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Oncolipidomics: Mass spectrometric quantitation of lipids in cancer research

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ABSTRACT

This review summarizes available mass spectrometry (MS) based approaches for the quantitative analysis of lipids in biological samples in the cancer research, which is termed here as oncolipidomics. The methodological part shows possible configurations of stand-alone MS or MS coupled to liquid-phase separation techniques. For the characterization of various lipids with the special emphasis on methods convenient for robust high-throughput lipidomic quantitation of biological samples, such as body fluids, tissues, and cell lines. The critical assessment of lipid species dysregulated in various cancer types is provided with the goal to summarize and generalize the typical up and down regulated lipids associated with the progress of tumor growth and evaluate possible future use of lipidomic analysis in the early cancer diagnosis.

1. Introduction

Lipids are constituents of cell membranes, which are involved in various cellular functions, for example cell signaling, energy storage, etc. These various biological functions of lipids make them interesting candidates for monitoring of the metabolic state of the organism and may allow the identification of characteristic profiles for various healthy and disease states. At present, the low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and total triacylglycerols (TG) are representative examples of routine analyses of lipids in common clinical practice. The fast proliferation of cells and altered energy metabolism in cancer may be assumed as a suitable example, where the changes in the lipid profile could be anticipated. Several studies presented within this review showed the potential of oncolipidomics for diagnostic purposes. The term oncolipidomics is used here for the description of the quantitative and comprehensive analysis of lipids by MS for cancerous samples in comparison to healthy samples. The comparison of results obtained from the literature highlights discrepancies with regard to the reported nomenclature and quantitation strategies including the quality control (QC) and the method validation, which suggests that some level of harmonization and guidelines of recommended approaches would be beneficial for the lipidomic community. The most common biological materials, sample preparation protocols, and MS based analysis methodologies are discussed in this review. Furthermore, some considerations for oncolipidomics with regard of the harmonization of quantitative lipid analysis and an overview on the most regulated lipid species in cancer research obtained from the literature search are highlighted towards the future investigation to possible disease diagnosis and therapy monitoring.

1.1. Lipid classification and nomenclature

The lipidome of mammals and other organisms exhibits a huge structural diversity, which requires the systematic nomenclature. For this purpose, the LIPID MAPS classification system has been introduced in 2005 [1], where lipids are divided into eight main categories, i.e., fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, saccharolipids, prenol lipids, and polyketides. The last three mentioned categories are less common for mammals and human, therefore they will be not discussed in this review. Each category further involves its own hierarchy including particular lipid classes and subclasses. Lipidomics is still a

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Abbreviations

2D	two-dimensional
APCI	atmospheric-pressure chemical ionization
BUME	butanol – methanol
CE	cholesterol ester
Cer	ceramide
CL	cardiolipin
CN	carbon number
DB	double bond number
DESI	desorption electrospray ionization
DG	diacylglycerol
DI	direct infusion
ECN	equivalent carbon number
EDTA	ethylenediaminetetraacetic acid
ESI	electrospray ionization
FA	fatty acid
FT	Fourier transformation
GalCer	galactosylceramide
Gb3Cer	globotriaosylceramide
GC	gas chromatography
HDL	high-density lipoprotein
HexCer	hexosylceramide
HILIC	hydrophilic liquid chromatography
HR	high-resolution
IS	internal standard
LacCer	lactosylceramide
LC	liquid chromatography
LDL	low-density lipoprotein
LPC	lysophosphatidylcholine
LPE	lysophosphatidylethanolamine
MALDI	matrix-assisted laser desorption/ionization
MG	monoacylglycerol
MS	mass spectrometry
MSI	mass spectrometry imaging
MTBE	methyl *tert*-butyl ether
NARP	non-aqueous reversed-phase
NIST	National Institute of Standards and Technology
NLS	neutral loss scan
NMR	nuclear magnetic resonance
NP	normal phase
O-	ether
P-	plasmalogen
PA	phosphatidic acid
PC	phosphatidylcholine
PE	phosphatidylethanolamine
PG	phosphatidylglycerol
PI	phosphatidylinositol
PIS	precursor ion scan
PS	phosphatidylserines
PUFA	polyunsaturated fatty acid
QC	quality control
QqQ	triple quadrupoles
QTOF	quadrupole time-of-flight
QTRAP	quadrupole - linear ion trap
RP	reversed-phase
S1P	sphingosine-1-phosphate
SFC	supercritical fluid chromatography
SM	sphingomyelin
SRM	selected reaction monitoring
TG	triacylglycerol
TLC	thin layer chromatography
UHPLC	ultrahigh-performance liquid chromatography
UHPSFC	ultrahigh-performance supercritical fluid chromatography

developing field and several updates and improvements have been made to the nomenclature [2,3] in the last decade.

Another problem is the necessity of proper annotation and the unification of structure-derived information from MS data for particular lipid species to help the lipid research community with the understanding of the complex lipidomic data obtained by mass spectrometric and chromatographic approaches. The solution is the shorthand notation [4], where the rules for particular levels of structural information are derived from the experimental data. In the following text, the shorthand notation is briefly described on the example of sphingomyelin (SM) 36:1 (lipid species level) for a better understanding. The abbreviation SM reflects the sphingomyelin lipid class. Subsequently, the colon separated numbers 36:1 provide the information on the carbon number and double bond number (CN:DB) of N-linked fatty acyl and the sphingoid base of ceramide part. Another possibility is the addition of the prefix d before the carbon number (SM d36:1) based on the common assumption of a sphingoid base with two hydroxyl groups in mammals (hydroxyl group level). If the type of sphingoid base and linked N-acyl are known from tandem mass spectra, then the fatty acyl/alkyl level notation can be applicable, i.e., SM d18:1/18:0. Finally, the LIPID MAPS sphingoid base/fatty acyl structure level, such as SM d18:1 (4E) (1OH, 3OH)/18:0, can be reported in case of known stereochemistry. Although the shorthand notation for most lipids was developed within this article [4], the abbreviation of some more complex lipids is still missing, e.g., complex acidic glycosphingolipids. Recommended nomenclature and abbreviations for these compounds have been suggested elsewhere [5,6].

1.2. Biological materials in clinical lipidomics

Lipids can be analyzed in all common human biological materials. For a better understanding of the biological role of lipids in the cancer development, various tumor cell lines were analyzed as well as tumor tissues and surrounding non-affected normal tissues for breast and kidney cancers [7–9]. However, non-invasive methods are preferred in clinical diagnosis, such as the analysis of body fluids. Blood, especially plasma and serum, is the most commonly used type of human biological material in the lipidomic analysis. EDTA plasma has been suggested as the most convenient body fluid material for the lipidomic analysis [10]. Urine, saliva, and cerebrospinal fluid are investigated as well in the biomarker discovery research of several diseases including cancer [11]. In recent years, the lipidomic analysis of extracellular vesicles (exosomes) secreted by mammalian cells isolated from body fluids gained a special attention [12] due to their importance in the communication between cells.

It is assumed that lipid concentration differences are observed between cancer and healthy states. However, lipid concentrations also depend on various exogenous factors, such as dietary intake and circadian rhythm [13] as well as endogenous factors (e.g., hormonal rhythm), therefore differences in the lipid concentration profile reflecting the health state may be difficult to detect. Furthermore, lipid concentrations may be influenced by sample collection and storage protocols, for example collection tubes (heparin *vs.* EDTA tubes for plasma collection). The time needed to isolate the serum as well as the centrifugation speed used to isolate

plasma may also affect the concentration profile of lipids. All these factors illustrate how important the sample quality and the harmonization of sample isolation protocols are in order to have a chance to come to diagnostic conclusions. In fact, research laboratories strongly depend on samples what they obtain from external providers and have limited influence on sample collection conditions. On the other hand, clinical employees are occupied by their daily routines with the patient treatment, therefore the sample collection protocol has to be as simple as possible and harmonized among different collection places. Consequently, systematic studies of the influence of sample collection, storage, sample material, collection time point, and the lipid profile depending on the health state with reliable lipid quantitation obtained by various laboratories are necessary in order to provide oncolipidomics a real chance in the clinical practice. The availability of statistical relevant sample sizes for clinical lipidomic studies is often challenging, because inclusion and exclusion criteria should be followed, such as the type of collecting tubes, no hemolysis of samples, the match of gender, age, and body-mass-index, etc. Effects of other comorbidities should be investigated as well. Furthermore, samples before and after treatment or surgery and several collecting points of the same patients would be desired. Biobanks may be applicable, but the quality of the samples collected at various hospitals should be monitored.

1.3. Sample preparation in lipidomics

Robust, reproducible, and fast sample preparation protocols with high coverage for a broad range of lipid classes are essential for the comprehensive, reliable, and quantitative analysis of lipids in biological samples. For the quantitative analysis, the addition of exogenous internal standards (IS) prior to the sample preparation is necessary [14]. The liquid-liquid extraction is the most commonly used sample preparation method covering relatively broad range of lipid classes. Folch [15] and Bligh-Dyer [16] methods or modifications of those using chloroform and methanol (Folch - 2:1, v/v, Bligh-Dyer - 1:2, v/v) are prevailing. Other approaches are based on methyl *tert*-butyl ether (MTBE) [17] as well as on butanol – methanol (BUME) [18]. For the ether-based extraction, a mixture of methanol and MTBE (1.5:5, v/v) and water is employed. The BUME extraction involves two steps, where one-phase extraction using the mixture of butanol and methanol (3:1, v/v) is followed by two-phase extraction by adding heptane: ethyl acetate (3:1, v/v) and 1% acetic acid.

If higher selectivity and sensitivity are needed, then solid-phase extraction can be applied, especially for highly polar to ionic lipids obtained from the aqueous phase [19]. Depending on the properties of the employed extraction material, i.e., pure silica or octadecylsilica, lipids of interest can be enriched and fractionated [19]. The simplest sample preparation approach for the analysis of lipids is the protein precipitation of body fluids with organic solvents prior to the analysis. Even though it is by far the fastest approach, it bears the risk of low efficiency for the removal of impurities, which may result in higher background signal and faster contamination of the system.

2. Common analytical methodologies in lipidomic quantitation

MS using the direct infusion (DI) or its coupling with liquid-phase separation techniques strongly dominates the field of lipidomic quantitation [20] with possible applicability for high-throughput clinical studies including the biomarker discovery and early diagnosis screening. The liquid-phase separation techniques have a high separation power to resolve numerous intact lipid molecules including various types of lipid isomers depending on the applied chromatographic mode. For quantitation purposes, the lipid class separation techniques are preferred due to the fact that the exogenous lipid class IS coelutes with analytes from the same lipid class, which guarantees the same matrix and suppression effects for both IS and analytes. The situation is similar in case of direct infusion (so called shotgun approach) with triple quadrupole (QqQ) instruments, where characteristic scan events enable the distinction of individual lipids classes, and again IS and analytes are ionized at the same time. Fig. 1 is an example of PC measured by shotgun MS. In case of lipid species separation techniques, such as reversed-phase (RP) liquid chromatography (LC), special care with regard to internal standards should be paid due to different matrix and suppression effects during the chromatographic run based on lipid species separation. Independent of the employed methodology for lipid quantitation, the emphasis should be given on the full method validation and the use of a sufficient number of QC samples after the certain number of injections, typically 20–50 samples [20–22]. In general, any quantitative lipidomic study based on MS should be fully validated using at minimum one IS per each lipid class and the real biological matrix [23]. The best approach is the use of a pooled sample including the lipid class IS added before the extraction [24]. The extract of the pooled sample containing the IS may be also used as QC sample during the measurements of the sample batch.

Individual steps of the whole analytical methodology, such as the sample collection, the sample preparation, the mass spectrometric analysis, and the data processing, should be carefully monitored to obtain reliable quantitative data for large-scale clinical studies. Sample preparation variances can be improved by automated sample preparation protocols by using robotic systems. The signal response in MS can significantly vary due to the contamination, therefore the use of a system suitability standard in addition to IS should be regularly measured and evaluated. This may allow the evaluation of mass spectrometer state and may help with the decision, if the sequence of valuable samples has to be stopped in order to investigate the signal loss by employing cleaning steps. The sequence of samples must be randomized during the sample preparation and measurements in order to avoid bias during the statistical analysis. Generally, the whole lipidomic quantitation methodology should be validated in accordance with European Medicine Agency [25], Food and Drug Administration [26] or other convenient guidelines. For biomarker discovery studies, it is recommended to use training and validation sets. The training set is used to build up a statistical model, and the validation set to evaluate the performance of the statistical model with regard to sensitivity and specificity. Additionally, the use of blinded samples may further improve the method confidence.

2.1. Direct infusion MS

2.1.1. Low resolution shotgun MS

One approach to determine lipids in biological samples is the shotgun MS analysis using low resolution MS, which does not use any separation technique prior to MS analysis, but uses specific MS/MS scans for the global analysis of the lipidome at the constant ion suppression between lipid classes and individual species within the lipid class, because all lipids are ionized together [24,27,28]. Every common lipid class is characterized by particular fragments or neutral losses after collision-induced dissociation allowing the determination of specific lipid species in biological samples (e.g., glycerophospholipids are divided to several subclasses, and every subclass has specific product ions suitable for their determination) [27–30]. The most common scan types during shotgun analysis are precursor ion scans (PIS) and neutral loss scans (NLS), and the best

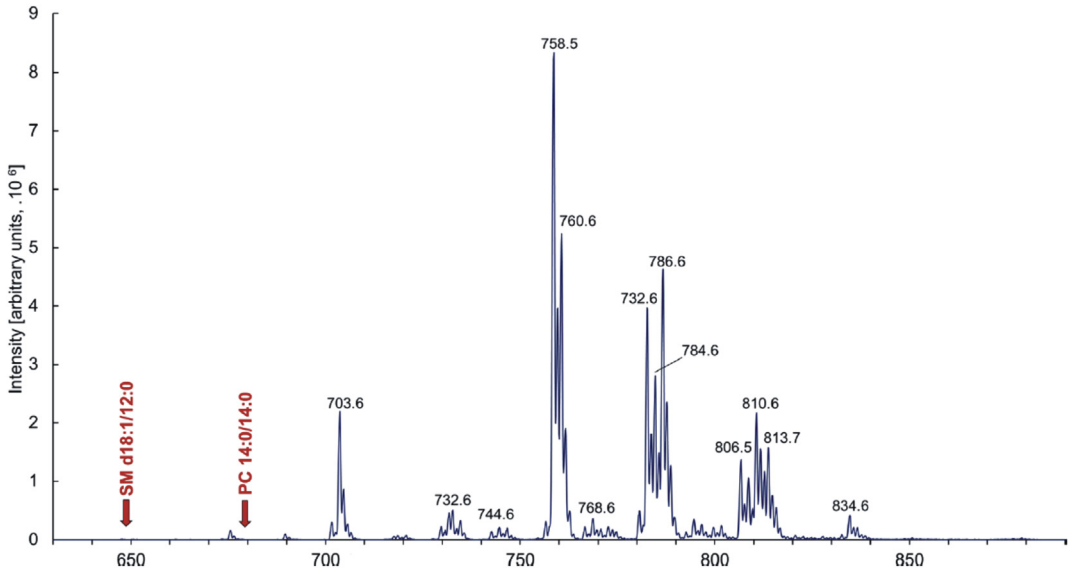

Fig. 1. Selection of internal standards for PC and SM based on the analysis of pooled human plasma using shotgun MS with precursor ion scan of *m/z* 184. Reproduced from [20] with permission from American Chemical Society.

instrument for these scan types are triple quadrupoles (QqQ) and quadrupole - linear ion trap (QTRAP) mass spectrometers [24,27–29]. An example of PIS is the determination of phosphatidylcholines (PC), lysophosphatidylcholines (LPC), and sphingomyelins (SM) with PIS of *m/z* 184 corresponding to the product ion of polar head group of choline. On the other hand, examples of NLS are the determination of phosphatidylethanolamines (PE), phosphatidylinositols (PI), phosphatidylserines (PS), phosphatidic acids (PA), phosphatidylglycerols (PG), and their lyso-forms. The neutral loss Δ*m/z* 141 is specific for determination of PE, Δ*m/z* 185 for PS, Δ*m/z* 115 for PA, Δ*m/z* 277 for PI, and Δ*m/z* 189 for PG. These neutral losses also correspond to the loss of the polar head group [27]. Another possibility is the addition of lithium salt to induce lithium adducts with subsequent characteristic fragmentation [31]. The method is easy to automate with robotic systems providing reproducible and accurate data, allowing the lipidomic analysis of large sample sets required in the clinical research, but the disadvantage of this approach is the impossibility to determine isomers or trace isobaric lipid species in the mixture.

