INTRODUCTION

Plasma lipid profile is the index to ascertain hyperlipidemia. Additionally, vascular cells, including platelets, engaged in a dynamic interaction with circulatory lipids, offer secluded intracellular compartments for lipid synthesis. This “Trojan horse” of lipid repertoire is overlooked in the conventional lipid profile but has profound pathophysiological significance. Platelets can deliver atherogenic lipids while seeding atheroprogression1 and contribute to chronic manifestations of cardiovascular disease (CVD).2 Lately, advanced lipidomic analyses3 have started to unravel the multifaceted aspects of the platelet lipidome.4,5 This review highlights the intriguing features of the platelet lipidome that govern thrombotic and pro-coagulant activities, platelet bioenergetics and its dependence on exo/endogenous lipids, transcellular lipid metabolism driving thromboinflammation, and the translational impact of exploring the platelet lipidome for biomarkers and lipid therapeutics.

PLATELETS AND LIPIDS: AGE-OLD ACCOMPlices

The concurrence of dyslipidemia and coronary atherothrombosis,8,9 in combination with reduced occurrence of acute myocardial infarction...
(AMI) following administration of lipid-lowering therapies\textsuperscript{10,11} advocate that circulatory lipids may modulate platelet functions. Platelets express scavenger receptors (SRs)- CD36, LOX-1, CXL16-PS/SR, and ApoER2 for low-density lipoprotein (LDL).\textsuperscript{12} Increased CD36 expression correlates with enhanced reactivity to oxidized LDL (oxLDL), and thrombotic propensity in humans,\textsuperscript{13-15} whereas platelet activation and thrombosis in hyperlipidemic mice are normalized by CD36 deficiency.\textsuperscript{13} In acute coronary syndrome (ACS) patients oxLDL binding to platelets correlates with activation status.\textsuperscript{16} Intraplatelet oxLDL levels are elevated in coronary artery disease (CAD) patients, particularly in ACS patients diagnosed with intracoronary thrombi,\textsuperscript{5} suggesting that platelet-lipid associations may enhance thrombotic risk.\textsuperscript{17}

\subsection{Lipid agonists}

Platelet interaction with plasma lipids through SRs lowers their activation threshold.\textsuperscript{11,18-20} Platelets from hyperlipidemic patients show increased secretion, aggregation, and enhanced superoxide generation, corroborating with elevated plasma \textit{β}-thromboglobulin and CD40L levels. On the contrary, patients with abetalipoproteinemia lacking ApoB100 show impaired aggregation and TXA2 production.\textsuperscript{18} LDL binding triggers rapid phosphorylation of ApoER2 by Src family kinases leading to p38MAPK activation\textsuperscript{21} upstream of cPLA2, and subsequently calcium mobilization, TxA2 production, inside out-\textit{αIIbβ3} signaling that synergizes with agonist-induced stimulation. This pathway is eventually terminated through PECAM-1, leading to Ser/Thr-phosphatase-PPA2 recruitment and dephosphorylation of effector kinases.\textsuperscript{22} ApoER2 occupancy activates focal adhesion kinase serving as a docking site for adaptor protein Grb2 and PI3K-p85\textsuperscript{23,24}; it also activates small GTPase Rap-1b, which triggers \textit{αIIbβ3} activation, which sensitizes platelets to agonist-induced secretion and aggregation.\textsuperscript{25} The priming effect of LDL is greatly enhanced upon oxidation.\textsuperscript{26} OxLDL engages CD36 and Scavenger receptor A (SR-A)\textsuperscript{26,27} driving p38MAPK activation, TXA2 production, enhanced adhesion to fibrinogen,\textsuperscript{28} shape change, and spreading through myosin light chain (MLC) phosphorylation.\textsuperscript{29} OxLDL can suffice as an independent agonist by engaging CD36, instigate reactive oxygen species (ROS) production through gp91\textsuperscript{phox}/NOX2 (Figure 1); an effect counteracted by CD36 inhibitor and absent in CD36\textsuperscript{−/−} and NOX2\textsuperscript{−/−} murine platelets.\textsuperscript{30} While oxLDL ligation of CD36 triggers the activatory signaling cascade, platelet sensitivity toward cGMP imposed inhibition is reduced.\textsuperscript{30} Such mechanisms, by which circulatory lipids desensitize platelets to inhibitory brakes, as validated by Naseem’s group, justify the correlation of hyperlipidemia

