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The role of lipids and fatty acid metabolism in the development of prostate cancer

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The reprogramming of lipid metabolism and signaling pathways is the central aspect of cancer biology. It is hypothesized that tumor cells can alter the lipid spectrum in order to fulfill their metabolic requirements. Furthermore, they can alter potential tumors and suppressive mechanisms in which lipids' involvement is essential. Recently, more attentions have been given on the alteration of lipid metabolism during prostate cancer development, and investigations have shown unique regulation of "*de novo*" lipid synthesis in cancer cells. Cancer cells often use newer pathways and enzymes to simplify the synthesis of fatty acids, and the newly synthesized lipids affect cellular processes, which impacts cancer cell proliferation and survival outcomes. Herein, we aimed to study the influence of lipid profile alterations on the development of prostate cancer. We found that the total amounts of lipids and phospholipids were increased within tissues from men with the malignant prostate tumor as compared with the benign prostate tissue. Significant changes were also observed in the composition of saturated and unsaturated fatty acids within the malignant tumor tissues. Intensification of lipid peroxidation has also been observed in malignant prostate tumors compared to benign prostate tumors. Collectively, these findings further highlights the fact that lipid and fatty acids play unique regulatory roles in the cellular development of prostate malignant transformation.

Keywords: Analytical assessments, *De novo* synthesis, Free fatty acids, Lipids, Metabolism, Peroxidation, Phospholipids, Prostate cancer

Lipids are the source of energy and one of the basic building blocks for all living cells. According to recent studies, alterations in the lipid spectrum and their metabolism play significant role(s) in cancer development[1,2]. The cancerous cells may alter the lipid profile in order to satisfy their metabolic requirements. They can also affect the potential tumors' suppressor mechanisms, in which lipids are also involved[3]. Notably, by controlling the lipid metabolism, it is possible to induce (as well as inhibit) the tumor progression[4]. Besides, the lipids also contribute in the tumor cell proliferation and metastasis[5]. Nowadays, the lipid alterations and reprogramming of the signaling pathways are considered as critical aspects for cancer biology[6]. Recent studies also suggest that lipid alterations contribute towards prostate cancer development[7].

Notably, in prostate tumors, the unique regulation of the *de novo* lipid synthesis occurs by tumor cells. The process is caused by changes in lipid metabolism, during which tumor cells use alternative pathways and enzymes to simplify the synthesis of fatty acids. Newly synthesized lipids can induce some specific cellular processes in order to enhance proliferation and survival of tumor cells. Epidemiological studies have shown thatdietary fats can also provoke prostate cancer development[8]. However, the given pathology is caused by dietary fats or "*de novo*" synthesized lipids, remains still unknown. The studies however suggest that fatty acids are involved in numerous metabolic processes during prostate carcinogenesis. According to some authors, this could be due to the presence or absence of double bonds in the fatty acid molecules[8]. The investigation indicates the high concentrations of palmitic acid in patients with prostate cancer, proliferative mastopathy and breast cancer, *etc*.[9,10]. Notably, in the cell membrane, an abnormal amount of terminal carbonic acids reduces membrane permeability and viscosity. As a result, the intercellular adhesion forces are also reduced, thereby promoting tumor cell migration and dissemination[11].

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Furthermore, saturated fatty acids play essential role(s) in the proliferation of cancerous cells. Previous study suggested that this could be due to several reasons: the ability of saturated fatty acids to inhibit the activity of anti-oncogene - P53 (tumor suppressor gene)[12] alter the induction of P21 (a cyclin-dependent kinase inhibitor), which plays a vital role in developing cellular response regarding DNA damage[12]. As for unsaturated fatty acids and their metabolites, besides their characteristic function, they are significant mediators and modulators in the process of transmitting intracellular signals that are involved in oxidative metabolism and alter the gene expression mechanism[13]. They act as ligands for specific nuclear receptors[14]. Unsaturated fatty acids can also bind the peroxisomal transcription factors [*e.g.*, peroxisome proliferator- activated receptor gamma (PPAR-γ)], which play crucial role(s) in lipid homeostasis[15,16].