2.1.2. High-resolution (HR) shotgun MS

Shotgun lipidomic approaches may also rely on mass analyzers with high (e.g., QTOF) [29] or ultrahigh mass resolving power employing Fourier transformation (FT) [32–36]. The high mass resolution is accompanied by high mass accuracy and thus the elemental composition of lipid species can be determined for the measurement of precursor ions in full scan mass spectra as well as their particular product ions in tandem mass spectra (MS/MS) [32]. This approach allows the automatic database matching using very narrow Δ*m/z* tolerance setting. Precursor ions are linked to their corresponding product ions, such as either present fatty acyls or head group moieties during the identification procedure for the elimination of possible false positive results. FT instrumentation is mainly applied for the direct infusion HRMS quantitation with the aim to distinguish very small mass differences between lipid compounds or present mass interferences. Similarly as for low resolution shotgun lipidomics, the extract is infused directly to the ion source at a low flow rate using either flow injection or chip-based robotic systems, such as TriVersa NanoMate [32,33,35,36] for the direct-infusion HRMS.

Various laboratory-made software packages are available for the processing of these complex MS and MS/MS data, e.g., ALEX [37] or LipidXplorer [38]. Characteristic product ions and neutral losses obtained from tandem mass spectra are used for the lipid identification, while their quantitation is usually performed based on the IS normalization in positive- or negative-ion full scan mass spectra. Another possibility is the comparison of the sum of intensities of identified lipid fragments of the ion to that of selected IS. These strategies, termed as top-down lipidomics, bottom-up shotgun lipidomics, and MS^{ALL} [32,35,36], can be based on targeted or untargeted analyses. The bottleneck of HRMS quantitation is that the presence of thousands of peaks results in huge dataset size, where only a very small percentage of those peaks belong to lipids. Specific noise filtering and data compression steps are thus performed to reduce the processing time and data size [39]. Although HRMS strategies enable reliable quantitation, identification of new lipid classes, extension of lipid databases, and better description of lipid metabolic pathways, special effort should be devoted to possible *m/z* overlaps during the validation procedure with regard to applied mass resolution [40].

2.2. Separation – MS coupling

The chromatographic separation prior to MS analysis can provide not only higher sensitivity for lipids in biological samples but also additional criterion for the structural confirmation. Biological samples are of high complexity, containing enormous number of species of different origin, properties and abundances, so the ionization efficiency can be influenced by these factors. The chromatographic separation before the introduction to the ion source of mass spectrometer can significantly reduce the complexity, which results in the reduced ion suppression and matrix effects. Thin-layer chromatography (TLC), gas chromatography (GC), and liquid chromatography are well-established methods for the analysis of lipids [20]. The separation efficiency, resolution and retention time depends on the properties of lipids and employed stationary phases.

Various types of lipid isomeric and isobaric species can be separated by the proper selection of the separation mechanism convenient for the targeted selectivity. The separation mode also

enables to select the resolution of lipid classes or lipid species inside classes. The lipid class separation is achieved in hydrophilic liquid chromatography (HILIC) and normal-phase (NP) modes, which are applicable to either LC or supercritical fluid chromatography (SFC). On the other hand, the lipid species separation is achieved by hydrophobic interactions of fatty acyl chains of lipid molecules with non-polar stationary phases in RP mode. Significant improvements in the chromatographic resolution and the speed of analysis are achieved by ultrahigh-performance approaches like ultrahigh-performance liquid chromatography (UHPLC) and ultrahigh-performance supercritical fluid chromatography (UHPSFC), where the columns with sub-2 μm particles and higher operational pressure are used [21,24,41].

Two major approaches are used for the separation based coupling to MS, either traditional approach using selected reaction monitoring (SRM) transitions on triple quadrupole mass spectrometer or newer approach using high-resolution mass analyzers based on time-of-flight [21,22,24] or Orbitrap [34], however, the mass resolution has to be optimized with regard to the separation speed. Commercial or open-source softwares for metabolomics [22,42] or dedicated for the lipidomic analysis [43,44] are used for data processing including lipid peak detection, baseline correction, noise reduction, lipid alignment, IS normalization, etc. Despite the fact that many laboratories are using different liquid chromatography/mass spectrometry (LC/MS) conditions and instrumentation, comparable quantitative results can be achieved among various instrumentation in case of proper analytical validation [45], where quantitative lipidomic analysis across nine LC/MS platforms with high-resolution showed comparable results. Although HRMS can distinguish many isobaric species, the application of mass resolution of only several tens thousands, that is usually used in case of fast high-throughput chromatographic analyses, still does not allow the distinction between M and M+2 isotopes of lipids differing in one double bond. Thus, the isotopic correction should be also performed in case of HRMS class lipid separation approaches [24,40,41]. The use of a tandem mass spectrometer combined with chromatographic separation is preferred, when the high sensitivity especially for targeted lipid species is required, by selecting precursor ions together with those characteristic fragments.

2.2.1. Lipid class separation

UHPLC/MS methods can be divided according to the separation power of lipids of various polarity into HILIC suitable for polar lipid classes and normal-phase suitable for non-polar lipid classes [46], whereas UHPSFC shows applicability for non-polar and polar lipid classes [41] (Fig. 2). Typical stationary phases are classical bare silica or silica gels modified with polar functional groups (e.g., diol, cyano, amino, and amide bonded phases). Typical mobile phases used in HILIC mode are polar solutions miscible with water, whereby acetonitrile with small amounts of water, including additives such as ammonium acetate in order to control the pH, is the most widely used mobile phase [47]. Generally, almost all stationary phases used in UHPLC can be used in UHPSFC as well, even though polar stationary phases, as used in NP chromatography are more common than hydrophobic stationary phases like C18 columns [41]. The most common mobile phase in UHPSFC is carbon dioxide with modifiers (acetonitrile, propanol, or methanol) for the control of solvation, elution strength and polarity of the mobile phase [41].

2.2.2. Lipid species separation

RP mode is the most widespread chromatographic mode in the omics research. Individual molecules are separated according to their hydrophobic interactions with the hydrophobic stationary phase, which results in stronger retention for lipids with longer fatty acyl chains in RP chromatographic systems. Columns typically have the length of 50–150 mm with C18 or C8 sorbent and sub-2 μm or 2.6–2.8 μm core-shell particles [21]. Over 400 lipids from 14 classes were identified in human plasma, urine and porcine brain together with the description of the retention behavior of lipids on the carbon number and the double bond number (Fig. 3A) [48]. The quantification is demanding, because IS do not coelute with analytes unlike in HILIC or NP methods. The addition of isotopically labeled standards, i.e., fully isotopically labeled yeast extracts or isotopic labelling may overcome quantitation issues. Köfeler et al. [49] illustrated the advantage of ultra-high resolution and mass accuracy of Orbitrap mass analyzer for the identification and quantification of lipids in different biological matrices using RP-UHPLC/MS.

Non-aqueous reversed-phase (NARP) LC is the technique used for the separation of triacylglycerols by various mixture of organic solvents [50–53]. The retention is increasing with the increase of equivalent carbon number (ECN) (Fig. 3B). The mechanism of silver-ion chromatography is based on the stability of silver complex, which is more stable for *cis*-isomers than *trans*-isomers. The stability is increased for higher number of double bonds [53,54] with possible resolution of regioisomers (Fig. 3C). Two-dimensional (2D) LC combines two different techniques (Fig. 3B), often techniques for the separation of lipid classes (NP, HILIC) and lipid species (RP) with off-line or online coupling. Continuous comprehensive 2D-LC method was also used for the lipidomic characterization of porcine brain and human plasma [55]. The chiral separation is possible by chemical derivatization or using special columns (Fig. 3D) [56]. Itabashi and Kuksis used HPLC with two columns having chiral phases for the determination of stereochemical configuration of phosphatidylglycerols [57].

2.3. Desorption ionization and mass spectrometry imaging (MSI)

Many desorption ionization techniques, working either at ambient pressure or under vacuum conditions, have been developed and applied for the lipid characterization [58–63]. The most common ionization technique in this group is matrix-assisted laser desorption/ionization (MALDI) followed by desorption electrospray ionization (DESI). Lipids are one of the most abundant compounds in biological tissues, and it is no wonder that desorption MS is often used for the tissue characterization in one [6,60] or two dimensions using MSI [58,59,62,63]. Histology-driven approaches are often applied to show the specific distribution of lipids in particular tissue area [62,64]. The comparison of lipid profile in tumor and non-affected tissue parts directly from the tissue [6,59,63] or after lipid extraction [6] is another widespread application of desorption ionization MS (Fig. 4).

There are some limitation in terms of quantitation, because the signal in desorption ionization MS is less stable compared to LC/ESI-MS, and such techniques suffer from extensive matrix effects (especially in case of MSI) [64–66], but semi-quantitation can be achieved [6]. Various types of lipid signal correction have been described for the lipid semi-quantitation using MALDI and DESI-MS, such as normalization to total ion current [67], median of peak intensity [67,68], root mean square [68], or most reliable normalization to IS [6,68]. The standard procedure of IS addition to the sample before the extraction is performed in case of tissue or body fluids extract analysis, but the more problematic situation is to achieve homogenous distribution of IS within all pixels of tissue sample for direct tissue MSI quantitation. The IS can be deposited under [68] or on the top of the tissue [68,69], applied together with matrix or alone for MALDI [68] or added to the solution in case of DESI [68,70]. Another possibility of semi-quantitation using desorption ionization techniques is the relative quantitation, where

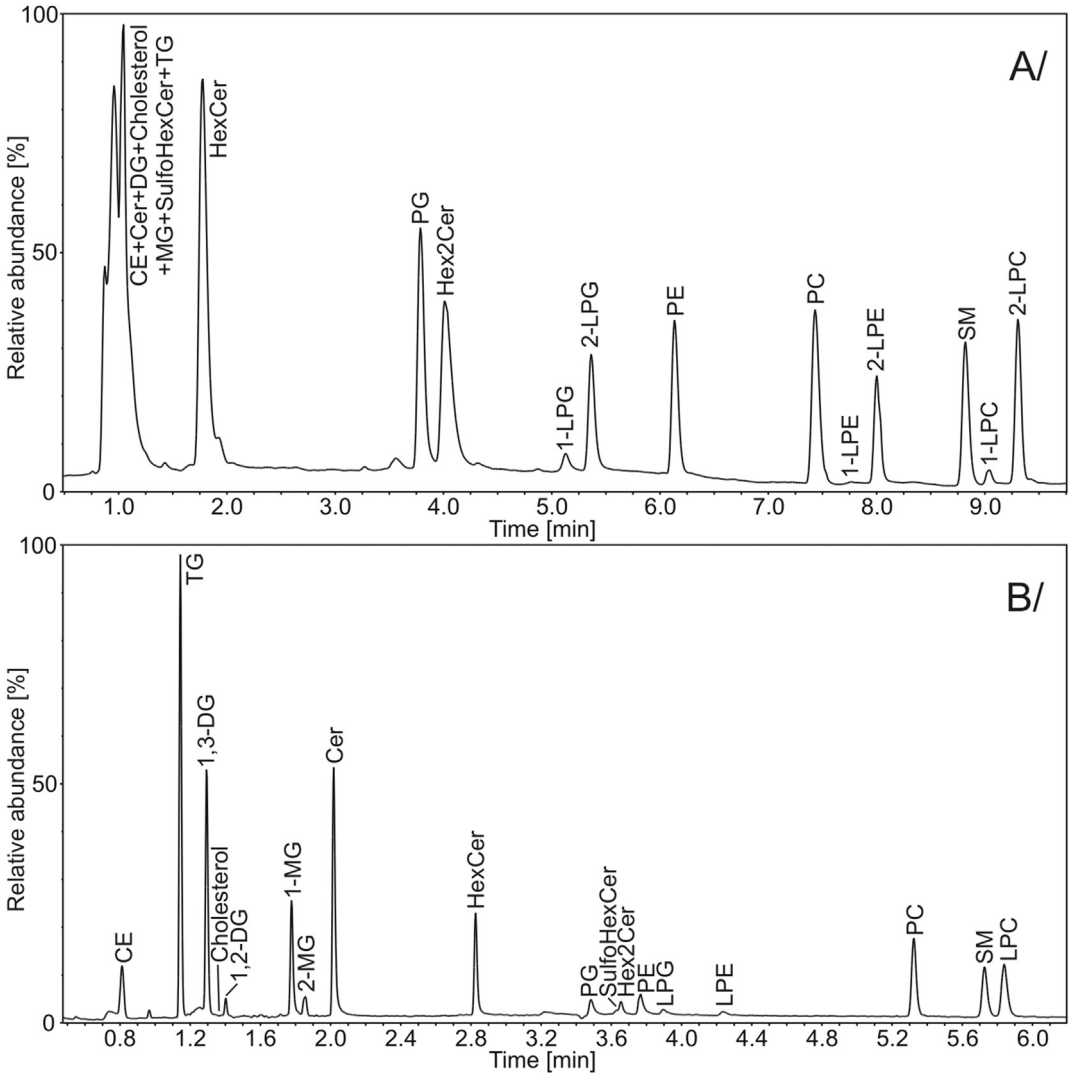

Fig. 2. Separations of lipid class representative standards in various chromatographic modes: (A) HILIC/MS separation of polar lipid classes and (B) UHPSFC/MS separation of both nonpolar and polar lipid classes. Reproduced from Ref. [24] with permission from Elsevier.

particular lipid species are expressed as the percentage within a particular lipid class or particular ratios of intensities of lipids from the identical lipid class can be evaluated [6].