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\caption{Binding of oxidized low-density lipoprotein (oxLDL) or oxPC\textsubscript{CD36} species to CD36, other oxidized phospholipids (oxPLs) to platelet-activating factor receptor (PAFR) and lysophosphatidylcholine to G2AR activates platelet. Signaling pathway downstream of CD36 ligation releases the platelet inhibitory break otherwise executed through soluble guanylate cyclase (GC), cGMP, and protein kinase G (PKG), but enhances the activatory signaling mechanisms leading to an enhanced thrombotic response. Non-enzymatically derived oxPLs enhance tissue factor (TF) generation, counteract the tissue factor pathway inhibitor (TFPI) to promote coagulation. Reactive oxygen species (ROS)-triggered activation of redox-sensitive ERK5 downstream of CD36 ligation activates the caspase driven apoptotic machinery to promote externalization of PS, and facilitates coagulation, fibrin deposition. Platelet liberated ROS also mediates extracellular lipid oxidation into oxidized derivatives.}
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and thrombotic disposition.\textsuperscript{30} We observed that both LDL and oxLDL instigate a pro-thrombotic response. LDL/oxLDL triggers intraplatelet ROS generation, like in the oxLDL-CD36 axis;\textsuperscript{21} induces lipid peroxidation; and LDL modifications, which enriches the repertoire of oxidized lipids.\textsuperscript{3} OxLDL-CD36 potentiates arterial thrombosis in hyperlipidemic ApoE\textsuperscript{−/−} mice through activation of redox-sensitive ERK5.\textsuperscript{32} This eventually promotes externalization of thrombogenic-PL, PS, in a caspase-dependent manner, followed by assembly of the prothrombinase complex and fibrin generation (Figure 1).\textsuperscript{33} Extracellular conversion of LDL to oxLDL (Figure 1) is seen in the microenvironment of stimulated platelets; in carotid plaque homogenate; even more so with platelets from hyperlipidemic individuals, but not from patients with X-linked chronic granulomatous disease lacking NOX2, suggesting a ROS-mediated process.\textsuperscript{34} Extracellular oxLDL thus generated engages CD36 or LOX-1 to enhance aggregation, 8-iso-prostaglandinF\textsubscript{2α}-III, TXA\textsubscript{2} production, and thrombus formation.\textsuperscript{34} Extracellular oxidation may also generate lysophosphatidic acid (LPA), richly deposited at atherosclerotic plaques. Lysophosphatidic acid activates platelets through G\textsubscript{q}-coupled LPA receptor, induces Ca\textsuperscript{2+} mobilization, and calmodulin-kinase mediated phosphorylation of MLC, which facilitates shape change.\textsuperscript{35,36} Activated platelets generate LPA, and contribute to serum levels during blood clotting.\textsuperscript{37} Given its effect on vascular smooth muscle cells (VSMCs), platelet-derived LPA may substantially contribute to atheroprogession. Recent LPC has been suggested as a surrogate marker of plaque instability in atherosclerotic mice, and as a principal component of platelet-derived microvesicles.\textsuperscript{38} LPC activates platelets through G2AR\textsuperscript{38} (Figure 1). Lysophosphatidylcholine (LPC) enrichment in platelets from CAD patients,\textsuperscript{3} and highest LPC concentration at vulnerable plaque regions,\textsuperscript{38} demonstrates its atherothrombotic attributes. Moreover, prominent oxLDL immunoreactivity in platelet-enriched areas of intracoronary thrombus, corresponding to increased intraplatelet oxLDL levels in ACS patients,\textsuperscript{5} suggests that platelets are lipid depositories in thrombus and may perpetrate thromboinflammation.

2.2 Thromboinflammatory lipids and platelet lipid cargo

Lipids can act as pro/anti-inflammatory effectors. Leukotrienes (LTs) cause inflammation in asthma, while lipoxins terminate inflammation.\textsuperscript{39} LPC as a platelet chemoattractant promotes the formation of platelet-monocyte aggregates,\textsuperscript{39} the predominance of which is seen in peripheral circulation of ACS patients.\textsuperscript{40} Monocytes are a prime source of soluble tissue factor (TF) in blood, further substantiated by cardiovascular risk factors, eg, hypercholesterolemia; exaggerated by the presence of platelets; and reverted by statin administration.\textsuperscript{41} Monocyte TF expression is associated with clinical manifestations of deep vein thrombosis (DVT), antiphospholipid syndrome (APS), and CAD. Moreover, platelets may acquire TF from monocyte-derived microparticles or during platelet-monocyte interaction mediated through P-selectin, Mac-1, enhancing their thrombogenicity.\textsuperscript{42} OxLDL upregulates p-selectin expression on platelets,\textsuperscript{5} enabling aggregate formation, preferentially with CD16\textsuperscript{+} monocytes.\textsuperscript{43} Lipid-laden, “eat-me” signal-exhibiting apoptotic platelets are phagocytosed by CD34\textsuperscript{+} progenitor cells, monocytes, and M1-M2-macrophages, promoting their differentiation into foam cells.\textsuperscript{44} Such phagocytic processes accelerate lipid loading in monocytes involving CD36, SR-A, while aspirin, P2Y1, P2Y12 antagonist, ticagrelor, counteract it.\textsuperscript{43} Lipid-activated platelets generate pro-inflammatory chemokines like CXCL4, which also support monocyte lipid uptake.\textsuperscript{43} LDL/oxLDL uptake in platelets themselves is increased by CXCL12, which enhances ApoER2 and CXCL16-PS/OX-5R surface expression.\textsuperscript{5} CXCL12 also boosts the phagocytic clearance of lipid-loaded platelets by monocytes and macrophages.\textsuperscript{44} Thus, a combination of circulatory lipids and atherogenic chemokines may exaggerate the inflammatory potential of lipid-laden platelets. Activated platelets may also direct the course of inflammation by generating both pro- and anti-inflammatory lipid mediators. Platelet eicosanoids (TXA\textsubscript{2}, 12-HETE) and prostaglandins (PGF\textsubscript{2}E, PGD\textsubscript{2}) regulate monocyte and neutrophil functions. Activated platelets also release dioxolane A3 (DXA\textsubscript{3}) following PAR1-PAR4 activation or by collagen, ionophore, or collagen-thrombin combination employing cPLA\textsubscript{2} and AA metabolism\textsuperscript{45} (Figure 2A), independent of TXa\textsubscript{2} synthesis. DXA\textsubscript{3} generation is affected by genetic deficiency of cPLA\textsubscript{2}, by cPLA\textsubscript{2}, and COX-1 inhibitors (aspirin, indomethacin), but is enhanced in 12-L0X\textsuperscript{−/−} murine platelets.\textsuperscript{45} DXA\textsubscript{3} is rapidly esterified to 16:0-, 18:1-, 18:0-PE-plasmalogen, and 18:0-acyl-PE by lysophospholipid acyltransferases (Figure 2A); so mostly remains platelet associated, while free DXA\textsubscript{3} adds to serum levels during clotting. Platelet-derived/associated DXA\textsubscript{3} enhances neutrophil Mac-1 expression (CD11b/CD18),\textsuperscript{46} which might exaggerate neutrophil-platelet or endothelial associations, transendothelial migration, and phagocytosis. Discovery of more platelet-derived lipids and their pathophysiological relevance will uncover novel thromboinflammatory mediators and therapeutic targets.

