shah, S.U. Shah, S.A.A. Rizvi, Y. Shahzad, Co-delivery strategies to overcome multidrug resistance in ovarian cancer, Int. J. Pharm. 533 (2017) 111–124.
[177] F. Tomao, C. Marchetti, A. Romito, A. Di Pinto, V. Di Donato, O. Capri, I. Palaia, M. Monti, L. Muzii, P. Benedetti Panici, Overcoming platinum resistance in ovarian cancer treatment: from clinical practice to emerging chemical therapies, Expert Opin. Pharmacother. 18 (2017) 1443–1455.
[178] B. Dziegielewska, E.V. Casarez, W.Z. Yang, L.S. Gray, J. Dziegielewski, J.K. Slack-Davis, T-type Ca2+ channel inhibition sensitizes ovarian Cancer to carboplatin, Mol. Cancer Ther. 15 (2016) 460–470.
[179] P. Samuel, R.C. Pink, D.P. Caley, J.M. Currie, S.A. Brooks, D.R. Carter, Over-expression of miR-31 or loss of KCNMA1 leads to increased cisplatin resistance in ovarian cancer cells, Tumour Biol. 37 (2016) 2565–2573.
[180] M.L. Bonnefond, R. Florent, S. Lenoir, B. Lambert, E. Abeilard, F. Giffard, M.H. Louis, N. Elie, M. Briand, D. Vivien, L. Poulain, P. Gauduchon, M. N'Diaye, Inhibition of store-operated channels by carboxyamidotriazole sensitizes ovarian carcinoma cells to anti-BclxL strategies through Mcl-1 down-regulation, Oncotarget 9 (2018) 33896–33911.
[181] L. Pelzl, Z. Hosseinzadeh, K. Alzoubi, T. Al-Maghout, S. Schmidt, C. Stournaras, F. Lang, Impact of Na+/Ca2+ exchangers on therapy resistance of ovary carcinoma cells, Cell. Physiol. Biochem. 37 (2015) 1857–1868.
[182] Y.C. Yung, N.C. Stoddard, J. Chun, LPA receptor signaling: pharmacology, physiology, and pathophysiology, J. Lipid Res. 55 (2014) 1192–1214.
[183] X. Fang, D. Gaudette, T. Furui, M. Mao, V. Estrella, A. Eder, T. Pustilnik, T. Sasagawa, R. Lapushin, S. Yu, R.B. Jaffe, J.R. Wiener, J.R. Erickson, G.B. Mills, Lysophospholipid growth factors in the initiation, progression, metastases, and management of ovarian cancer, Ann. N. Y. Acad. Sci. 905 (2000) 188–208.
[184] E.K. Kim, J.M. Ha, Y.W. Kim, S.Y. Jin, H.K. Ha, S.S. Bae, Inhibitory role of polyunsaturated fatty acids on lysophosphatidic acid-induced cancer cell migration and adhesion, FEBS Lett. 588 (2014) 2971–2977.
[185] T. Gudermann, T. Hofmann, M. Mederos y Schnitzler, A. Dietrich, Activation, subunit composition and physiological relevance of DAG-sensitive TRPC proteins, Novartis Found. Symp. 258 (2004) 103–118 discussion 118-22, 155-9, 263-6.
[186] J.A. Rosado, S.O. Sage, Protein kinase C activates non-capacitative calcium entry in human platelets, J. Physiol. (Paris) 529 (Pt 1) (2000) 159–169.
[187] X. Zhang, M. Gueguinou, M. Trebak, Store-Independent Orai Channels Regulated by STIM, (2018), pp. 197–214.
[188] H. Zhang, L. Zhou, W. Shi, N. Song, K. Yu, Y. Gu, A mechanism underlying the effects of polyunsaturated fatty acids on breast cancer, Int. J. Mol. Med. 30 (2012) 487–494.
[189] A. Fiorio Pla, H.L. Ong, K.T. Cheng, A. Brossa, B. Bussolati, T. Lockwich, B. Paria, L. Munaron, I.S. Ambudkar, TRPV4 mediates tumor-derived endothelial cell migration via arachidonic acid-activated actin remodeling, Oncogene 31 (2012) 200–212.
[190] P. Goswamee, T. Pounardjian, D.R. Giovannucci, Arachidonic acid-induced Ca (2+) entry and migration in a neuroendocrine cancer cell line, Cancer Cell Int. 18 (2018) 30.
[191] C. Dubois, F. Vanden Abeele, V. Lehen'kyi, D. Gkika, B. Guarmit, G. Lepage, C. Slomianny, A.S. Borowiec, G. Bidaux, M. Benahmed, Y. Shuba, N. Prevarskaya, Remodeling of channel-forming ORAI proteins determines an oncogenic switch in prostate cancer, Cancer Cell 26 (2014) 19–32.
[192] J.L. Tanyi, A.J. Morris, J.K. Wolf, X. Fang, Y. Hasegawa, R. Lapushin, N. Auersperg, Y.J. Sigal, R.A. Newman, E.A. Felix, E.N. Atkinson, G.B. Mills, The human lipid phosphate phosphatase-3 decreases the growth, survival, and tumorigenesis of ovarian cancer cells: validation of the lysophosphatidic acid signaling cascade as a target for therapy in ovarian cancer, Cancer Res. 63 (2003) 1073–1082.
[193] T. Yamada, K. Sato, M. Komachi, E. Malchinkhuu, M. Tobo, T. Kimura, A. Kuwabara, Y. Yanagita, T. Ikeya, Y. Tanahashi, T. Ogawa, S. Ohwada, Y. Morishita, H. Ohta, D.S. Im, K. Tamoto, H. Tomura, F. Okajima, Lysophosphatidic acid (LPA) in malignant ascites stimulates motility of human pancreatic cancer cells through LPA1, J. Biol. Chem. 279 (2004) 6595–6605.
[194] T.E. Crane, B.R. Khulpateea, D.S. Alberts, K. Basen-Engquist, C.A. Thomson, Dietary intake and ovarian cancer risk: a systematic review, Cancer Epidemiol. Biomarkers Prev. 23 (2014) 255–273.
[195] H. Kemilainen, K. Huhtinen, A. Auranen, O. Carpen, L. Strauss, M. Poutanen, The expression of HSD17B12 is associated with COX-2 expression and is increased in high-grade epithelial ovarian Cancer, Oncology 94 (2018) 233–242.