2.4. Other spectroscopic methods

Several studies reported the use of other spectral techniques than MS for the analysis of lipids, such as Raman, infrared, and nuclear magnetic resonance (NMR) spectroscopy. Lipid classes have characteristic bands in Raman spectra, where the connection of Raman spectroscopy with optical or imaging techniques were reported for the lipid analysis of cells, tissues, and body fluids [71–74]. Fiber-optic Raman probes allows *ex vivo* and *in vivo* studies for diagnostic purposes [73]. Various Raman techniques have been used for the differentiation of normal and various cancer samples [73] as well as for normal, benign, and malignant tissues samples [75,76]. Fourier transform infrared spectroscopy is another spectroscopic technique, where the quantitation is based on the Lambert-Beer law [77,78]. Lipid quantitation for cholesterol, sphingomyelins, and phospholipids in brain [78] and prostate cancer cells were reported by infrared spectroscopy [77]. Habartová et al. [79] used the combination of chiroptical and vibrational spectroscopies for the identification of pancreatic cancer from human plasma. They discovered differences in the lipid metabolism and the protein secondary structures with specificity and sensitivity above 90%.

NMR spectroscopy is a powerful tool for structural elucidation with high reproducibility and directly applicable for the quantitation. NMR spectroscopy is completely free of matrix and suppression effects known in MS. However, the trace and multicomponent analysis may be very challenging due to the high complexity of NMR spectra for complex biological samples. ^{1}H and ^{13}C NMR are suitable for non-polar and polar lipids, while ^{31}P NMR is applicable for all lipids containing phosphorous, i.e., phospholipids and sphingolipids [80–82]. For differentiation of cancerous and healthy samples, the comparison of NMR spectra is a commonly used approach leading to the identification of characteristic disease and healthy fingerprints [82].

3. Clinical applications of oncolipidomics

In order to ensure comparable quantitative results within various laboratories performing lipidomic analysis, some guidelines are necessary for possible applicability in clinical and diagnostic

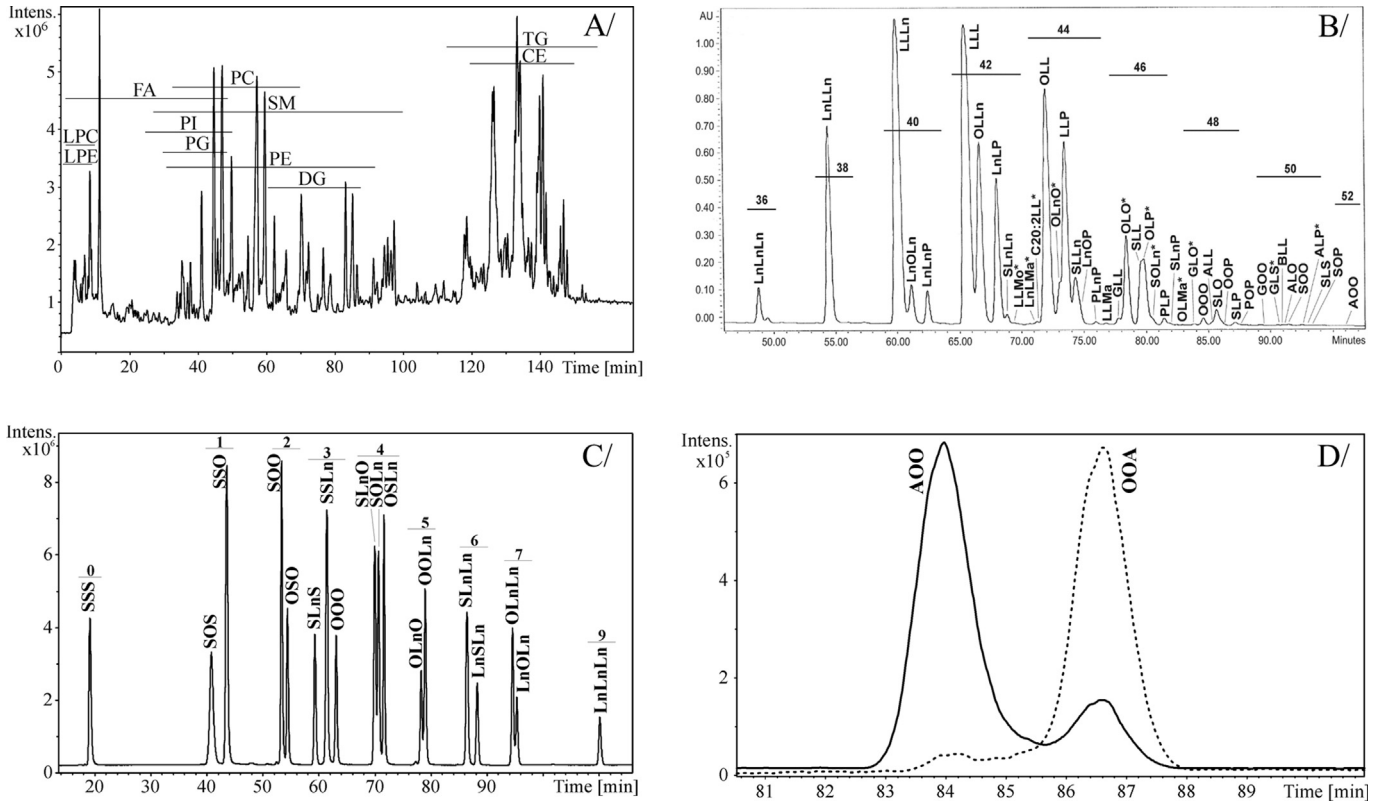

Fig. 3. Lipid species separation by various chromatographic techniques. (A) Positive-ion RP-UHPLC/ESI-MS chromatogram of total lipid extracts of human plasma. Reproduced from Ref. [48] with permission from Elsevier. (B) NARP chromatographic separation of walnut oil. Reproduced from Ref. [52] with permission from Wiley and Sons. (C) Silver-ion HPLC/APCI-MS chromatogram of triacylglycerols. Reproduced from Ref. [54] with permission from Elsevier. (D) Chiral HPLC/APCI-MS chromatogram of enantiomers synthesized by the stereospecific esterification of 2,3- and 1,2-isopropylidene-sn-glycerols. Reproduced from Ref. [56] with permission from American Chemical Society.

purposes. The physiological concentration ranges of studied lipids should be determined for healthy population to enable future diagnostic applications. Therefore, it is important that within the lipidomic community results for lipids should always be reported in the same way with regard of classification, nomenclature, and concentration units in order to compare quantitative results obtained in various laboratories. Furthermore, the quality of methodologies used for lipidomics can be controlled by applying a universal reference material, such as the NIST 1950 plasma and quantified results can be compared to already published data from various laboratories [83,84]. The use of isotopically labeled standards for the quantitation of various lipid classes is costly especially for high number of investigated samples. Consequently, the use of less expensive non-endogenous internal standards may be preferable. However, all used internal standards should be tested for their applicability for quantitation and results should again be compared to already published data as well as the comparison of exogenous standards to isotopically labeled ones may further confirm the reliability of quantitative results. The verification of the lipidomic data by the use of different MS based methods may further enhance reliability. All mentioned strategies may lead to comparable and reproducible results obtained by various research

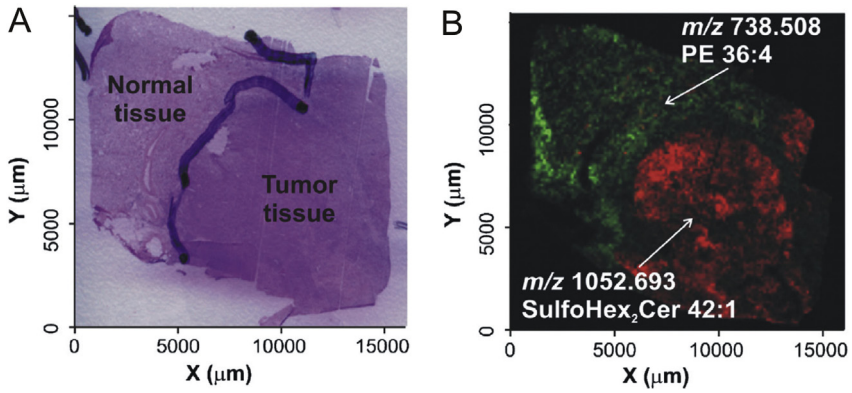

Fig. 4. Comparison of hematoxylin and eosin staining (a) with MALDI-MS imaging (b) of two slices of normal and tumor tissue. Reproduced from Ref. [6] with permission from American Chemical Society.

Table 1
List of dysregulated lipids for various types of cancer.

Cancer type	Sample type	Number of subjects (H = healthy, C = cancer)	Upregulated lipids[a]	Downregulated lipids[a]	Method (IS)	Reference
Bladder cancer	Tissue	20 H + 20 C	PS 36:1, PI 38:4, FA 18:1	–	DESI-MSI	[85]
	Urine	345 H + 95 C	SM with 16:0	–	UHPLC/MS/MS, GC/MS (IS:xeniobiotic compounds)	[86]
		26 H + 25 C	TG 52:4, TG 50:2, TG 52:3, TG 54:4, TG 50:1, TG 52:2, TG 54:3, CE 20:4, CE 16:1, CE 18:2, CE 16:0, CE 18:1, SM 32:1	–	LC/QTOF-MS (IS:inorganic phosphorous)	[87]
Breast cancer	Plasma	25 H + 55 C	SM 40:3, SM 32:2, SM 34:2, SM 40:2, SM 38:3, C4 carnitine	PC 34:2, PC 40:3, PC 42:5, LPC 16:0, LPC 18:0	LC/MS (IS: Biocrates IDQ p180)	[88]
		110 H + 84 C	PC 32:1, PC 34:4, PC 38:3, PC 40:5, PC 40:3, PC 44:11, PC O-32:2, PC O-38:3	LPC 18:3, LPC 20:2, LPC 20:1, LPC 20:0, CE 19:1, CE 19:0, CE 20:0	LC/QqQ MS (IS: 2 per class)	[89]
		41 H + 37 C	PC 40:7, PC 46:1, DG 36:3	PE 34:1	UHPLC/QTOF-MS	[90]
		29 H + 29 C	LPC 16:1, LPC 18:1, LPC 18:4, LPC 20:4, LPE 18:0, LPE 18:1, PA 32:0, PA P-31:1, PG 22:0, FA 14:0, FA 16:1, FA 16:0, FA 18:2, FA 18:1, FA 20:4, FA 18:0, SM 41:2, SM 42:2, MG 18:1, MG 18:2, DG 32:1, DG 34:1, DG 34:2, DG 34:3, DG 36:2, DG 36:4, DG 38:3, DG 40:4, TG 48:0, TG 48:1, TG 48:2, TG 48:3, TG 50:0, TG 50:1, TG 50:2, TG 50:3, TG 50:4, TG 52:0, TG 52:1, TG 52:2, TG 52:3, TG 52:4, TG 52:4, TG 52:5, TG 54:2, TG 54:3, TG 54:4, TG 54:5, TG 54:6, TG 56:5, TG 56:6, TG 56:7, TG 56:8, TG 58:9, PC P-31:1, PC 32:1, PC 36:0, PC 36:1, PC O-36:4, PC 38:4, PC P-38:4, PC 38:6, PC 38:7, PC 40:5, PC 40:6	cyclic LPA 18:1	LC/QTOF-MS, GC/TOF-MS	[91]
	Serum	25 H + 50 C	PC O-34:2, PC O-36:4, PC O-36:3	–	DI/TOF-MS (IS: PC 28:0)	[92]
		20 H + 20 C	LPE 18:1, LPE 18:0, LPE 22:0, SM 38:0, PC 38:0, DG 34:2, DG 44:5	Cer 44:1, Cer 38:1, Cer 41:1, LPC 18:0	LC/QTOF-MS	[93]
	Tissue	10 H + 267 C	PC 30:0, PC 32:0, PE 36:4, GlcCer 42:0(2OH), PC 32:1, PC 36:4, PE 38:4, PC 40:6, PE P-36:4, PI 38:4, PE P-34:2, SM 42:1, PC 38:5, PC 38:4, PE 38:3, PE P-38:4, PE 34:1, PC 32:1, PE 36:1	–	UHPLC/QTOF-MS (IS: LPC 17:0, Cer 35:1, PC 34:0, PE 34:0, TG 51:0 + labeled IS)	[94]
		32 H + 50 C	PC 32:1, PC 34:1, PC 36:1, PA 36:2, FA 16:1, FA 18:1, FA 20:1	PC 38:4, PC 38:6, PC 38:4, PA 38:3, PA 40:5, SM 40:1, SM 42:2, PI 38:4, PE 38:4, FA 20:4, FA 22:4, FA 22:5	MALDI-FTICR-MS	[95]
		10 H + 10 C	PI 34:1, PI 32:1, PI 32:0, PE 34:1, PE 36:2, SM 34:1	PI 36:4, PI 38:4, PE P-36:4, PE-P-38:5/O-38:6, PE P-38:4/O-38:5, SM 36:2, SM 40:2	HPLC/ESI-MS (IS: PE 29:1)	[7]
		10 H + 10 C	PI 32:1, PE 32:1, PC 32:1, PI 34:1, PE 34:1, PC 34:1, PI 40:6, PE 40:6, PC 40:6, PE 38:4	PI 36:4, PE 36:4, PC 36:4, PI 38:4, PC 38:4, PE P-38:4, PC P-38:4, PE P-38:5, PE P-36:4	HPLC/ESI-MS (IS: PE 29:1)	[9]
	Urine	29 H + 31 C	PG O-36:1, PA O-16:0, PC 34:1, DG 32:0, PA 37:6, PA 33:3	LPE 18:2, LPE 20:4, LPC 14:1	LC/QTOF-MS, GC/TOF-MS	[96]
Colorectal cancer	Plasma	125 H + 133 C	–	LPC 18:1, LPC 18:2	DI/ESI-QqQ-MS (IS: LPC 12:0)	[97]
		18 H + 23 C	PC 32:0, PE 35:0, PC 31:3, PE 34:3, PC P-38:5, PC O-38:6, PC P-40:5, PC O-40:6	LPC 16:0, LPC P-18:1, LPC P-18:2, LPC 18:0, LPC P-16:1	DI/QTOF-MS	[98]
		20 H + 48 C	FA 10:0	–	GC/TOF-MS (IS: d3-8,8,8-decanoic acid)	[99]
		10 H + 25 C	PG 34:0, SM 42:2, Cer 44:5	LPC 18:3, LPC 18:2, PE O-36:3, PE O-38:3, SM 38:8	2D-LC/QTOF-MS (IS: FA 17:0, PE 28:0, PC 28:2, PG 28:0, LPS 17:1, LPC 17:0, LPE 17:1, LPG 17:1, SM 35:1, Cer 30:1, GluCer 30:1, GalCer 26:1, LacCer 26:1, MG 17:0, DG 24:0, TG 49:3)	[100]
	Serum	110 H + 112 C	–	two or three hydroxylated ultra-long chain fatty acids C28	FTICR-MS	[101]
		52 H + 52 C	Palmitic amide, oleamide, FA 14:0, FA 18:0, FA 20:3, hexadecanedioic acid	LPC 16:0, LPC 18:2, LPC 18:1, LPC 18:0, LPC 20:4, LPC 22:6, PC 34:1, LPA 16:0, LPA 18:0	DI/FTICR-MS (IS: reserpine, haloperidol, lidocaine, 2,4-dichlorophenoxyacetic acid)	[102]
		102 H + 101 C	Oleamide, FA 18:1, FA 18:2	LPC 14:0, LPC 16:1, LPC 20:0, LPC 18:1, LPA 18:0	UHPLC/QTOF-MS, GS/MS (IS: L-2-chlorophenylalanin, heptadecanoic acid)	[103]
		20 H + 20 C		Polyunsaturated fatty acids PC and LPC, LPA 18:2		[104]

