Progress in Lipid Research 95 (2024) 101276

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review Article

Oxylipin profiling for clinical research: Current status and future perspectives☆

Karol Parchem [a,b], Sophia Letsiou [c], Toni Petan [d], Olga Oskolkova [e], Isabel Medina [f], Ondrej Kuda [g], Valerie B. O'Donnell [h], Anna Nicolaou [i], Maria Fedorova [j], Valery Bochkov [e], Cécile Gladine [k,*]

[a] Department of Food Chemistry, Technology and Biotechnology, Faculty of Chemistry, Gdańsk University of Technology, 11/12 Gabriela Narutowicza St., 80-233 Gdańsk, Poland
[b] Department of Analytical Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 53210 Pardubice, Czech Republic
[c] Department of Biomedical Sciences, University of West Attica, Ag. Spiridonos St. Egaleo, 12243 Athens, Greece
[d] Department of Molecular and Biomedical Sciences, Jožef Stefan Institute, Jamova cesta 39, SI-1000 Ljubljana, Slovenia
[e] Institute of Pharmaceutical Sciences, University of Graz, Humboldtstrasse 46/III, 8010 Graz, Austria
[f] Instituto de Investigaciones Marinas-Consejo Superior de Investigaciones Científicas (IIM-CSIC), Eduardo Cabello 6, E-36208 Vigo, Spain
[g] Institute of Physiology, Czech Academy of Sciences, Videnska 1083, 14200 Prague, Czech Republic
[h] Systems Immunity Research Institute, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK
[i] School of Health Sciences, Faculty of Biology Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester M13 9NT, UK
[j] Center of Membrane Biochemistry and Lipid Research, University Hospital and Faculty of Medicine Carl Gustav Carus of TU Dresden, 01307 Dresden, Germany
[k] Université Clermont Auvergne, INRAE, UNH, Clermont-Ferrand, France

ARTICLE INFO

Keywords:
Lipid mediators
Epilipids
Lipidomics
Oxylipins
Eicosanoids
Clinical translation

ABSTRACT

Oxylipins are potent lipid mediators with increasing interest in clinical research. They are usually measured in systemic circulation and can provide a wealth of information regarding key biological processes such as inflammation, vascular tone, or blood coagulation. Although procedures still require harmonization to generate comparable oxylipin datasets, performing comprehensive profiling of circulating oxylipins in large studies is feasible and no longer restricted by technical barriers. However, it is essential to improve and facilitate the biological interpretation of complex oxylipin profiles to truly leverage their potential in clinical research. This requires regular updating of our knowledge about the metabolism and the mode of action of oxylipins, and consideration of all factors that may influence circulating oxylipin profiles independently of the studied disease or condition. This review aims to provide the readers with updated and necessary information regarding oxylipin metabolism, their different forms in systemic circulation, the current limitations in deducing oxylipin cellular effects from in vitro bioactivity studies, the biological and technical confounding factors needed to consider for a proper interpretation of oxylipin profiles.

Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; BLT, leukotriene B4 receptor; CE, cholesteryl ester; COX, cyclooxygenase; CYP, cytochrome P450 monooxygenase; DHA, docosahexaenoic acid; EP, prostaglandin E2 receptor; EpOME, epoxyoctadecamonoenoic acid; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxyoctadecadienoic acid; LA, linoleic acid; LLE, liquid-liquid extraction; LOX, lipoxygenase; lysoPL, lysophospholipid; LT, leukotriene; LX, lipoxin; MS, mass spectrometry; NSAIDs, non-steroidal-anti-inflammatory-drugs; Oxo-ODE, oxooctadecadienoic acid; PG, prostaglandin; PGI, prostacyclin; PL, phospholipid; PLA_2, phospholipase A_2; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; RP-(U)HPLC, reverse-phase (ultra)high-performance liquid chromatography; SPE, solid-phase extraction; SPM, specialized proresolving mediator; TG, triacylglycerol; TX, thromboxane; TXAS, thromboxane synthase; VLDL, very-low-density lipoprotein..

☆ This article is a contribution to the EpiLipidNET Virtual Special Issue on Analysis and Biological Importance of Lipids and Modified Lipids coordinated by Corinne M. Spickett * Dr Cécile Gladine. E-mail: cecile.gladine@inrae.fr

* Corresponding author.
E-mail addresses: parchem.karol@gmail.com (K. Parchem), sletsiou@uniwa.gr (S. Letsiou), toni.petan@ijs.si (T. Petan), o.oskolkova@uni-graz.at (O. Oskolkova), medina@iim.csic.es (I. Medina), Ondrej.Kuda@fgu.cas.cz (O. Kuda), O-DonnellVB@cardiff.ac.uk (V.B. O'Donnell), anna.nicolaou@manchester.ac.uk (A. Nicolaou), maria.fedorova@tu-dresden.de (M. Fedorova), valery.bochkov@uni-graz.at (V. Bochkov), cecile.gladine@inrae.fr (C. Gladine).

https://doi.org/10.1016/j.plipres.2024.101276
Received 12 December 2023; Received in revised form 24 April 2024; Accepted 29 April 2024
Available online 30 April 2024

1. Introduction

Lipidomics, and in particular epilipidomics, focused on oxidized or otherwise modified lipids, has strong potential for biomedical applications. In this field, eicosanoids and other oxylipins hold a central position thanks to their significant role in the regulation of a diverse set of homeostatic and inflammatory processes, also linked to numerous diseases and therapeutic treatments (e.g. non-steroidal-anti-inflammatory-drugs (NSAIDs)) [1]. The term "oxylipins" refers to a large family of lipids derived from the oxygenation of polyunsaturated fatty acids (PUFAs) by various enzymatic and non-enzymatic pathways, many of which are potently bioactive [2,3]. These include the eicosanoids, derived from 20-carbons PUFAs, but also octadecanoids and docosanoids derived from 18-carbon and 22-carbon PUFAs, respectively. Nowadays, mass spectrometry (MS) lipidomic platforms are used for routine workflows that enable the quantitative profiling of up to 150-200 oxylipins from all pathways and substrate PUFAs. This allows relevant system biology approaches to capture the biological and metabolic complexity of oxylipins. Various case-control studies based on these approaches have proven the utility of comprehensive oxylipin profiling to support a new understanding of various diseases. For instance, specific oxylipin signatures have been recently associated with metabolic syndrome, liver diseases or COVID-19 [4–6]. Analyzing large number of oxylipins even in extensive studies is technically feasible, but it is now essential to improve the biological interpretation of complex profiles of circulating oxylipins. This review aims to summarize what we currently know about the biological origins and mode of action of circulating oxylipins as well as key information that should be considered for a correct biological interpretation of their profiles. We will also point out factors that may influence the circulating oxylipin profiles, and discuss how analytical choices can affect oxylipin profiles and their biological significance.