3 LIPIDS AS AN ENERGY SOURCE

Plasma lipid intake may enrich intraplatelet free fatty acid (FA) reserve following lipase activity, to fuel the metabolic drive. Thrombin-activated platelets generate FAs for mitochondrial \(\beta\)-oxidation, a process orchestrated by cPLA\textsubscript{2}.\textsuperscript{47} Thrombin-induced oxygen consumption rate, both basal and thrombin, triggered adenosine triphosphate (ATP)-linked oxidative respiration are affected by cPLA\textsubscript{2} inhibition, as it abrogates the generation and flux of FAs and eicosanoids through mitochondrial \(\beta\)-oxidation.\textsuperscript{7} The high rate of glycolysis (extracellular acidification rate [ECAR]) under basal or thrombin stimulated state, which principally depends on glucose utilization, remains unaltered.\textsuperscript{7} However, FA and eicosanoid synthesis are affected in the absence of glucose or following inhibition of glycolysis, which presumably supplies ATP for kinase activities (eg, Src) substantiating cPLA\textsubscript{2} catalysis. Platelets exhibit metabolic plasticity in switching between glycolysis and mitochondrial oxidative phosphorylation at basal conditions.\textsuperscript{48} Glycolysis is triggered upon thrombin stimulation following rapid uptake of exogenous
glucose or utilizing endogenous glycogen reserves in its absence, with slight increment in mitochondrial oxygen consumption. Under nutrient-limiting conditions, platelets may use glucose, glycogen, or FA to support energy demands. Mitochondrial oxidation is flexible in terms of substrate utilization, and while oxidation of one is restricted, consumption of the other is enhanced. The strength and duration of stimuli may also influence the choice of fuels. At a later stage of activation, when FAs become limiting, mitochondrial \( \beta \)-oxidation is retarded, ATP consuming maintenance of membrane asymmetry is compromised, leading to the exposure of procoagulant PS, otherwise confined

**FIGURE 2** A, Platelet-derived thromboinflammatory lipids influence the function of immune cells like monocytes and neutrophils. Platelet-derived DXA3 is a recently discovered eicosanoid that acts on neutrophils. DXA3 is synthesized upon platelet activation through the AA-COX-1 metabolic pathway. DXA3 thus generated is esterified to membrane phospholipids by lysophospholipid acyl transferase, and remains membrane-associated. B, Platelets equipped with COX-1 and 12-LOX are involved in transcellular lipid metabolism with endothelial cells, 5-LOX expressing monocytes and neutrophils.
to the inner leaflet of plasma membrane. Another investigation validates the utility of lipogenesis in platelet bioenergetics. Acetyl Co-A carboxylase (ACC), a key regulator of FA metabolism when in (ACC1) cytosol synthesizes malonyl-Co-A for de novo lipogenesis; whereas ACC2 on the outer mitochondrial membrane prevents FA transport into mitochondria. AMPK, which is sensitive to ATP depletion and rise in AMP levels, is activated upon platelet stimulation. AMPK phosphorylates and inactivates ACC possibly to halt energy-demanding lipogenesis and release the brake on FA channeling into the mitochondrial powerhouse. Absence of an AMPK-ACC inactivation axis exaggerates thrombotic response to collagen but has no bearing on basal or thrombin and collagen stimulated bioenergetics. Exogenous plasma energy reserves may also influence platelet bioenergetics. Guppy et al addressed metabolic fuel consumption by platelets from plasma and estimated an ATP turnover of 25 µmol/1010 platelets/h, a quarter of which is attributed to aerobic glycolysis and the rest to oxidation of various substrates. However, the majority of oxygen consumption is due to lipid oxidation. Therefore, the metabolic profile of platelets from hyperlipidaemic individuals or mice, accustomed to SR-instigated signals from exogenous lipids, besides an altered endogenous lipidome is likely to be different. Modern lipidomic approaches to monitor generation, from exogenous lipids, besides an altered endogenous lipidome is likely to be inflicted by metabolic disorder (hyperlipidaemia, diabetes) and consumption and enzymatic transformation of lipids as a function of time might elaborate the flux of lipids during thrombotic activities as discussed in the context of fluxolipidomics of PUFAs. Platelet bioenergetics has significant bearing on platelet hyper-reactivity. Platelets from pulmonary hypertension patients show enhanced respiratory reserve capacity, which correlates with mean pulmonary artery pressure, pulmonary vascular resistance, and right ventricular stroke work index. Increased FA oxidation in these platelets is associated with augmented activity of carnitine palmitoyltransferase-1, responsible for the formation of acylcarnitines, and ETC -complex II. Increased levels of acyl-carnitine in CAD patients also indicates a metabolic shift in platelets, likely to be inflicted by metabolic disorder (hyperlipidaemia, diabetes) frequently leading to CAD.

