2 Applications of Lipidomics in Tumor Diagnosis and Therapy

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Abstract

Lipids have many critical biological functions in cancer. There are characteristic changes of lipid metabolism and metabolites in different physiological and pathological processes. Lipidomics is an emerging discipline of metabolomics for systematic analysis of lipids in organisms, tissues, or cells and the molecules that interact with them. With the development of new analytical techniques, especially the application and development of mass spectrometry techniques, the determination of lipids can be carried out quickly and accurately and has a high throughput. A large number of studies have shown that abnormal lipid metabolism is closely related to the occurrence and development of tumors. The application of lipidomics technology can reveal changes in lipids and relative abnormal metabolic pathways associated with tumors. Moreover, it shows a wide range of application prospects in the identification of tumor lipid biomarkers, early tumor diagnosis, and the discovery of antitumor drug targets. This chapter mainly introduces the application and development direction of lipidomics in the diagnosis and therapy of different tumors.

Keywords

Lipidomics · Lipid · Tumor · Diagnosis Therapy

Lipids are a class of essential biomolecules that are involved in many critical cellular processes. Because of their hydrophobicity, lipids are the main components of biofilms (Fig. 2.1). They are, therefore, the physical basis of all organisms because they provide the ability to separate organisms from the natural environment. Lipids not only provide energy for cells [1], but they are also involved in both extracellular and intracellular signaling processes in which lipids conduct signals and amplify regulatory cascade reactions.

Clinical lipidomics is a novel extension of lipidomics that investigates lipid profiles, pathways, and networks by characterizing and quantifying complete lipid molecules in patient cells, biopsy tissues, or body fluids. It is expected to be more stable during treatment, more sensitive to changes, and targeted to disease and to enable more efficient data analysis and more standardized measurements to meet clinical needs [2]. Lipidomics is projected to become a more critical method in clinical application and an important

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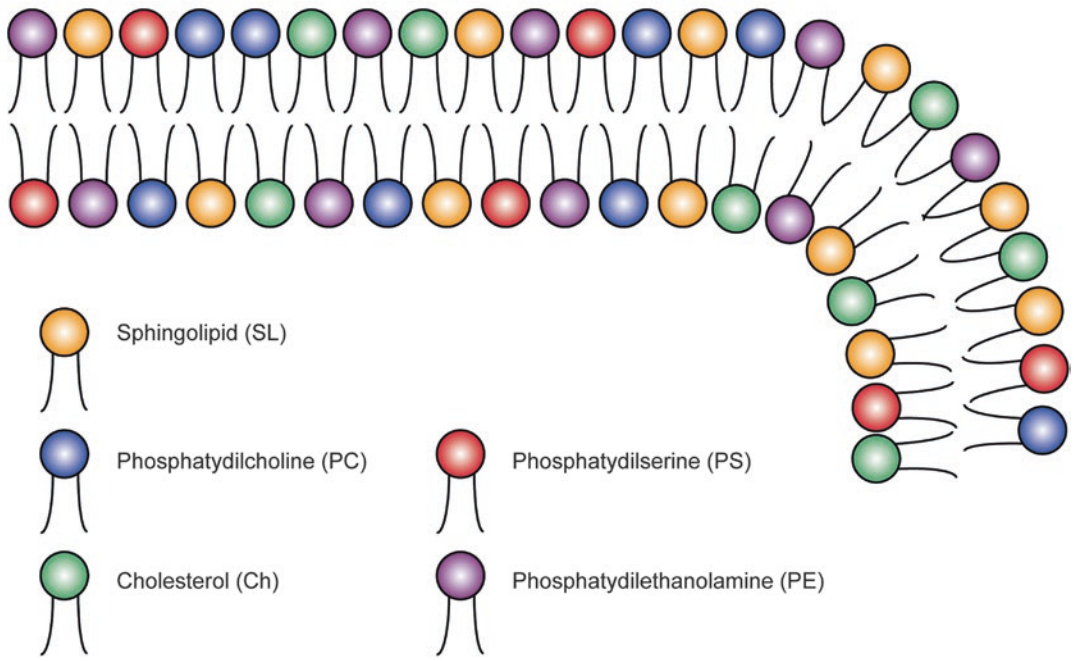

Fig. 2.1 Schematic representation of the cell membrane of phospholipids in the bilayer

tool for the early diagnosis and evaluation of disease progression of cancers (Fig. 2.2).

Because of the role of lipid molecules in cell structure, energy, and signal transduction, the characterization of cellular and extracellular lipid composition changes is critical for understanding cancer biology. Moreover, several mass spectrometry-based analyses and imaging studies have shown that lipid molecules may help enhance existing biochemical and histopathological approaches for cancer diagnosis, staging, and prognosis [3]. Therefore, the analysis of lipid metabolic changes associated with cancer cells and tumor tissues is useful for both basic and translational research. In the field of tumor lipidomics, scientists mainly focus on the applications in the diagnosis and treatment of tumors, which will be overviewed in this chapter.

2.1 Tumor Diagnosis

Lipids undergo subtle metabolic changes during the early stages of tumorigenesis. Accordingly, capturing the signals of the changes in these molecular profiles will greatly benefit the early diagnosis of cancer. Most clinical serum biomarkers for cancer detection were established in the early 1980s when the Nobel Prize in Physiology or Medicine was awarded for "discovering the principles of monoclonal antibody production." Using this "Nobel" technique, various monoclonal antibodies were developed, and the ligands on the surface of cancer cells were characterized. Abnormal sugar chain structures and abnormal sugar chain-associated glycoproteins have been identified as standard features of cancer cell surface through specific interactions with monoclonal antibodies. Subsequently, sugar-related biomarkers were detected in the serum of cancer patients and developed into serum biomarkers such as CA125, CA153, CA195, CA199, CA242, and CA724, which are popular in clinical use today [4].