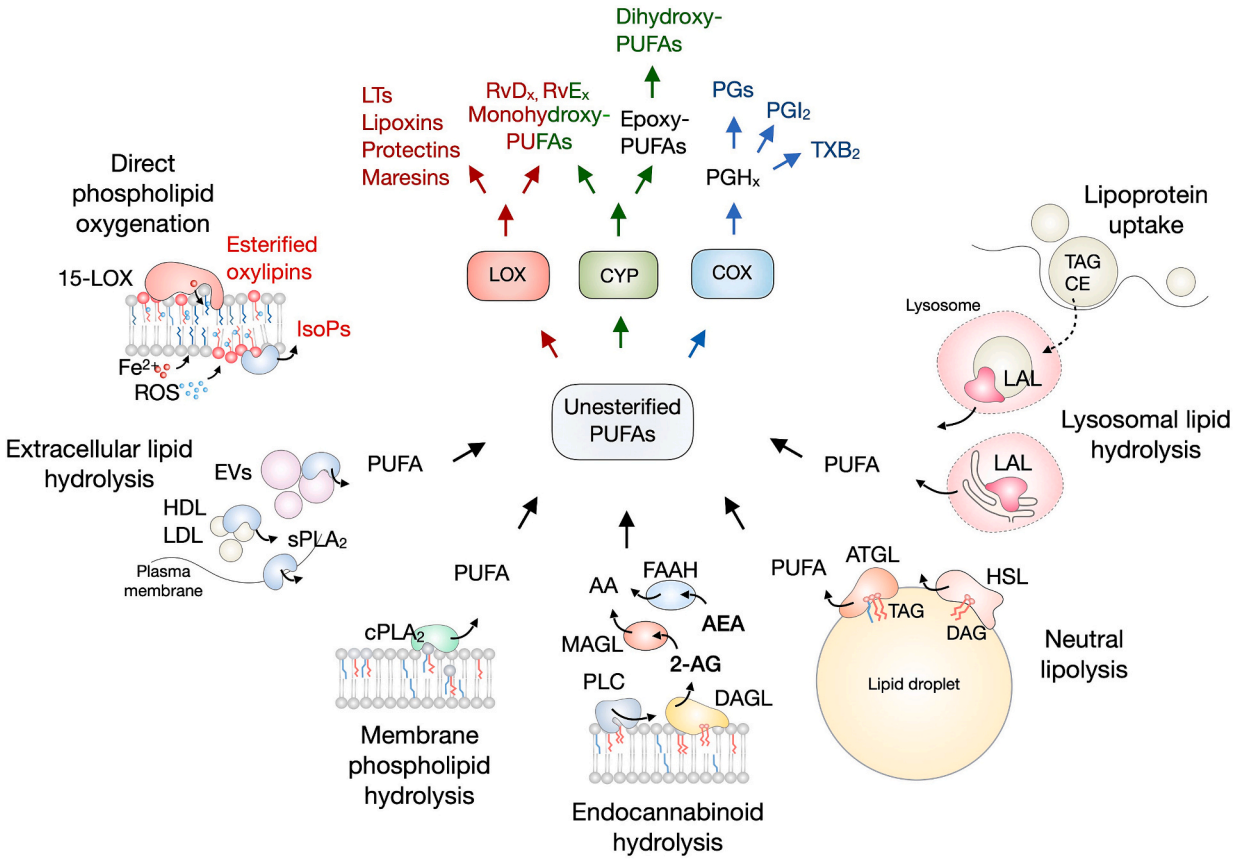

Fig. 1. Overview of oxylipin biosynthesis pathways. Substrate PUFAs for oxylipin biosynthesis can be released from various lipid pools, including: (i) membrane phospholipids by intracellular PLA_2 enzymes, including the group IVA cytosolic PLA_2 ($cPLA_2\alpha$); (ii) extracellular phospholipids present in the plasma membrane, lipoproteins (HDL, LDL) or EVs by extracellular PLA_2s, including the group X secreted PLA_2; (iii) non-polar lipids stored in cytosolic lipid droplets mediated by cytosolic lipases, such as ATGL or HSL, and lysosomal lipids, derived from (iv) lipoprotein uptake or (v) intracellular lipid recycling, by acid lipolysis mediated by LAL. (vi) Hydrolysis of endocannabinoids, such as 2-AG or AEA, by MAGL and FAAH can be another source of AA for eicosanoid biosynthesis. Unesterified PUFAs serve as substrates for three enzymatic pathways forming: (i) COX-derived oxylipins such as PGHx, the precursors of PGs, PGI_2 and TXB_2, (ii) LOX-derived oxylipins, including LTs and monohydroxy-FAs (e.g. HEPEs, HETEs), and (iii) CYP-derived oxylipins, including epoxy-, mono- and dihydroxy-PUFA derivatives. Specialized pro-resolving mediators, such as the D- and *E*-series resolvins, protectins and maresins, can be produced by the LOX enzymes or by various combinations of COX, LOX and CYP enzyme activities. PUFAs esterified in phospholipids can be directly oxygenated by enzymes such as 15-LOX. Moreover, both non-esterified and esterified PUFAs are susceptible to ROS-mediated non-enzymatic peroxidation giving rise to isoPs and other oxygenated species. Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; AEA, anandamide; ATGL, adipose triglyceride lipase; CE, cholesteryl ester; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase A_2; CYP, cytochrome P450 monooxygenases; DAG, diacylglycerol; DAGL, diacylglycerol lipase; EV, extracellular vesicles; FAAH, fatty acid amid hydrolase; HDL, high-density lipoprotein; HEPE, hydroxyeicosapentaenoic acid; HETE, hydroxyeicosatetraenoic acid; HSL, hormone-sensitive lipase; IsoPs, isoprostanes; LAL, lysosomal acid lipase; LDL, low-density lipoprotein; LOX, lipoxygenase; LTs, leukotrienes; MAGL, monoacylglycerol lipase; PG, prostaglandin; PGE, prostaglandin E; PGI, prostaglandin PGI; PGHx, prostaglandin Hx; PLC, phospholipase C; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; $sPLA_2$, secreted phospholipase A_2; TG, triacylglycerol; TXB_2, thromboxane B_2; RvE_x, E-series resolvins; RvD_x, D-series resolvins.

2. Biological origins of circulating oxylipins

2.1. Metabolism of oxylipins

2.1.1. Biosynthesis of oxylipins

A detailed description of the biosynthesis of oxylipins is beyond the scope of this work as this has been described in several excellent reviews [2,7–10]. Here, we will point out specific and updated aspects of oxylipin biosynthesis that should be considered for a correct biological interpretation of their circulating profiles.

The canonical pathway of oxylipin biosynthesis starts with the release of PUFAs from membrane phospholipids (PLs) by phospholipase A_2 (PLA_2) enzymes (Fig. 1). In particular, the cytosolic $PLA_2\alpha$ (also called group IVA PLA_2, encoded by *PLA2G4A*) has been widely recognized as the primary source of arachidonic acid (AA) for oxylipin production [11–14]. This enzyme acts primarily on phosphatidylcholines and displays a significant preference for PLs containing AA found at the *sn*-2 position [15]. However, over the years, this biosynthetic pathway has evolved to include more members of the PLA_2 superfamily (for a recent comprehensive review see [16]), but also various lipases (including the adipose triglyceride lipase, hormone-sensitive lipase, lysosomal acid lipase, endothelial and lipoprotein lipase) that may release PUFAs from non-polar lipids stored in cytosolic lipid droplets and/or lipoproteins [17–23]. Once released, non-esterified PUFAs serve as substrates for three main enzymatic reactions catalysed by cyclooxygenases (COXs), lipoxygenases (LOXs) or cytochrome P450 monooxygenases (CYPs, more precisely families CYP1A1, CYP2C8, CYP4A11 and CYP4F2) (see [2,9] for a detailed description of oxylipin biosynthesis from major precursor PUFAs). Each one of these enzymatic pathways generates a large range of oxylipins functioning either as end products, or intermediates further transformed via a cascade of downstream enzymes. The resulting oxylipins can regulate various signaling pathways in an autocrine or paracrine manner. Alternatively, non-esterified oxylipins, upon activation to acyl-CoAs, can be esterified into membrane PLs. This mechanism requires the involvement of Lands'cycle enzymes and contributes to the formation of oxidized PLs [24–26]. The latter can also originate from the direct oxidation of membrane PLs through both non-enzymatic and enzymatic mechanisms. For instance, in monocytes and airway epithelia, enzymatically oxidized PLs, which comprise oxylipins attached to PLs, can be formed via the direct action of human 15-LOX on PLs [26].

Another potential source of AA for eicosanoid production are the endocannabinoids such as 2-arachidonoylglycerol and anandamide, which can be hydrolysed by monoacylglycerol lipase and fatty acid amide hydrolase, respectively [27]. Interestingly, the hydrolysis of 2-arachidonoylglycerol by monoacylglycerol lipase simultaneously deactivates endocannabinoid signaling by reducing the concentration of 2-arachidonoylglycerol in the brain and some other tissues [28,29].

The major COX-derived oxylipins are the prostanoids: prostaglandins (PGs), thromboxanes (TXs) and prostacyclin (PGI), while low levels of monohydroxy-PUFAs (e.g. 11- and 15-hydroxyeicosatetraenoic acids (11- and 15-HETE) are also formed by COX-2. The LOX pathway produces hydroperoxy-PUFAs, which are rearranged into monohydroxy-PUFAs or further converted to leukotrienes (LTs), while transcellular metabolism including LOX-LOX or LOX-CYP reactions has been proposed to produce numerous dihydroxy- and trihydroxy-PUFAs including the specialized proresolving mediators (SPMs), lipoxins (LXs), resolvins, maresins and protectins. While generation of many of these lipids in purified systems has been shown [10], their cellular formation under physiological conditions is currently a subject of discussion [30,31] [32–39]. The CYP pathway primarily produces epoxy-PUFAs, as well as mid- and ω carbon atom-chain monohydroxy-PUFAs, with the epoxides being further transformed to vicinal (i.e., adjacent or 1,2-) dihydroxy-PUFAs by the enzyme soluble epoxide hydrolase (Fig. 1).

The biosynthesis of major oxylipins such as monohydroxy fatty acids and the classic PGs, PGI, TXs and LTs, derived from the COX, LOX and CYP pathways, has been well established for decades. However, it should be noted that tissue formation and analytical detection of multiple oxygenated oxylipin species, such as SPMs, has been recently discussed in publications and online preprints [30,40–43]. This highlights the need for a collaborative effort to standardise the analytical requirements for reporting oxylipins in biological and clinical samples. While many papers reported multiple SPMs [10,44–48], others report that these oxylipins species were not detectable in plasma and other biological tissues [49–52].

The reactive oxygen species (ROS)-mediated biosynthesis of oxylipins should also be considered, as it is an important contributor of circulating species, and can provide a reliable assessment of oxidative stress. Notably, F2-isoprostanes, derived from the ROS-mediated oxidation of AA, are recognized as a reference biomarker of oxidative stress [53]. ROS oxidation usually occurs directly on esterified PUFAs and is induced by nonradical ROS (singlet oxygen), or by free radicals, which either penetrate the cell/tissue from the environment, or are produced endogenously by enzymes, such as NADPH oxidase, myeloperoxidase, nitric oxide synthase, xanthine oxidase or the mitochondrial respiratory chain [54,55]. ROS oxidation generates a mixture of oxylipins, including hydroxides, ketones, epoxides, aldehydes as well as iso- and neuroprostanes (Fig. 1) [56]. Some of these ROS-mediated oxylipins are structurally close or even identical to enzymatically-produced species (*e.g* PGs and isoprostanes), while most LOX- and CYP-derived mid chain hydroxides (e.g. 5-HETE, 8-HETE, 11-HETE or 12-HETE) could also arise from ROS oxidation. However, enzymatic formation of oxylipins is regioselective and enantioselective, whereas ROS-mediated formation proceeds with no stereoselectivity [2,10].