4 | LIPIDS THAT FINE-TUNE AND ORCHESTRATE PLATELET RESPONSE

4.1 | The reservoir of membrane lipids and oxidized phospholipids (oxPLs)

The platelet membranous network incorporates endogenously generated lipids and those endocytosed from plasma. They constitute a large part of membrane ultrastructure including lipid rafts and additionally they are used as a source of energy, mediate signaling processes and provide a procoagulant surface. Cholesterol and glycosphingolipid enriched lipid rafts regulate the spatial distribution of membrane tethered proteins eg CD36, ADP receptors (P2Y1, P2Y12). Specific extraction procedures are required for these membrane microdomains to extrapolate their native composition and track the dynamic changes during platelet activation. Proteins within lipid rafts interact with coagulation factor XII (FXIII), which influence the pro-coagulant efficacy of activated platelets, and mediate clot retraction. Moreover, ADP stimulation or p2Y12 antagonism by ticagrelor triggers redistribution of cholesterol and sphingomyelin within these microdomains, which may regulate platelet responsiveness. This is of particular significance in ACS patients where ticagrelor is a preferred antiplatelet therapy. Physiological regulators, eg, PGI2, reduce platelet responsiveness to von Willebrand factor (VWF) by phosphorylation of GPIIb mediated through PKA-I. GPIIb is localized to lipid rafts. Membrane lipid composition and consequently, thrombotic functions, can also be influenced by diet. Dietary intake of γ-linolenic acid (18:3n-6)-containing borage oil, ω-3-FA in fish/fish oil/DHA or similar marine and olive oil supplements enrich antithrombotic lipid precursor ω-3-FA (linoleic acid), dihomo-γ-linolenic acid-(DGLA, 20:3n-6) conjugated but not thrombogenic arachidonic acid (20:4n-6) containing phospholipids (PLs), alters mean platelet volume, and decreases thromboxane and β-thromboglobulin production.

Membrane lipids include glycerolipids, glycerophospholipids, sterols, sphingolipids, prenols, and several FAs. PLs constitute the bulk of platelet membranes altered by enzymatic (phospholipases, ligases), and non-enzymatic processes. Both uncontrolled non-enzymatic oxidation of PLs, and stringently regulated enzymatic oxidation, generate oxPLs. Phosphatidylcholines are more prone to non-enzymatic modifications producing hydroperoxides and fragmented oxPLs. Synthesis and biological significance of non-enzymatically derived oxPLs is reviewed elsewhere. The complex mixture of oxPAPC, oxPLPC, oxDL, collectively referred to as oxPCCD36, is detected at atherosclerotic plaques, and released upon plaque rupture. Plasma levels of oxPCCD36 are elevated in hyperlipidaemia. oxPCCD36 directly activates platelets. PAPC-derived PGPC promotes endothelial tissue factor secretion and PLPC-derived PONPC, PAzPC counteracts the tissue factor pathway inhibitor. oxPFPFR are PAF like non-enzymatically derived ether PLs that activate platelets through platelet-activating factor receptor (PAFR). Concomitantly they promote thrombosis (Figure 1). We observed increased intraplatelet levels of several oxPLs, particularly in ST-elevation myocardial infarction (STEMI) patients possibly resulting from oxidative stress, which may prompt intraplatelet oxPL generation.