Lipid metabolic reprogramming is an essential marker of tumorigenesis and development. Alterations in the tumor metabolism, including the accumulation of metabolites, lead to local immunosuppression of the tumor microenvironment. Hao et al. conducted a systematic analysis

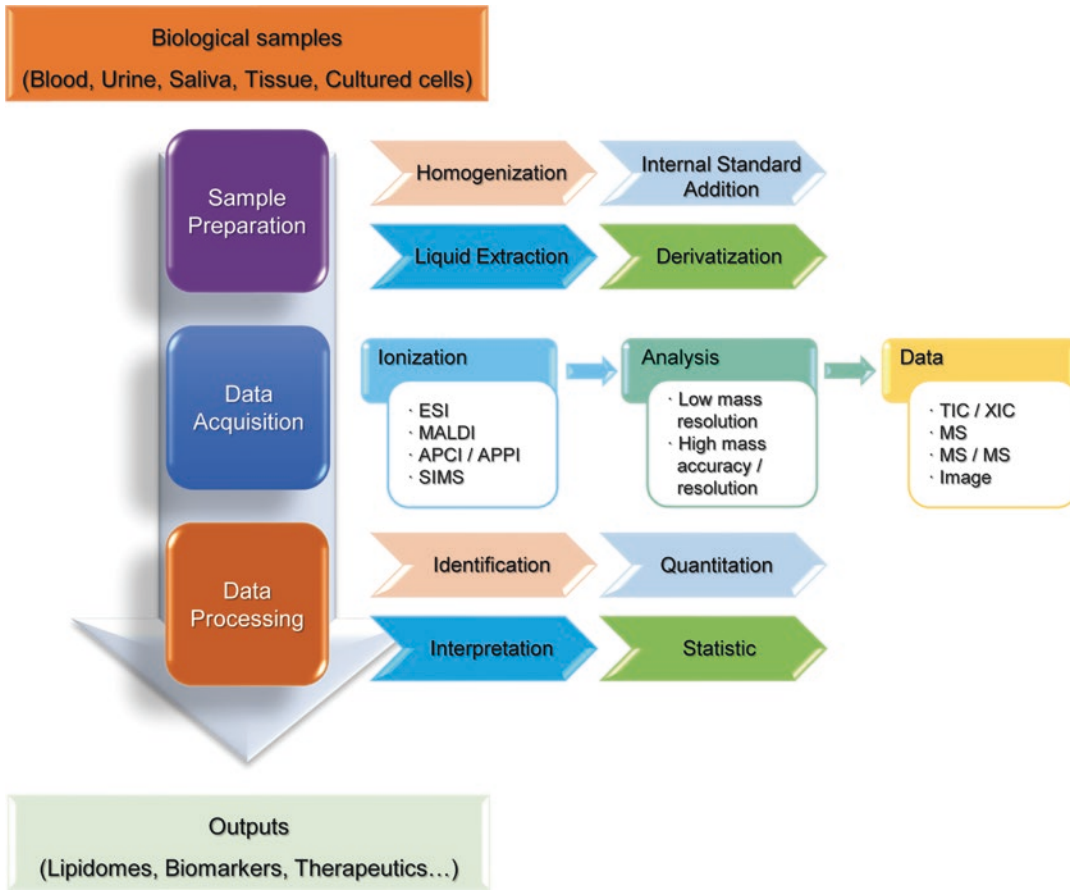

Fig. 2.2 Clinical lipidomics workflow, including all basic steps from samples to biological results

of The Cancer Genome Atlas (TCGA) multiple-omics data and found that the most widely altered lipid metabolic pathways in pan-cancer are fatty acid metabolism, arachidonic acid metabolism, cholesterol metabolism, and PPAR signaling [5].

Recent reports about lipidomics in tumor diagnosis have covered most organs of the human body, which will be discussed below (Fig. 2.3).

2.1.1 Lung Cancer

Lung cancer is the leading cause of cancer death worldwide [6]. Therefore, lipidomics studies are relatively centered on the diagnosis of lung cancer. Small-cell lung cancer (SCLC) is a type of aggressive lung cancer with low survival rates. Although kinases commonly play a crucial role in tumorigenesis, very few kinases are currently known to promote SCLC development. Cristea et al. reported that MEK5 and ERK5 are necessary for optimal survival and amplification of SCLC cell lines in vitro and in vivo. In-depth lipidomics analysis suggests that the loss of MEK5/ERK5 disrupts several lipid metabolic pathways, including the mevalonate pathway that controls cholesterol synthesis [7].