Herein, our research work aimed to investigate potential alterations/differences in the lipids and fatty acid metabolism in prostatic tissues (benign versus malignant) to demonstrate their contribution towards prostate cancer development. We primarily investigated the total amount of tissues' (prostate benign and malignant) lipids and the levels of phospholipids in the total lipids. We also evaluated the changes in the spectrum of free fatty acids and the lipid peroxidation intensity within the prostatice tumor tissues.

Material and Methods

Samples

In the present study, we collected sample from men with benign and malignant prostate tumors (15 cases in each group). The age of all subjects ranged from 60-75 years in each group. The disease status and clinicalstage of the subjects was determined based on the rectal, histomorphological, and ultrasound examinations of the prostate gland at the A. Tsulukidze Urology National Center, Tbilisi, Georgia. The study was approved by the National Council on Bioethics of Georgia and written informed consent was obtained from all subjects.

Methods

The tumor tissues were homogenized in a chloroform-methanol mixture. The total amount of lipids and phospholipids in total lipids were determined by using the Kates method from tissue homogenates[17]. The analysis of fatty acids was performed using high-performance liquid chromatography (HPLC)[18]. We determined the lipid peroxidation levels according to the method described by Uchiyama and Mihara[19].

The obtained data were analyzed using the statistical methods by MINITAB (Basic Statistic), and *P* value of ≤0.05 was considered statistically significant.

Results and Discussion

In the first stage of the study,total amount of lipids in the benign and malignant tumor tissues of the prostate was evaluated. We observed the total amount of lipids in the prostate tissues with adenocarcinoma was elevated (≈1.5 times) as compared to the benign prostatic tissues (Table 1). We found that level of phospholipids in the total amount of lipids was also elevated (≈1.65 times) within the malignant tumors as compared with the benign tumors (Table 1).

According to our previous studies, there was a sharp increase in the total amount of lipids, phospholipids, and fatty acids in the blood and erythrocytes within prostate adenocarcinoma compared to the control group[20,21] (Table 2).

These results can be explained with the following potential mechanisms: changes in lipid metabolismand altered regulation of the metabolism[1] by mobilizing the body's fat deposits during malignant growth[12], and also the alterations in hormonal balance[8], leading towards the development of prostate tumors. As noted earlier, one of the characteristic features of malignant tumor isthe intensification of lipid biosynthesis[8]. Previous study suggest that the mentioned fact may be due to the hyper-expression of sterol-regulatory protein within the malignant tissue cells, which controls the activity of genes that encode important enzymes involved in the biosynthesis of fatty acids, such as the enzyme, fatty acid synthase (FAS)[22]. The study indicated that this multifunctional enzyme complex (*i.e.*, FAS) is highly expressedin

Table 1 — Comparative assessments of the total amount of lipids, total amount of phospholipids and the intensity of lipid peroxidation within the prostate tumors' tissues.

Study parameters	Benign prostatic hyperplasia	Adenocarcinoma of the prostate
Total amount of lipids (mg/100 mg per tissue)	0.75±0.25	1.13±0.09
Amount of total phospholipids (mg/mg lipid)	0.38±0.19	0.63±0.02
Intensity of lipid peroxidation (μM/mL per 1 mg protein)	0.3±0.15	0.6±0.12

n=15, number of patients in each study group; $P< 0.05$; The age range of the patients 60-75 years.

Table 2 — A comparative evaluation ofthe total amount of lipids, amounts of phospholipids, and individual fatty acids in blood and erythrocytes of the men with prostate tumors

Study parameters	Control group	Benign prostatic hyperplasia	Adenocarcinoma of the prostate
Total blood lipids (dry weight in mg per mL, in the blood)	3.32	3.57	3.8
Blood total phospholipids (dry weight in mg per mL, in the blood)	1.6	1.3	2.2
Total amount of phospholipids in the erythrocyte membrane (dry weight in mg 1 mL, in erythrocytes)	0.35	0.5	0.9
Stearic acid (C18: 0) (mg%, in blood plasma)	208.7±5.6	176.6±4.0	249.0±4.1
Linolenic acid (C18:3) (mg%, in blood plasma)	516.6±3.4	632.0±4.8	693.0±4.4
Arachidonic acid (C20:0) (mg%, in blood plasma)	351.2±1.2	383.2±1.6	383.8±0.9

n=15, number of patients in each study group; $P< 0.05$; The age range of the patients 60-75 years

many types of human solid tumors, including prostate cancer[22]. Taken this into consideration, we suggest that the increase in FAS enzyme activity and the involvement of newer pathways of lipid metabolism in prostate cancer cells should increase the amount of total lipids and phospholipids in the total lipid mass compared to the benign tumor.