Phosphatidylethanolamines are enzymatically modified by COX-1 and 12-LOX either through direct oxidation, or esterification of preformed oxidized FAs. One hundred and three species of enzymatically oxidized PLs have been characterized in thrombin-activated platelets. Platelet activation triggering cPLA2 activity liberates AA and DGLA from PLs, which are metabolized by COX-1 into PGE2, PGE2, PGD2, thromboxane, PGE1, PGD1, and by 12-LOX into 12-HpETE, and 12-HpETE, respectively. PL-derived lipid signaling intermediates have been extensively explored and will be in the future. Meanwhile, the focus has shifted to unravelling the role of esterified PLs and plasmalogens. 12-HETE is generated upon thrombin, and collagen stimulation, and rapidly esterified to PEs (16:0p, 18:1p, 18:0p, 18:0a/12-HETE-PE) and PCs (16:0a, 18:0a/12-HETE-PC) by Co-A dependent ligases. 12-HETE-PEs substanitate coagulation like other anionic PLs (PS), by positioning their negatively
charged hydroxyl group near the membrane to facilitate binding of calcium and coagulation factors, prompting thrombin generation. Antiphospholipid syndrome patients show significantly enhanced levels of 12-HETE-PLs, exaggerating their prothrombotic disposition. Moreover, 12-HETE-PLs enable binding of β2-glycoprotein1 to increase autoimmune reactivity associated with APS. A considerable enrichment of AA containing PE-plasmalogens (16:0/20:4, 18:1/20:4) is also observed upon the gain of ACC function. This, together with a concomitant increase in TXa2 synthesis, confers a prothrombotic phenotype in ACC1/2DKI mice. Angiotensin II-induced abdominal aortic aneurysm (AAA) models in ApoE- mice also show elevated levels of HETE-PL (12-, 5-, 15-HETE-PEs and PCs) along with several eoxPLs, eg, HODE, HDOHE, and non-enzymatic fragments of eoxPLs, that substantiate procoagulant functions. On the contrary, a potential therapeutic implication of HETE-PLs is demonstrated by 12-HETE-PE liposome administration, which restores hemostasis in murine hemophilia A by stimulating the extrinsic coagulation cascade and thrombin generation in factor VIII- (FVIII), factor IX- (FIX)-, and factor X (FX)-deficient human plasma. Platelets from patients having undergone cardiopulmonary bypass generate less 12-HETE-PE and externalize less 12-HETE-PE/PS upon stimulation. They exhibit less thrombin generation and increased bleeding risk. 12-HETE-PLs restore thrombin generation in postoperative plasma in vitro exemplifying its clinical benefits.

DHA-derived 12-LOX metabolite 14-HDOHE can also be esterified to PE to produce diacyl and plasmalogen-PEs. Additionally, COX-1 generated PGE2 and PGD2 are promptly PE-esterified following activation with thrombin, collagen, or ionophore, in a calcium-dependent manner. However, the physiological significance of esterified prostaglandins remains undefined. Free eicosanoids copiously generated and released during activation regulate platelet responsiveness.

Once hydrolyzed from the sn-2 position of membrane PLs by phospholipases, the oxygenation of polyunsaturated fatty acids (PUFAs) by COX-1, 12-LOX, and cytochrome p450 (CYP) generates short-lived oxylipins to orchestrate intracellular signaling, act as paracrine/autocrine G-protein coupled receptors (GPCR) agonists. Genetic deficiency of cPLA2 in humans compromises oxylipin generation and coagulation. AA-PLs are differentially processed in response to thrombin and collagen. AA release upon thrombin stimulation is mediated through cPLA2, which prefers AA-PL and AA-PS as targets; while collagen activation triggers all three cPLA2, iPLA2, and sPLA2 and prefer AA-PE-plasmalogens. In addition, different AA pools in platelets may be preferentially processed by COX-1 or 12-LOX. The action of COX-1 on oxylipin precursors DGLA, AA, EPA, generates prostanooids of series 1-(PGD1, PGE1), series 2-(PGD2, PGE2, PG2, TXA2), and series 3-(PGD3, PGE3, TXA3). PGD2 and PGE2 are also non-enzymatically derived from PGH2. Prostanoids diffuse through plasma-membranes and act on prostanoid D-(DP)/E receptors-(EP), prostacyclin-(IP), and thromboxane-(TP) receptors to regulate platelet responsiveness. While TXA2-TP potentiates the prothrombotic drive, endothelium and leukocyte derived PGI2, PGE1, exercise antithrombotic effects. PGE2 at low doses while engaging EP3 is proaggregatory, and at high doses when bound to EP4 is antiaggregatory.

12-LOX catalyzes hydroperoxidation of PUFAs to generate 12-HpETE (AA-derived), and 12-HpETE (DGLA-derived), which exert pro- and antithrombotic actions, respectively. 12-HpETE is reduced to 12-HETE by glutathione reductase and synergistically enhances aggregatory response to collagen, ADP, and PAR activation, but counteracts that of AA. Myeloproliferative patients, and those with RUNX1 haploinsufficiency show decreased 12-LOX expression, decreased thrombotic complications, but increased bleeding.

The contribution of CYPs to oxylipin synthesis in platelets is relatively unexplored, although expression of several CYPs (CYP1A1, CYP5A1, CYP2U1, CYP2J2, CYP4A11, CYP4F2) is evidenced in platelets and megakaryocytes (DAMI cells). CYP metabolites (ETEs, 20-HETE) have been identified in platelets; in addition, both washed platelets and DAMI cells generate these oxylipins in the presence of exogenous AA. Recently the generation of AA-derived metabolite 8,9-EET, also the release of EPA derived metabolite 14(15)-HpETE can be shown from murine platelets, although their functional impact remain unspecified. Given the diversity of oxylipins, attaining a balance between pro- and antithrombotic mediators is the intended therapeutic target to preserve hemostasis but reduce pathological thrombosis.