			(Saturated fatty acids in DG and LPC), LPC 18:0, LPC 16:0		UHPLC/QTOF-MS (IS: LPC 17:0, PC 34:0, PE 34:0, PG 34:0, PS 34:0, PA 34:0)	
		95 H + 95 C	Very long-chain FA	–	LC/HRMS (IS: ^{13}C-cholic acid)	[105]
		1449 H + 144 C	SM 34:1, PC 34:2, PC 34:1, PC 36:4, PC 36:2	–	DI-FTICR-MS (IS: PC 36:0)	[106]
	Tissue	12 H + 12 C	PC 34:1, LPC 16:0, LPC 18:1	–	MALDI-IMS	[107]
Esophageal cancer	Plasma	53 H + 53 C	PI, PS 30:0, LPC 22:2, GM2 42:2, PI, PE, PC, PA	–	UHPLC/TOF-MS	[108]
		24 H + 44 C	Octanoylcarnitine, LPC 16:1, LPC 16:0, LPC 18:0, decanoylcarnitine	FA 18:2, uric acid	HPLC/QTOF-MS (IS: levofloxacin, hesperidin, rhein)	[109]
	Serum	10 H + 40 C	LPC 20:4, PC 34:2, PC 36:2	PC 36:3, PC O-36:3, LPC 18:2	LC/QTOF-MS	[110]
Gastric cancer	Serum	1449 H + 94 C	SM 34:1, PC 34:2, PC 34:1, PC 36:4, PC 36:3, PC 36:2	–	DI/FTICR-MS (IS: PC 36:0 + calibration standards SM 34:1, PC 34:2, PC 34:1, PC 36:4, PC 36:2)	[106]
	Tissue	16 H + 19 C	PC 32:1, PC 34:1, PC 36:1, PA 36:2, SM 34:1, PC 36:3	PC 38:4, PC 38:6, PC 38:4, PA 38:3, PA 40:5, SM 40:1, SM 42:2, PE 38:4, PI 38:4	MALDI-FTICR-MS	[95]
Liver cancer	Serum	90 H + 82 C	–	LPC 16:0, LPC 18:0; PC 16:0, PC 18:0, PC 34:1, PC 34:2, PC 38:6, PC 36:4, PC 36:2	UHPLC/QTOF-MS	[111]
	Urine and serum	71 H + 82 C	–	FA	GC/QTOF-MS, UHPLC/QTOF-MS	[112]
Kidney cancer	Serum	20 H + 31 C	GM3	LPC 16:0, LPC 18:0, LPC 18:1, LPC 18:2, LPC 20:2, LPC 20:1	DI/MS + LC/MS	[113]
		25 H + 33 C	GM3 43:1, GM3 40:2, sphinganine	LPC 16:0, LPC 18:0, SM 34:1, SM 42:2, SM 40:2, SM 32:1, LPC 18:1, LPC 18:2, LPC 15:0, LPC 17:0, LPC P-18:0, LPC P-16:0, LPC 14:0, LPC 20:2, LPC 20:1, LPE 22:0, LPE 22:1, SM 38:1, carnitine, thromboxanes, PC	RP-LC/MS, HILIC-LC/MS	[114]
		24 H + 24 C	GM3 40:2, C17 sphinganine	PE P-16:0, SM 34:1, PC	LC/TOF-MS	[115]
	Tissue	11 H + 11 C	PI 38:4, PI 40:4, PS 36:1, PG 36:2	FA 12:0	DESI-MSI	[116]
		10 H + 10 C	PC 30:3	PC 26:0, PC 30:2	MALDI-FTICR-MS	[117]
		20 H + 20 C	PI 38:5, PI 36:2, PI 40:5, PI 40:4, PI 36:0, PC 38:4, PC 36:2, PC 32:0, PE P-38:4, PE P-38:5, PE 36:1	PI 36:1, PI 36:4, PI 34:1, PC 34:2, PC 36:4, PC 34:1, PE 38:4, PE 36:4, PE 34:2, SM 36:2, SM 36:1, SM 38:2, SM 38:1	HPLC/ESI-MS (IS: PE 29:1)	[8]
		49 H + 49 C	O-PC, O-PE, CE, TG, Cer	PE, DG, PI, CL, SM	LC/TOF-MS (IS: PC 32:0-d6, TG 34:2, LTB4-d4)	[118]
		78 H + 80 C	$SHex_2Cer$ 44:2, $SHex_2Cer$ 43:2, $SHex_2Cer$ 43:1, $SHex_2Cer$ 42:0(OH), $SHex_2Cer$ 44:1, $SHex_2Cer$ 41:2, $SHex_2Cer$ 40:0(OH), $SHex_2Cer$ 34:2(OH), $SHex_2Cer$ 42:3(OH)	SHexCer 40:1(OH), SHexCer 40:0(OH), SHexCer 41:0(OH), SHexCer 42:1(2OH), SHexCer 42:0(2OH), SHexCer 41:1(OH), SHexCer 41:0(2OH), SHexCer 43:1(OH)	MALDI-Orbitrap-MS (IS: SHexCer 30:1)	[6]
		20 H + 20 C	PI 40:5, PI 40:4; GM3 41:1, GM3 36:2, GM3 41:2, GM3 34:1, GM3 42:3, GM3 42:2	SHexCer 41:1(OH), SHexCer 38:1(OH), SHexCer 40:1(OH), SHexCer 42:0(2OH), SHexCer 42:1(OH), PS 36:4; PI 34:0, LPI 16:0	HPLC/QTOF-MS (IS: SHexCer 30:1, PS 28:0, GM3 30:1)	[119]
Lung cancer	Plasma	12 H + 12 C	–	LPC 16:0, LPC 18:1, LPC 18:2, LPC 18:0	UHPLC/QTOF-MS	[120]
		200 H + 100 C	S1P, ceramides		LC/MS/MS	[121]
		28 H + 31 C	–	PC 34:4, PE 34:2, PE 36:1, PE 36:2, PE 36:4, PE 38:4, PE 38:6, PE 40:4, PE 40:5, PS 38:4, Cer 42:0	LC/MS, GC/MS	[122]
		17 H + 17 C	PS 36:1, PE 40:6, FA 20:1, FA 22:1, TG 62:13, DG 40:8, TG 60:7, FA 18:2	PE 40:5, DG 42:8, DG 40:6, PE 38:5, LPE 18:0, PE P-38:4, PE P-36:2, PE P-38:5, PE P-36:1	LC/HRMS	[123]
		22 H + 22 C	LPE 18:1, PE P-40:3	CE 18:2, SM 22:0	ESI-MS	[124]
	Serum	495 H + 58 C	LPC 18:1, LPC 20:4, LPC 20:3, LPC 22:6, SM 34:1	Oleamide	DI/FTICR-MS (IS: LPC 18:0, LPC 18:1, PC 36:2, SM 16:0)	[125]
		23 H + 23 C	LPC 16:0, LPC 18:0, LPC 18:2, LPC 20:4, LPC 20:5, LPC 22:3, DG 38:8, SM 32:1, fatty acid amides: C20:1, C20:0, C22:2, C24:1, C22:1	Carnitine 10:1, carnitine 8:1, FA 16:0, FA 18:0, FA 18:1, FA 18:2, FA 20:4, FA 16:1	UHPLC/QTOF-MS	[126]
		487 H + 474 C + 479 benign disease	FA 16:0, FA 16:1, FA 18:0, FA 18:1, FA 18:3, FA 20:3, FA 22:6 (nonesterified and esterified)	FA 20:5 (nonesterified and esterified)	MALDI-ICR-MS (IS: FA 17:0, FA 21:0)	[127]
		29 H + 61 C	PE 34:2, PE 36:2, PE 38:4	–	GC/TOF-MS, HILIC/QTOF-MS	[128]
		599 H + 246 C	SM 34:1, PC 34:2, PC 34:1, PC 36:3, PC 36:2	–	DI/FTICR-MS (IS: PC 36:0)	[106]
		300 H + 100 C	LPC 18:2, LPC 18:1, LPC 18:0, LPC 16:0	–	MALDI-TOF-MS, LC/MS (IS: LPC 17:1)	[129]
	Tissue	21 H + 21 C	PC 34:1, PC 36:2, PC 36:3	–	MALDI-TOF-MS	[130]
		21 H + 52 C	PC 38:2, PC 36:4, PC 36:3, PC 34:1, PC 38:4	PC 36:1, PC 34:2, PC 36:2	DESI-MSI, LC-Orbitrap-MS	[131]
		73 H + 73 C	PI 38:3, PI 40:3, PI 38:2	SM 40:1, SM 42:1, SM 36:1		[132]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Sample type	Number of subjects (H = healthy, C = cancer)	Upregulated lipids[a]	Downregulated lipids[a]	Method (IS)	Reference
					ESI-MS/MS (IS: PC 25:0, PC 43:6, SM 30:1, PE 25:0, PE 43:6, PI 25:0, PI 31:1, PI 43:6, PS 25:0, PS 31:1, PS 37:4); MALDI-FTICR	
Ovarian cancer	Plasma	27 H + 117 C	LPA 16:0, LPA 20:4	–	TLC, ESI-MS (IS: LPA 18:1, LPC 18:1)	[133]
		50 H + 50 C	–	LPS O-18:0, CE 18:3, TG 48:2, PG P-32:0, TG 48:3, PS O-34:1, TG 54:9, TG 50:5, TG 50:4, PE 38:4, TG 48:1, LPS O-20:0, PE 38:4, TG 50:1	LC/MS (IS: LPC 17:0, PC 34:0, PE 34:0, TG 51:0, Cer 35:1)	[134]
		31 H + 39 C	PC 31:2, PE P-42:4	LPC P-15:0, LPC O-16:0, LPC 18:1, LPC 18:0, LPG 20:5, LPC 20:3, LPC 22:6, Cer 41:1, SM 32:2, SM 32:1, PC P-34:4, PC 34:4, PC P-36:3, PE P-40:6, PC 36:3, PC 36:1, PC 38:6, PC 38:4, PC 38:3, PC 38:2, PC P-40:6, PG 39:1, PC 40:5, PC 42:11, LacCer 34:1, PS 32:6, PI 40:9, PI 42:9, PI 40:7	UHPLC/QTOF-MS	[135]
	Serum	55 H + 50 C	LPA 16:0, LPA 18:1, LPA 18:0, LPA 20:4	–	LC/ESI-MS (IS: LPA 17:0)	[136]
	Tissue	12 H + 12 C	SHexCer	–	MALDI-MS, LC/MS (IS: C12 ST, C12 GalCer, C12 GlcCer)	[137]
Pancreatic cancer	Plasma	100 H + 100 C	Glycoholic acid	Galactitol, LPC 14:0, propionylcarnitine	LC/TOF-MS, GC/TOF-MS (IS: p-chlorophenylalanine)	[138]
	Serum	599 H + 115 C	–	PC 36:4, SM 34:1, PC 34:2, PC 36:3, PC 36:2, SM 34:1	DI/FTICR-MS (IS: PC 36:0)	[106]
Prostate cancer	Plasma	36 H + 105 C	SM 36:1, PC 40:7, LPC 20:4, LPC 18:1, LPC 18:0, LPC 16:0, PC 38:5, PC 38:4, SM 36:2, SM 34:2, SM 34:1, PC O-36:4, PC O-36:2, PC O-36:1	–	DI/QqQ-MS (IS: PC 24:0, PC 48:2, LPC 13:0, LPC 19:0, PE 24:0, PE 46:0, LPE 14:0, LPE 18:0, LPG 14:0, LPG 18:0, PA 28:0, PA 40:0, PS 28:0, PS 40:0, PI 34:0, CE 13:0, CE 23:0)	[139]
		51 H + 80 C	–	SM 34:1, SM 36:1, SM 36:2, SM 38:1, SM 40:1, SM 40:2, SM 41:1, SM 41:2, SM 42:1, SM 42:2, SM 42:3	UHPLC/MS (IS: IS Mix)	[140]
	Serum	76 H + 57 C	PC 40:3, PC 42:4	PC P-38:4	DI/MS/MS (IS: PC 24:0, PC 48:2, LPC 13:0, LPC 19:0, PE 24:0, PE 46:0, LPE 14:0, LPE 18:0, LPG 14:0, LPG 18:0, PA 28:0, PA 40:0, PS 28:0, PS 40:0, PI 34:0, PI 36:0, CE 13:0, CE 23:0)	[141]
		18 H + 18 C	PA 32:1, PC 37:3, PC 39:6, PE 29:1, PE 42:4, PE 42:5, FA 18:3, FA 19:1, DG 40:9, DG 41:0, TG 52:3, TG 59:5, TG 60:11, TG 61:5, TG 45:2	PA 14:0, PE 31:3, FA 16:3, FA 20:2, FA 20:4, FA 22:0, FA 22:3, DG 30:2, DG 32:3	ESI-MS/MS, GC/MS (IS: heptadecanoate, heptadeconoic acid)	[142]
	Tissue	14 H + 14 C	PI 36:1, PI 38:3, PI 38:2	–	MALDI-MSI	[143]
		31 H + 31 C	–	LPC 16:0(OH), SM 34:1	MALDI-MSI	[144]
		76 H + 76 C	CE 18:1, CE 24:5, CE 24:4, CE 20:1, Cer 40:2, FA 22:3, CE 22:6, TG 58:1, Cer 38:2	–	UHPLC/TOF-MS (IS: PC 38:0, PE 34:0, LPC 19:0, SM 30:1, TG 45:0, Cer 35:1, FA 16:0-d3, CE 13:0)	[145]
	Urine	13 H + 15 C	PS 36:2, SM 34:1, HexCer 34:1, HexCer 40:1, HexCer 42:1, HexCer 42:2, LacCer 34:1, LacCer 42:2, Gb3 34:1, PC 34:1, PC 34:2, PS 36:2, PE-P-34:2 (PE-O-34:3), PE-P-36:2 (PE-O-36:3), PE-P-36:3	PS 34:1, PS 36:1, PS 36:2, SM 40:1, SM 42:1, SM 42:2, Gb3 42:1, Gb3 42:2, PC 36:2, PE P-36:0, PE P-34:1 (PE O-34:2), PE P-36:4 (PE O-36:5), PE P– 36:1 (PE O-36:2), PE P-38:4 (PE O-38:5), PE P-36:2, PE P-38:5	DI/QTRAP-MS (IS: LPC 17:0, PC 34:0, PE 34:0, PS 34:0, PG 34:0, PA 34:0, Cer 35:1, SM 30:1, DG 34:1, CE 18:0-d6, GlcCer 34:1-d3, LacCer 34:1-d3, Gb3 35:1)	[146]
Thyroid cancer	Serum	122 H + 167 C	PC 34:2, PC 36:3, SM 42:2, PC 34:1, PC 36:1, PC 35:2, PC 32:0	PA 36:3, PA 38:4 PA 38:3, PA 40:5, SM 34:1, PA 42:10, PA 38:5, LPC 20:4, PC 38:5, PC 40:6, PC 38:6, PC 36:2, SM 40:1	MALDI-FTICR-MS	[147]
		30 H + 30 C	FA 20:1, FA 18:1, FA 16:0, FA 16:1, FA 17:0	LPC P-16:0, LPC 22:6, LPC 22:5, LPC 20:5, LPC 20:4, LPC 20:2, LPC 20:1, LPC 18:3, LPC 18:1, LPC 18:0, LPC 16:1, LPC 16:0, LPC 22:4, FA 22:4, FA 14:0	LC/MS	[148]
	Tissue	15 H + 21 C	PC 34:1, 36:1, 32:0, SM 34:1, PC 34:1, PC 32:0, PC 36:1, PA 36:3, PA 36:2, PC 38:6, PA 38:5, PA 38:4	SM 36:2, PA 40:5, PC 34:2, PC 36:3, PC 36:2, PC 38:3, PC 38:4, PA 38:3, SM 42:2, SM 40:1	MALDI-FTICR-MS	[147]
		12 H + 18 C	PC 32:1, PC 34:1, PC 36:1, PA 36:2, PC 38:6	PC 38:4, PC 38:6, PC 38:4, PC 38:3, PC 40:5, SM 40:1, SM 42:2, PA 38:3, PA 40:5, PE 38:4, PI 38:4	MALDI-FTICR-MS	[95]