The expression of enzymes of the oxylipin pathways has cell and tissue specificity, although many of these enzymes are ubiquitously expressed [57]. Enzymes of the COX pathway include 2 isoforms, COX-1 and COX-2. Both have constitutive expression in various tissues that may directly contribute to the circulating pool of oxylipins. These include blood vessels (both COX-1 and COX-2), immune cells (monocytes, T-cells) and platelets [58]. Moreover, COX-2 is inducible by inflammatory signals (via NFκB pathway) in T-cells, B-cells and monocytes [59,60]. The downstream terminal prostanoid synthases have relatively specific expression sites. For instance, TXs synthase (generating TXA_2/B_2) is particularly highly expressed in activated platelets, while endothelium is a major expression site for PGI synthase (generating PGI_2). LOX enzymes also have preferential sites of expression. Platelets express 12-LOX (generating 12(*S*)-HETE), whereas activated leukocytes (e.g. monocytes, neutrophils) are a privileged site for 5-LOX expression (generating 5-HETE). The production of LTB_4 through LTA4 hydrolase can occur in various tissues, but LTC4 synthase is mainly expressed in eosinophils and monocytes [57]. Of note, CYP enzymes are poorly expressed in circulating cells and their major sites of expression are liver, kidney, brain, heart, and lung [2].

2.1.2. Catabolism of oxylipins

Non-esterified oxylipins do not accumulate within cells or in biofluids, but are synthesized upon demand, secreted and have a short half-life (from seconds to a few minutes) [57,61]. The primary active compounds are either converted to non-active or less active downstream metabolites. Knowledge of the potential degradation pathways of oxylipins and metabolic connections between precursors and products is important for the biological interpretation of the circulating oxylipin profiles.

Various oxylipin subclasses are degraded by a combination of initial β-oxidation followed by ω-oxidation/β-oxidation to polar metabolites that are excreted in urine or conjugated to glutathione [62,63]. β-Oxidation can occur in either the mitochondria or peroxisomes, with the same reactions mediated via different gene products. However, the relative involvement of these pathways in controling oxylipin signaling is not yet well understood. PGs and TXs are mainly chain shortened to their dinor- or tetranor- equivalents by two rounds of β-oxidation, chain

saturation and oxidation of the alcohol group [62]. PGs are deactivated via prostaglandin dehydrogenase to 15-keto- and 13,14-dihydro-15-keto PGs that are also found in circulation [64]. Degradation of HETEs is more complex, because the hydroxyl position represents an obstacle for a simple β-oxidation. In general, HETEs can be metabolized via three distinct metabolic pathways: β-oxidation, ω-oxidation and further hydroxylation given the presence of polyunsaturated hydroxylated chain. Overall, balance between the pathways and the major end products appears to be tissue-specific.

LTs and LXs are degraded by a combination of step-wise ω-carbon atom oxidation to first form the carboxylic group followed by β-oxidation from the ω-carboxyl terminus. LXB_4 was oxidized in human neutrophils from the ω-carboxy terminus [65], and it was chain-shortened from the ω-carboxyl terminus in rat hepatocytes as well [66,67]. However, the 3-hydroxy-LTB_4 intermediate was identified in the extract, suggesting that also β-oxidation from the α-carboxyl group is operational (with ~1% yield) for the LT structure similar to standard β-oxidation of HETEs [66,67]. This supports the notion that β-oxidation of LTB_4 from the carboxylic terminus is potentially a problematic reaction for acyl-CoA oxidase due to the close proximity of the 5-hydroxyl group and the α-carboxylic terminus [67–69]. Moreover, 5-HETE, sharing the same structural pattern at the carboxylic terminus with LTB_4, does not undergo β-oxidiation either in intestinal epithelial Caco-2 cells or renal tubular cells [68,69]. The substrate preferences of the acyl-CoA oxidase regarding the proximity of hydroxyl group and/or position of (conjugated) double bonds to the terminal carboxylic functions remains unexplored. It is unknown why the degradation of some oxylipins terminates with the residual chain hydroxylated at carbon number 4 or 5 or why the β-oxidation of polyunsaturated and polyhydroxylated chains partially ends with a hydroxyl group at carbon number 6 or 8.

In addition, the specific subcellular orchestration of oxylipin β-oxidation remains unclear. Data from patients suffering from Zellweger syndrome showed that peroxisomes are crucial for eicosanoid β-oxidation [62,70,71]. However, chain-shortened acyl intermediates can be transported to the mitochondria for final degradation, a step that requires coordination between peroxisomes and mitochondria. In some cells, β-oxidation truncates 12-HETE to only C18 or C16 metabolites following two or three cycles of β-oxidation [69], while other cells proceed to form C12 4-hydroxydodecenoic acid [72]. These findings suggest an unknown cell type-specific interplay between mitochondrial and peroxisomal degradation pathways, which might define what end products are released into circulation.

Overall, findings suggest that many oxylipins can be converted to shorter, more polar products depending on the specific enzymes present in various cells and tissues. These enzymatic reactions are sensitive to the position of double bond and the position of the hydroxyl group. The challenge is to deduce a biological interpretation based on the concentration of the parent oxylipins and degradation products. Relevant to this, it was recently shown that macrophages rapidly degrade high levels of diverse oxylipins to reduce the local inflammatory response and that this process can be modulated via cooperation between mitochondrial and peroxisome β-oxidation pathways and export/reuptake of the intermediates [73]. Thus, the active removal of oxylipins is likely to contribute to limiting their bioactivity, and how this dynamically operates in vivo is not well understood.

Overall, although the general oxylipin degradation pathways are known, there is limited information about cell-specific pathways, substrate specifities for the key enzymes, and identities of degradation intermediates. Further studies are needed to clarify to which extent catabolism of individual oxylipins is tissue/cell-specific and whether targeted analysis of their degradation products could assist in the identification of (patho)physiological conditions.

2.2. Different forms of circulating oxylipins

In systemic circulation, oxylipins are found esterified to complex lipids, accociated with blood proteins or in a non-esterified form. Here, we will briefly discuss the current knowledge about the origin of these different forms and their potential biological role.

2.2.1. Esterified oxylipins

Lipoproteins. In plasma, >90% of detected oxylipins are esterified into lipoprotein lipids [21]. These include PLs found at the surface of lipoproteins, but also triacylglycerols (TGs) and cholesteryl esters (CEs) found in the non-polar lipid core. Of note, each lipoprotein class has specific oxylipin profile that is differentially affected by metabolic disorders [74,75]. The formation of esterified oxylipins in lipoproteins can be induced by ROS acting directly on the surface lipoprotein PLs. Furthermore, the liver is actively involved in the production of enzymatically esterified oxylipins found in lipoproteins. This has been recently described with epoxy-fatty acids and hydroxy-fatty acids generated in response to an inflammatory stimulus and packaged into complex lipids contained in very-low-density lipoprotein (VLDL) [76]. For more details about the formation and metabolic fate of oxylipins in lipoproteins, see the recent review of Liang et al. [77].

Circulating cells and extracellular vesicles. Leukocyte and platelet membranes contain enzymatically oxidized PLs that are generated through coupling of COX and LOX pathways with the Lands' cycle enzymes or by direct enzymatic oxidation of PLs [24,78]. Similar lipids can also be generated by incorporation of exogenous oxylipins into membrane lipids [79]. This metabolic pathway has been well described in activated platelets and neutrophils generating various PL-esterified HETEs and PGs (e.g. PGD_2 and PGE_2) [80–83]. As mentioned earlier, ROS can also generate esterified oxylipins through direct oxidation of esterfied PUFAs. In a second pathway, 15-LOX can oxygenate PUFAs chains in CEs, which in turn can be released and re-esterified into lysophospholipids (lysoPLs) [84]. Recent studies also found that COX-2, 15-LOX-2 and platelet 12S-LOX can act on lysoPLs released by calcium-independent $PLA_2\gamma$ in response to calcium ionophore stimulation [85], generating oxylipin-bound lysoPLs. Furthermore, the synergistic activity of 15-LOX and group IIA secretory PLA_2 results in the formation of hydroxy, hydroperoxy, and keto products of 2-arachidonoyl-lysophosphatidylinositol that promote Toll-like receptor 4 activation and inflammation in arthritis [86]. Although their signaling pathways are just beginning to be revealed, recent studies suggest that oxylipin-lysoPLs may act as damage-associated molecular patterns that can promote sterile inflammation and contribute to autoimmune, chronic and aging-related diseases [25].

Because extracellular vesicles are released as fragments of their precursor cells, it is expected that esterified oxylipins found on cellular membranes might be also found on extracellular vesicles. Furthermore, several studies have shown that oxylipins are present in extracellular vesicles membranes. Briefly, in circulation, extracellular vesicles derived from T-cells, mast cells and intestinal mucosa have been shown to contain PGE_2, 15-$dPGJ_2$, LTC_4 and LTB_4 [87]. A recent targeted lipidomic study also identified various hydroxy-fatty acids (e.g. tetranor-12-HETE, 13-hydroxyoctadecadienoic acid (13-HODE), 9-HODE, 11-HETE, 8-HETE, 12-HETE) and tetranor derivatives of PGE_2 and PGD_2 in macrophage-derived extracellular vesicles [88].

In healthy subjects, it was shown that esterified oxylipins in plasma mainly consist of AA-derived oxylipins and linoleic acid (LA)-derived oxylipins (51% and 41%, respectively), while oxylipins derived from n-3 fatty acids (α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) represent only 8% of the esterified pool (Fig. 2). Concerning the chemical classes, the relative concentration of hydroxy-, epoxy- and dihydroxy-fatty acids represent 83%, 14% and 3% of esterified oxylipins. Prostanoids are also likely to be esterified as it has been shown for $PGF_{2,\alpha}$ which was found to be esterified at 40% in the plasma of healthy individuals [89].