4.2 | Thromboinflammatory communication through lipids

Platelets also engage in transcellular lipid metabolism. Platelets, erythrocytes, and endothelial cells lacking 5-LOX engage in transcellular metabolism with 5-LOX expressing cells (neutrophils, monocytes) generating lipid mediators in amplified amounts, or a unique metabolite. Thus, the AA metabolome is influenced by the transcellular exchange of substrates between (5-,12-,15-,)-LOX enzymes, which diversifies eicosanoid biosynthesis and their pathophysiological influence. Platelet-derived PGH2 is converted into the antiplatelet and vasodilatory prostacyclin PGI2 by endothelial cells.

Platelets also utilize leukocyte-derived LTA4 to generate pro-inflammatory peptido-leukotrienes (LTs) (Figure 2B) and anti-inflammatory lipoxins. AA generated in activated neutrophils is oxygenated by 5-LOX to produce the 5-HpETE intermediate, which is converted to LTA4 by 5-LOX and to 5-HETE by glutathione peroxidase. Unstable LTA4 is rapidly hydrolyzed to LTE4 and further converted into less active 20-OH-LTE4 and inactive 20-COOH-LTB4. However, co-stimulation of neutrophils with platelets generates LTC4. Platelets act as donor cells by providing AA and 12-HETE, or acceptor cells utilizing leukocyte-derived substrates.
and neutrophils by calcium ionophore (A23187) platelet-released AA is utilized by neutrophil 5-LOX to generate 5-HETE, LTB4, or by 15-LOX to produce 15-HETE. Some neutrophil-derived 5-HETE and LT4 is transported back to platelets, where 12-LOX metabolizes 5-HETE to 5-12-diHETE, and LTC4-synthase (LTC4S) converts LTB4 into LTC4. Neutrophil-derived LTC4 is also processed by 12-LOX to produce lipoxins. Neutrophil-derived LTB4 consumption by platelets increases proportionately with substrate concentration, time, and the number of platelets in the neutrophil-platelet mix. Co-incubation of neutrophils primed with inflammatory stimuli (FMLP and opsonized zymosan) triggers LTC4 synthesis, which is metabolized by platelets. Similarly, GMCSF primed, and FMLP challenged, neutrophils when co-incubated with thrombin activated platelets, prompt generation of LTC4 (using neutrophil-derived LTB4 by platelets), 5-12-diHETE (by neutrophils using platelet-derived 12-HETE), and LXA4/LXB4. A correlation between LTC4 and 5-12-diHETE suggests simultaneous production of the transcellular metabolites (Figure 2B). Thrombin activated platelets are more efficient in converting neutrophil-derived LTA4 into cysLTs as compared to 12-LOX-generated lipoxins. Unstimulated neutrophils as acceptor cells can also metabolize 12-HETE from thrombin-activated donor platelets and hydroxylate it into 12-20-diHETE. Thus, different modes of transcellular lipid metabolism ensue in response to diverse triggers. While calcium ionophore activates both cells and immunogens (FMLP, opsonized zymosan particles) stimuli neutrophils, thrombin acts primarily on platelets. Vascular thrombin has a profound impact on transcellular eicosanoid metabolism. With advanced lipidomics platforms at our disposal nowadays, these old chapters are worth revisiting.

Transcellular eicosanoid biosynthesis is not limited to platelets and neutrophils. Eosinophils, lung resident macrophages, and mast cells expressing LTC4S also produce LTC4. Although monocytes express 5-LOX, the transcellular exchange of substrates with platelet 12-LOX differs considerably. LTC4 and 5-12-diHETE are generated upon co-stimulation of monocytes-platelets with calcium ionophore. Interestingly, radiolabeling experiments with 3H and 14C-AA reveal that monocytes provide the substrates AA, 5-HETE, and LXA4/LXB4 for platelet 12-LOX. However, monocytes, unlike neutrophils, cannot utilize platelet-derived metabolites to a detectable extent, exemplifying distinct modes of transcellular metabolism operating across different cell lineages.

Biophysical interaction between cells also coordinates transcellular metabolism. Exchange of substrates whereby 3H-TxB2 is synthesized in 3H-AA-labeled neutrophil/unlabeled platelets (platelets as acceptor), and 3H-LTC4 is generated from unlabeled neutrophil/3H-AA-labeled platelets (platelets as AA donor and LT4 acceptor), is disrupted by GE12 antibody against P-selectin. Presumably, FMLP-activated neutrophil-derived mediators, eg, cathepsin G, induce P-selectin expression on platelets to establish intercellular contact and facilitate transcellular lipid synthesis. On the contrary, autologous unstimulated neutrophils or FMLP-challenged, or A23187-stimulated neutrophils counteract 12-HETE and 12-HHT generation in thrombin activated platelets through CD62P that is abolished upon removal of sialic acid from sialyl Lewis(x) structure on neutrophils. Interaction of platelet-GPIIb/IIIa with neutrophil-CD11b/CD18, bridged through fibrinogen, also delays and decreases LT and 5-HETE generation from ionophore-treated neutrophils. This is counteracted by peptides interfering with fibrinogen binding to platelet-GPIIb/IIIa. These mechanisms may resolve the inflammatory response initially mounted by platelet-neutrophil interaction.