[a] In some cases, lipid annotation from original references is changed here to provide the uniform style for easier data comparison.

Table 2
Summary of lipid species most frequently upregulated in cited references in this review.

Cited	Upregulated lipid species
15 times	PC 34:1
10 times	SM 34:1
8 times	PC 32:1
7 times	PC 36:1
6 times	FA 18:1, PC 32:0, PC 34:2, PC 36:2, PC 36:3, LPC 16:0
5 times	LPC 18:1, LPC 20:4, PC 38:4, LPC 18:0
4 times	PA 36:2, PC 36:4
3 times	FA 16:0, FA 16:1, FA 18:0, FA 18:2, FA 20:1, LPE 18:1, PC 38:6, PC 40:6, PC P-36:3, PE 34:1, LPC 16:1, PE 38:4, PI 38:4, PI 40:4, PS 36:1, SM 42:2, TG 52:3, TG 52:4
twice	CE 18:1, DG 34:2, FA 14:0, FA 18:3, FA 20:3, GM3 40:2, LPA 16:0, LPA 20:4, LPC 18:2, LPE 18:0, oleamide, PC 38:5, PC 40:3, PC 40:5, PC 40:7, PE 36:1, PE 36:2, PE 40:6, PE P-38:4, PI 32:1, PI 34:1, PI 38:2, PI 38:3, PI 40:5, PS 36:2, SM 34:2, SM 32:1, TG 50:1, TG 50:2, TG 52:2, TG 54:3, TG 54:4

groups and may allow the identification of lipid profiles or lipid biomarkers characteristic for various diseases giving lipidomics in clinics a real chance.

3.1. Dysregulated lipids in cancer research

The overview of published papers on the analysis of dysregulated lipids in human samples is shown in Table 1 for these cancer types: bladder [85–87], breast [7,9,88–96], colorectal [97–107], esophageal [108–110], gastric [95,106], liver [111,112], kidney [6,8,113–119], lung [106,120–132], ovarian [133–137], pancreatic [106,138], prostate [139–146], and thyroid [95,147,148]. The following types of biological materials were studied in cited references: serum (15 times), plasma (12 times), tissues (13 times), and urine (4 times). This overview suggests a potential for the future application of lipidomics as a tool for the differentiation of cancer and healthy samples, but on the other hand, the literature search revealed also limitations of the current state-of-art, because the presented data are not consistent among all studies. The key problems identified in numerous cited references are that many reported methods do not use any method validation, QC samples, IS for the lipidomic quantitation, etc., which contributes to this heterogeneity in reported data. It is clear that there is a significant space for the improvement, as already mentioned in some previous papers [10,20,149] and formulated by the Lipidomics Standards Initiative [23].

The threshold criterion for Table 1 was set to have at minimum 10 subjects per each cancer patient and healthy control groups. The information provided in Tables 1–3 has been unified in line with the shorthand notation for lipids for MS [4]. In some references, more detailed information were provided, for example including the identification of fatty acyls, but for the better mutual comparison of presented information, we unified the reporting style in our review. The full version of the information can be found in original papers. Table 1 lists all dysregulated lipids in individual cited references sorted according to the type of cancer and analyzed biological sample. The most frequently upregulated and downregulated lipid species in these papers are highlighted in Tables 2 and 3, respectively. The most frequently reported dysregulated lipid classes are PC, LPC, and SM, which is probably strongly affected by the fact that these lipid classes are most abundant in cells and body fluids, and therefore most frequently analyzed.

The complexity of lipidomic analysis for clinical samples can be illustrated by LPC 16:0 and LPC 18:0, which are reported as downregulated in 8 and 10 cases, respectively (Table 3), while the opposite behavior is observed in 6 and 5 papers, respectively (Table 2). It is not clear, whether this behavior reflects the different dysregulation patterns for different cancer types or whether it could be caused by shortcomings in individual methods applied, because they often lack the right method validation, QC, and IS. In case of mono- and diunsaturated PC, frequently reported upregulated species are PC 34:1, PC 32:1, PC 36:1, PC 34:2, and PC 36:2 (Table 2), while polyunsaturated ones (PC 38:4, PC 38:6, and PC 36:4) are mostly downregulated (Table 3). Similar trends are observed for some other phospholipid classes, for example SM 34:1 are reported as upregulated in cancer, and PE 36:4, PI 38:4, and PA 40:5 are downregulated. In case of two or three references, several other upregulated lysophospholipids, triacylglycerols, and cholesterol esters were reported (Table 2). Table 4 shows, how frequently the individual cancer types were investigated. The top three are lung cancer with 14 references followed by breast cancer (11 references) and colorectal cancer (11 references).

4. Summary and future outlooks

This review shows that in some cases similar trends in the regulation pattern of lipids can be observed even for different types of cancer, which is a positive sign for possible future screening of multiple cancer types using one analytical platform. Some generic trends are observed based on multiple citations of the same dysregulated lipids, such as the strong dysregulation of LPC in both directions, the upregulation of several mono- and diunsaturated PC,

Table 3
Summary of lipid species most frequently downregulated in cited references in this review.

Cited	Downregulated lipid species
10 times	LPC 18:0, PE 36:4
9 times	PC 38:4, SM 40:1
8 times	LPC 16:0, LPC 18:1
7 times	LPC 18:2, SM 34:1, SM 42:2
6 times	PC 34:2, PC 36:2, PC 38:6
5 times	PA 38:3, PA 40:5, PI 38:4
4 times	LPC 20:1, LPC 20:2, PC 36:3, PC 36:4, PE P-36:2, PE P-38:4, PE P-38:5, SM 36:2
3 times	FA 20:4, LPC 14:0, LPC 18:3, LPC 20:4, LPC 22:6, PC 34:1, PC 38:3, PE P-36:4, PI 36:4, SM 36:1, SM 38:1, SM 40:2, SM 42:1
twice	Cer 41:1, FA 18:2, FA 22:4, LPA 18:0, LPC 16:1, LPC 20:0, LPC P-16:0, PC 34:4, PC 36:1, PC 40:5, PC P-38:4, PE 34:2, PE 40:5, PE P-36:1, SHexCer 40:1(OH), SHexCer 41:1(OH), SHexCer 42:0(2OH), SM 32:1

Table 4
Cancer types sorted according to the number of citations in this review.

Cited	Type of cancer
14 times	Lung cancer
11 times	Breast cancer, colorectal cancer
9 times	Kidney cancer
8 times	Prostate cancer
5 times	Ovarian cancer
4 times	Thyroid cancer
3 times	Bladder cancer, esophageal squamous cell carcinoma,
twice	Hepatocellular carcinoma, gastric cancer, pancreatic cancer

and the downregulation of polyunsaturated PC. However, it should not be overlooked that sometimes different research groups report completely opposite dysregulation of lipids even for the same cancer type, which is probably caused by shortcomings in the methodology, because many papers (especially earlier published works) underestimate the importance of the method validation, QC, and the appropriate selection of IS. It is surprising how many studies do not use any IS, which should be a basic prerequisite for any MS based quantitation. These discrepancies confirm the urgent need of harmonization of analytical approaches used for the lipidomic quantitation to make sure that all laboratories follow the minimum standards for reporting reliable data, which should result in the same trends observed at all sites, otherwise the confusion may compromise the biomarker research. Another issue is the mismatch of various annotation styles for reporting lipid molecules, which increases the level of confusion especially for less experienced researchers. These issues should be discussed within the lipidomic community with the goal to harmonize minimum requirements for the analytical methodology and data reporting in lipidomics, which is the goal of recently established the Lipidomics Standard Initiative [23].

Declaration of competing financial interests

The authors declare no financial interests.