It is to be noted that androgens may also significantly affect the process of lipid biogenesis in cells[8]. Literature suggests that activation of lipid synthesis facilitates the androgen signal[8], which is also confirmed by our data[20,21]. The androgens activate androgen receptors by activating the sterol regulatory element-binding protein (SREBP)-1C-dependent multifunctional enzyme complex (*i.e.*, FAS) thereby enhancing lipid synthesis within the malignant cells[8]. Moreover, altering the amount of lipids in tumor tissue is also significantly affected by the developed oxidative stress and lipid peroxidation[23]. We also examined the intensity of lipid peroxidation within tissues of prostate tumors and found that there was 2-fold increase in the intensity of lipid peroxidation in the tumor tissue with prostate adenocarcinoma patients as compared with the benign prostatic hyperplasia (Table 1).

Several possiblemechanisms are suggested for the activation of lipid peroxidation within prostate malignant tumor tissue. Recent studies have demonstrated that the process of energy transformation in normal prostate epithelial cells is specific, particularly in the normal prostate cells, the energy is generated in the epithelium by glycolysis[24]. During tumor growth, epithelial cells switch from glycolysis (ineffective system) to oxidative phosphorylation (effective system),while most of the tumor processes (for example in breast cancer, uterine tumors, *etc.*) are characterized by reverse energy transformation[24]. An increase in Krebs cycle activity in the prostate malignant epithelial cells may cause increased electron production for the mitochondrial electron transport chain. Thus, the probability of transferring the electrons directly to oxygen increases, which leads to the formation of large amounts of reactive oxygen species (ROS)[25]. Considering the fact that prostate epithelial cells are not adapted to ROS and free radicals, it becomes clearer that during prostate malignant transformation free radical processes within the prostate epithelial cells have greater significance compared to other malignant tumors. Thus, the formation and/or accumulation of ROS must be followed by the intensification of lipid peroxidation, which is confirmed by our studies (Table 1).

Additionally, it is also known that oxidative stress in tumor cells leads to enhanced lipogenesis[22,26]. Notably, the oxidative stress activates the multifunctional enzyme complex-FAS in an SREBP-1C-dependent pathway[22]. Moreover, the main reason for the activation of lipid peroxidation process can also be the development of oxidative stress in tumor cells on the background of reduced activities of antioxidant systems[25]. Lipids, and particularly phospholipids, contain a wide spectrum of biomolecules with unique structures due to the fatty acids and the length of their chains, also the number of double bonds, the variety of bond locations, and the chain structure[1].

Our goal was to investigate the alterations in the spectrum of free fatty acids in prostate tumor tissues (benign and malignant) asfatty acids are involved in numerous biochemical processes within tumors[9,15,26]. To achieve this goal, we studied free unsaturated and saturated fatty acids, particularly assessed the levels

of following individual saturated fatty acids: lauric (C12:0), myristic (C14: 0), palmitic (C16: 0) and stearic (C18: 0) acids. Also, for unsaturated fatty acids the following individual fatty acid levels were evaluated: oleic (C18: 1), linoleic (C18: 2), linolenic (C18: 3), arachidonic (C20: 0), eicosanoid (C22: 0), and lignoceric acids (C24: 0).

Our analyses showed that the individual fatty acids were decreased within prostate malignant tissues as compared to a benign tumor in the following order: lauricacid (C12: 0) (~ 2.56 times), myristicacid (C14: 0) (~ 8.7 times), palmiticacid (C16: 0) (~ 2.76 times), and stearic acids (C18: 0) (~1.97 times) (Fig. 1).