Preliminary data from recent studies suggest that lipid profiling has high specificity for evaluating the stage, severity, subtype, and drug response in lung cancer. The heterogeneity of lipid profiles and lipid metabolism may be part of the heterogeneity of lung cancer and leads to drug resistance [8]. Malignant pleural effusion (MPE) is an essential marker of advanced metastasis of lung cancer. However, current

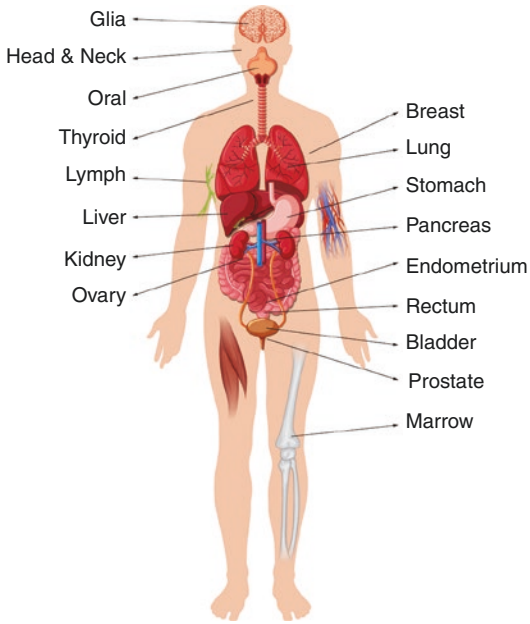

Fig. 2.3 Reported lipidomics diagnosis of human tumors (anatomy vector is from Vecteezy)

diagnostic methods entail a tedious process to distinguish between malignant pleural effusions and benign pleural effusions (BPE). Yang et al. conducted a global metabolomics and lipidomics analysis based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) to characterize the metabolic characteristics of lung cancer MPE and identify the potential metabolite biomarkers diagnostic of MPE. During MPE, 25 ether lipids, including phosphatidylcholine (PC), lysophosphatidylcholines (LPC), and phosphatidylethanolamine (PE), were significantly downregulated. This supported the diagnostic potential of the upregulated expression of oxidized polyunsaturated fatty acids (PUFAs) in MPE [9].

Noreldeen HAA et al. reported other lipidomics methods based on ultrahigh-performance liquid chromatography other than intended targets plus quadrupole time-of-flight mass spectrometry (UHPLCQ-TOF/MS). Two machine learning methods (genetic algorithm and binary logical regression) were also used to screen candidates for different lipids and to establish a combined lipid biomarker to distinguish between women with non-small-cell lung cancer (NSCLC) and healthy controls. The results showed that fatty acids (FA) (20:4), FA (22:0), and LPE (204) could be used as a combination biomarker to distinguish NSCLC from healthy tissues in women, with excellent sensitivity and specificity [10]. Klupczynska et al. conducted targeted lipid group screening to select potential molecules for the early detection of lung cancer. Of the lipids tested, there were significant differences between the PC group and the lysophosphatidylcholines (lysoPC) group in NSCLC patients and healthy controls, especially a C26:0; lysoPC a C26:1; PC aa C42:4; and PC aa C34:4 [11].

Yu et al. used MS to analyze the lipids of 390 individuals from 44 plasma samples obtained from the training lung cancer cohort. C18:2 cholesterol ester and sphingomyelin 22:0 as lipid markers were identified to be useful for distinguishing between squamous cell lung carcinoma (SqCC) patients and high-risk individuals, with 95.5% sensitivity, 90.9% specificity, and 95.2% accuracy [12]. Using UHPLCQ-TOF/MS through targeted lipid profiling, Chen et al. identified PCs and phosphatidylethanolamine (PEs) as biomarkers of early-stage NSCLC. The levels of PCs and PEs were abnormal during glycerophospholipid metabolism, which is the most altered pathway in early NSCLC [13].

2.1.2 Breast Cancer

Breast cancer (BC) is a heterogeneous malignancy. It is the most frequent malignancy and the leading cause of cancer-related death in American women. Compared with other major BC subtypes, triple-negative breast cancer has a lower survival rate and a higher metastasis rate, thus highlighting the need for more sensitive and specific methods for early-stage TNBC (ES-TNBC) detection. However, early diagnosis remains challenging because of the high pathological level, and thus the survival rate remains relatively low. Eghlimi et al. reported that LC-tandem MS can detect lipids with high specificity and sensitivity. Two diagnostic biomarker panels were proposed for TNBC/ES-TNBC [14]. Terao et al. evaluated all-trans retinoic acid (ATRA)-treated BC cell lines and found that ATRA disrupted the

homeostasis of many lipids, the most significant of which was in the mitochondrial intima and those involved in the oxidative phosphorylation of cardiac phospholipids. ATRA can reduce the level of cardiac phospholipid, and this can inhibit the growth activity of retinoid. ATRA exerts its antiproliferative activity by reducing tumor cell respiration and energy balance, thus its important role in breast cancer [15].

Kang et al. investigated the role of lipid metabolic alterations in malignant phenotypes of BC. They found significant homeostatic interference of various complex lipid substances (including ceramide, sphingomyelin, ether-linked phosphatidylcholine, and ether-linked phosphatidylethanolamine) in the mesenchymal state of cancer cells. The polyunsaturated fatty acid composition in spherical cells was significantly reduced, and SCD, ACOX3, and FADS1 were upregulated. Meanwhile, PTPLB, PECR, and ELOVL2 were downregulated. The ratio of C226n3 (docosahexaenoic acid, DHA) to C225n3 was significantly reduced in globular cells, like ELOVL2 downregulation. ELOVL2 expression is associated with a malignant phenotype and appears to be a novel prognostic biomarker in breast cancer [16]. Zhao et al. investigated the toxic effects of bisphenol F (bp F) in BC xenografts and the potential mechanisms for tumor metastasis-related tissues (e.g., in the liver and kidney). They found that BPF exposure disrupts the metabolic and lipid groups in the liver and kidney. Exposure induces reprogramming of glutathione (GSH) biosynthesis and glycolysis metabolism by activating glycine, serine, cysteine, glutamine, lactate, and pyruvate in the liver and kidney tissues. This also interferes with the biosynthesis and degradation of glycerol phospholipids (GPs) and glycerol phospholipids (GLs), resulting in abnormal renal tissue membrane homeostasis and cellular function [17].

