Association of lipid metabolism with ovarian cancer

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ABSTRACT

Defects in lipid metabolism have been found to be linked to several diseases, among which atherosclerosis, hypertension, obesity, and diabetes are the most important. Although cancer is chiefly a genetic disease, dietary lipid intake and metabolism are related to some cancer risks, including the risk for ovarian cancer. Higher intake of dietary lipids, systemic lipid metabolism malfunction, and abnormal serum lipid levels are somehow related to ovarian cancer. Overexpression of some lipid metabolic enzymes are also found in ovarian cancer. In this review article, we summarize the relationships between lipid intake, lipid metabolism, and ovarian cancer.

KEY WORDS

Ovarian cancer, lipids, metabolism, cholesterol, fatty acid synthase, phospholipids

1. INTRODUCTION

Lipids are the major macromolecules essential for various biologic functions, including energy production, signalling, and cell growth and division. Defects in lipid metabolism are associated with several diseases, among which atherosclerosis, hypertension, obesity, diabetes, and cancer are the most important [1]. Among the factors that contribute to the appearance of cancer, diet has a fundamental role, and lipids are the main components that have been related to increases in the incidence of cancerous diseases, particularly breast, colorectal, ovarian, and prostate cancers [2]. Data from animal studies have shown that some lipids have different effects on cancer risk than do others; for example, the omega-6 family of unsaturated fatty acids enhances tumour growth, whereas the omega-3 family delays or reduces tumour development [3].

Cholesterol in tissue and blood has consistently been found to have a prime role in the pathogenesis of coronary artery disease, but an association of cholesterol with cancers such as colorectal and breast cancer and leukemia has also been reported [4,5]. The cholesterol content of cell membranes is tightly regulated, and this process of regulation involves the uptake of cholesterol-rich low-density lipoprotein (LDL). However, interestingly, cholesterol accumulation has been reported in various solid tumours, especially oral and prostate cancers [6,7]. In addition, cholesterol metabolism is dysregulated in many malignancies, including myeloid leukemia and lung and breast cancers [7–10]. Although a high level of serum triglycerides (TGS) does not appear to be mechanically involved in the development of most cancers, reduction of serum TGS and intensive surveillance with total colonoscopy in colon cancer may have benefit in men with hypertriglyceridemia [11]. An association between high serum TGS and colon cancer has also been reported by McKeown–Eyssen [12].

Among the lipids, the phospholipids are probably the ones most frequently and significantly reported to be associated with cancer. Since the year 2000, elevations in phosphocholine and total choline-containing compounds have been observed in almost every type of cancer studied with nuclear magnetic resonance spectroscopy [13–15]. Fatty acid synthase (FAS), a key enzyme in the synthesis of long-chain fatty acids, has been found to be overexpressed in breast and prostate cancers relative to its expression in adjacent normal tissue [16]. That finding supported the role of FAS as a prostate cancer oncogene in the presence of androgen receptor and the oncogenic effect exerted by FAS in inhibiting the intrinsic pathway of apoptosis [17]. Recently, Nomura *et al.* [18] showed that the enzyme monoacylglycerol lipase (MAGL) is highly expressed in aggressive human cancer cells and primary tumours, in which it regulates a fatty acid network enriched in oncogenic signalling lipids that promote migration, invasion, survival, and *in vivo* tumour growth. Overexpression of MAGL in nonaggressive cancer cells reconstitutes this fatty acid network and increases cell phenotypes of pathogenicity that are reversed by a MAGL inhibitor.

Ovarian cancer is a neoplastic growth arising from various parts of the ovary, mainly the outer lining and the Fallopian tube. Ovarian cancer is the fifth leading cause of death from cancer in women and the

leading cause of gynecologic cancer death [19]. Dietary lipids, malfunctions of systemic lipid metabolism, and abnormal serum lipid profiles are all associated with ovarian cancer in multiple ways.