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References

[1] E. Fahy, S. Subramaniam, H.A. Brown, C.K. Glass, A.H. Merrill, R.C. Murphy, C.R.H. Raetz, D.W. Russell, Y. Seyama, W. Shaw, T. Shimizu, F. Spener, G. van Meer, M.S. VanNieuwenhze, S.H. White, J.L. Witztum, E.A. Dennis, A comprehensive classification system for lipids, Eur. J. Lipid Sci. Technol. 107 (2005) 337–364.
[2] E. Fahy, S. Subramaniam, R.C. Murphy, M. Nishijima, C.R.H. Raetz, T. Shimizu, F. Spener, G. van Meer, M.J.O. Wakelam, E.A. Dennis, Update of the LIPID MAPS comprehensive classification system for lipids, J. Lipid Res. 50 (2009) S9–S14.
[3] LIPID MAPS Lipidomics Gateway. http://www.lipidmaps.org, (accessed April 23, 2019).
[4] G. Liebisch, J.A. Vizcaino, H. Kofeler, M. Trotzmuller, W.J. Griffiths, G. Schmitz, F. Spener, M.J.O. Wakelam, Shorthand notation for lipid structures derived from mass spectrometry, J. Lipid Res. 54 (2013) 1523–1530.
[5] M.A. Chester, IUPAC-IUB joint commission on biochemical nomenclature (JCBN) nomenclature of glycolipids - recommendations 1997, Eur. J. Biochem. 257 (1998) 293–298.
[6] R. Jirásko, M. Holčapek, M. Khalikova, D. Vrána, V. Študent, Z. Prouzová, B. Melichar, MALDI Orbitrap mass spectrometry profiling of dysregulated sulfoglycosphingolipids in renal cell carcinoma tissues, J. Am. Soc. Mass Spectrom. 28 (2017) 1562–1574.
[7] E. Cífková, M. Holčapek, M. Lísa, D. Vrána, J. Gatěk, B. Melichar, Determination of lipidomic differences between human breast cancer and surrounding normal tissues using HILIC-HPLC/ESI-MS and multivariate data analysis, Anal. Bioanal. Chem. 407 (2015) 991–1002.
[8] E. Cífková, M. Holčapek, M. Lísa, D. Vrána, B. Melichar, V. Študent, Lipidomic differentiation between human kidney tumors and surrounding normal tissues using HILIC-HPLC/ESI-MS and multivariate data analysis, J. Chromatogr. B 1000 (2015) 14–21.
[9] E. Cífková, M. Lísa, R. Hrstka, D. Vrána, J. Gatěk, B. Melichar, M. Holčapek, Correlation of lipidomic composition of cell lines and tissues of breast cancer patients using hydrophilic interaction liquid chromatography/electrospray ionization mass spectrometry and multivariate data analysis, Rapid Commun. Mass Spectrom. 31 (2017) 253–263.
[10] B. Burla, M. Arita, M. Arita, A.K. Bendt, A. Cazenave-Gassiot, E.A. Dennis, K. Ekroos, X.L. Han, K. Ikeda, G. Liebisch, M.K. Lin, T.P. Loh, P.J. Meikle, M. Oresic, O. Quehenberger, A. Shevchenko, F. Torta, M.J.O. Wakelam, C.E. Wheelock, M.R. Wenk, MS-based lipidomics of human blood plasma: a community-initiated position paper to develop accepted guidelines, J. Lipid Res. 59 (2018) 2001–2017.
[11] A. Ghosh, K. Nishtala, Biofluid lipidome: a source for potential diagnostic biomarkers, Clin. Transl. Med. 6 (2017).
[12] G. Pocsfalvi, C. Stanly, A. Vilasi, I. Fiume, G. Capasso, L. Turiák, E.I. Buzas, K. Vékey, Mass spectrometry of extracellular vesicles, Mass Spectrom. Rev. 35 (2016) 3–21.
[13] E.C.-P. Chua, G. Shui, I.T.-G. Lee, P. Lau, L.-C. Tan, S.-C. Yeo, B.D. Lam, S. Bulchand, S.A. Summers, K. Puvanendran, S.G. Rozen, M.R. Wenk, J.J. Gooley, Extensive diversity in circadian regulation of plasma lipids and evidence for different circadian metabolic phenotypes in humans, Proc. Natl. Acad. Sci. Unit. States Am. 110 (2013) 14468.
[14] M. Wang, C. Wang, X. Han, Selection of internal standards for accurate quantification of complex lipid species in biological extracts by electrospray ionization mass spectrometry—what, how and why? Mass Spectrom. Rev. 36 (2017) 693–714.
[15] J. Folch, M. Lees, G.H. Sloane Stanley, A simple method for the isolation and purification of total lipides from animal tissues, J. Biol. Chem. 226 (1957) 497–509.
[16] E.G. Bligh, W.J. Dyer, A rapid method of total lipid extraction and purification, Can. J. Biochem. Physiol. 37 (1959) 911–917.
[17] V. Matyash, G. Liebisch, T.V. Kurzchalia, A. Shevchenko, D. Schwudke, Lipid extraction by methyl-tert-butyl ether for high-throughput lipidomics, J. Lipid Res. 49 (2008) 1137–1146.
[18] L. Löfgren, G.-B. Forsberg, M. Ståhlman, The BUME method: a new rapid and simple chloroform-free method for total lipid extraction of animal tissue, Sci. Rep. 6 (2016) 27688.
[19] M. Chocholoušková, R. Jirásko, D. Vrána, J. Gatěk, B. Melichar, M. Holčapek, Reversed phase UHPLC/ESI-MS determination of oxylipins in human plasma: a case study of female breast cancer, Anal. Bioanal. Chem. 411 (2019) 1239–1251.
[20] M. Holčapek, G. Liebisch, K. Ekroos, Lipidomic analysis, Anal. Chem. 90 (2018) 4249–4257.
[21] T. Čajka, O. Fiehn, Comprehensive analysis of lipids in biological systems by liquid chromatography-mass spectrometry, Trac. Trends Anal. Chem. 61 (2014) 192–206.
[22] T. Čajka, O. Fiehn, Toward merging untargeted and targeted methods in mass spectrometry-based metabolomics and lipidomics, Anal. Chem. 88 (2016) 524–545.
[23] Lipidomics Standard Initiative. https://lipidomics-standards-initiative.org, (accessed April 23, 2019).
[24] M. Lísa, E. Cífková, M. Khalikova, M. Ovčačíková, M. Holčapek, Lipidomic analysis of biological samples: comparison of liquid chromatography, supercritical fluid chromatography and direct infusion mass spectrometry methods, J. Chromatogr. A 1525 (2017) 96–108.
[25] European Medicines Agency, Guideline on Bioanalytical Method validation,Committee for Medicinal Products for Human Use, 192217/2009, Rev. 1 Corr, vol. 2, 21 July 2011.
[26] Food and Drug Administration, Guidance for Industry on Bioloanalytical Method Validation, Federal Register, 23 May 2001.
[27] X. Han, K. Yang, R.W. Gross, Multi-dimensional mass spectrometry-based shotgun lipidomics and novel strategies for lipidomic analyses, Mass Spectrom. Rev. 31 (2012) 134–178.
[28] M. Wang, C.Y. Wang, R.H. Han, X.L. Han, Novel advances in shotgun lipidomics for biology and medicine, Prog. Lipid Res. 61 (2016) 83–108.
[29] B. Simons, D. Kauhanen, T. Sylvänne, K. Tarasov, E. Duchoslav, K. Ekroos, Shotgun lipidomics by sequential precursor ion fragmentation on a hybrid quadrupole time-of-flight mass spectrometer, Metabolites 2 (2012) 195–213.
[30] M. Ståhlman, C.S. Ejsing, K. Tarasov, J. Perman, J. Borén, K. Ekroos, High-throughput shotgun lipidomics by quadrupole time-of-flight mass spectrometry, J. Chromatogr. B 877 (2009) 2664–2672.
[31] F.F. Hsu, Mass spectrometry-based shotgun lipidomics - a critical review from the technical point of view, Anal. Bioanal. Chem. 410 (2018) 6387–6409.
[32] R. Almeida, J.K. Pauling, E. Sokol, H.K. Hannibal-Bach, C.S. Ejsing, Comprehensive lipidome analysis by shotgun lipidomics on a hybrid quadrupole-orbitrap-linear ion trap mass spectrometer, J. Am. Soc. Mass Spectrom. 26 (2015) 133–148.
[33] S. Gallego, K. Hojlund, C. Ejsing, Easy, fast, and reproducible quantification of cholesterol and other lipids in human plasma by combined high resolution MSX and FTMS analysis, J. Am. Soc. Mass Spectrom. 29 (2018) 34–41.
[34] M. Ghaste, R. Mistrik, V. Shulaev, Applications of fourier transform ion cyclotron resonance (FT-ICR) and Orbitrap based high resolution mass spectrometry in metabolomics and lipidomics, Int. J. Mol. Sci. 17 (2016).

[35] K. Schuhmann, R. Herzog, D. Schwudke, W. Metelmann-Strupat, S.R. Bornstein, A. Shevchenko, Bottom-up shotgun lipidomics by higher energy collisional dissociation on LTQ Orbitrap mass spectrometers, Anal. Chem. 83 (2011) 5480–5487.
[36] D. Schwudke, J.T. Hannich, V. Surendranath, V. Grimard, T. Moehring, L. Burton, T. Kurzchalia, A. Shevchenko, Top-down lipidomic screens by multivariate analysis of high-resolution survey mass spectra, Anal. Chem. 79 (2007) 4083–4093.
[37] P. Husen, K. Tarasov, M. Katafiasz, E. Sokol, J. Vogt, J. Baumgart, R. Nitsch, K. Ekroos, C.S. Ejsing, Analysis of lipid experiments (ALEX): a software framework for analysis of high-resolution shotgun lipidomics data, PLoS One 8 (2013) e79736.
[38] R. Herzog, K. Schuhmann, D. Schwudke, J.L. Sampaio, S.R. Bornstein, M. Schroeder, A. Shevchenko, LipidXplorer: a software for consensual cross-platform lipidomics, PLoS One 7 (2012) e29851.
[39] K. Schuhmann, H. Thomas, J.M. Ackerman, K.O. Nagornov, Y.O. Tsybin, A. Sheychenko, Intensity-Independent noise filtering in FT MS and FT MS/MS spectra for shotgun lipidomics, Anal. Chem. 89 (2017) 7046–7052.
[40] C. Bielow, G. Mastrobuoni, M. Orioli, S. Kempa, On mass ambiguities in high-resolution shotgun lipidomics, Anal. Chem. 89 (2017) 2986–2994.
[41] M. Lísa, M. Holčapek, High-throughput and comprehensive lipidomic analysis using ultrahigh-performance supercritical fluid chromatography–mass spectrometry, Anal. Chem. 87 (2015) 7187–7195.
[42] J.L. Ren, A.H. Zhang, L. Kong, X.J. Wang, Advances in mass spectrometry-based metabolomics for investigation of metabolites, RSC Adv. 8 (2018) 22335–22350.
[43] J. Hartler, A. Triebl, A. Ziegl, M. Trotzmuller, G.N. Rechberger, O.A. Zeleznik, K.A. Zierler, F. Torta, A. Cazenave-Gassiot, M.R. Wenk, A. Fauland, C.E. Wheelock, A.M. Armando, O. Quehenberger, Q.F. Zhang, M.J.O. Wakelam, G. Haemmerle, F. Spener, H.C. Kofeler, G.G. Thallinger, Deciphering lipid structures based on platform-independent decision rules, Nat. Methods 14 (2017) 1171–1174.
[44] B. Peng, R. Ahrends, Adaptation of skyline for targeted lipidomics, J. Proteome Res. 15 (2016) 291–301.
[45] T. Čajka, J.T. Smilowitz, O. Fiehn, Validating quantitative untargeted lipidomics across nine liquid chromatography-high-resolution mass spectrometry platforms, Anal. Chem. 89 (2017) 12360–12368.
[46] M. Holčapek, B. Červená, E. Cífková, M. Lísa, V. Chagovets, J. Vostálová, M. Bancířová, J. Galuszka, M. Hill, Lipidomic analysis of plasma, erythrocytes and lipoprotein fractions of cardiovascular disease patients using UHPLC/MS, MALDI-MS and multivariate data analysis, J Chromatogr B-Anal Technol Biomed Life Sci 990 (2015) 52–63.
[47] B. Buszewski, S. Noga, Hydrophilic interaction liquid chromatography (HILIC)—a powerful separation technique, Anal. Bioanal. Chem. 402 (2012) 231–247.
[48] M. Ovčačíková, M. Lísa, E. Cífková, M. Holčapek, Retention behavior of lipids in reversed-phase ultrahigh-performance liquid chromatography–electrospray ionization mass spectrometry, J. Chromatogr. A 1450 (2016) 76–85.
[49] A. Triebl, M. Trötzmüller, J. Hartler, T. Stojakovic, H.C. Köfeler, Lipidomics by ultrahigh performance liquid chromatography-high resolution mass spectrometry and its application to complex biological samples, J. Chromatogr. B 1053 (2017) 72–80.
[50] S.-S. Cai, L.C. Short, J.A. Syage, M. Potvin, J.M. Curtis, Liquid chromatography-atmospheric pressure photoionization-mass spectrometry analysis of triacylglycerol lipids–effects of mobile phases on sensitivity, J. Chromatogr. A 1173 (2007) 88–97.
[51] E. Hvattum, Analysis of triacylglycerols with non-aqueous reversed-phase liquid chromatography and positive ion electrospray tandem mass spectrometry, Rapid Commun. Mass Spectrom. 15 (2001) 187–190.
[52] M. Holčapek, M. Lísa, P. Jandera, N. Kabátová, Quantitation of triacylglycerols in plant oils using HPLC with APCI-MS, evaporative light-scattering, and UV detection, J. Sep. Sci. 28 (2005) 1315–1333.
[53] M. Lísa, K. Netušilová, L. Franěk, H. Dvořáková, V. Vrkoslav, M. Holčapek, Characterization of fatty acid and triacylglycerol composition in animal fats using silver-ion and non-aqueous reversed-phase high-performance liquid chromatography/mass spectrometry and gas chromatography/flame ionization detection, J. Chromatogr. A 1218 (2011) 7499–7510.
[54] M. Holčapek, H. Dvořáková, M. Lísa, A.J. Giron, P. Sandra, J. Cvačka, Regioisomeric analysis of triacylglycerols using silver-ion liquid chromatography atmospheric pressure chemical ionization mass spectrometry: comparison of five different mass analyzers, J. Chromatogr. A 1217 (2010) 8186–8194.
[55] M. Holčapek, M. Ovčačíková, M. Lísa, E. Cífková, T. Hájek, Continuous comprehensive two-dimensional liquid chromatography–electrospray ionization mass spectrometry of complex lipidomic samples, Anal. Bioanal. Chem. 407 (2015) 5033–5043.
[56] M. Lísa, M. Holčapek, Characterization of triacylglycerol enantiomers using chiral HPLC/APCI-MS and synthesis of enantiomeric triacylglycerols, Anal. Chem. 85 (2013) 1852–1859.
[57] Y. Itabashi, A. Kuksis, Reassessment of stereochemical configuration of natural phosphatidylglycerols by chiral-phase high-performance liquid chromatography and electrospray mass spectrometry, Anal. Biochem. 254 (1997) 49–56.
[58] G. Arentz, P. Mittal, C. Zhang, Y.Y. Ho, M. Briggs, L. Winderbaum, M.K. Hoffmann, P. Hoffmann, Applications of mass spectrometry imaging to cancer, Adv. Cancer Res. 134 (2017) 27–66.
[59] T.J.A. Dekker, E.A. Jones, W.E. Corver, R.J.M. van Zeijl, A.M. Deelder, R.A.E.M. Tollenaar, W.E. Mesker, H. Morreau, L.A. McDonnell, Towards imaging metabolic pathways in tissues, Anal. Bioanal. Chem. 407 (2015) 2167–2176.
[60] D.R. Ifa, L.S. Eberlin, Ambient ionization mass spectrometry for cancer diagnosis and surgical margin evaluation, Clin. Chem. 62 (2016) 111–123.
[61] R.C. Murphy, J.A. Hankin, R.M. Barkley, Imaging of lipid species by MALDI mass spectrometry, J. Lipid Res. 50 (2009) S317–S322.
[62] A. Rompp, B. Spengler, Mass spectrometry imaging with high resolution in mass and space, Histochem. Cell Biol. 139 (2013) 759–783.
[63] Z. Takats, N. Strittmatter, J.S. McKenzie, Ambient mass spectrometry in cancer research, Adv. Cancer Res. 134 (2017) 231–256.
[64] M.M. Gessel, J.L. Norris, R.M. Caprioli, MALDI imaging mass spectrometry: spatial molecular analysis to enable a new age of discovery, J. Proteomics 107 (2014) 71–82.
[65] I. Lanekoff, S.L. Stevens, M.P. Stenzel-Poore, J. Laskin, Matrix effects in biological mass spectrometry imaging: identification and compensation, Analyst 139 (2014) 3528–3532.
[66] A.J. Taylor, A. Dexter, J. Bunch, Exploring ion suppression in mass spectrometry imaging of a heterogeneous tissue, Anal. Chem. 90 (2018) 5637–5645.
[67] J.M. Fonville, C. Carter, O. Cloarec, J.K. Nicholson, J.C. Lindon, J. Bunch, E. Holmes, Robust data processing and normalization strategy for MALDI mass spectrometric imaging, Anal. Chem. 84 (2012) 1310–1319.
[68] I. Lanekoff, J. Laskin, Quantitative mass spectrometry imaging of molecules in biological systems, Adv. Chromatogr. 54 (2018) 43–72.
[69] R. Angelini, R. Vitale, V.A. Patil, T. Cocco, B. Ludwig, M.L. Greenberg, A. Corcelli, Lipidomics of intact mitochondria by MALDI-TOF/MS, J. Lipid Res. 53 (2012) 1417–1425.
[70] H.M. Bergman, I. Lanekoff, Profiling and quantifying endogenous molecules in single cells using nano-DESI MS, Analyst 142 (2017) 3639–3647.
[71] S.E.J. Bell, N.M.S. Sirimuthu, Quantitative surface-enhanced Raman spectroscopy, Chem. Soc. Rev. 37 (2008) 1012–1024.
[72] K. Czamara, K. Majzner, M.Z. Pacia, K. Kochan, A. Kaczor, M. Baranska, Raman spectroscopy of lipids: a review, J. Raman Spectrosc. 46 (2015) 4–20.
[73] K. Kong, C. Kendall, N. Stone, I. Notingher, Raman spectroscopy for medical diagnostics — from in-vitro biofluid assays to in-vivo cancer detection, Adv. Drug Deliv. Rev. 89 (2015) 121–134.
[74] M.C. Potcoava, G.L. Futia, J. Aughenbaugh, I.R. Schlaepfer, E.A. Gibson, Raman and coherent anti-Stokes Raman scattering microscopy studies of changes in lipid content and composition in hormone-treated breast and prostate cancer cells, J. Biomed. Opt. 19 (2014) 111605.
[75] M.V.P. Chowdary, K.K. Kumar, J. Kurien, S. Mathew, C.M. Krishna, Discrimination of normal, benign, and malignant breast tissues by Raman spectroscopy, Biopolymers 83 (2006) 556–569.
[76] C.M. Krishna, G.D. Sockalingum, R.A. Bhat, L. Venteo, P. Kushtagi, M. Pluot, M. Manfait, FTIR and Raman microspectroscopy of normal, benign, and malignant formalin-fixed ovarian tissues, Anal. Bioanal. Chem. 387 (2007) 1649–1656.
[77] A. Derenne, O. Vandersleyen, E. Goormaghtigh, Lipid quantification method using FTIR spectroscopy applied on cancer cell extracts, Biochim. Biophys. Acta 1841 (2014) 1200–1209.
[78] I. Dreissig, S. Machill, R. Salzer, C. Krafft, Quantification of brain lipids by FTIR spectroscopy and partial least squares regression, Spectrochim. Acta Part A Mol. Biomol. Spectrosc. 71 (2009) 2069–2075.
[79] L. Habartová, B. Bunganič, M. Tatarkovič, M. Zavoral, J. Vondroušová, K. Syslová, V. Setnička, Chiroptical spectroscopy and metabolomics for blood-based sensing of pancreatic cancer, Chirality 30 (2018) 581–591.
[80] J. Schiller, M. Muller, B. Fuchs, K. Arnold, D. Huster, 31P NMR spectroscopy of phospholipids: from micelles to membranes, Curr. Anal. Chem. 3 (2007) 283–301.
[81] J. Li, T. Vosegaard, Z. Guo, Applications of nuclear magnetic resonance in lipid analyses: an emerging powerful tool for lipidomics studies, Prog. Lipid Res. 68 (2017) 37–56.
[82] T. Whitehead, T. Kieber-Emmons, Applying in vitro NMR spectroscopy and 1 H NMR metabonomics to breast cancer characterization and detection, Prog. Nucl. Magn. Reson. Spectrosc. 47 (2005) 165–174.
[83] J.A. Bowden, A. Heckert, C.Z. Ulmer, C.M. Jones, J.P. Koelmel, L. Abdullah, L. Ahonen, Y. Alnouti, A.M. Armando, J.M. Asara, T. Bamba, J.R. Barr, J. Bergquist, C.H. Borchers, J. Brandsma, S.B. Breitkopf, T. Cajka, A. Cazenave-Gassiot, A. Checa, M.A. Cinel, R.A. Colas, S. Cremers, E.A. Dennis, J.E. Evans, A. Fauland, O. Fiehn, M.S. Gardner, T.J. Garrett, K.H. Gotlinger, J. Han, Y.Y. Huang, A.H.P. Neo, T. Hyotylainen, Y. Izumi, H.F. Jiang, H.L. Jiang, J. Jiang, M. Kachman, R. Kiyonami, K. Klavins, C. Klose, H.C. Kofeler, J. Kolmert, T. Koal, G. Koster, Z. Kuklenyik, I.J. Kurland, M. Leadley, K. Lin, K.R. Maddipati, D. McDougall, P.J. Meikle, N.A. Mellett, C. Monnin, M.A. Moseley, R. Nandakumar, M. Oresic, R. Patterson, D. Peake, J.S. Pierce, M. Post, A.D. Postle, R. Pugh, Y.P. Qiu, O. Quehenberger, P. Ramrup, J. Rees, B. Rembiesa, D. Reynaud, M.R. Roth, S. Sales, K. Schuhmann, M.L. Schwartzman, C.N. Serhan, A. Shevchenko, S.E. Somerville, L.S. John-Williams, M.A. Surma, H. Takeda, R. Thakare, J.W. Thompson, F. Torta, A. Triebl, M. Trotzmuller, S.J.K. Ubhayasekera, D. Vuckovic, J.M. Weir, R. Welti, M.R. Wenk, C.E. Wheelock, L.B. Yao, M. Yuan, X.Q.H. Zhao, S.L. Zhou, Harmonizing lipidomics: NIST interlaboratory comparison exercise for lipidomics using SRM 1950-Metabolites in Frozen Human Plasma, J. Lipid Res. 58 (2017) 2275–2288.