Reprogramming of lipid metabolism is a hallmark of many cancers and has been shown to promote BC progression. Purwaha et al. showed that higher sphingomyelin levels were significantly associated with better disease-free survival in patients with TNBC [18]. LC-MS and environmental mass spectrometry imaging (MSI) have been shown to be robust and reproducible diagnostic techniques for BC. Silva et al. investigated whether the lipid features observed in cancer tissues via desorption electrospray ionization (DESI)-MSI correspond to those detected in LC-MS plasma samples. A comparison of the plasma and tissue lipid profiles suggests that each matrix studied (e.g., blood or tumor) has its particular molecular characteristics [19]. Nishida-Aoki et al. performed an extensive targeted quantitative lipid group analysis of cells and extracellular vesicles (EV) from high-metastatic and low-metastatic TNBC cell lines using supercritical fluid chromatography rapid scanning tripolar mass spectrometry. They confirmed that EV between different lipid components is associated not only with their origin cells but also with high- and low-metastatic cell lines. Moreover, compared with those of low-metastatic cells, the EV of high-metastatic BC cells accumulated unsaturated diacylglycerol (DGs) and did not increase in the cells. DG enrichment of EVs activates protein kinase D signaling pathways in endothelial cells, leading to angiogenesis stimulation [20].

2.1.3 Colorectal Cancer

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide. Reliable biomarkers for early CRC diagnosis are crucial for reducing mortality. Liu et al. used the combined lipid group method to study the differences in blood lipid profiles between 101 CRC patients and 52 healthy volunteers. A total of 11 lipid species, including glycerophosphoethanolamine, ethanolamine plasmalogens, plasmanyl glycerophosphatidylethanolamine, fatty acids, fatty acid ester of hydroxyl fatty acid, and diacylglycerophosphates, were identified to distinguish healthy controls at an early stage [21]. Bestard-Escalas et al. described the characteristics of membrane lipid groups and their EV in five commercial colonic cell lines. Moreover, the results showed that both cells and EV lipid groups could be separated according to the degree of cell malignancy. Furthermore, the effects of all CRC lines on ether

lipids were specific and significantly homogeneous [22].

Solid tumors are characterized by overall metabolic alterations in their growth and progression. Wang et al. measured the molar abundance of 342 species of 20 lipids in biopsy-matched CRC and adjacent normal mucosa samples. Compared with the findings of previous reports, CRC samples showed a large amount of preserved lipid composition similar to that in the normal colonic mucosa samples. Significant exceptions include increased levels of phosphatidylinositol in CRC and decreased phosphatide abundance in late CRC [23]. Serafim et al. examined patients with stage I–III CRC, patients with adenomatous polyps, and individuals who underwent routine colonoscopy. All patients underwent peripheral blood lipid extraction, and the lipids of the samples were identified via MALDI-MS technology. The polyketide group (810.1) is the lipid represented in the tumor, and the polyp and control group are mostly represented. We observed differences in the lipid profile between patients with lymph node invasion (N1–2) and those without lymph node infiltration (N) in CRC patients [24].

Kitamura et al. studied the level of lysophospholipids in colorectal cancer tissues and found that lysophosphatidylinositol and lysophosphatidylserine levels were significantly higher than those in normal tissues. Meanwhile, lysophosphatidic acid levels were significantly lower than those in normal tissues. The fatty acid analysis showed that lysophospholipids 18:0 and 18:0 were the dominant lipids in colon cancer [25]. Choi et al. used MS to analyze the lipid groups of colon cancer stem cells (CSCs) and large cancer cells (BCCs) and reported that CSCs contain a unique lipid profile. The free MUFA was higher in CSCs than that in BCCs, whereas the levels of free SFA were lower. In addition, all identified MUFAs containing phosphatidylethanolamine had high levels in CSCs. Interestingly, low phosphatidyl-serine (18:1/18:0), phosphatidyl-choline (PC; p-18:0/18:1), and sphingomyelin (SM; d18:1/20:0 or d16:1/22:0) levels in CSCs were observed. The specific PC, SM, and MUFAs in CSCs can be increased rapidly. Collectively, these results suggest that these specific lipid components are essential for the maintenance of CSCs [26].