2. DIETARY LIPIDS AND THEIR METABOLISM IN OVARIAN CANCER

Several case–control and cohort studies have found positive associations between ovarian cancer and an intake of foods with high levels of saturated fats or cholesterol, such as red meat, eggs, and dairy products [20–22]. Pan *et al.* [23] reported that ovarian cancer risk is positively associated with higher consumption of dietary cholesterol and eggs, and inversely associated with a higher intake of vegetables overall and of cruciferous vegetables and with supplementation of vitamin E, beta-carotene, and vitamin B complex. High consumption of fats may increase circulating estrogen levels, thus increasing the possibility of cell damage and proliferation that is responsible for cancerous growth [24]. Risch *et al.* [19] suggested that dietary cholesterol may influence the risk of ovarian cancer through elevated circulating estrogen or progesterone. The repeated rupture of the follicle associated with ovulation is believed to expose the ovarian epithelium to hormones in the surrounding fluid; high estrogen concentrations may increase the likelihood of tumour development [25]. However, Bertone *et al.* [24] found that the association of fat-rich food intake and ovarian cancer risk was not significant, although an increase in risk with frequent intake of eggs was observed. A weakly positive, but nonlinear association was observed for saturated fat intake and ovarian cancer risk in an Italian case–control study [26] in which intake of monounsaturated and polyunsaturated fatty acids was inversely correlated with ovarian cancer.

Numerous investigations have demonstrated altered systemic lipid metabolism in cancer patients and aberrant lipid utilization by tumour cells. The most common measure of altered systemic lipid metabolism in these individuals is hyperlipidemia. In a study by Taylor *et al.* [27] of peritoneal fluid from ovarian cancer patients and control subjects, isolation and analysis of lipids revealed four consistently altered lipid parameters in the cancer patients: elevated monoglycerides, diglycerides, and free fatty acids, and decreased triacylglycerides. Memon *et al.* [28] found an inverse relationship between total serum cholesterol and increased incidence of ovarian tumours in pre- and postmenopausal Pakistani women. In another study [29], oxidized LDL in serum was found to be higher in breast and ovarian cancer patients than in control subjects, but total cholesterol and high-density lipoprotein showed no such association. One nested case–control study in the United States found that women with a higher serum cholesterol level had an increased risk of ovarian cancer as compared with women who had a lower cholesterol level [30]. A study by Pirozzo *et al.* [31] reported that cholesterol from eggs was associated with an increased risk of ovarian cancer, but that cholesterol from other sources was not. Those authors suggested that the association was not with the cholesterol in the eggs, speculating that it could be with the highly lipophilic organochlorine residues. However, an involvement of LDL with cancer was also supported by a recent study in which phytosterol and stanol consumption reduced blood levels of LDL cholesterol and lowered not only cancer risk but also cardiovascular disease risk [32].

A clear correlation between TG metabolism and ovarian cancer has not yet been reported. Li *et al.* [33] reported elevated TG levels (32%) in ovarian cancer patients, but previously, Ostroumova *et al.* [34] reported lower TG levels.

3. LIPID METABOLISM IN OVARIAN CANCER

Various lipid metabolic pathways, especially those involving fatty acid biosynthesis, and phospholipids and their enzyme systems, have been found to be involved in ovarian cancer.

3.1 Fatty Acid Synthase

High levels of FAS expression have been found in ovarian cancer patients [35]. In hormone-dependent endometrial cells, FAS expression is part of the estrogen-driven cellular response that leads to proliferation [36]. Also, together with neoplastic stage, FAS is regarded as a reliable predictor of recurrence and disease-free survival in common epithelial ovarian tumours [37].

Increased FAS activity plays an active role in cancer evolution by regulating oncogenic proteins closely related to malignant transformation. Fatty acid synthase–dependent signalling regulates the expression, activity, and cellular localization of the human epidermal growth factor receptor 2 [HER2 (cErbB-2)] oncogene in ovarian cancer cells [38]. It was suggested that HER2 plays a role as a cellular energy sensor in the response of tumour cells to a non-genotoxic metabolic stress (such as a perturbation of FAS-dependent endogenous fatty acid biosynthesis), thus offering a rationale for the therapeutic targeting of FAS in HER2-overexpressing carcinomas [38].