[84] O. Quehenberger, A.M. Armando, A.H. Brown, S.B. Milne, D.S. Myers, A.H. Merrill, S. Bandyopadhyay, K.N. Jones, S. Kelly, R.L. Shaner, C.M. Sullards, E. Wang, R.C. Murphy, R.M. Barkley, T.J. Leiker, C.R.H. Raetz, Z.Q. Guan, G.M. Laird, D.A. Six, D.W. Russell, J.G. McDonald, S. Subramaniam, E. Fahy, E.A. Dennis, Lipidomics reveals a remarkable diversity of lipids in human plasma, J. Lipid Res. 51 (2010) 3299–3305.
[85] A.L. Dill, L.S. Eberlin, A.B. Costa, C. Zheng, D.R. Ifa, L.A. Cheng, T.A. Masterson, M.O. Koch, O. Vitek, R.G. Cooks, Multivariate statistical identification of human bladder carcinomas using ambient ionization imaging mass spectrometry, Chem. Eur J. 17 (2011) 2897–2902.
[86] B.M. Wittmann, S.M. Stirdivant, M.W. Mitchell, J.E. Wulff, J.E. McDunn, Z. Li, A. Dennis-Barrie, B.P. Neri, M.V. Milburn, Y. Lotan, R.L. Wolfert, Bladder cancer biomarker discovery using global metabolomic profiling of urine, PLoS One 9 (2014) e115870.
[87] G. Cruciani, R.M. Pellegrino, A. Di Veroli, S. Cataldi, D. Marocco, E. Costantini, A. Sidoni, M. Viola-Magni, Diagnostic application of lipidomics fingerprints to bladder carcinoma, Transl. Cancer Res. 6 (2017) 1197–1206.
[88] Y.P. Qiu, B.S. Zhou, M.M. Su, S. Baxter, X.J. Zheng, X.Q. Zhao, Y. Yen, W. Jia, Mass spectrometry-based quantitative metabolomics revealed a distinct lipid profile in breast cancer patients, Int. J. Mol. Sci. 14 (2013) 8047–8061.
[89] X.L. Chen, H.K. Chen, M.Y. Dai, J.M. Ai, Y. Li, B. Mahon, S.M. Dai, Y.P. Deng, Plasma lipidomics profiling identified lipid biomarkers in distinguishing early-stage breast cancer from benign lesions, Oncotarget 7 (2016) 36622–36631.
[90] N. Jiang, G.F. Zhang, L.J. Pan, C.P. Yan, L.W. Zhang, Y. Weng, W.J. Wang, X.Y. Chen, G.S. Yang, Potential plasma lipid biomarkers in early-stage breast cancer, Biotechnol. Lett. 39 (2017) 1657–1666.
[91] M.P. Cala, J. Aldana, J. Medina, J. Sanchez, J. Guio, J. Wist, R.J.W. Meesters, Multiplatform plasma metabolic and lipid fingerprinting of breast cancer: a pilot control-case study in Colombian Hispanic women, PLoS One 13 (2018) e0190958.
[92] L.A. Hammad, G.X. Wu, M.M. Saleh, I. Klouckova, L.E. Dobrolecki, R.J. Hickey, L. Schnaper, M.V. Novotny, Y. Mechref, Elevated levels of hydroxylated phosphocholine lipids in the blood serum of breast cancer patients, Rapid Commun. Mass Spectrom. 23 (2009) 863–876.
[93] M. Cui, Q.L. Wang, G. Chen, Serum metabolomics analysis reveals changes in signaling lipids in breast cancer patients, Biomed. Chromatogr. 30 (2016) 42–47.
[94] M. Hilvo, C. Denkert, L. Lehtinen, B. Muller, S. Brockmoller, T. Seppanen-Laakso, J. Budczies, E. Bucher, L. Yetukuri, S. Castillo, E. Berg, H. Nygren, M. Sysi-Aho, J.L. Griffin, O. Fiehn, S. Loibl, C. Richter-Ehrenstein, C. Radke, T. Hyotylainen, O. Kallioniemi, K. Iljin, M. Oresic, Novel theranostic opportunities offered by characterization of altered membrane lipid metabolism in breast cancer progression, Cancer Res. 71 (2011) 3236–3245.
[95] S. Guo, Y.M. Wang, D. Zhou, Z.L. Li, Significantly increased monounsaturated lipids relative to polyunsaturated lipids in six types of cancer microenvironment are observed by mass spectrometry imaging, Sci. Rep. 4 (2014) 5959.
[96] M. Cala, J. Aldana, J. Sanchez, J. Guio, R.J.W. Meesters, Urinary metabolite and lipid alterations in Colombian Hispanic women with breast cancer: a pilot study, J. Pharm. Biomed. Anal. 152 (2018) 234–241.
[97] Z.W. Zhao, Y.J. Xiao, P. Elson, H.Y. Tan, S.J. Plummer, M. Berk, P.P. Aung, I.C. Lavery, J.P. Achkar, L. Li, G. Casey, Y. Xu, Plasma lysophosphatidylcholine levels: potential biomarkers for colorectal cancer, J. Clin. Oncol. 25 (2007) 2696–2701.
[98] M.C.F. Messias, G.C. Mecatti, C.F.F. Angolini, M.N. Eberlin, L. Credidio, C.A.R. Martinez, C.S.R. Coy, P.D. Carvalho, Plasma lipidomic signature of rectal adenocarcinoma reveals Potential Biomarkers, Front. Oncol. 7 (2018).
[99] S. Crotti, E. Agnoletto, G. Cancemi, V. Di Marco, P. Traldi, S. Pucciarelli, D. Nitti, M. Agostini, Altered plasma levels of decanoic acid in colorectal cancer as a new diagnostic biomarker, Anal. Bioanal. Chem. 408 (2016) 6321–6328.
[100] S.S. Shen, L. Yang, L.N. Li, Y. Bai, C. Cai, H.W. Liu, A plasma lipidomics strategy reveals perturbed lipid metabolic pathways and potential lipid biomarkers of human colorectal cancer, J. Chromatogr. B 1068 (2017) 41–48.
[101] S.A. Ritchie, P.W.K. Ahiahonu, D. Jayasinghe, D. Heath, J. Liu, Y.S. Lu, W. Jin, A. Kavianpour, Y. Yamazaki, A.M. Khan, M. Hossain, K.K. Su-Myat, P.L. Wood, K. Krenitsky, I. Takemasa, M. Miyake, M. Sekimoto, M. Monden, H. Matsubara, F. Nomura, D.B. Goodenowe, Reduced levels of hydroxylated, polyunsaturated ultra long-chain fatty acids in the serum of colorectal cancer patients: implications for early screening and detection, BMC Med. 8 (2010).
[102] F. Li, X.Z. Qin, H.Q. Chen, L. Qiu, Y.M. Guo, H. Liu, G.Q. Chen, G.G. Song, X.D. Wang, F.J. Li, S. Guo, B.H. Wang, Z.L. Li, Lipid profiling for early diagnosis and progression of colorectal cancer using direct-infusion electrospray ionization Fourier transform ion cyclotron resonance mass spectrometry, Rapid Commun. Mass Spectrom. 27 (2013) 24–34.
[103] B.B. Tan, Y.P. Qiu, X. Zou, T.L. Chen, G.X. Xie, Y. Cheng, T.T. Dong, L.J. Zhao, B. Feng, X.F. Hu, L.X. Xu, A.H. Zhao, M.H. Zhang, G.X. Cai, S.J. Cai, Z.X. Zhou, M.H. Zheng, Y. Zhang, W. Jia, Metabonomics identifies serum metabolite markers of colorectal cancer, J. Proteome Res. 12 (2013) 3000–3009.
[104] L.F. Chen, C.X. Zhang, Q.F. Gui, Y. Chen, Y.M. Yang, Ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry-based metabolic profiling of human serum prior to and following radical resection of colorectal carcinoma, Mol. Med. Rep. 12 (2015) 6879–6886.
[105] K. Perttula, W.M.B. Edmands, H. Grigoryan, X.M. Cai, A.T. Iavarone, M.J. Gunter, A. Naccarati, S. Polidoro, A. Hubbard, P. Vineis, S.M. Rappaport, Evaluating ultra-long-chain fatty acids as biomarkers of colorectal cancer risk, Cancer Epidemiol. Biomark. Prev. 25 (2016) 1216–1223.
[106] Y.M. Guo, J.L. Ren, X.O. Li, X.F. Liu, N. Liu, Y.M. Wang, Z.L. Li, Simultaneous quantification of serum multi-phospholipids as potential biomarkers for differentiating different pathophysiological states of lung, stomach, intestine, and pancreas, J. Cancer 8 (2017) 2191–2204.
[107] R. Mirnezami, K. Spagou, P.A. Vorkas, M.R. Lewis, J. Kinross, E. Want, H. Shion, R.D. Goldin, A. Darzi, Z. Takats, E. Holmes, O. Cloarec, J.K. Nicholson, Chemical mapping of the colorectal cancer microenvironment via MALDI imaging mass spectrometry (MALDI-MSI) reveals novel cancer-associated field effects, Mol. Oncol. 8 (2014) 39–49.
[108] R. Liu, Y. Peng, X.B. Li, Y. Wang, E.C. Pan, W. Guo, Y.P. Pu, L.H. Yin, Identification of plasma metabolomic profiling for diagnosis of esophageal squamous-cell carcinoma using an UPLC/TOF/MS platform, Int. J. Mol. Sci. 14 (2013) 8899–8911.
[109] J. Xu, Y.H. Chen, R.P. Zhang, Y.M. Song, J.Z. Cao, N. Bi, J.B. Wang, J.M. He, J.F. Bai, L.J. Dong, L.H. Wang, Q.M. Zhan, Z. Abliz, Global and targeted metabolomics of esophageal squamous cell carcinoma discovers potential diagnostic and therapeutic biomarkers, Mol. Cell. Proteomics 12 (2013) 1306–1318.
[110] S.A. Mir, P. Rajagopalan, A.P. Jain, A.A. Khan, K.K. Datta, S.V. Mohan, S.S. Lateef, N. Sahasrabuddhe, B.L. Somani, T.S.K. Prasad, A. Chatterjee, K.V.V. Kumar, M. VijayaKumar, R.V. Kumar, S. Gundimeda, A. Pandey, H. Gowda, LC-MS-based serum metabolomic analysis reveals dysregulation of phosphatidylcholines in esophageal squamous cell carcinoma, J. Proteomics 127 (2015) 96–102.
[111] B.H. Wang, D.Y. Chen, Y. Chen, Z.H. Hu, M. Cao, Q. Xie, Y.F. Chen, J.L. Xu, S.S. Zheng, L.J. Li, Metabonomic profiles discriminate hepatocellular carcinoma from liver cirrhosis by ultraperformance liquid chromatography-mass spectrometry, J. Proteome Res. 11 (2012) 1217–1227.
[112] T.L. Chen, G.X. Xie, X.Y. Wang, J. Fan, Y.P. Qiu, X.J. Zheng, X. Qi, Y. Cao, M.M. Su, X.Y. Wang, L.X. Xu, Y. Yen, P. Liu, W. Jia, Serum and urine metabolite profiling reveals potential biomarkers of human hepatocellular carcinoma, Mol. Cell. Proteomics 10 (2011).
[113] L. Lin, Q.A. Yu, X.M. Yan, W. Hang, J.X. Zheng, J.C. Xing, B.L. Huang, Direct infusion mass spectrometry or liquid chromatography mass spectrometry for human metabonomics? A serum metabonomic study of kidney cancer, Analyst 135 (2010) 2970–2978.
[114] L. Lin, Z.Z. Huang, Y. Gao, X.M. Yan, J.C. Xing, W. Hang, LC-MS based serum metabonomic analysis for renal cell carcinoma diagnosis, staging, and biomarker discovery, J. Proteome Res. 10 (2011) 1396–1405.
[115] L. Lin, Z.Z. Huang, Y. Gao, Y.J. Chen, W. Hang, J.C. Xing, X.M. Yan, LC-MS-based serum metabolic profiling for genitourinary cancer classification and cancer type-specific biomarker discovery, Proteomics 12 (2012) 2238–2246.
[116] A.L. Dill, L.S. Eberlin, C. Zheng, A.B. Costa, D.R. Ifa, L.A. Cheng, T.A. Masterson, M.O. Koch, O. Vitek, R.G. Cooks, Multivariate statistical differentiation of renal cell carcinomas based on lipidomic analysis by ambient ionization imaging mass spectrometry, Anal. Bioanal. Chem. 398 (2010) 2969–2978.
[117] E.E. Jones, T.W. Powers, B.A. Neely, L.H. Cazares, D.A. Troyer, A.S. Parker, R.R. Drake, MALDI imaging mass spectrometry profiling of proteins and lipids in clear cell renal cell carcinoma, Proteomics 14 (2014) 924–935.
[118] K. Saito, E. Arai, K. Maekawa, M. Ishikawa, H. Fujimoto, R. Taguchi, K. Matsumoto, Y. Kanai, Y. Saito, Lipidomic signatures and associated transcriptomic profiles of clear cell renal cell carcinoma, Sci. Rep. 6 (2016).
[119] R. Hájek, M. Lísa, M. Khalikova, R. Jirásko, E. Cífková, V. Študent, D. Vrána, L. Opálka, K. Vávrová, M. Matzenauer, B. Melichar, M. Holčapek, HILIC/ESI-MS determination of gangliosides and other polar lipid classes in renal cell carcinoma and surrounding normal tissues, Anal. Bioanal. Chem. 410 (2018) 6585–6594.
[120] J. Dong, X.M. Cai, L.L. Zhao, X.Y. Xue, L.J. Zou, X.L. Zhang, X.M. Liang, Lysophosphatidylcholine profiling of plasma: discrimination of isomers and discovery of lung cancer biomarkers, Metabolomics 6 (2010) 478–488.
[121] A.J. Alberg, K. Armeson, J.S. Pierce, J. Bielawski, A. Bielawska, K. Visvanathan, E.G. Hill, B. Ogretmen, Plasma sphingolipids and lung cancer: a population-based, nested case-control study, cancer epidemiol, Biomark. Prev. 22 (2013) 1374–1382.
[122] T. Wen, L. Gao, Z.M. Wen, C.Y. Wu, C.S. Tan, W.Z. Toh, C.N. Ong, Exploratory investigation of plasma metabolomics in human lung adenocarcinoma, Mol. Biosyst. 9 (2013) 2370–2378.
[123] S. Ravipati, D.R. Baldwin, H.L. Barr, A.W. Fogarty, D.A. Barrett, Plasma lipid biomarker signatures in squamous carcinoma and adenocarcinoma lung cancer patients, Metabolomics 11 (2015) 1600–1611.
[124] Z.T. Yu, H.K. Chen, J.M. Ai, Y. Zhu, Y. Li, J.A. Borgia, J.S. Yang, J.C. Zhang, B. Jiang, W. Gu, Y.P. Deng, Global lipidomics identified plasma lipids as novel biomarkers for early detection of lung cancer, Oncotarget 8 (2017) 107899–107906.
[125] Y.M. Guo, X.M. Wang, L. Qiu, X.Z. Qin, H. Liu, Y.Y. Wang, F. Li, X.D. Wang, G.Q. Chen, G.G. Song, F.J. Li, S. Guo, Z.L. Li, Probing gender-specific lipid metabolites and diagnostic biomarkers for lung cancer using Fourier transform ion cyclotron resonance mass spectrometry, Clin. Chim. Acta 414 (2012) 135–141.