2.1.4 Gastric Cancer

Malignant tumor growth is characterized by significant changes in metabolites. Sun et al. found that palmitic acid (PA) was significantly downregulated in gastric carcinoma. Cell proliferation in gastric cancer (GC) cell lines, such as AGS, SGC-7901, and MGC-803, was inhibited by the high concentration of PA in vitro, impairing cell invasiveness and migration ability. In addition, sterol regulatory element-binding protein 1 (SREBP-1c) is activated in human GC, promoting the expression of various genes such as SCD1 and FASN, which are associated with fatty acid synthesis. SREBP-1c downregulation rescued migration and invasion defects of AGS and SGC-7901 GC cells [27]. Based on a breakthrough in genomics, TCGA recently proposed an integrated genome analysis approach wherein GC is divided into four subtypes according to the chromosomal instability (CIN) states. Hung et al. collected GC tissue specimens and noncancer tissue specimens from cancer patients and conducted an analysis following TCGA classification. They identified 409 oncogene and tumor suppressor gene sequences, and the samples were divided into CIN and non-CIN types. Using LC-MS, the authors identified the lipid profiles of GC samples and adjacent noncancerous tissue samples. Compared with adjacent noncancerous tissues, gas chromatography samples showed distinct features of lysophospholipid, phosphocholine, phosphatidylethanolamine, phosphatidylinositol, phosphoserine, sphingomyelin, ceramide, and triglycerides. The levels of GPs (choline phosphate, phosphatidylethanolamine, and phosphatidylinositol) increased by 1.4–2.3 times in the CIN group compared with those in the non-CIN group ($P < 0.05$). These changes in the glycerol and glycerophospholipid pathways indicated GC progression to CIN [28].

2.1.5 Prostate Cancer

EVs of non-tumorigenic cells in prostate cancer (PCa) patients are rich in fatty acids, glycolipids, and precursor oils. In contrast, EVs of tumorigenic or metastatic cells are abundant in glycolipids, sphingolipids, and glycerol phospholipids [29]. Zhou et al. compared PCa with benign prostate tissue (BPT). The results showed that the total fatty acid content, monounsaturated fatty acid content, polyunsaturated fatty acid content, and $n-6$ total fatty acid content of the PCa group were significantly higher than those of the BPT group. A significantly higher PCa $n-6$FFA and $n-3$FFA concentration of most fatty acid parameters was associated with Gleason grade and clinical stage [30]. However, the fatty acids associated with the occurrence, progression, and ethnic differences between African American (AA) and Caucasian American (CA) populations as well as the fatty acids that are differentially expressed remain unclear. Kregel et al. observed that both bromine-containing and external (BET) degraders inhibited PCa cell growth in vivo and in vitro. These drugs preferentially affect AR-positive PCa cells (22 Rv1, LNCaP, VCaP) rather than AR-negative cells (PC3 and DU145). The increase in PUFAs and thioredoxin-interacting proteins (TXNIP) indicate their potential as pharmacological biomarkers for targeting BET proteins [31].

2.1.6 Endometrial Carcinoma

In endometrial cancer, preoperative biomarkers for identifying patients with low risk of disease progression can help establish the appropriate degree of surgery required and avoid possible complications from radical surgery. Using electrospray ionization tandem mass spectrometry, Knific et al. conducted a quantitative analysis of 163 metabolites in 126 plasma samples from 61 patients with endometrial cancer and 65 controls. Three levels of single phosphatidylcholine decreased significantly in patients with endometrial cancer [32]. Cummings et al. discussed the changes of epithelial eicosane metabolism gene expression in endometrial carcinogenesis. These were combined with eicosane-like profiles in matched clinical specimens. The expression of candidate eicosane metabolic enzymes, that is, low HPGD combined with high ALOX5 expression, was associated with worse overall survival and progression-free survival, emphasizing that HPGD and ALOX5 are potential therapeutic targets for invasive EC subtypes [33].

2.1.7 Bladder Cancer

Bladder cancer is an elusive disease because of its rapid recurrence and drug resistance. The prognosis of BC patients with recurrence and hyperthermia is extremely poor. Lee et al. conducted a lipid group comparison analysis of two homogeneous human T24 bladder cancer cell lines. Ultrahigh-performance liquid chromatography-mass spectrometry (UPLC-MS) analysis of 1864 lipids identified differentially expressed lipid levels suspected to be associated with cisplatin resistance [34]. Vantaku et al. used the NIST MS metabolomics outline and lipid blast MS/MS library to identify 519 metabolites and 19 lipids differentially expressed between low- and high-grade bladder cancer, respectively. They identified metabolic features of high-grade bladder cancer by integrating unbiased metabolomics, lipidomics, and transcriptomics to predict patient survival and identify novel therapeutic targets [35].

2.1.8 Ovarian Cancer

Cheng et al. reported the findings from the protein and lipid group analyses of exosomes from ovarian cancer cells (SKOV-3) and ovarian surface epithelial cells (HOSEPiC). A total of 1433 proteins and 1227 lipids were identified from the exocrine derived from both cell lines. The exocrine extracted from the SKOV-3 was more abundant than the ChE and ZyE species extracted from

the HOSEPiC. V collagen chains (COL5A2) and lipoprotein lipase (LPL) in the exocrine from SKOV-3 sources were significantly higher [36]. Wefers et al. analyzed 109 lipid mediators of ascites in patients with ovarian cancer and found that the lipid involved in ascites inhibition was different from that in normal peritoneal fluid. In addition, there were lipid intermediates in the ascites of ovarian cancer patients, which is consistent with T cell dysfunction [37].