Selective FAS inhibition activates adenosine monophosphate–activated protein kinase (AMPK) in ovarian cancer cells, inducing cytotoxicity while sparing most normal human tissues from the pleiotropic effects of AMPK activation [39]. Thus, FAS has become a target for anticancer therapy.

Xenograft studies suggest that FAS inhibition is not substantially toxic to normal tissues. Using a novel small-molecule FAS inhibitor, FAS 31, in preliminary toxicity studies, Meskini *et al.* [40] reported that no observable toxicity to normal tissues occurred in rat or mouse.

3.2 Phospholipids

Alterations of choline phospholipid metabolism have been reported in ovarian cancer [41], a finding that also supported the involvement of FAS in ovarian cancer. Because the drop in the level of phosphatidylcholine (59%) was significantly correlated with a drop in *de novo* synthesized fatty acid levels, phosphatidylcholine was identified as a potential noninvasive magnetic resonance spectroscopy–detectable biomarker of FAS inhibition *in vivo* [42]. Phospholipids have been found to be involved in ovarian cancer in several forms, including lysophosphatidic acid (LPA), phospholipase A2 (PLA2), phospholipase D (PLD), and autotoxin (ATX), among others.

3.2.1 Lysophosphatidic Acid

The LPAS, with their various fatty acid side chains, are the constituents of a growth-stimulating factor—ovarian cancer activating factor—that has been identified from ascites in patients with ovarian cancer [43]. As a bioactive compound, LPA induces cell proliferation or differentiation, prevents apoptosis induced by stress or stimuli, induces platelet aggregation and smooth muscle contraction, and stimulates cell morphology changes, cell adhesion, and cell migration. It thus is involved in a broad range of biologic processes in a variety of cellular systems [44,45]. As an established mitogen, LPA also promotes the invasiveness of hepatoma cells into monolayers of mesothelial cells, and it stimulates proliferation of ovarian and breast cancer cell lines even in the absence of other growth promoters such as serum. Furthermore, LPA stimulates rapid neurite retraction and rounding of the cell body in serum-deprived neuroblastoma cells [46], and it plays a critical role in regulation of gene expression in normal and neoplastic cells. It is a potent modulator of the expression of genes involved in inflammation, angiogenesis, and carcinogenesis such as interleukin 6 [47], interleukin 8 [47,48], vascular endothelial growth factor (VEGF) [49], urokinase plasminogen activator [50], and cyclooxygenase-2 [51], among others. Thus LPA may contribute to cancer progression by triggering expression of those target genes, resulting in a more invasive and metastatic microenvironment for tumour cells [47,52]. A significant increase in the expression of LPA receptors (LPA_2 and LPA_3) with VEGF was found by Fujita *et al.* [53], who suggested that LPA receptors might be involved in VEGF expression mediated by LPA signals in human ovarian oncogenesis. The recent identification of the metabolizing enzymes that mediate the degradation and production of LPA and the development of receptor selective-analogs has opened a potential new approach to the treatment of ovarian cancer [54]. Lysophosphatidic acid also stimulated VEGF expression independent of hypoxia-inducible factor 1, promoting tumour angiogenesis by activation of the c-Myc and Sp-1 transcription factors [55].

3.2.2 Phospholipase A2

The PLA2 enzyme has been implicated in the activation of cell migration and the production of LPA in ovarian carcinoma cells [56]. Autonomous replication and growth-factor-stimulated proliferation of ovarian cancer cells are highly sensitive to inhibition of calcium-independent PLA2 (iPLA2), but are refractory to inhibition of cytosolic PLA2 [56]. Activation of iPLA2 plays a critical role in cell migration, which is involved in many important biologic processes such as development, the immunologic and inflammatory responses, and tumour biology [56]. When ovarian cancer cells were grown under growth-factor-independent conditions, suppression of iPLA2 activity led to an accumulation of cell populations in both the S and the G2/M-phases [57]. Supplementation with exogenous growth factors such as LPA and epidermal growth factor in culture released the S-phase arrest, but did not affect the G2/M arrest associated with inhibition of iPLA2. In addition to the prominent effect on the cell cycle, inhibition of iPLA2 also induced weak-to-modest increases in apoptosis [57]. Downregulation of iPLA2β with lentivirus-mediated RNA interference targeting iPLA2β expression inhibited cell proliferation in culture and decreased tumorigenicity of ovarian cancer cell lines in athymic nude mice [57].