The biological role of esterified oxylipins is not fully understood. They could serve as sinks that remove non-esterified oxylipins from cellular pools or act as a passive oxidant sink. They could also serve as a

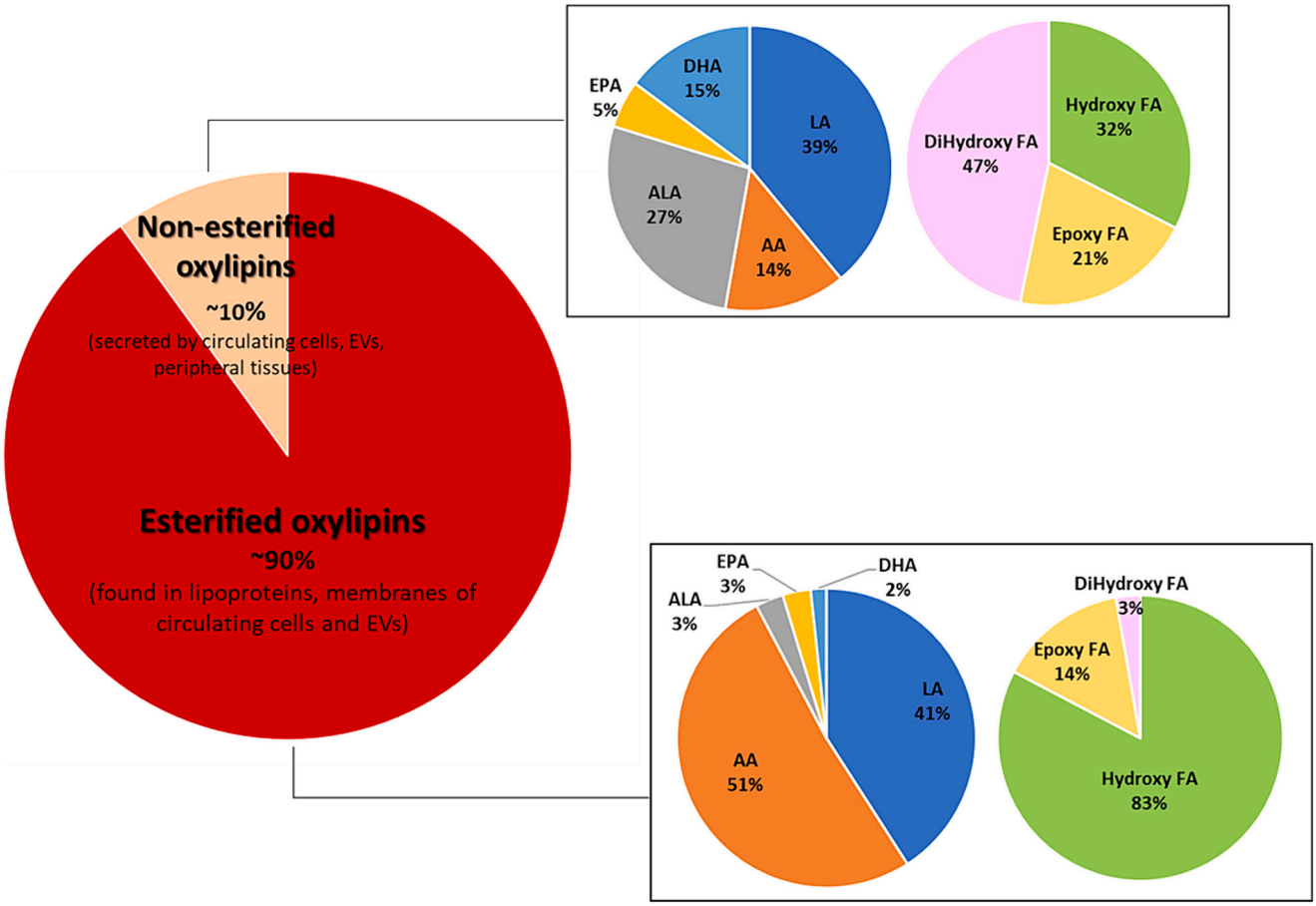

Fig. 2. Relative distribution of oxylipins between the esterified and the non-esterified pools (data reported in plasma of healthy humans by *Schebb* et al., *2014*).

cellular reservoir for rapid release of oxylipins upon cell stimulation. Esterified oxylipins can also directly act as signaling molecules in their own right [90].

2.2.2. *Non-esterified oxylipins*

In most lipidomics studies, circulating oxylipins are measured in their non-esterified form [91]. Similarly to non-esterified fatty acids, non-esterified oxylipins are found in circulation non-covalently bound to serum proteins, such as albumin, that has been shown to bind 13-HODE, 15-hydroxyeicosatetraenoic acid (15-HETE) PGH_2, TXA_2 and LTB_4 [92–94]. The source of non-esterified circulating oxylipins is not clear as they may originate from circulating blood cells, the vascular endothelium, liver, adipose tissue and other organs. Activated circulating cells (e.g. immune cells and platelets) produce a range of PGs, TXs and HETEs, while the endothelium generates PGI_2 [95]; indeed the interplay TXB_2 and PGI_2 is important for blood pressure regulation and controlling plateled activation. Extracellular vesicles could also contribute to the circulating pool of non-esterified oxylipins as they have been shown to contain functional enzymes releasing and oxidizing PUFAs (e.g. cytosolic PLA_2, calcium-independent PLA_2, secretory PLA_2, LTA4 hydrolase, LTC4 synthase, COX1/2, PGE synthase) [96]. Finally, adipose tissue lipolysis could be a significant contributor of non-esterified circulating oxylipins during the fasting state [97], especially LA- and ALA-derived species as these fatty acids are abundant in adipose tissues [98,99]. Decreased circulating levels of these oxylipins during the postprandial state [100], when adipose tissue lipolysis is inhibited, corroborate this notion.

The relative distribution of non-esterified oxylipins in plasma is very different from esterified oxylipins. In healthy subjects, it was shown that AA- and LA-derived oxylipins represent 14% and 39% of the quantified oxylipins respectively, while the n-3 PUFA derived oxylipins together accounted for up to 47%, more that half being ALA-derived species. Concerning the chemical classes, the relative concentration of hydroxy-, epoxy- and dihydroxy-fatty acids represent 32%, 21% and 47% of non-esterified oxylipins, respectively.

Non-esterified oxylipins are produced upon cell stimulation to regulate cell responses through autocrine or paracrine modes of action. They have half-lives from seconds to a few minutes suggesting that non-esterified oxylipins found in circulation might reflect recent cell or tissue activation.

3. Analytical parameters influencing circulating oxylipin profiles

Analytical parameters including sampling, storage, sample preparation, and MS analysis, can strongly influence oxylipin profiles. However, protocols used are still very diverse making the direct comparison of various studies quite challenging. The specific influence of various analytical parameters has been recently reviewed [101,102], therefore, this review article will only cover those key parameters (briefly summarized in Fig. 3) that should be carefully considered in oxylipidomic workflows aiming to generate biologically relevant data.

3.1. *Sampling*

The type of blood fraction sample (plasma or serum) used for oxylipin profiling should be carefully considered, as the two matrices are neither quantitatively nor qualitatively comparable. This has been demonstrated for esterified and non-esterified oxylipins, notably the platelet derived oxylipins (i.e. COX and 12-LOX derived oxylipins) [103]

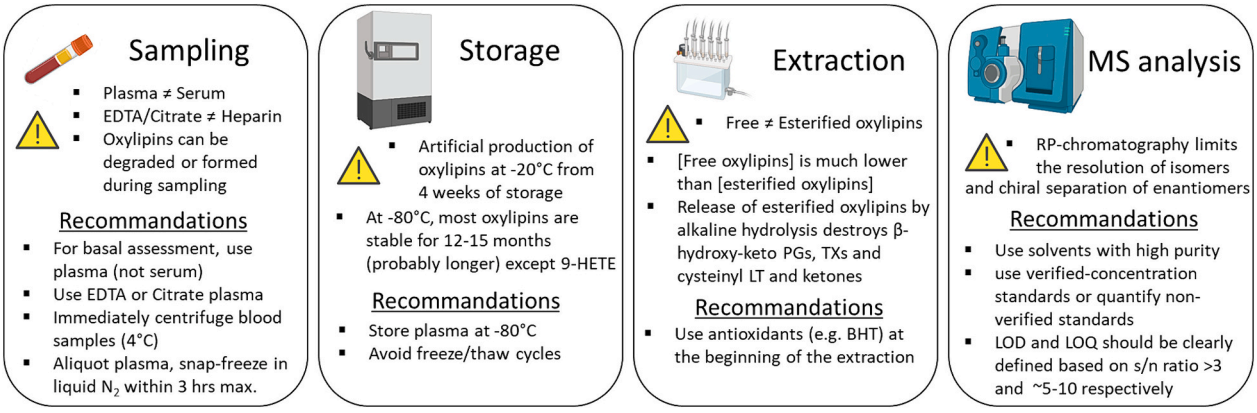

Fig. 3. General points of consideration and recommandations regarding the major experimental steps included in a typical workflow to profile circulating oxylipins (Created with BioRender.com, ≠ means "different).

but also some 15-LOX and 5-LOX derived oxylipins including SPMs [104]. When aiming to assess basal circulating oxylipin profiles, it is recommended to use plasma, not serum. During serum preparation, blood coagulation activates platelets and leukocytes, resulting in the activation of COX-1/-2, TXAS and 12-LOX generating mainly large amounts of TXA_2/B2, 12-HHT and 12-HETE [103,105,106]. As a result, serum does not provide data on basal circulating oxylipins but rather a functional evaluation of COX/TXAS/12-LOX activity during the coagulation process [107,108]. Furthermore, the type of anticoagulant used for plasma preparation can also modulate the oxylipin profile. To avoid artificial production of oxylipins during this process, it is recommended to use ethylenediaminetetraacetic acid (EDTA) that chelates Ca^{2+} ions inhibiting both coagulation and cell activation [109]. Sodium citrate can be also used to prepare plasma, but heparin should be avoided as it only blocks coagulation, not cell activation, allowing platelets to form 12-LOX oxilipins [110]. Heparin was also shown to activate lipoprotein lipases [111].