The significance of platelet-derived AA in transcellular metabolism during acute inflammation is demonstrated in fMLP treated rabbits that show elevated plasma levels of TxB2 suggesting platelet activation, and LTB4, LTE4 production. This is significantly affected in immunologically thrombocytopenic rabbits. Clinical evidence comes from patients undergoing percutaneous transluminal coronary angioplasty. Sampling of intracoronary blood at the plaque rupture site in situ reveals elevated levels of intraluminal LTC4, LTA4, particularly in aspirin-treated patients, which directs AA metabolism through LOX. Moreover, the presence of 5-12-diHETE adds to the evidence of transcellular eicosanoid synthesis exemplifying its clinical significance.

5 | EMPOWERING PLATELET LIPIDOMICS

Platelet lipidome has stirred interest for several decades starting with the categorization of membrane-PLs, to the pioneering discovery of platelet eicosanoids, and characterization of lipid signaling intermediates. Early studies using thin-layer chromatography (TLC), gas chromatography (GC), mass spectrometry (MS), and high performance liquid chromatography (HPLC) coupled to ultraviolet (UV), fluorescence, or radiochemical detection have paved the way for modern lipidomics approaches. Lipidomics has evolved through invention of "shotgun" lipidomics, and liquid chromatography with tandem mass spectrometry (LC/MS/MS) approaches. High throughput shotgun lipidomics, ideally suited to detect abundant lipids but not those with poor ionization efficiencies, involves direct infusion of samples into MS without chromatographic separation and their detection by MS scanning over a defined mass window. Although highly sensitive mass resolution capacity is essential, it may be affected by interference from isotopes and isomers. LC/MS/MS lipidomic analysis involves specified chromatographic separation of lipids by their characteristic m/z ratio, resolving much of isomeric and isobaric interferences. In addition, LC resolution reduces the number of analytes presented simultaneously for electrospray ionization. Samples are processed by high resolution mass spectrometry (HR-MS) fortified with tandem mass analyzer, eg, Q-TOF or Q-Orbitrap systems. Targeted lipidomic analysis of predefined lipids, commonly employs QqQ and hybrid QLIT instruments. Untargeted lipidomics provides a comprehensive overview of all lipids without preselection, employing quadrupole time-of-flight (QqTOF), quadrupole Orbitrap (Q-Orbitrap), and Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS; as represented in Table 1). O’Donnell’s
| Lipids of interest | Lipidomics approach | Platelet source and or conditions | Ref. |
|--------------------|---------------------|-----------------------------------|------|
| **Abundant lipids** |                     |                                   |      |
| Glycerolipids (TG, DG), glycerophospholipids (PL, PS, PG, PE, PC, CL) Cholesterol, CholE | Shotgun lipidomics-HR-MS | Human and murine platelets; murine platelets and platelet releasate following activation with CRP, thrombin, or CRP + Thrombin | 90 |
| TG, DG, LPC, LPE, LPI, PL | Untargeted analysis-UHPLC-qTOF-MS/MS-DIA with SWATH | Human platelets from CAD patients and age-matched control subjects | 5,6 |
| LPC, PC, PS, PI, PE | LC-ESI-MS/MS-Q-TRAP | Resting, thrombin, ADP, collagen activated human platelets, platelet-derived microvesicles, DAMI cells | 38 |
| PC, PE, PEP, LPC, PLE, DG, TG, CholE | Differential mobility spectroscopy for separating lipid classes followed by MS/MS-QTRAP in MRM mode | Murine platelets from ACC1/2-DKI mice under resting, thrombin, collagen, and thrombin + collagen stimulated state | 49 |
| **Low abundant lipids** |                     |                                   |      |
| Lipid mediators |                     |                                   |      |
| 12-HETE, 8-HETE, 12-HETE, 12-HEPE, TxA2, PGE2, 8,9-EET, AA | Targeted analysis: Reverse phase LC-MS-QTRAP; HR-MS | Murine platelets from wild type and smprd⁻/⁻ mice following CRP stimulation | 90 |
| 12--HETE, AA, PGE2 | LC-DT-MMS analysis | Resting and thrombin activated human platelets from healthy donors with/without aspirin administration | 131 |
| Sphingolipids, Sphingosine, sphinganine, SM, Cer, HexCer, SPC | Targeted analysis: Reverse phase LC-MS-QTRAP; HR-MS | Murine platelets from wild type and smprd⁻/⁻ mice following CRP stimulation | 90 |
| SM, Cer | Untargeted analysis-UHPLC-ESI-QTOF-MS/MS-DIA with SWATH | Human platelets from CAD patients and age-matched control subjects | 5,6 |
| SM, Cer | LC-ESI-MS/MS-Q-TRAP | Resting, thrombin, ADP, collagen activated human platelets, platelet-derived microvesicles, DAMI cells | 38 |
| **Nonenzymatically derived oxPLs** |                     |                                   |      |
| POVPC, PGPC, PONPC, POAzPC | Untargeted analysis-UHPLC-ESI-QTOF-MS/MS-DIA with SWATH | Human platelets from CAD patients and age-matched control subjects | 5,6 |
| **Oxylipins** |                     |                                   |      |
| AA derived |                     |                                   |      |
| 8-HETE, PGE2, 12-HETE, 12-HEPE, TxB2, 12-HETE, 12-OxoETE, | Targeted analysis: Reverse phase LC-MS-QTRAP; HR-MS | Murine platelets and platelet releasate following activation with CRP, thrombin or CRP + Thrombin | 90 |
| 8,9-EET, HHT, KHT | Simultaneous targeted and untargeted profiling, UHPLC-ESI-MS/MS using DIA-SWATH | Thrombin activated platelet releasate | 112 |
| EPA derived |                     |                                   |      |
| 12-HEPE, 14(15)EpEET | Targeted analysis: Reverse phase LC/MS-QTRAP; HR-MS | Murine platelets and platelet releasate following activation with CRP, thrombin or CRP + Thrombin | 90 |
| **EoxPLs- HODE, HDOHE, eoxPLs** | LC-MS/MS-QTRAP | Clots from AAA mice and thrombus from AAA patients | 71 |
| **DGLA induced oxylipin** |                     |                                   |      |
| 12-LOX derived 12-HETE, 12-HETE and COX-1 derived TxB1, TxB2, PGE1, PGE2 | LC-ESI-MS²-IonTrap | Human platelets pre-treated with DGLA and after that stimulated with PAR4-activating peptide | 82 |
| 12-HETE | LC-ESI-TQ-S-MS/MS | 12-HETE in FcγRlla-stimulated human platelets in presence/absence of 12-LOX inhibitor ML355 | 132 |
| **Esterified oxPLs** |                     |                                   |      |
| 12-HETE-PLs (12-HETE-PC, 12-HETE-PE) | LC-MS/MS-MRM mode-QTRAP | Wild-type and ALOX12⁻/⁻ mice. | 70,133 |
| 31, significantly enhanced 12-LOX-derived HETE-PEs | LC-MS/MS-MRM mode-QTRAP | APS patients. Platelets under resting and thrombin stimulated condition | 72,133 |
| HETE-PLs (12-HETE-PE, PC) | LC-MS/MS-MRM mode-QTRAP | Platelets from patients after cardiopulmonary bypass | 72,133 |