3.2.3 Phospholipase D

In ovarian cancer cells, PLD is involved in the formation of phosphatidic acid (PA), which is a source of LPA [58]. It was suggested that PLD is also involved in cancer progression and metastasis: elevated PLD expression has been reported in various cancer tissues [58]. Moreover, PLD was found to stimulate cell protrusions in v-Src–transformed cells [59]. Furthermore, PLD activity was elevated by the integrin receptor signalling pathway in OVCAR-3 cells, and PLD block was found to inhibit integrin-mediated Rac translocation in, and the spreading and migration of, OVCAR-3 cells [60]. Thus, the PLD-PA-Rac pathway plays an important role in the metastasis of cancer cells, and it might provide a means for integrin and PLD-mediated cancer metastasis [60].

3.2.4 Autotaxin

The ATX protein is a member of the ectonucleotide pyrophosphatase and phosphodiesterase family of enzymes, but unlike other members of this group, ATX possesses lysophospholipase D activity. This enzymatic activity hydrolyzes lysophosphatidylcholine (LPC) to generate the potent tumour growth factor and mitogen LPA. Exogenous addition of VEGFA to cultured cells induces ATX expression and secretion, resulting in increased extracellular LPA production [61]. This elevated LPA, acting through LPA_4, modulates VEGF responsiveness by inducing VEGF receptor 2 expression. Downregulation by antisense morpholino oligomers of ATX secretion in SKOV3 cells significantly attenuates cell motility responses to VEGF, ATX, LPA, and

LPC [61]. Through their respective G protein–coupled receptors, LPC and LPA have both been reported to stimulate migration [62]. By itself, LPC was unable to stimulate the migration of either cell type; ATX had to be present. Knocking down ATX secretion, or inhibiting its catalytic activity, blocked cell migration by preventing lysophosphatidate production and the subsequent activation of LPA receptors [62].

4. SUMMARY

As is the case for most complicated diseases, lipid intake and defective lipid metabolism are somehow involved in cancer. Ovarian cancer is the most dangerous disease of the female reproductive system, and so understanding its pathophysiology and therapeutics is a major concern. More and more research is being focused in this field to evaluate the appropriate dietary status of lipids, to manipulate lipid metabolism in the quest for a better life without ovarian cancer, and to discover new therapeutic strategies. More specifically, FAS, LPA, and ATX should receive closer scrutiny. Targeting FAS, LPAS, LPA receptors, and the enzymes of LPA metabolism may be the future of successful cancer therapy—especially ATX, which may be a novel target for cancer therapy because blockage of this enzyme inhibits LPA production.

