

Prospective Application of Lipidomics in Prostate Cancer

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Abstract

Lipidomics, a rapidly developing research field, has been widely studied in many non-cancer areas, and in some cancers. Taking prostate cancer as an example, this article has concisely reviewed applications of lipidomics in cancer research. Lipidomics is able to identify a few out of thousands individual lipid species in bio-fluids as biomarkers in diagnosis of prostate cancer with high sensitivity, specificity and accuracy. This technology has been also used in studying the pathogenesis of prostate cancer by combining data of lipid profiling with lipid metabolites and pathways strategy. Importantly, lipidomics can provide details of lipid compositions different between prostate cancer and benign prostate, which will greatly help to make strategy in prevention and treatment of prostate cancer.

Keywords: Lipid; Lipidomics; Prostate cancer; Biomarker

Introduction

Prostate cancer is a disease that affects men worldwide and places a medical and socioeconomic burden on modern society. Significant challenges remain in understanding the oncogenesis of prostate cancer, finding sensitive and specific methods for early diagnosis, and, in identifying effective interventions for prevention and treatment of prostate cancer. Lipidomics, a rapidly developing research field, is able to identify, quantify and profile thousands of individual lipid species at one time from a small specimen. Lipidomics is extremely sensitive technology; it can detect less abundant lipid species at pmol level [1]. With highly automated nanoLC-MS-based approach, the detecting sensitivity can reach to attomol level [2]. Lipidomics has been widely studied in many non-cancer areas, and in some cancers, such as in pancreatic adenocarcinoma, thyroid cancer, colon cancer, hepatocellular carcinoma, glioblastoma, [2-6] and prostate cancer [1,7,8]. Taking prostate cancer as an example, discussed here are the applications of lipidomics in cancer research.

Lipidomics in Diagnosis of Prostate Cancer

Turnover of lipids is accelerated in prostate cancer cells, in order to meet the needs of proliferating cells in building blocks for cellular membrane and other structures, and in signals transduction. Therefore, lipid profile, in the context of composition, configuration and quantity of individual species, groups and classes of lipids in prostate cancer cells must be distinguishable from that in normal prostate cells. Such a distinctive lipid profile could be reflected in the bio- fluids of patients with prostate cancer. Using shotgun lipidomics, Min et al. [7] performed qualitative and quantitative profiling of urinary phospholipids from urine samples of healthy patients ($p < 0.05$, with concentration changes of more than three-fold). Our group [1] performed lipid profiling of 390 individual apparent lipid species on 141 plasma samples (36 male controls, 105 patients with prostate cancer). Analyzing 390 apparent lipid species, 12 were identified as individual plasma lipid biomarkers useful in the diagnosis of prostate cancer. Each of these individual lipid species can be independently serve as a plasma lipid biomarker for the diagnosis of prostate cancer: its plasma concentration in patients is at least 10-fold higher than cutoff value of instruments and ≥ 2 -fold higher than in controls, with a sensitivity above 80%, specificity above 50%, and accuracy above 80%. When more than one of these identified lipid markers are combined, their diagnostic power dramatically increases. For example, if three lipid species, LPC(18:1), LPC(20:4) and PC(40:7) are used together, the combination would provide a sensitivity of 91.5%, specificity of 84.3% and accuracy (ROC area) of 95.9% in differentiating patients with prostate cancer from controls.

Based on reported diagnostic powers, minimal invasiveness in the collection of samples from patient urine and blood, and applicability in detection of a few lipid species in routine medical laboratory settings, the reported lipid biomarkers could easily become clinically useful as screening biomarkers in the early diagnosis of prostate cancer. Of course, further validation and clinical trials for these lipid markers are necessary before they can be used clinically. In the two studies mentioned above, the number of detected lipid species is less than four hundred, and most of these lipid species are polar lipids. Performing a global lipid profile including a wider range of lipid classes, groups, as well as their metabolites, such as free fatty acids, eicosanoids and their derivatives, could identify additional lipid markers useful for the diagnosis of prostate cancer.

Lipidomics in study of pathogenesis of prostate cancer classes are associated with the development of normal prostate and progression of prostate cancer. For example, the risk of prostate cancer is increased with elevations in particular plasma phospholipids and fatty acids, such as myristic acid, α -linolenic acid, and eicosapentaenoic acids. Decreases in total polyunsaturated fatty acids (PUFA), omega-3, arachidonic and steric acids, and increases in total monounsaturated fatty acids and oleic acid, are associated with chemical recurrence of prostate cancer [9,10]. Cholesterol relates to the incidence of prostate cancer, possibly through the formation of lipid rafts [10], which further activate the PI3K/Akt signaling pathway to drive tumor progression [11,12]. Due to the limits in technology and cost/effectiveness, previous studies are only able to focus on a few lipid species at one time or on the level of classes or groups collectively, such as total cholesterol, phospholipids, triacylglycerides (TAG), or ω -3/6 fatty acids. Lipidomics provides a unique opportunity to detect, both quantitatively and qualitatively, numerous individual lipid species in parallel, which informs us as to which individual lipid species contribute to an overall increase of total cholesterol, phospholipids, TAG, or ω -3/6 fatty acids, etc. Lipid profiles provide useful information to determining the metabolic pathways of altered lipids in prostate cancer. In our previous studies, we found that the concentrations of all 14 detected lysophosphatidylcholine species