2.1.9 Pancreatic Cancer

Pancreatic cancer is one of the most aggressive malignancies. Early diagnosis of pancreatic cancer is difficult, leading to its poor prognosis. Tao et al. evaluated possible prognostic or diagnostic metabolite biomarkers in serum exocrine of pancreatic cancer patients and found that 270 of the 20 lipids showed significant abnormalities. Of them, 61 were verified in a larger sample size. LysoPC 22:0, PC (P-14:0/22:2), and PE (16:0/18:1) were associated with tumor stage, CA19–9 expression, CA242 expression, and tumor diameter. PE (16:0/18:1) was also significantly correlated with overall survival [38]. Arnoletti et al. collected portal vein plasma samples during the intraoperative period from 29 patients undergoing pancreaticoduodenectomy and used multidimensional mass spectrometry-based shotgun lipid histology to analyze lipid changes. The unique characteristic analysis of 20 lipids and 235 lipids was found to reliably identify PDAC (stage I–IV), intraductal papillary mucosa (IPMN), and nonmalignant pancreatitis [39].

The carnitine palmitoyltransferase (CPT) family is essential for fatty acid oxidation. Guan et al. found that carnitine palmitoyltransferase 1C (CPT1C), one of the subtypes, plays an essential role in the aging of tumor cells. However, whether other subtypes (CPT1A, CPT1B, and CPT2) have the same effect on cellular senescence remains unclear [40]. CPT1C has the most significant effect on cell senescence. Using lipidomics analysis, we further found that the downregulation of CPTs alters lipid content involved in mitochondrial function and induces lipid accumulation.

2.1.10 Liver Cancer

The cellular heterogeneity of tumor tissue is one of the causes of tumor recurrence after chemotherapy. Thus, identification of specific tumor tissue cell subtypes is critical for precision medicine and prognostic prediction. Lipids, as structural and functional components of cells, are closely related to the apparent morphology of cells. They are biomarkers of potential cancer species that can be used to classify different cancer cell types. Wang et al. described a lipid spectrum analysis method based on nanostructured laser desorption/ionization mass spectrometry (NALDI-MS). This method can classify five HCC cell lines and distinguish the subtypes of mixed cells and tumor tissues. The molecular structures of these biomarkers were classified into two categories as phosphatidylcholine (i.e., PE, PI, PG, PA, and PS) and phospholipids (i.e., LacCer, ST) [41].

2.1.11 Glial Tumor

Isocitrate dehydrogenase (IDH)1 mutation is a highly frequent event in low-grade gliomas and secondary glioblastomas. Zhou et al. found marked changes in glycolysis and lipid metabolism in IDH1 mutant glioma tissues compared with IDH1 wild-type glioma through comprehensive metabolic studies on clinical IDH1 mutant glioma specimens. More pyruvate was found to enter the TCA cycle in IDH1 mutant gliomas presenting with reduced triglycerides and sphingolipids [42].

2.1.12 Thyroid Cancer

The difference between papillary thyroid carcinoma and benign thyroid lesions is of great significance for clinical management. Histopathological classification can be supported by molecular biomarkers, including lipid group features, identified using high-throughput mass spectrometry techniques. Wojakowska et al. used a high-resolution MALDI-Q-Ion mobility-TOF-MS technique to analyze lipid groups in

formalin-fixed thyroid tissue samples. Multiple phosphatidylcholine (32:0, 32:1, 34:1, and 36:3), sphingomyelin (34:1 and 36:1), and phosphatidic acid (36:2 and 36:3) were detected in cancer tissues. Moreover, they were significantly more abundant in cancer tissue than in noncancerous tissue [43].

2.1.13 Head and Neck Cancer

Fanconi anemia (FA) gene mutations are common in sporadic head and neck squamous cell carcinoma (HNSCC). We have previously demonstrated that FA pathway deletion stimulates invasion of HNSCC cell lines. Zhao et al. used a systematic approach to define FA pathway-dependent lipid metabolism and to extract lipid-based features and invasive effectors in FA defective cells. The most notable element in the lipid profile results was the consistent elevation of glycolipid, especially ganglioside accumulation. In contrast, such lipids were inhibited with genetic correction of HNSCC cells from FA patients [44].

2.1.14 Myeloma

Multiple myeloma (MM) is a blood malignancy characterized by clonal expansion of malignant plasma cells. Although long-term palliative treatment is possible, MM is incurable and most patients develop recurrence. Mohamed et al. evaluated the feasibility of simultaneous lipidomics and proteomics analysis of plasma cells. The results showed that PCs were significantly downregulated in recurrent MM. PC, ceramide, cardiac phospholipid, arachidonic acid, and cholesterol metabolic pathways were significantly correlated only in patients with recurrence, but not in those who were newly diagnosed [45].

2.1.15 Oral Cancer

Metabolic recombination as one of the characteristics of cancer is beneficial to rapid energy production, biosynthetic ability, and therapeutic resistance. We previously found that balsam pear extract (BME) could prevent carcinogen-induced oral cancer in mice. RNA sequence analysis of the mouse tongue showed that compared with other cancers, BME significantly regulated the metabolic process by altering glycolysis and lipid metabolic pathways in oral cancer [46]. Bednarczyk et al. compared the usefulness of proteome and lipidome components to distinguish between oral cancer cells and normal mucosa. The tumor regions were more heterogenous than the normal epithelium, and the distribution of peptide components was more uneven than that of lipid components. Furthermore, there were significant differences in the abundance of peptide components and lipid components between the tumor and the normal epithelium (for peptide and lipid components, the median effect of Cohen was 0.49 and 0.31, respectively). In addition, compared to normal epithelial cells, a multicomponent cancer classifier was detected using tissue samples from three patients and then validated with tissue samples from the fourth patient. The weighted accuracy of cancer classification for peptide-based signature and lipid-based signature was 0.85 and 0.69, respectively. Although the molecular differences between cancerous and normal mucosa were higher in the proteome domain than in the analyzed lipidome subdomain, imaging of lipidome components can also distinguish between oral cancer and normal epithelium. Therefore, both tumor proteome and lipidome are promising sources of biomarkers for oral malignancies [47].