5. REFERENCES

1. Nelson DL, Cox MM. Bioenergetics and metabolism. In: Lehninger AL, Nelson DL, Cox MM, eds. *Lehninger Principles of Biochemistry.* 3rd ed. New York: Worth Publishers; 2000: 598–619,770–814.
2. Granados S, Quiles JL, Gil A, Ramírez–Tortosa MC. Dietary lipids and cancer [Spanish]. *Nutr Hosp* 2006;21:42–52.
3. Araki E. Dietary lipid intake and cancer [Japanese]. *Bull Saitama Prefectural Univ* 2000;1:89–97.
4. Halton JM, Nazir DJ, McQueen MJ, Barr RD. Blood lipid profiles in children with acute lymphoblastic leukemia. *Cancer* 1998;83:379–84.
5. Simo CE, Orti LA, Sena FF, Contreras BE. Blood cholesterol in patients with cancer [Spanish]. *An Med Interna* 1998;15:363–6.
6. Freeman MR, Solomon KR. Cholesterol and prostate cancer. *J Cell Biochem* 2004;91:54–69.
7. Kolanjiappan K, Ramachandran CR, Manoharan S. Biochemical changes in tumor tissues of oral cancer patients. *Clin Biochem* 2003;36:61–5.
8. Li HY, Appelbaum FR, Willman CL, Zager RA, Banker DE. Cholesterol-modulating agents kill acute myeloid leukemia cells and sensitize them to therapeutics by blocking adaptive cholesterol responses. *Blood* 2003;101:3628–34.
9. Duncan RE, El-Sohemy A, Archer MC. Mevalonate promotes the growth of tumors derived from human cancer cells *in vivo* and stimulates proliferation *in vitro* with enhanced cyclin-dependent kinase-2 activity. *J Biol Chem* 2004;279:33079–84.
10. El-Sohemy A, Archer MC. Inhibition of *N*-methyl-*N*-nitrosourea- and 7,12-dimethylbenz[*a*]anthracene–induced rat mammary tumorigenesis by dietary cholesterol is independent of Ha-Ras mutations. *Carcinogenesis* 2000;21:827–31.
11. Tabuchi M, Kitayama J, Nagawa H. Hypertriglyceridemia is positively correlated with the development of colorectal tubular adenoma in Japanese men. *World J Gastroenterol* 2006;12:1261–4.
12. McKeown–Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 1994;3:687–95.
13. Daly PF, Lyon RC, Faustino PJ, Cohen JS. Phospholipid metabolism in cancer cells monitored by ^{31}P NMR spectroscopy. *J Biol Chem* 1987;262:14875–8.
14. Ackerstaff E, Glunde K, Bhujwalla ZM. Choline phospholipid metabolism: a target in cancer cells? *J Cell Biochem* 2003;90:525–33.
15. Glunde K, Ackerstaff E, Mori N, Jacobs MA, Bhujwalla ZM. Choline phospholipid metabolism in cancer: consequences for molecular pharmaceutical interventions. *Mol Pharm* 2006;3:496–506.
16. Kuhajda FP. Fatty acid synthase and cancer: new application of an old pathway. *Cancer Res* 2006;66:5977–80.
17. Migita T, Ruiz S, Fornari A, Fiorentino M, Priolo C, Zadra G. Fatty acid synthase: a metabolic enzyme and candidate oncogene in prostate cancer. *J Natl Cancer Inst* 2009;101:519–32.
18. Nomura DK, Long JZ, Niessen S, Hoover HS, Ng SW, Cravatt BF. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* 2010;140:49–61.
19. Risch HA, Jain M, Marrett LD, Howe GR. Dietary fat intake and risk of epithelial ovarian cancer. *J Natl Cancer Inst* 1994;86:1409–15.
20. Kushi LH, Mink PJ, Folsom AR, *et al.* Prospective study of diet and ovarian cancer. *Am J Epidemiol* 1999;149:21–31.
21. La Vecchia C, Decarli A, Negri E, *et al.* Dietary factors and the risk of epithelial ovarian cancer. *J Natl Cancer Inst* 1987;79:663–9.
22. Knekt P, Steineck G, Jarvinen R, Hakulinen T, Aromaa A. Intake of fried meat and risk of cancer: a follow-up study in Finland. *Int J Cancer* 1994;59:756–60.
23. Pan SY, Ugnat AM, Mao Y, Wen SW, Jhonson KC. A case–control study of diet and the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:1522–7.
24. Bertone ER, Rosner BA, Hunter DJ, *et al.* Dietary fat intake and ovarian cancer in a cohort of US women. *Am J Epidemiol* 2002;156:22–31.
25. Hill MJ, Goddard P, Williams RE. Gut bacteria and aetiology of cancer of the breast. *Lancet* 1971;2:472–3.
26. Bidoli E, La Vecchia C, Montella M, *et al.* Nutrient intake and ovarian cancer: an Italian case–control study. *Cancer Causes Control* 2002;13:255–61.
27. Taylor CG, Doering DL, Kraemer FB, Taylor DD. Aberrations in normal systemic lipid metabolism in ovarian cancer patients. *Gynecol Oncol* 1996;60:35–41.
28. Memon NQ, Memon JQ, Khan AW. Serum cholesterol levels and incidence of ovarian tumours in Pakistani women. *Pak J Physiol* 2007;3:23–5.
29. Delimaris I, Faviou E, Antonakos G, Stathopoulou E, Zachari A, Dionyssiou–Asteriou A. Oxidized LDL, serum oxidizability and serum lipid levels in patients with breast or ovarian cancer. *Clin Biochem* 2007;40:1129–34.