In case of prostate malignant tissue, decreased levels of saturated fatty acids in the total amount of free fatty acids may be due to the replacement of unsaturated membrane fatty acids with saturated fatty acids on the basis of enhanced lipid peroxidation[23]. Epithelial cells of malignant prostate tissues are characterized with a different energy metabolism compared with benign prostate tissue[24]. As noted earlier, this metabolic alteration also causes numerous changes within the malignant prostate tumors, including increase in the number of mitochondria in cancer cells[27]. Interestingly, outer and inner membranes of the mitochondria are mostly composed of phospholipids rich in saturated fatty acids[8]. It is therefore suggested that the decrease in free saturated fatty acids in malignant tumor tissues compared to benign tumor may be due to an increase in the number of mitochondria, which should lead to decrease of saturated fatty acids portion in total amount of free fatty acids.

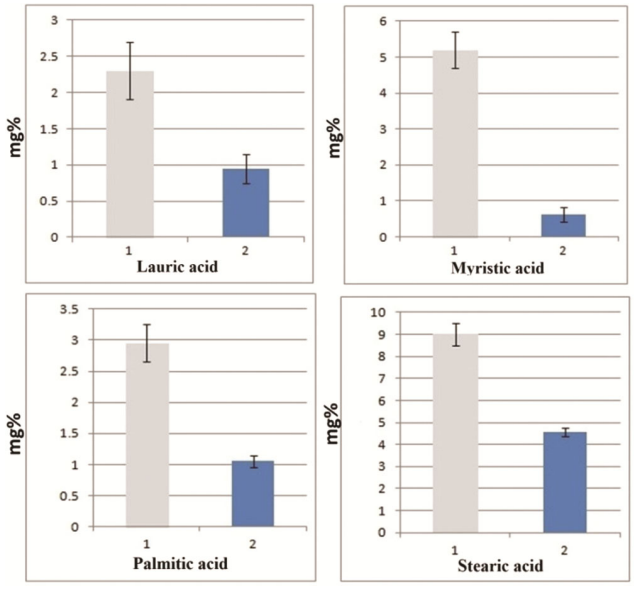

Fig. 1 — A comparative representation of the total amount of *"individual"*free saturated fatty acids in the total amount of free fatty acids in the tumor tissue of men with prostate cancer (mg/%). 1. Benign prostatic hyperplasia; 2. Adenocarcinoma of the prostate

Generally, tumor tissue is characterized by overexpression of FAS[26], and the activity of FAS directly correlates with protein palmitoylation and myristoylation[28].

It is hypothesized that these types of protein lipid modifications play crucial role(s) in the mechanism of receptor signal transmission in the cell[28]. Moreover, palmitoylation and myristoylation reactions play essential roles in the regulation of transmembrane transport of solutes as well as in the implemention of some signaling pathways such as WNt/β-catenin pathways[28]. It is well known that intensity of this signal pathway is an oncogenic factor during the development of prostate cancer, hepatocarcinoma, and melanoma as well[8].

We speculate that the reduced levels of myristic and palmitic acids inprostate adenocarcinoma cases may also be due to the activation of this signaling pathway and involvement of these fatty acids in protein lipid modification reactions, whichshould also cause a decrease in saturated fatty acids in the total amount of free fatty acids inprostate malignant tissues (Table 3).

In the next stage of our study, we investigated the quantitative alteration of free unsaturated fatty acids in the total amount of fatty acids within benign and malignant prostate tumor tissues. We found that the total amount of free unsaturated fatty acids was lowered significantly (~1.9 times) within malignant prostate tissue compared to benign tumor tissue (Table 3). A significant decrease in the level of unsaturated fatty acids in the total amount of free fatty acids should be caused by a change in the amount of separate unsaturated fatty acids. Consequently, we investigated the amount of individual unsaturated fatty acids within the prostate tumor tissues, which

Table 3 — Comparative determination of the levels of free saturated and unsaturated fatty acids in prostate tumors.

Study parameters	Benign prostatic hyperplasia	Adenocarcinoma of the prostate
Total amount of free saturated fatty acids (mg/%)	19.5±3.5	7.19±2.8
Total amount of free unsaturated fatty acids (mg/%)	35.03±4.5	18.42±3.8

n=15, number of patients in each study group; $P< 0.05$; The age range of the patients: 60-75 years.