Timing and temperature during sampling and storage are also important parameters to consider in order to avoid artificial production or degradation of oxylipins. Overall, it is recommanded to centrifuge the blood, collect, aliquot and freeze plasma samples as quickly as possible. Ideally, blood samples should be immediately centrifuged (at 4 °C), plasma should be collected, aliquoted, snap-frozen in liquid nitrogen within 3 h, and stored at -80 °C until further analysis. Methanol or other organic solvents can be added to plasma samples to stabilize it, although this has minor effect when plasma is stored at -80 °C (except for 12-HETE and TXB_2 that are artificillay increased if methanol is not added) [112]. Overall, small deviations from these ideal conditions generally does not appear to affect most oxylipins with the exception of epoxy-PUFAs that artificially increase if inappropriate sample preparation and processing are performed (i.e. blood hemolysis, delays in blood centrifugation and plasma sample freezing) [110,113]. The temperature of blood collection (4 °C vs room temperature) also has limited influence on F2-isoprostanes [114].

3.2. Sample storage

The conditions under which the plasma samples are stored (temperature, time and freeze/thaw cycles) are also important as oxylipins may be degraded or artificially formed during long-term storage. As plasma preparations may contain small number of platelets, residual enzymatic activityand/or non-enzymatic autoxidation induced by free transition metals coming from disrupted cells can modify oxylipin patterns; storing the samples at -80 °C is highly recommended to avoid these problems. When stored at -20 °C, most oxylipins levels were found increased over time, starting with 4 weeks of storage [112,114]. When kept at -80 °C, others and we have showed that most oxylipins are stable (within the analytical variance of +/- 20-30%) over a period of 12-15 months. It is reasonable to conclude that longer periods of storage without freeze and thaw cycles should have minor impact on oxilipin stability. Additionally, freeze/thaw cycle should be avoided as it can cause cell activation and release of free metal ions. Although this does not seem to affect most oxylipins, there is an impact on 12-HETE, 5-HETE, 18-hydroxyeicosapentaenoic acid (18-HEPE) and 14- hydroxydocosahexaenoic acid (14-HDHA) [110,113], and additional studies are necessary to confirm the impact on other species.

3.3. Oxylipin extraction

Several of the steps included in lipid extraction and sample preparation protocols, can influence the oxylipin patterns. The most important question to address when designing the study is which type of oxylipins (non-esterified or esterified) should be measured. As discussed, esterified oxylipins are much more abundant in plasma than non-esterified oxylipins (10 to 350 times higher) [115], therefore easier to obtain and quantify from small volumes of plasma. However, the alkaline hydrolysis step used to release esterified oxylipins from complex lipids, destroys β-hydroxy-keto PGs (e.g. PGEs, PGDs) and TXs, as well as cysteinyl leukotrienes and ketones (i.e. oxo-eicosatetraenoic acid (oxo-ETE), oxo-ODE and oxo-eicosadienoic acid (oxo-EDE) from the LOX pathway), although it does not affect β-hydroxy-alcohols (PGFs) and LTB_4 [89]. Therefore, circulating concentrations of these species can only be quantified from the pool of non-esterified oxylipins, if present. Another important issue is the use of antixidants and enzyme inhibitors during sample preparation and lipid extraction. They should be added at the beginning of sample preparation to avoid degradation or artificial formation of oxylipins during storage. A recent study comparing the effect of different additives on the quantification of esterified oxylipins, showed that adding butylated hydroxytoluene (BHT) at the beginning of sample preparation prevents artificial production of oxylipins, mainly hydroxy-PUFAs [113]. It should nevertheless be noted that BHT might cause matrix effects.

A number of detailed standard operative procedures for the analysis of non-esterified and/or esterified oxylipins have been published [116,117]. Typically, sample preparation starts with a step of lipid extraction applying liquid-liquid extraction (LLE) or protein precipitation with organic solvents. Then, oxylipins are semi-purified by solid phase extraction (SPE) to reduce matrix effects and concentrate low abundant species. The choice of the lipid extraction and SPE protocols should be carefully considered as they can impact on all aspects of the analysis, including the removal of ion suppressing matrix components, process efficiency and oxylipin recovery, as well as degradation and/or the artificial production of lipid species. For esterified oxylipins, LLE with acidified solvents or protein precipitation are both appropriate, but

protein precipitation is less labor-intensive and could therefore be prefered for its simplicity [118]. Concerning the choice of SPE, there is a choice of resins including reverse phase, polymeric stationary phase with embeded polar groups or materials with anion exchange properties and solvents used to remove impurities and elute oxylipins; all these factors can impact upon the extraction and recovery of oxylipins [119]. Ostermann et al. compared the efficacy of six well-estabished protocols and concluded that using silica-based bonded phase (e.g. SepPak tC18 SPE column) and methyl formate for the elution of oxylipins is very efficient for the analysis of non-esterified oxylipins in plasma [119]. Of note, Ostermann et al. showed that when analyzing esterified oxylipins (using base hydrolysis), this also releases large amounts of PUFAs leading to artificial formation of cis-epoxy-PUFAs during the drying of cartridge. It is therefore recommended to control precisely the drying time (exactly 30 s) to avoid this technical bias [118,120]. Once eluted, the solvent(s) is usually evaporated in the dark and under nitrogen to avoid further oxidation, or using a vacuum system. The lipid residue is then reconstituted using the appropriate volume and type of solvent. Glycerol (30% in solvent) could be added to stabilize the oxylipin extract and reduce column sensitivity to the organic solvents, respectively. Although this is a common practice in many labs [121–125], the impact of this practice has not been assessed. Once reconstituted, the oxylipin extracts should be transferred in a tighltly sealed amber glass vial and stored at -80 °C to prevent oxylipin degradation by the atmospheric oxygen or light.

3.4. MS analysis of extracted oxylipins

Oxylipins are usually analyzed by reversed-phase (ultra)high-performance liquid chromatography (RP-(U)HPLC) coupled to electrospray ionization tandem mass spectrometry (ESI-MS/MS) [101,102]. As RP-(U)HPLC does not permit the resolution of isomers, separate protocols employing chiral separation of enantiomeric compounds may be required to determine the biological origin (enzymatic or free-radical) of oxylipins of interest [116]. This approach is becoming more popular and was recently developed for the quantitative profiling of octadecanoid species [126].

ELISAs have been available for many years for the detection of oxylipins, including prostaglandins and more recently SPMs. However, due to the small size of these lipids, there are issues of specificity, and these kits have been known to overestimate the levels of oxylipins present [127] Two recent examples relating to PGE_2 are cited, where the kit was used as an assay to indicate a prostaglandin pathway, rather than to specifically measure PGE_2 due to overestimation of the amount of lipid present [128,129].

The purity of solvents and internal standards can also affect the liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of oxylipins, as they may induce ion suppression resulting in reduced sensitivity and increased variability. It is recommended to use the highest purity solvents and lipid standards of verified concentration, or to quantify non-verified standards as recently described [130]. Procedures of analyte identification and requirements for peak quality should also be standardized to avoid inconsistent or questionable results, as it was recently highlighted with SPMs [101]. Importantly, the limits of detection and quantitation should be clearly defined, e.g. by using an appropriate signal to noise ratio (e.g. typically, between 5 and 10 for quantitation and >3 for detection). When product ion spectra are used to confirm the identity of an oxylipin, they must visually resemble that of the relevant synthetic standard. As this might not feasible for lipids found close to the analytical limit of detection, providing a series of multiple reaction monitoring transitions based on structure-specific fragment ions, and showing the analyte peak eluting at the same retention time, can provide the required confidence for accurate identification. An example of this approach can be found in Rund et al. [133].

3.5. Harmonization and comparability of oxylipin analysis

Although multiple analytical choices (i.e., type of biofluid, type of anticoagulant, non-esterified or esterified oxylipins, sample preparation, MS analysis) can influence the detection and quantification of oxylipins, there are currently no internationaly harmonized protocols. This makes difficult the comparison of results obtained from independent clinical studies. Harmonization will be also crucial for future clinical applications that require highly precise and reproducible analysis [134]. Additionally, it is also important to pursue analytical developments in the field of oxylipin analysis to determine which methodologies and workflows are best for which set of oxylipins, tissue type being analyzed, and for which clinical application.

There is only one interlaboratory study that precisely investigated the comparability of oxylipin analysis [50]. In this study, five independent laboratories assessed the technical variability and comparability of 133 oxylipins (including octadecanoids, eicosanoids and docosanoids from various biochemical pathways) using a harmonized and standardized protocol, common biological materials (i.e., seven quality control plasmas), standard calibration series, and analytical methods. Using this experimental design and the consensus value approach (based on the median of the mean) to assess the interlaboratory comparability, this study shows that reliable, reproducible, and comparable oxylipin concentrations can be measured in independent laboratories. It would be interesting to reproduce this type of interlaboratory study using different sets of oxylipins.

4. Release and action of oxylipins

4.1. Non-esterified oxylipins

The mechanism of oxylipin release is not yet fully described for all oxylipins classes but, for instance, prostanoids, once produced intracellularly, they can passively diffuse through the plasma membrane or be actively transported by ATP binding cassette transporters, in particular the multidrug resistance-associated proteins [135]. In the extracellular environnement, non-esterified oxylipins can act on the producing cells (autocrine action) or neighbouring cells (paracrine action) by binding to a wide range of cell membrane receptors. Oxylipin receptors are typically G-protein coupled receptors that induce different signals depending on the relevant coupled G-proteins (see [136,137]). Although less documented, non-esterified oxylipins can also act intracellularly by binding to nuclear recepetors such as the family of peroxisome proliferator-activated receptors (PPARs) or by interacting with proteins such as IκB kinase or Kelch-like ECH-associated protein 1, therefore modulating the NFκB and Nrf2 signaling pathways [138,139].