[126] Y.J. Li, X. Song, X.J. Zhao, L.J. Zou, G.W. Xu, Serum metabolic profiling study of lung cancer using ultra high performance liquid chromatography/quadrupole time-of-flight mass spectrometry, J. Chromatogr. B 966 (2014) 147–153.
[127] J.L. Ren, D. Zhang, Y.J. Liu, R.Q. Zhang, H.L. Fang, S. Guo, D. Zhou, M. Zhang, Y.P. Xu, L. Qiu, Z.L. Li, Simultaneous quantification of serum nonesterified and esterified fatty acids as potential biomarkers to differentiate benign lung diseases from lung cancer, Sci. Rep. 6 (2016) 34201.
[128] J.F. Fahrmann, D. Grapov, B.C. DeFelice, S. Taylor, K. Kim, K. Kelly, W.R. Wikoff, H. Pass, W.N. Rom, O. Fiehn, S. Miyamoto, Serum phosphatidylethanolamine levels distinguish benign from malignant solitary pulmonary nodules and represent a potential diagnostic biomarker for lung cancer, Cancer Biomark. 16 (2016) 609–617.
[129] M. Ros-Mazurczyk, K. Jelonek, M. Marczyk, F. Binczyk, M. Pietrowska, J. Polanska, R. Dziadziuszko, J. Jassem, W. Rzyman, P. Widlak, Serum lipid profile discriminates patients with early lung cancer from healthy controls, Lung Canc. 112 (2017) 69–74.
[130] G.K. Lee, H.S. Lee, Y.S. Park, J.H. Lee, S.C. Lee, J.H. Lee, S.J. Lee, S.R. Shanta, H.M. Park, H.R. Kim, I.H. Kim, Y.H. Kim, J.I. Zo, K.P. Kim, H.K. Kim, Lipid MALDI profile classifies non-small cell lung cancers according to the histologic type, Lung Canc. 76 (2012) 197–203.
[131] T.G. Li, J.M. He, X.X. Mao, Y. Bi, Z.G. Luo, C.G. Guo, F. Tang, X. Xu, X.H. Wang, M.R. Wang, J. Chen, Z. Abliz, In situ biomarker discovery and label-free molecular histopathological diagnosis of lung cancer by ambient mass spectrometry imaging, Sci. Rep. 5 (2015) 14089.
[132] E. Marien, M. Meister, T. Muley, S. Fieuws, S. Bordel, R. Derua, J. Spraggins, R. Van de Plas, J. Dehairs, J. Wouters, M. Bagadi, H. Dienemann, M. Thomas, P.A. Schnabel, R.M. Caprioli, E. Waelkens, J.V. Swinnen, Non-small cell lung cancer is characterized by dramatic changes in phospholipid profiles, Int. J. Cancer 137 (2015) 1539–1548.
[133] R. Sutphen, Y. Xu, G.D. Wilbanks, J. Fiorica, E.C. Grendys, J.P. LaPolla, H. Arango, M.S. Hoffman, M. Martino, K. Wakeley, D. Griffin, R.W. Blanco, A.B. Cantor, Y.J. Xiao, J.P. Krischer, Lysophospholipids are potential biomarkers of ovarian cancer, Cancer Epidemiol. Biomark. Prev. 13 (2004) 1185 (+).
[134] M.F. Buas, H.W. Gu, D. Djukovic, J.J. Zhu, C.W. Drescher, N. Urban, D. Raftery, C.I. Li, Identification of novel candidate plasma metabolite biomarkers for distinguishing serous ovarian carcinoma and benign serous ovarian tumors, Gynecol. Oncol. 140 (2016) 138–144.
[135] J.N. Li, H.Y. Xie, A. Li, J.L. Cheng, K. Yang, J.T. Wang, W.J. Wang, F. Zhang, Z.Z. Li, H.S. Dhillon, M.S. Openkova, X.H. Zhou, K. Li, Y. Hou, Distinct plasma lipids profiles of recurrent ovarian cancer by liquid chromatography-mass spectrometry, Oncotarget 8 (2017) 46834–46845.
[136] M. Meleh, B. Pozlep, A. Mlakar, H. Meden-Vrtovec, L. Zupancic-Kralj, Determination of serum lysophosphatidic acid as a potential biomarker for ovarian cancer, J. Chromatogr. B 858 (2007) 287–291.
[137] Y. Liu, Y.F. Chen, A. Momin, R. Shaner, E. Wang, N.J. Bowen, L.V. Matyunina, L.D. Walker, J.F. McDonald, M.C. Sullards, A.H. Merrill, Elevation of sulfatides in ovarian cancer: an integrated transcriptomic and lipidomic analysis including tissue-imaging mass spectrometry, Mol. Canc. 9 (2010) 186.
[138] G. Xie, L. Lu, Y. Qiu, Q. Ni, W. Zhang, Y.-T. Gao, H.A. Risch, H. Yu, W. Jia, Plasma metabolite biomarkers for the detection of pancreatic cancer, J. Proteome Res. 14 (2015) 1195–1202.
[139] X.C. Zhou, J.H. Mao, J.M. Ai, Y.P. Deng, M.R. Roth, C. Pound, J. Henegar, R. Welti, S.A. Bigler, Identification of plasma lipid biomarkers for prostate cancer by lipidomics and bioinformatics, PLoS One 7 (2012) e48889.
[140] H.M. Awwad, C.H. Ohlmann, M. Stoeckle, R. Aziz, J. Geisel, R. Obeid, Choline-phospholipids inter-conversion is altered in elderly patients with prostate cancer, Biochimie 126 (2016) 108–114.
[141] N. Patel, R. Vogel, K. Chandra-Kuntal, W. Glasgow, U. Kelavkar, A novel three serum phospholipid panel differentiates normal individuals from those with prostate cancer, PLoS One 9 (2014) e88841.
[142] D. Duscharla, S.R. Bhumireddy, S. Lakshetti, H. Pospisil, P.V.L.N. Murthy, R. Walther, P. Sripadi, R. Ummanni, Prostate cancer associated lipid signatures in serum studied by ESI-tandem mass spectrometryas potential new biomarkers, PLoS One 11 (2016) e0150253.
[143] T. Goto, N. Terada, T. Inoue, K. Nakayama, Y. Okada, T. Yoshikawa, Y. Miyazaki, M. Uegaki, S. Sumiyoshi, T. Kobayashi, T. Kamba, K. Yoshimura, O. Ogawa, The expression profile of phosphatidylinositol in high spatial resolution imaging mass spectrometry as a potential biomarker for prostate cancer, PLoS One 9 (2014) e90242.
[144] T. Goto, N. Terada, T. Inoue, T. Kobayashi, K. Nakayama, Y. Okada, T. Yoshikawa, Y. Miyazaki, M. Uegaki, N. Utsunomiya, Y. Makino, S. Sumiyoshi, T. Yamasaki, T. Kamba, O. Ogawa, Decreased expression of lysophosphatidylcholine (16:0/OH) in high resolution imaging mass spectrometry independently predicts biochemical recurrence after surgical treatment for prostate cancer, Prostate 75 (2015) 1821–1830.
[145] J. Li, S. Ren, H.-l. Piao, F. Wang, P. Yin, C. Xu, X. Lu, G. Ye, Y. Shao, M. Yan, X. Zhao, Y. Sun, G. Xu, Integration of lipidomics and transcriptomics unravels aberrant lipid metabolism and defines cholesteryl oleate as potential biomarker of prostate cancer, Sci. Rep. 6 (2016) 20984.
[146] T. Skotland, K. Ekroos, D. Kauhanen, H. Simolin, T. Seierstad, V. Berge, K. Sandvig, A. Llorente, Molecular lipid species in urinary exosomes as potential prostate cancer biomarkers, Eur. J. Cancer 70 (2017) 122–132.
[147] S. Guo, L. Qiu, Y.M. Wang, X.Z. Qin, H. Liu, M.W. He, Y.P. Zhang, Z.L. Li, X.H. Chen, Tissue imaging and serum lipidomic profiling for screening potential biomarkers of thyroid tumors by matrix-assisted laser desorption/ionization-Fourier transform ion cyclotron resonance mass spectrometry, Anal. Bioanal. Chem. 406 (2014) 4357–4370.
[148] Z.Z. Yao, P.Y. Yin, D.W. Su, Z.J. Peng, L.N. Zhou, L. Ma, W. Guo, L. Ma, G.W. Xu, J.Y. Shi, B.H. Jiao, Serum metabolic profiling and features of papillary thyroid carcinoma and nodular goiter, Mol. Biosyst. 7 (2011) 2608–2614.
[149] O. Vvedenskaya, Y. Wang, J.M. Ackerman, O. Knittelfelder, A. Shevchenko, Analytical challenges in human plasma lipidomics: a winding path towards the truth, Trac. Trends Anal. Chem. (2019). in press, https://doi.org/10.1016/j.trac.2018.1010.1013.