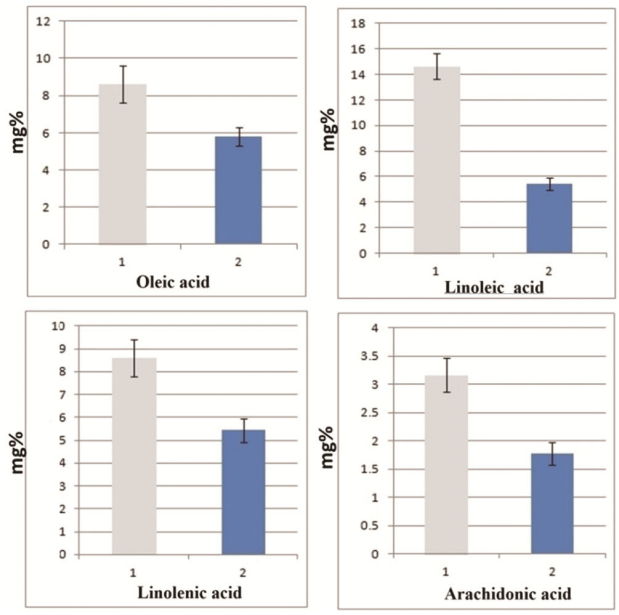

Fig. 2 A comparative demonstration of the levels of *"individual"*unsaturated fatty acids in the total amount of free fatty acids (mg/%). 1. Benign prostatic hyperplasia; 2. Adenocarcinoma of the prostate

demonstrated sharp decreased levels within the prostate malignant tumor tissues as compared to the benign tissue samples (in the following order): oleic acid (C18: 1) (~1.5 times), linoleic acid (C18: 2) (~2.7 times), linolenic acid (C18: 3) (~ 1.58 times), and arachidonicacids (C20: 0) (~ 1.78-fold) (Fig. 2).

We speculate that numerous factors may be contributing to the observed decreased amount of individual unsaturated fatty acids in the total free fatty acids within malignant prostate tissue. One such factors can be the 'intensification' of lipid peroxidation, and consequently the enhanced peroxidation of unsaturated fatty acid. Moreover, unsaturated fatty acids and their metabolites such as arachidonic acid (C20:4ω6) and its metabolites (prostaglandins and leukotrienes) play significant synergistic role(s) in the malignant transformation of prostate[29].

In numerous malignancies of epithelial tissues (such as neuroblastoma and embryonic tumors), increased activity of cyclooxygenase-2 has been demonstrated. It is known that these enzymes are involved in the synthesis of prostaglandins from unsaturated fatty acids. It is regarded that increased activity of this enzyme is directly associated with the processes such as cell proliferation, tumor invasion, angiogenesis, metastasis, and immunosuppression[30]. Enhanced metabolism of arachidonic acid via 5-lipoxygenase pathwayhas also been observed in cases of other epithelial malignancies (*i.e*., malignancies of colon, esophagus, lungs, and breast, *etc*.)[31,32]. If we consider that prostate cancer belongs to malignancies of the epithelial origin, there is a high probability that the activity of the given enzyme can also be increased within the malignant tumor tissue of the prostate.An increased activity of the enzyme should lead to the activation/enhancement of unsaturated fatty acid metabolism by lipoxygenase pathway, which should cause reduction in the amount of unsaturated fatty acids[6]. The alterations in the amount of single fatty acids (unsaturated and saturated) indicates a qualitative change within the membrane lipid pool and in general within the lipid spectrum of the tumor tissue cells, significantly altering the structure andfunctional status of membrane[1].

We therefore highlight that the given alterations within lipid profile may be due to the unique regulation of *de novo* lipid synthesis by prostate cancer cells. Thus, these changes can be considered as a precondition for prostate malignant transformation.