4.2. Esterified oxylipins

Until recently, only non-esterified oxylipins were considered as being biologically active, but it is now well established that esterified oxylipins exert bioactivities. Contrary to non-esterified oxylipins that only act on surrounding cells through autocrine or paracrine actions, esterified oxylipins can act at distance of their site of production therefore allowing endocrine action. The lipolytic release of esterified oxylipins is a mean by which esterified oxylipins can exert their action [22]. This reaction is catalysed by lipoprotein lipase [21], which is expressed in heart, skeletal muscle and adipose tissue, and allows delivery of fatty acids and oxylipins from TG-rich lipoproteins (chylomicron and VLDL). Endothelial lipase may also be involved in the hydrolysis of esterified oxylipins from high density lipoprotein (HDL) to the endothelium [22]. The second way, by which esterified oxylipins could exert their bioactivity is through direct binding to cell surface or nuclear receptors. Non-enzymatically produced oxylipins esterified to PLs were shown to stimulate several types of signal-transducing receptors including G protein-coupled receptors, tyrosine kinase receptors, Toll-like receptors,

receptors coupled to endocytosis, and nuclear ligand-activated transcription factors such as PPARs [140,141]. A third way of action is linked to the conformational change induced by the presence of oxylipins in membrane PLs. For instance, several in vitro and in vivo studies have reported that various types of esterified HETEs promote coagulation by enhancing the ability of phosphatidylserine to interact with clotting factors [142–144].

5. Challenges in understanding the biological significance of circulating oxylipins

Oxylipins have important regulatory functions in various biological processes such as inflammation, vascular tone or coagulation. Thanks to the increasing number of analytical platforms enabling routine oxylipin profiling, the use of plasma oxylipin profile in clinical research is spreading supporting the identification of (patho)physiological dysregulations or monitoring the effects of nutritional or pharmacological interventions or generation of new research hypotheses (see Table 1 and supplementary file). Usually, oxylipin profiling is used to identify shifts in the oxylipin signature in patients in comparison with control/healthy subjects. These shifts can give a first indication about the activation or inhibition of a given oxylipin pathway and/or cell type. However, it it should be kept in mind that metabolic or cell specificity is not absolute in oxylipin metabolism. Assessment of strereochemistry using chiral chromatography could be useful in appreciating the metabolic origin of a species of interest supporting biological interpretation, as *S* or *R* configurations are indicative of enzymatic or non-enzymatic origin, respectively. Moreover, it is advisable to check all oxylipins derived from the same pathway or related to the same biological function, in order to confirm the involvement of a specific pathway or functional activation. Having an indication on the activation or inhibition of a given oxylipin pathway, and/or a given cell type, can be extrapolated as these are well-documented biological processes. For example, high levels of the 5-LOX products 5-HETE and LTB4 that are both produced by activated monocytes, can be reasonably interpreted as an activation of inflammatory processes. Similarly, high levels of 12-HETE and TXA_2, that are both produced by activated platelets, may reflect activation of the coagulation process. It is also important to appreciate the presence of feedback control mechanisms. For instance, it has been shown that 15-HETE can suppress 5-LOX activity in human polymorphonuclear leucocytes [145], and this may help to understand the biological significance of high 15-HETE and/or low 5-HETE and LTB4 plasma levels.

Furthermore, many attempts have been made in clinical research to identifiy oxylipins that may be specific disease biomarkers. However, this should be considered with caution as a shift in oxylipin signatures may be indicative of underlying physiopathological processes such as inflammation or thrombosis, that are common conditions in a wide range of diseases.

Another level of biological interpretation of shifting oxylipin profiles would be to deduce any potential cellular effects of circulating oxylipins. However, most of our knowledge about the biological action of oxylipins on target cells is derived from experimental studies using specific cell models or genetically modified animal models and pharmacological doses of purified or synthetic lipids. Moreover, the complexity of pharmacokinetics, pharmacodynamics, and pharmacogenomics of oxylipins should be considered to avoid over-interpretation of their role. This issue is especially well illustrated by data on the production and action of PGs, which are briefly described in the following paragraphs. PGs are usually present in circulation at very low concentrations [146]. For example, PGE_2 is present at 3-12 pg/mL (8.5–34 pM) [147], while in experimental models, PGE_2 is active at concentrations above 10,000 pM [148,149]. Thus, concentration of circulating oxylipins may be too low to regulate cells directly or at least it is difficult to predict which cells and to what extent they may be (or have recently been) affected by circulating oxylipins. Another stumbling block in establishing straightforward links between circulating concentrations of oxylipins and

Table 1
Selected publications* illustrating the biological significance and potential of oxylipins in clinical research.

Disease/Disorder	Reference	Objective of the study
Cardiovascular disorders	Palmu et al., 2020 [182]	Assessment of the correlation between plasma inflammatory eicosanoids and related oxylipin mediators and blood pressure in a cohort of 8099 Finish participants.
	Caliguiri et al., 2017 [183]	Determination of the influence of plasma fatty acids and oxylipins on the odds of cardiovascular/ cerebrovascular events in a cohort of 98 patients with peripheral artery disease.
	Sun et al., 2016 [184]	Examination of the association between plasma fatty acids, oxylipins, and risk of acute myocardial infarction in a cohort of 744 case and 744 control Singapore Chinese individuals.
	Strassburg et al., 2012 [185]	Assessment of the changes of plasma oxylipin profile before and 24 h after cardiac surgery in male patients ($n = 5$).
Cardiometabolic disorders	Shearer et al., 2018 [186]	Comparison of oxylipin composition of VLDL, LDL, and HDL in 14 health individuals and 31 metabolic syndrome patients and determination of the effect of metabolic syndrome patient treatment with prescription omega-3 fatty acids on lipoprotein oxylipin profile.
	Dalle et al., 2022 [187]	Identification and validation the oxylipin signature of metabolic syndrome in two independent nested case/control studies involving 476 participants.
	Schuchardt et al., 2013 [188]	Comparison of serum concentrations of 44 oxylipins in 20 normolipidemic with 20 hyperlipidemic male individuals.
Obesity	Jiménez-Franco et al., 2024 [189]	Comparison of plasma oxylipin profiles in 116 patients with severe obesity with 63 overweight/obese healthy controls and determination of the impact of surgical weight loss on the levels of oxylipins in plasma.
	Grapov et al., 2020 [190]	Assessment of the weight loss and fitness interventions on exercise-associated plasma oxylipin patterns in sedentary obese, insulin-resistant women ($n = 12$).
	Hernandez-Carretero et al., 2018 [191]	Assessment of changes of PGD2 levels in patients ($n = 9$) before, 6 and 12 months after bariatric surgery ($n = 9$).
Diabetes	Tuomisto et al., 2022 [192]	Investigation of the correlation between plasma eicosanoid and related oxylipin profiles and the risk of incident type 2 diabetes in a cohort of 1070 Finnish participants.
	Tans et al., 2020 [193]	Determination of changes of plasma COX oxylipin levels between lean ($n = 9$), obese ($n = 10$), and type 2 diabetes ($n = 11$) individuals.
	Grapov et al., 2012 [194]	Comparison of plasma non-esterified fatty acids, oxylipins and endocannabinoids levels in overweight to obese, non-diabetic ($n = 12$) and type 2 diabetic ($n = 43$) African-American women.
	Buckner et al., 2021 [195]	Examination of the association between plasma oxylipin profiles and incident type 1 diabetes in a

(*continued on next page*)

Table 1 (*continued*)

Disease/Disorder	Reference	Objective of the study
		cohort of 71 case and 71 control children.
Liver disease	Li et al., 2020 [196]	Evaluation of the oxylipin role in non-alcoholic fatty liver disease (NAFLD) in a cohort of 35 case and 8 healthy control individuals.
Cancer	Chocholoušková et al., 2019 [197]	Comparison of plasma oxylipin concentrations in cohort of female breast cancer patients (n = 20) and healthy volunteers (n = 20).
	Saboda et al., 2021 [198]	Determination of relationship between oxylipin plasma levels and colorectal adenoma characteristics, the development of a metachronous adenoma, and evaluation whether the selenium intervention influenced plasma oxylipin levels in a cohort of 256 subjects.
Neurological disorders	Chistyakov et al., 2024 [199]	Assessment of the correlation between Parkinson's disease stage and plasma oxylipin profiles in a cohort of patients in early (n = 29) or advanced (n = 44) disease stage and healthy volunteers (n = 36).
	Gouveia-Figueira et al., 2017 [200]	Comparison of plasma levels of endocannabinoid anandamide, related N-acylethanolamines, and linoleic acid-derived oxylipins in women suffering for migraine with aura (n = 26) or without aura (n = 12) and 26 healthy women.
	Borkowski et al., 2021 [201]	Comparison of plasma and cerebrospinal fluid levels of non-esterified polyunsaturated fatty acids, oxylipins, and endocannabinoids in a cohort of approximately 150 patients with Alzheimer's disease and approximately 135 healthy controls.
	Hennebelle et al., 2017 [202]	Determination the difference in plasma oxylipin profiles and fatty acid precursors in patients with major depressive disorder with seasonal pattern between summer and winter (n = 9).
Ocular disorders	Rhee et al., 2021 [203]	Investigation of differences in plasma oxylipin profiles in type 2 diabetes patients with a disease duration ≥15 years with or without diabetic macular edema in a cohort of 60 participants.
	Xu et al., 2024 [204]	Comparison of plasma oxylipin levels in patients with primary open-angle glaucoma (POAG) (n = 10) and healthy controls (n = 10).
	Ren et al., 2023 [205]	Comparison of plasma oxylipin and fatty acids precursor concentrations in adult patients with retinal vein occlusion (n = 44) with normal controls (n = 36).
Infectious diseases	Biagini et al., 2023 [206]	Examination of the association between plasma oxylipin and precursor fatty acid profiles and SARS-CoV-2 variants (Wild-type (n = 14), Alpha (n = 9), Delta (n = 11), and Omicron (n = 14)) in cohort of a 48 patients.
	Deme et al., 2022 [207]	Assessment the correlation between plasma eicosanoid levels and immune, viral, and cognitive outcomes in people with HIV (n = 95) compared to seronegative controls (n = 25).
	Surowiec et al., 2017 [208]	Comparison of plasma oxylipin and endocannabinoids in children with uncomplicated and severe malaria (n = 40) with healthy controls (n = 20).
Others		
Crohn's disease	Ben-Mustapha et al., 2023 [209]	Comparison of mucosal and plasma polyunsaturated fatty acid, oxylipin, and endocannabinoid levels in Crohn's disease patients (n = 28) and healthy controls (n = 30).
Preterm birth	Svenvik et al., 2021 [210]	Evaluation of the association between plasma oxylipin levels and preterm birth in preterm labor in a cohort of 80 pregnant women.
Nephropathy	Deng et al., 2022 [211]	Comparison of plasma oxylipin levels in IgA nephropathy patients (n = 30) and healthy controls (n = 30).
Sarcopenia	Dalle et al., 2019 [212]	Investigation of the correlation between plasma oxylipin signatures and characterization of the early phases of sarcopenia in a cohort of subjects with decreased (n = 12), stable (n = 16), or increased (n = 14) appendicular muscle mass.