30. Helzlsouer KJ, Alberg AJ, Norkus EP, Morris JS, Hoffman SC, Comstock GW. Prospective study of serum micronutrients and ovarian cancer. *J Natl Cancer Inst* 1996;88:32–7.
31. Pirozzo S, Purdie D, Kuiper–Linley M, *et al.* Ovarian cancer, cholesterol, and eggs: a case-control analysis. *Cancer Epidemiol Biomarkers Prev* 2002;11:1112–14.
32. Woyengo TA, Ramprasath VR, Jones PJ. Anticancer effects of phytosterols. *Eur J Clin Nutr* 2009;63:813–20.
33. Li AJ, Elmore RG, Chen IY, Karlan BY. Serum low-density lipoprotein levels correlate with survival in advanced stage epithelial ovarian cancers. *Gynecol Oncol* 2010;116:78–81.
34. Ostroumova MN, Kovalenko IG, Bershtein LM, Tsyrlina EV, Dil'man VM. Characteristics of dyslipidemia in cancer patients [Russian]. *Vopr Onkol* 1986;32:34–43.
35. Gansler TS, Hardman W, Hunt DA, Schaffel S, Hennigar RA. Increased expression of fatty acid synthase (OA-519) in ovarian neoplasms predicts shorter survival. *Hum Pathol* 1997;28: 686–92.
36. Pizer ES, Lax SF, Kuhajda FP, Pasternack GR, Kurman RJ. Fatty acid synthase expression in endometrial carcinoma. *Cancer* 1998;83:528–37.
37. Alò PL, Visca P, Framarino ML, *et al.* Immunohistochemical study of fatty acid synthase in ovarian neoplasms. *Oncol Rep* 2000;7:1383–8.
38. Menendez JA, Vellon L, Mehmi I, *et al.* Inhibition of fatty acid synthase (FAS) suppresses HER2/*neu* (ErbB-2) oncogene overexpression in cancer cells. *Proc Natl Acad Sci U S A* 2004;101:10715–20.
39. Zhou W, Han WF, Landree LE, *et al.* Fatty acid synthase inhibition activates AMP-activated protein kinase in SKOV3 human ovarian cancer cells. *Cancer Res* 2007; 67:2964–71.
40. El Meskini R, Medghalchi SM, Vadlamudi A, *et al.* Fatty acid synthase inhibition for ovarian cancer. Presented at the 99th Annual Meeting of the American Association for Cancer Research; San Diego, CA; April 15, 2008. [Available online at: www.fasgen.com/Fatty-Acid-Synthase-Inhibition-for-Ovarian-Cancer.pdf; cited July 21, 2010]
41. Ricci A, Podo EIF. Alterations of choline phospholipid metabolism in ovarian tumor progression: a NMR study. *Biophy Bioeng Lett* 2008;1:1–8.
42. Ross J, Najjar AM, Sankaranarayanapillai M, Tong WP, Kaluarachchi K, Ronen SM. Fatty acid synthase inhibition results in a magnetic resonance-detectable drop in phosphocholine. *Mol Cancer Ther* 2008;7:2556–65.
43. Lu J, Xiao Y, Baudhuin LM, Hong G, Xu Y. Role of ether-linked lysophosphatidic acids in ovarian cancer cells. *J Lipid Res* 2002;43:463–76.
44. Moolenaar WH. Bioactive lysophospholipids and their G protein–coupled receptors. *Exp Cell Res* 1999;253:230–8.
45. Liscovitch M, Cantley LC. Lipid second messengers. *Cell* 1994;77:329–34.
46. Westermann AM, Havik E, Postma FR, *et al.* Malignant effusions contain lysophosphatidic acid (LPA)–like activity. *Ann Oncol* 1998;9:437–42.
47. Fang X, Yu S, Bast RC, *et al.* Mechanisms for lysophosphatidic acid-induced cytokine production in ovarian cancer cells. *J Biol Chem* 2004;279:9653–61.