Conclusion

Based on the data obtained from our research investigations it can be concluded that: i) alterations in the lipid metabolism regulation takes place within the prostate cancer cells that may be caused by the mobilization of newer fatty acid depots; ii) enhancement of lipogenesis occurs, which is induced by oxidative stress within the prostate malignant cells; and iii) reduction in the levels of individual fatty acids (saturated and unsaturated) in prostate malignant tissue, is a valid indicator for a qualitative alterations in lipid composition of plasma membrane and within the general lipid profile of prostate malignant tissue cells.

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Conflict of interest

All authors declare no conflicts of interest.

References

1 Beloribi-Djefaflia S, Vasseur S & Guillaumond F, Lipid metabolic reprogramming in cancer cells. *Oncogenesis*, 5 (2016) e189.

2 Long J, Zhang CJ, Zhu N, Du K, Yin YF, Tan X, Liao DF & Qin L, Lipid metabolism and carcinogenesis, cancer development. *Am J Cancer Res*, 8 (2018) 778.

3 Wu X, Qin L, Fako V & Zhang JT, Molecular mechanisms of fatty acid synthase (FASN)-mediated

resistance to anti-cancer treatments. *Adv Biol Regul*, 54 (2014) 214.
4 Lim JY & Kwan HY, Roles of lipids in cancer. In (Ed.): *Advances in Lipid Metabolism.* (Intech Open) (018.
5 Luo X, Zhao X, Cheng C, Li N, Liu Y & Cao Y, The implications of signaling lipids in cancer metastasis. *Exp Mol Med*, 50 (2018) 1.
6 Yi M, Li J, Chen S, Cai J, Ban Y, Peng Q, Zhou Y, Zeng Z, Peng S, Li X, Xiong W, Li G & Xiang B, Emerging role of lipid metabolism alterations in cancer stem cells. *J Exp Clin Cancer Res*, 37 (2019) 118.
7 Dang Q, Chen YA & Hsieh JT, The dysfunctional lipids in prostate cancer. *Am J Clin Exp Urol*, 7 (2019) 273.
8 Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, Meyskens FL Jr, Goodman GE, Minasian LM, Parnes HL, Klein EA & Kristal AR, Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst*, 105 (2013) 1132.
9 Thors L, Bergh A, Persson E, Hammarsten P, Stattin P, Egevad L, Granfors T & Fowler CJ, Fatty acid amide hydrolase in prostate cancer: Association with disease severity and outcome, CB1 receptor expression and regulation by IL-4. *PLoS One*, 5 (2010) e12275.
10 Shannon J, King IB, Lampe JW, Gao DL, Ray RM, Lin MG, Stalsberg H & Thomas DB, Erythrocyte fatty acids and risk of proliferative and non-proliferative fibrocystic disease in women in Shanghai, China. *Am J Clin Nutr*, 89 (2009) 265.
11 Hilvo M, Denkert C, Lehtinen L, Müller B, Brockmöller S, Seppänen-Laakso T, Budczies J, Bucher E, Yetukuri L, Castillo S, Berg E, Nygren H, Sysi-Aho M, Griffin JL, Fiehn O, Loibl S, Richter-Ehrenstein C, Radke C, Hyötyläinen T, Kallioniemi O, Oresic M, Novel theranostic opportunities offered by characterization of altered membrane lipid metabolism in breast cancer progression. *Cancer Res*, 71 (2011) 3236.
12 Zeng L, Wu GZ, Goh KJ, Lee YM, Ng CC, You AB, Wang J, Jia D, Hao A, Yu Q & Li, B, Saturated fatty acids modulate cell response to DNA damage: Implication for their role in tumorigenesis. *PLoS One*, 3 (2008) e2329.
13 Yu XH, Ren XH, Liang XH & Tang YL, Roles of fatty acid metabolism in tumourigenesis: Beyond providing nutrition. *Mol Med Rep*, 18 (2018), 5307.
14 Wang X, Lin H & Gu Y, Multiple roles of dihomo-γ-linolenic acid against proliferation diseases. *Lipids Health Dis*, 11 (2012) 25.