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are higher in both plasma and prostatic samples from patients with prostate cancer, as compared with samples from controls. Further, we found that expression level of secretory phospholipase A2 (sPLA2) is increased in cancerous prostate as compared with benign prostate, which may contribute to the accumulation of lysophospholipid species in cancer tissues and in plasma (data not published). Meanwhile, we also found that the expression level of lysophospholipid acyltransferase 1 (LPCAT1) is significantly higher in cancerous prostate as compared with benign prostate. Elevated expression of LPCAT1 also correlated with prostate cancer pathologic grade and clinical chemical recurrence in prostate cancer [13]. Taken together, cycle: tumor cells upregulate the expressions of both sPLA2 (which generate adequate lysophospholipid species, substrates for LPCAT1) and LPCAT1, in order to secure de novo synthesis of various phospholipid species for building cellular membranes of newly proliferated cancer cells. By combining data of lipid profiles in individual species, cluster, group and class of lipids with lipid MAPS, more lipid metabolic pathways critical to prostate cancer could be identified. Approaches have been developed to profile the lipidomes in subcellular compartments, such as in mitochondria, lipid drops, etc. Llorente et al. [8] performed sophisticated shotgun and targeted molecular lipidomic assays on a metastatic prostate cancer cell line, PC-3 cells, in order to provide an in-depth analysis of the lipidomes of these cells and their released exosomes. This study, based on the quantification of approximately 280 molecular lipid species, found that exosomes released from PC-3 cells show a remarkable enrichment of glycosphingolipids, sphingomyelin, cholesterol, and phosphatidylserine, as compared with their parent cells. Such advances in lipidomics could revolutionize biochemical analysis of structure diversity and functional complexity of lipids in prostate cancer in the near future. In addition, combining all -omics techniques, such as proteomics, glycomics and gene arrays, lipidomics could be very useful tool in unraveling the nature of prostate cancer, as well other cancers.

Lipidomics in exploration of preventive and therapeutic interventions of prostate cancer Research to date suggests that prostatic growth is influenced by dietary fatty acids with concurrent variation in the expression of androgen receptor and peroxisome proliferator activated receptor gamma (PPAR- γ). PPAR- γ might be the link between diet and prostate growth, and, AR expression and function. Since the levels of testosterone are altered, it is also possible that prostatic changes are secondary to the systemic effects of the diet [14]. Epidemiological and clinical studies suggest that TAG and low-density lipoprotein (LDL) are comorbid risk factors in both prostate cancer and cardiovascular diseases [15]. It is well-known that cardiovascular disease may be prevented by controlling the level of TAG, cholesterol and LDL, by diet, exercise and medication. Whether these findings imply that prostate cancer, as cardiovascular disease, is preventable needs further study. Actually, several lipid-lowering statins have been used in treatment of prostate cancer; however, the outcome remains controversial [16]. One of the major flaws in these studies on the association of prostate cancer with lipids is that they lack data as to normal control lipid profiles in benign and proliferative prostatic disease, as well as for malignant prostates. Instead, these investigations use systemic (plasma) lipid profiles or cell lines as surrogates for prostatic tissues. While research has progressed, there still remains a significant lack of research effort focused on global lipid profiles from benign prostate, proliferative prostatic diseases, and in prostate cancer, including both primary and metastatic disease. Only with such information, can specific strategies be developed for the prevention and treatment of prostate cancer through regulation of lipid intake and metabolism.

Our group is performing global lipid profiling of more than one thousand lipid species in benign prostate and prostate cancer. Preliminary data show that prostate cancer has higher concentrations of all lipid classes, including free fatty acids, total fatty acids, diacylglycerides (DAG), TAG, cholesterol-esters and polar lipids. It is specially noted that individual lipid species vary dramatically within a given lipid class, between patient ethnicities, and among pathological grades of prostate cancer. Taking total fatty acids as example, overall total fatty acids is 1.8-fold higher in cancer prostate than that in benign prostate (C/B ratio=1.8, $p=0.02$). However, the range of C/B ratio among 16 total fatty acid species is from -1.5 to 9.7-fold. One of ω -3 fatty acids (18:3n3a) in cancer prostate is 6.8-fold higher than that in benign prostate; however the difference is not statistically significant ($p=0.15$) because of obvious individual variations. Then 18:3n3a is stratified by race and analyzed. Results indicate that the difference in 18:3n3 is significant between cancer prostate and benign prostate in White population ($p=0.043$), but not in that of Black population ($p=0.37$). These results suggest that lipidomics can provide more detailed information of lipids in prevention and treatment of prostate cancer.

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