2.1.16 Renal Carcinoma

The clear cell carcinoma (ccRCC) subtype of renal cell carcinoma (RCC) is characterized by lipid accumulation and metabolic alterations. However, data on ccRCC metabolic alterations are limited. Schaeffeler et al. assessed metabolic alterations and lipid composition of RCC subtypes and ccRCC-derived metastases. They found differences in lipid synergistic regulatory

networks between ccRCC and chromophobe RCC (chRCC) except for lysophospholipids and sphingolipids [48].

2.2 Tumor Therapy

The above content indicates that lipidomics and changes in lipid molecules have high potential for application in early tumor diagnosis. Tumor diagnosis is easier to establish through direct detection and analysis of clinical samples. However, owing to the standardized management of clinical research and clinical observation of long-term curative effects, there are fewer studies on the application of lipidomics in tumor treatment. Therefore, most tumor treatment-related research still stays at the stage of intervening tumor cells in the laboratory.

2.2.1 Lung Cancer

Zhang et al. identified CCL3 metabolic-related genes or inflammation-related genes in lung adenocarcinoma and small lung cancer cells, respectively. Palmitic acid C16:0 or stearic acid C18:0 upregulated ACSL5 or CSF2 expression in a time- and dose-dependent manner. Deletion of both genes resulted in cell insensitivity. By altering intracellular energy, the target lipid increased the expression of PDK4 genes and inhibited cell proliferation [49]. Bergqvist et al. compared the effects of microsomal prostaglandin E synthase (mPGES)-1 inhibitor complex III (ciii) with those of cyclooxygenase (COX)-2 inhibitor NS-398 on interleukin (IL)-1-induced cellular protein and lipid profiles in lung cancer. Compared to the NS-398 that activate these pathways, CIII downregulated eIF2, eIF4/P70S6K, and mTOR signals. There are nine phospholipid changes between the two inhibitors. Compared with CIII, NS-398 lysophospholipid (LPC) shows more profound changes in living cell imaging systems. We also found that CIII reduced cell proliferation and enhanced the cytotoxic effects of cisplatin, etoposide, and vincristine [50].

The recent introduction of targeted therapy and immunotherapy for NSCLC offers new hope for NSCLC patients. However, not all patients respond to these drugs, and the complete response is low. New therapeutic targets and novel antitumor drugs are still urgently needed in NSCLC. Sphingomyelin kinase 2 (SphK2) is one of the critical enzymes in sphingomyelin metabolism. Positive SphK2 expression predicts poor survival in NSCLC patients and is associated with gefitinib resistance. Dai et al. explored the NSCLC activity of ABC294640, which is the only oral SphK2 inhibitor. The results showed that ABC294640 could induce NSCLC apoptosis, cell cycle arrest, and tumor growth inhibition both in vitro and in vivo [51]. Lipotoxicity, caused by intracellular lipid accumulation, accelerates the degenerative process of cellular senescence, which is crucial in cancer development and treatment. CPT1C, a mitochondrial enzyme that catalyzes carnitinylation of fatty acids, has been found to be a key regulator of cancer cell senescence. Analysis of the LC/MS lipid groups of PANC-1, MDA-MB-231, HCT-116, and A549 cancer cells after the deletion showed significant changes in lipid groups of cpt1c depleted cells, including fatty acids, diacylglycerols, triacylglycerols, oxidized lipids, cardiac phospholipids, phosphatidylglycerols, phosphatidylcholine-phosphatidylethanolamine ratios, and sphingomyelins [52].

2.2.2 Prostate Cancer

Androgen deprivation therapy (ADT) is a primary treatment strategy in patients with metastatic PCa. ADT is associated with various metabolic disorders, including impaired glucose tolerance, insulin resistance, and weight gain, thus increasing the risk of diabetes and cardiovascular death. ADT exerts its therapeutic effect through several mechanisms. First, ADT treatment reduces steroid synthesis, which is reflected in lower androgen sulfate and other steroid hormones. Second, ADT consistently reduces 3-hydroxybutyric acid and ketone formation. Third, ADT reduces many

acylcarnitines, thus affecting fatty acid metabolism. Fourth, ADT is reduces 3-formylindole (also called indole-3-carboxaldehyde) [53]. Clendinen et al. used multi-platform (NMR + LC-MS) metabolomics to study PCa recurrence and preoperative metabolic changes. Lipid histology experiments showed that many classes of lipids, including triglycerides, lysophosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, diglyceride, acylcarnitine, and ceramide, are highly abundant in patients with recurrence [54].

2.2.3 Ovarian Cancer

Lipidomics is a promising approach to identify lipid profiles in malignant phenotypic cells. Using MS, Cadoni et al. revealed quantitative differences in phospholipid composition between cisplatin-resistant and cisplatin-sensitive model cancer cell lines. Further, in CCRF-CEM cisplatin-sensitive cells, phosphocholines PC P-34:0, PC 34:1, PC 20:2_16:0, LPC 18:1 and LPC 16:0 PLs were found treated with 200-400 μM cisplatin, but not in cisplatin-resistant A2780 cells. Similarly, the PC 34:1, LPC 18:1, and LPC 16:0 of cisplatin-reactive A2780 increased in cells, whereas cisplatin-resistant A2780 cells PC 20:2_16:0 downregulated. The development of lipid entities and therapeutic resistance shown in MS may be helpful for molecular diagnosis and provide a potential complementary cancer biomarker [55].