[*] The publications were selected according to a search on PubMed using the terms "*plasma oxylipins*" and filtering only human trials. The search raised 167 publications that were manually filtered to selected only the most relevant publications (n = 102). See the complete list of publications in the supplementary file. Of note, we did not intend here to perform a systematic research. We therefore intentionally limit our literature search to PubMed and to the terms "plasma oxylipins" providing a relevant list of studies but not representing the entire literature illustrating the biological significance and potential of oxylipins in clinical research.

biological effects is their complex pharmacodynamics. A well-studied example is PGE_2, which stimulates four PGE_2 receptor subtypes (EP1-4) including one (EP3) that exists as several functionally non-identical isoforms [150]. This heterogeneity significantly adds to the complexity of the whole system because the receptor subtypes are differentially expressed on various cell types, are coupled to different signal transduction pathways, and can induce different, often opposite, effects. For example, EP3 binds to Gi and promotes aggregation of platelets, while EP4 and EP2 are coupled to Gs thus elevating cyclic adenosine monophosphate and inhibiting aggregation [147]. Similar functional heterogeneity is characteristic of the regulation of vascular tone: PGE_2 can induce either constriction or dilatation of vascular smooth muscle through different receptor subtypes [151]. An additional factor complicating the prediction of functional effects of oxylipins on the basis of their circulating concentrations is the genetic variatiability in the expression of receptor subtypes. For example, expression of pro- and anti-aggregatory EP receptors can be different between individuals, which leads to quantitatively and qualitatively different responses to PGE_2 [152].

The historically classical view of ligand-receptor interactions suggests that one specific receptor recognizes one specific ligand acting as an agonist or antagonist [153]. This type of interaction falls under the definition of one-to-one ligand-receptor interaction. However, numerous studies have shown that individual oxylipins can bind and stimulate multiple receptors [154]. Furthermore, individual oxylipin receptors can be activated by multiple oxylipins with different affinities – a phenomenon known as receptor promiscuity. For example, EP4 is activated not only by its cognate ligand PGE_2, but also by other PGs, their metabolic products (e.g. deoxy-PGs), and isoprostanes [137]. Another example is the TX receptor that, in addition to its cognate ligand TXA_2, can bind $PGF_{2\alpha}$, PGD_2 and 8-isoprostaglandins E_1, E_2 and $F_{2\alpha}$ [155], while different ligands have variable affinities and intrinsic activities, i.e., some of them are partial agonists and may be expected to

inhibit effects of full agonists such as TXA_2. Thus, interactions of prostanoids with their receptors can be described as many-to-many reactions, in which each prostanoid binds to several receptors and vice versa. These promiscuous ligand-receptor interactions can significantly complicate understanding of the link between concentrations of circulating prostanoids and their biological effects.

Similar principles may apply to other types of oxylipins. For example, LTB_4 binds with high affinity to the LTB4 receptor 1 (BLT1) and, with lower affinity and specificity, to the BLT2 receptor. Cysteinyl leukotrienes have five receptors (CysLT1, CysLT2, P2Y12, GPR17 and GPR99), which are coupled to different effector systems and induce diverse physiological effects [136]. These receptors are variably expressed on different cell types, which makes the whole picture even more complex. The binding is also pharmacologically promiscuous as demonstrated by the ability of different oxylipins to activate the same receptor. For example, the octadecanoids 9,10-dihydroxyoctadecamonoenoic acid (9,10-DiHOME), 12,13-DiHOME, 9(10)-epoxyoctadecamonoenoic acid ((9(10)-EpOME), 12(13)-EpOME, 9- and 13-HODEs, keto-octadecadienoic acids (KODEs), 9-oxooctadecadienoic acid (9-oxoODEs) and 13-oxo-ODEs, as well as the eicosanoid epoxyeicosatrienoic acids have been shown to activate the capsaicin receptor TRPV1 [156–158]. Another example is LT receptor BLT2, which in addition to LTB4, also binds other hydroxy fatty acids derived from LOX, such as 12S-HETE, 12S-hydroperoxyeicosatetraenoic acid (12S-HPETE), 15S-HETE, as well as the TX synthase product 12-hydroxyheptadecatrienoic acid (12-HHT) [159].

6. Independent factors influencing circulating oxylipin profiles

When interpreting associations between plasma oxylipin profiles and diseases, one should keep in mind that several extrinsic and/or intrinsic factors may influence the oxylipin profile independently of the investigated disease. The influence of these factors has been recently discussed [101,102] and will be briefly summarized here. The diet and especially the type and amount of consumed PUFAs have a strong influence on plasma oxylipin profile. This is very well documented through various dietary intervention studies using n-3 PUFAs (mainly fish oil, or purified EPA and DHA) [160–162]. Although the effect of supplementation might vary depending on the experimental design, the change in plasma oxylipins generally corresponds to the observed changes in their precursor PUFA(s). Usually, increasing the amount of dietary n-3 PUFAs in healthy subjects induces increase of n-3PUFA-derived oxylipins at the expense of n-6PUFA species. However, these relationships are very heterogenous when considering non-esterified oxylipins [160]. A recent dietary intervention study in healthy adults suggests that these effects are dose-dependent [118]. Although dietary n-3 PUFAs induce changes in all pathways, it has been shown that the CYP-epoxygenase pathway is particularly impacted in healthy individuals because of the highest metabolic efficiency of these enzymes towards EPA and DHA, in comparison with AA [163].

Medication intake should also be considered when seeking associations between oxylipins and disease states, as certain medicines specifically inhibit (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)) or indirectly affect (e.g. statins) oxylipin synthesis [120,164]. Although less documented, physical exercise, fasting/postprandial status, gut microbiota composition, some phytochemicals, selenium suplementation, smoking, alcohol consumption, exposure to air pollution, and chemicals may also modulate oxylipin biosynthesis and contribute to the variability of plasma profiles [100,165–174].

Gender, age and genetics are other important intrinsic factors that may also contribute to the biological variability of plasma oxylipins [101,175], althought the impact of these factors remains to be investigated in large cohort studies. Therefore, when interpreting shifts in oxylipin profiles in case - control studies, interindividual varibility that might mask biologically significant differences in the oxylipin patterns should be taken into consideration. This can be done at the stage of the experimental design, for instance by matching the participants according to age, sex or smoking status, or later at the stage of biostatistical analysis, by including potential confunding factors in the relevant mathematical models.

7. How bioinformatics can support biological interpretation

Functional annotation is a critical process in oxylipin profile interpretation. Most oxylipins are not cell-specific or enzyme-specific compounds but can come from different cell or tissue types (e.g. platelets, monocytes, vascular endothelium, liver, adipose tissue, etc.). As different enzymes or free-radical mediated oxidation can produce the same oxylipin(s), an in-depth understanding of the relevant biochemical pathways is required to correctly interpret their profiles. Data interpretation should be supported by mechanistic studies, identifying oxylipins at a molecular species level, and pinpointing at the relevant enzymes. Interpretation of complex oxylipin datasets can be facilitated by bioinformatic tools and specialized databases. A pre-requisite is the proper identification of oxylipin species based on the level of confidence in the analytical platform (e.g. structure, accurate mass, stereochemistry etc.). For instance, a compound commonly reported as'12-HETE' can be a mixture of enantiomers, which may exert different biological effects. The Human Metabolome Database (HMDB, https://hmdb.ca/) contains only'12-HETE' record, while KEGG and ChEBI recognize '12(*S*)-HETE' and 12(*R*)-HETE molecules, and LIPID MAPS allow annotations of 5 different'12-HETE' isomers (LMFA03060063, LMFA03060064, LMFA03060008, LMFA03060007, LMFA03060088). LIPID MAPS allows users to pick the identification based on the levels of confidence (e.g. confguration on all stereo centers), thus critically evaluating the information provided by the analytical technique. Confidence in annotation can also be provided through biological information, for example, in washed platelets, only 12S-HETE (and not 12R-HETE) is generated, as proven decades ago.