15 Uray IP, Rodenberg JM, Bissonnette RP, Brown PH & Mancini MA, Cancer-preventive rexinoid modulates neutral lipid contents of mammary epithelial cells through a peroxisome proliferator-activated receptor γ-dependent mechanism. *Mol Pharmacol*, 81 (2012) 228.
16 Moore RG, Lange TS, Robinson K, Kim KK, Uzun A, Horan TC, Kawar N, Yano N, Chu SR, Mao Q, Brard L, DePaepe ME, Padbury JF, Arnold LA, Brodsky A, Shen TL & Singh RK, Efficacy of a non-hypercalcemic vitamin-D2 derived anti-cancer agent (MT19c) and inhibition of fatty acid synthesis in an ovarian cancer xenograft model. *PLoS One*, 7 (2012) e34443.
17 Hawthorne JN, Techniques of lipidology: Isolation, analysis,and identification of lipids (2nd Revised Ed.). KATES MORRIS. *Biochem Soc Trans*, 16 (1988) 906.
18 Fanali S, Haddad PR, Poole C, Schoenmakers P& Lloyd D (Editors), *Liquid chromatography: Fundamentals and Instrumentation* (Handbooks in Separation Science, 1st Ed., USA, Elsevier) 2013, 520.
19 Uchiyama M & Mihara M, Determination of malondialdehyde precursor in tissues by thiobarbituric acid test. *Anal Biochem*, 78 (1978) 271.
20 Tchelidze M, The study of alterations in physical and chemical characteristics of the blood of the men with prostate benign hyperplasia and prostate adenocarcinoma, PhD Thesis, Ivane Javakhishvili Tbilisi State University, Tbilisi, (1999).
21 Botchorishvili I, The study of the structural and physical-chemical properties of the blood lipids and proteins in the men with prostate tumors, PhD Thesis. Ivane Javakhishvili Tbilisi State University, Tbilisi, (2004).
22 Gelebart P, Zak Z, Anand M, Belch A & Lai R, Blockade of fatty acid synthase triggers significant apoptosis in mantle cell lymphoma. *PLoS One*, 7 (2012) e33738.
23 Koltai T, Nelfinavir and other protease inhibitors in cancer: Mechanisms involved in anticancer activity. *F1000 Res*, 4 (2015) 9.
24 Lima AR, Bastos M, Carvalho M & Guedes de Pinho P, Biomarker discovery in human prostate cancer: An update in metabolomics studies. *Transl Oncol*, 9 (2016) 357.
25 Han C, Wang Z, Xu Y, Chen S, Han Y, Li L, Wang M & Jin X, Roles of reactive oxygen species in biological behaviors of prostate cancer. *BioMed Res Int*, 2020 (2020) 1269624.
26 Buszewska-Forajta M, Pomastowski P, Monedeiro F, Walczak-Skierska J, Markuszewski M, Matuszewski M, Markuszewski MJ & Buszewski B, Lipidomics as a diagnostic tool for prostate cancer.*Cancers*, 13 (2021) 2000.
27 Grupp K, Jedrzejewska K, Tsourlakis MC, Koop C, Wilczak W, Adam M, Quaas A, Sauter G, Simon R, Izbicki JR, Graefen M, Huland H, Schlomm T, Minner S & Steurer S, High mitochondria content is associated with prostate cancer disease progression. *Mol Cancer*, 12 (2013) 145.
28 Yang Y, Wnt signaling in development and disease. *Cell Biosci*, 2 (2012) 14.
29 Wang D & Dubois RN, Eicosanoids and cancer. *Nat Rev Cancer*, 10 (2010) 181.
30 Maione F, Oliaro-Bosso S, Meda C, Di Nicolantonio F, Bussolino F, Balliano G, Viola F & Giraudo E, The cholesterol biosynthesis enzyme oxidosqualene cyclase is a new target to impair tumour angiogenesis and metastasis dissemination. *Sci Rep*, 5 (2015) 9054.
31 Uto Y, Recent progress in the discovery and development of stearoyl CoA desaturase inhibitors. *Chem Phys Lipids*, 197 (2016), 3.
32 Mohammad N, Malvi P, Meena AS, Singh SV, Chaube B, Vannuruswamy G, Kulkarni MJ & Bhat MK, Cholesterol depletion by methyl-β-cyclodextrin augments tamoxifen induced cell death by enhancing its uptake in melanoma. *Mol Cancer*, 13 (2014) 204.