2.2.4 Colorectal Cancer

Lipidome technique is a promising antigen delivery technique in cancer immunotherapy. The phospholipid content of the lipid group may act as immunostimulatory molecules in tumor immunotherapy [56]. The DOTAP and DOPE lipid groups (F1 lipid groups) stimulated a mixed immune response in Th1 and Th2 colon cancer mice without tumor-specific antigens.

2.2.5 Bone Marrow Tumor

Although the proteasome inhibitor bortezomib (BTZ) has shown excellent results in MM, a small number of patients experienced severe adverse events or did not respond to the drug. In addition, BTZ-induced peripheral neuropathy (BiPN) is a common side effect, thus limiting its application. Maekawa et al. identified 385 lipid metabolites in patients' serum and found that low levels of glycerophospholipids, sphingolipids, and cholesterol esters are associated with adverse therapeutic responses. Metabolites associated with platelet-activating factor biosynthesis and cholesterol metabolism appear to be particularly relevant. In addition, several lysophosphatidylcholines, phosphatidylcholine, ceramide, neutral lipids, and oxidized fatty acids were significantly increased or decreased in BiPN patients with grade G0–G3 disease [57].

2.2.6 Lymphoma

Monocarboxylic acid transporter 1 (MCT1) is a regulator of cell metabolism and a therapeutic target for cancer therapy. Beloueche-Babari et al. evaluated the effects of MCT1 inhibitor AZD3965 critical determinant of tumor biological function on tumor metabolism and immune cell infiltration in an MCT1-dependent model of lymphoma. Tumor growth was inhibited, and tumor choline was reduced in mice with severe combined immunodeficiency Raji xenograft tumors treated with AZD3965 [58].

2.2.7 Other

In the field of cancer treatment, lipid molecules are not only involved in antitumor effects through metabolism but can also affect the vitality of tumor cells through immune responses. Treatment with immune checkpoint inhibitors (ICI) requires the production of appropriate amounts of IL-6 and

TNF-cells to clear tumor cells. IL-6- and TNF-activated phospholipases induce the release of PUFAs in cell membrane phospholipid pools. PUFAs as a precursor of pro-inflammatory and anti-inflammatory eicosane can inhibit excess production of IL-6 and TNF. PUFAs can also selectively kill tumor cells by enhancing the production of free radicals and the accumulation of toxic lipid peroxides in tumors rather than in normal cells [59].

Bone marrow-derived suppressor cells (MDSCs) play an essential role in tumorigenesis; accordingly, their inhibition is key to the success of tumor immunotherapy. MDSCs induce oxidative phosphorylation resulting from glycolysis to fatty acid oxidation (FAO) and lipid accumulation in tumors through metabolic reprogramming. The increased uptake of exogenous fatty acids by tumor MDSCs enhances its immunosuppressive activity against T cells, thereby promoting tumor progression [60].

2.3 Conclusion and Remarks

Traditional studies on cancer cell metabolism mostly focus on glutamine decomposition and glycolysis. However, in the past decade, with the continuous development of lipidomics technology, new knowledge and new theories have deepened the understanding of the relationship between lipid metabolism and cancer biology [61, 62]. Recent studies have shown that the reprogramming of cell lipid metabolism is directly involved in the malignant transformation and progression of cells [63, 64]. For example, lipids synthesized de novo can provide phospholipid components for proliferation to form plasma membranes and organelle membranes of newly dividing cells [65]. In addition, the upregulated expression of mitochondrial microglobulin helps tumor cells maintain energy metabolism and redox homeostasis. Lipid-derived messenger molecules can regulate related signal pathways and coordinate immune suppression [66, 67]. Therefore, lipid metabolism is involved in various oncogenic processes, including proliferation, differentiation, migration, invasion, and drug resistance [68, 69]. However, whether we can safely and effectively regulate cancer treatment through lipid metabolism, the underlying mechanism remains unclear [70].

In addition to peripheral blood as a commonly used sample for early tumor diagnosis, other easily accessible body fluids have also received increasing research attention. Human saliva as a biological fluid is increasingly used for diagnosing diseases, monitoring systemic disease status, and predicting disease progression. The discovery of biomarkers in saliva provides a unique opportunity to assess patient health by using oral fluids, avoiding invasive blood collection. Salivary fluids are clinically relevant because their components can be found in plasma. Salivary lipids are one of the most important cellular components in human saliva, and thus they have high potential as biomarkers. Lipid components in cells and tissues change with physiological changes, and lipid components in normal tissues are different from those affected by disease. Lipid imbalance is strongly associated with many lifestyle-related diseases, such as atherosclerosis, diabetes, metabolic syndrome, systemic cancer, neurodegenerative diseases, and infectious diseases. Therefore, lipid biomarkers can be useful to diagnose disease and evaluate disease status and treatment response. However, whether saliva can be used as a substitute for serum lipid profiles requires further investigation as developing reliable diagnostic and salivary disease surveillance tests requires identifying saliva biomarkers using a high-sensitivity method with low detection limits [71]. The continuous development of mass spectrometry (MS) and the introduction of high-precision and high-resolution mass spectrometry detectors in recent years have also significantly improved lipidomics methods.

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