Once oxylipins have been properly identified, it can be useful to map their metabolic pathways showing both their PUFA substrate and the enzyme(s) involved in their production. Curated pathway maps tailored for specific species are critical for meaningful data interpretation. For instance, AA metabolism is different between humans and mice, with respect to enzymes and substrate preferences (see https://www.lipidmaps.org/resources/pathways/wikipathways). Table 2 summarizes the publically available curated oxylipin metabolism pathways in humans. LimeMap is a comprehensive overview of the major oxylipins [176] and LIPID MAPS-based pathways are focused on major enzymes and their products [2177]. Both pathway sources contain information about enzymes and metabolites and LIPID MAPS pathways are curated at the level of enzymes, including primary citations. LIPID MAPS-based pathways were generated in a joint project with WikiPathways, but have been made static to ensure further changes involve careful curation. WikiPathways are open to updates and modifications from all Internet users, changes and authors are recorded, but it is up to the user to evaluate their correctness. A future challenge would be to create metabolic maps that would include clinically relevant markers (e.g. ratio of metabolites, expression of critical enzymes, etc.) linked to pathophysiology, to quickly orient the user.

Software tools that allow the mapping of user data over a pathway scheme, significantly facilitates oxylipin profile interpretation for end-users. Two sources of pathway maps covering the oxylipin synthesis are available: 1) LimeMap [176] created in CellDesigner [178] in Systems Biology Markup Language (SBML) format, and 2) WikiPathways [177] created in PathVisio [179] in Graphical Pathway Markup Language (GPML) format. The major problem for users is that both CellDesigner and PathVisio were developed as diagram editors and do not support helpful data mapping. Although the pathway files can be converted to alternative formats, the orderly-arranged network layout is lost in most cases [180]. SMBL is the most frequently used community-driven format to encode molecular networks and allows storing layout

Table 2
Publicly available curated human oxylipin metabolism pathways.

Publication	Source	Metabolites of	Format
LimeMap: a comprehensive map of lipid mediator metabolic pathways	Doi: https://doi.org/10.1038/s41540-020-00163-5	AA, dihomo-γ-linolenic acid (DGLA), ALA, EPA, DHA	SBML
The Biosynthesis of Enzymatically Oxidized Lipids	Doi: https://doi.org/10.3389/fendo.2020.591819	AA, EPA	CYS
The Biosynthesis of Enzymatically Oxidized Lipids	Doi: https://doi.org/10.3389/fendo.2020.591819	DHA	CYS
Eicosanoid synthesis (*Homo sapiens*)	https://www.wikipathways.org/index.php/Pathway:WP167 https://www.lipidmaps.org/resources/pathways/wikipathways/WP167	AA	GPML
Metabolism of alpha-linolenic acid (*Homo sapiens*)	https://www.wikipathways.org/index.php/Pathway:WP4586	ALA	GPML
Eicosanoid metabolism via cyclooxygenases (COX) (*Homo sapiens*)	https://www.wikipathways.org/index.php/Pathway:WP4719	AA	GPML
Eicosanoid metabolism via cytochrome P450 monooxygenases (CYP) pathway (*Homo sapiens*)	https://www.wikipathways.org/index.php/Pathway:WP4720	AA	GPML
Eicosanoid metabolism via lipooxygenases (LOX) (*Homo sapiens*)	https://www.wikipathways.org/index.php/Pathway:WP4721	AA	GPML
Octadecanoid formation from linoleic acid (*Homo sapiens*)	https://www.lipidmaps.org/resources/pathways/wikipathways/WP5324 https://www.wikipathways.org/pathways/WP5324.html	LA	GPML

information as an extension [180]. GPML is the file format used to store pathway content at WikiPathways, but its layout information compatibility is very limited. Therefore, LimeMap is the most versatile option currently available.

8. Perspectives and conclusions

The potential of oxylipins in clinical research and the development of MS-based assays for their qualitative and quantitative analysis, have resulted in an increase of publications reporting oxylipidomic studies in the last decade. In this review article, we discussed the current state of biochemical, biological and analytical knowledge in the field, aiming to provide sufficient information to avoid mis- or overinterpretation of circulating oxylipin profiles. Although the major biochemical pathways, cellular sources, receptors, uptake and release mechanisms, and bioactivities of eicosanoids and leukotrienes have been well established and used to develop potent pharmacological agents such as a number of non-steroidal anti-inflammatory drugs, this is not the case for many other oxylipins, and further research is needed to address these questions. Validation studies and analytical process standardisation, as well as regular literature updates are necessary to guarantee a proper biological interpretation. It is important to note that a large number of circulating oxylipins are not cell or tissue type specific, and can be generated via more than one biochemical/metabolic pathways. Circulating profiles also include oxylipin metabolites, the cellular and enzymatic origins of which remain poorly described. Although these species may not be useful in clinical research, this picture may change as new discoveries advance the field. Further studies and complementary analytical approaches (e.g. chiral chromatography, synthetic lipid standards) are now necessary to accurately determine the biochemical pathways and cellular sources determining the biosynthesis and activities of less-well described or new oxylipins, including their metabolites. Another important aspect, currently not considered in clincal research, it is that the vast majority of circulating oxylipins seem to be esterified to complex lipids (e.g. TGs, PLs, CEs) in lipoproteins, circulating cells and extracellular vesicules membranes. Reporting the levels and profiles of esterified oxylipins can be informative as their profiles can be different to those of non-esterified oxylipins, with distinct biological activites, although they are more challenging to analyze due to the relative lack of primary standards. Interestingly, esterified oxylipins can act at a distance of their production site allowing endocrine action, whereas non-esterified oxylipins are produced on demand and only act on surrounding cells through autocrine and paracrine mode of action, before being degraded. The compositon of esterified oxylipins found in the lipid cargos of lipoproteins, circulating cells and extracellular vesicules, as well as and their links to various physiopathological conditions, are only beginning to be understood, raising exciting new questions that should be further adressed as we move forward. When it comes to the biological interpretation of circulating oxylipin profiles, it is important to keep in mind that most of our knowledge about their bioactivities comes from experimental studies that cannot not always be exptrapolated to reflect the outcome of oxylipidomic clinical or preclinical studies. Pharmacokinetics, pharmacodynamics and pharmacogenomics of oxylipins should also be taken into consideration to avoid mis- or over-interpretation of the data. Moreover, when comparing shifts in oxylipin profiles between case and control participants, various extrinsic (e.g. diet, medication) and intrinsic (genetics, age, sex) factors should be considered, as these could modulate oxylipin profiles independently of the studied disease or condition. Future oxylipidomic studies should systematically collect and report this type of information to support the study design and data analysis stages. Finally, analytical choices (e.g. type of sample, conditions of storage, sample preparation procedures, purity of solvents and lipid standards, MS data analysis protocols) can have a profound influence on the resulting oxylipin profiles. Adopting harmonized procedures to should help ensure the generation of high-quality intercomparable data. Currenltly, only a small number of bioinformatic tools and databases exist, that have been specifically designed to interpret oxylipin profiles. However, these tools can only provide metabolic information (e.g. substrate PUFAs and enzymatic pathways); therefore, a further collective effort is necessary to generate improved bioinformatics tools able to support integration of information representing the pleiotropic biological action of oxylipins. In this regard, generation of a searchable database containing oxylipin MS/MS data is a current aim for the International Lipidomics Society Oxylipin Interest Group, along with reporting guidelines that would align with the recently published checklist for lipidomics reporting in general [181].

CRediT authorship contribution statement

Karol Parchem: Writing – review & editing, Writing – original draft. **Sophia Letsiou:** Writing – review & editing, Writing – original draft. **Toni Petan:** Writing – review & editing, Writing – original draft, Visualization. **Olga Oskolkova:** Writing – review & editing, Writing – original draft. **Isabel Medina:** Writing – review & editing, Writing – original draft. **Ondrej Kuda:** Writing – review & editing, Writing – original draft. **Valerie B. O'Donnell:** Writing – review & editing, Writing – original draft. **Anna Nicolaou:** Writing – review & editing, Writing – original draft. **Maria Fedorova:** Writing – review & editing, Writing – original draft. **Valery Bochkov:** Writing – review & editing, Writing – original draft. **Cécile Gladine:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Acknowledgments

This article is based upon work from COST Action CA19105 - Pan-European Network in Lipidomics and EpiLipidomics (EpiLipidNET), supported by COST (European Cooperation in Science and Technology). K.P. would like to acknowledge the support of the Czech Health Research Council (Project No. NU21-03-00499). C.G. would like to acknowledge the support of the French Research Agency ANR (Project No. ANR-22-CE17-0018-01). I.M. would like to acknowledge the support of the Spanish Ministry of Science and Innovation (Project No. PLEC2022-009385). Work in the M.F. lab is supported by "Sonderzuweisung zur Unterstützung profilbestimmender Struktureinheiten 2021" by the SMWK, TG70 by Sächsische Aufbaubank and SMWK, the measure is co-financed with tax funds on the basis of the budget passed by the Saxon state parliament (to M.F.), Deutsche Forschungsgemeinschaft (FE 1236/5-1 to M.F.), and Bundesministerium für Bildung und Forschung (01EJ2205A, FERROPath to M.F.). O.K. was supported by a grant from the Czech Academy of Sciences [Lumina Quaeruntur LQ200111901], and by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104) – Funded by the European Union – Next Generation EU. A.N. acknowledges the support of British Heart Foundation (PG/2019/34923). T.P. would like to acknowledge the support of the Slovenian Research Agency (grants P1-0207 and J7-1818).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plipres.2024.101276.

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