48. Sivashanmugam P, Tang L, Daaka Y. Interleukin 6 mediates the lysophosphatidic acid–regulated cross-talk between stromal and epithelial prostate cancer cells. *J Biol Chem* 2004;279:21154–9.
49. Hu YL, Tee MK, Goetzl EJ, *et al.* Lysophosphatidic acid induction of vascular endothelial growth factor expression in human ovarian cancer cells. *J Natl Cancer Inst* 2001;93:762–8.
50. Pustilnik TB, Estrella V, Wiener JR, *et al.* Lysophosphatidic acid induces urokinase secretion by ovarian cancer cells. *Clin Cancer Res* 1999;5:3704–10.
51. Symowicz J, Adley BP, Woo MM, Auersperg N, Hudson LG, Stack MS. Cyclooxygenase-2 functions as a downstream mediator of lysophosphatidic acid to promote aggressive behavior in ovarian carcinoma cells. *Cancer Res* 2005;65:2234–42.
52. Oyesanya RA, Lee ZP, Wu J, *et al.* Transcriptional and post-transcriptional mechanisms for lysophosphatidic acid–induced cyclooxygenase-2 expression in ovarian cancer cells. *FASEB J* 2008;22:2639–51.
53. Fujita T, Miyamoto S, Onoyama I, Sonoda K, Mekada E, Nakano H. Expression of lysophosphatidic acid receptors and vascular endothelial growth factor mediating lysophosphatidic acid in the development of human ovarian cancer. *Cancer Lett* 2003;192:161–9.
54. Tanyi J, Rigó J Jr. Lysophosphatidic acid as a potential target for treatment and molecular diagnosis of epithelial ovarian cancers [Hungarian]. *Orv Hetil* 2009;150:1109–18.
55. Song Y, Wu J, Oyesanya RA, Lee Z, Mukherjee A, Fang X. Sp-1 and c-Myc mediate lysophosphatidic acid–induced expression of vascular endothelial growth factor in ovarian cancer cells via a hypoxia-inducible factor-1–independent mechanism. *Clin Cancer Res* 2009;15:492–501.
56. Zhao X, Wang D, Zhao Z, *et al.* Caspase-3–dependent activation of calcium-independent phospholipase A2 enhances cell migration in non-apoptotic ovarian cancer cells. *J Biol Chem* 2006;281:29357–68.
57. Song Y, Wilkins P, Hu W, *et al.* Inhibition of calcium-independent phospholipase A2 suppresses proliferation and tumorigenicity of ovarian carcinoma cells. *Biochem J* 2007;406:427–36.
58. Eder AM, Sasagawa T, Mao M, Aoki J, Mills GB. Constitutive and lysophosphatidic acid (LPA)–induced LPA production: role of phospholipase D and phospholipase A2. *Clin Cancer Res* 2000;6:2482–91.
59. Shen Y, Zheng Y, Foster DA. Phospholipase D2 stimulates cell protrusion in v-Src–transformed cells. *Biochem Biophys Res Commun* 2002;293:201–6.
60. Chae YC, Kim JH, Kim KL, *et al.* Phospholipase D activity regulates integrin-mediated cell spreading and migration by inducing GTP–Rac translocation to the plasma membrane. *Mol Biol Cell* 2008;19:3111–23.
61. Ptaszynska MM, Pendrak ML, Bandle RW, Stracke ML, Roberts DD. Positive feedback between vascular endothelial growth factor-A and autotaxin in ovarian cancer cells. *Mol Cancer Res* 2008;6:352–63.
62. Gaetano CG, Samadi N, Tomsig JL, Macdonald TL, Lynch KR, Brindley DN. Inhibition of autotaxin production or activity blocks lysophosphatidylcholine-induced migration of human breast cancer and melanoma cells. *Mol Carcinog* 2009;48:801–9.

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