(Continues)
| Lipids of interest | Lipidomics approach | Platelet source and or conditions | Ref. |
|-------------------|---------------------|----------------------------------|------|
| HETE-PL (12-, 5-, 15-HETE-PL, both PE and PC) | LC-MS/MS-QTRAP | Angiotensin II-induced abdominal aortic aneurysm (AAA) model in ApoE<sup>−/−</sup> mice. Aortic wall homogenate from AAA mice and AA patients, thrombus from AAA patients | 71 |
| Diacyl and plasmalogen PEs containing 14-HDOHE | Precursor scanning LC-MS/MS | Thrombin activated human platelets | 73 |
| PGE<sub>2</sub> and PGD<sub>2</sub> attached to four PEs | LC-MS/MS-MRM mode-QTRAP | Thrombin, collagen, or ionophore activated human platelets; inhibition by aspirin supplementation to blood donors | 74 |
| Thromboinflammatory lipids | | | |
| DXA3, esterified DXA3 | Reversed phase UHPLC-FTMS/MS (Orbitrap analysis using heated electrospray ionization) and LC/MS<sup>3</sup> (FTMS mode on the LTQ Ion Trap.) | Human platelets activated with thrombin, collagen, and calcium ionophore A23187 | 45,46 |
| Antiplatelet lipids | | | |
| 12-HETE | LC-ESI-MS<sup>2</sup>-IonTrap | Releaset from DGLA pretreated and PAR4-agonist activated human platelets | 82 |
| Sphingosine-1-Phosphate | Mass spectrometry | PRP and PPP from stable CAD and AMI patients | 123 |
| | TLC | Platelet lysate and releasate from healthy subjects | 124 |
| Sphingosine-1-Phosphate | TLC with [3H] sphingosine, NBD-sphingosine | S1P in human platelets and S1P export activity | 134 |
| Transcellular lipids | | | |
| LTC4 | RP-HPLC-UV absorbance | LTC4 synthase activity in platelets | 91 |
| LTC4 | RP-HPLC-UV absorbance | In platelet-neutrophil co-incubates and platelet metabolism of exogenously supplied LTA4 | 97 |
| Peptidoleukotrienes (LTC4, LTD4), 5,12-diHETE, LXA4 | Electron capture negative ion chemical ionization(NICI)-GC/MS | Intracoronary blood from patients undergoing percutaneous transluminal coronary angioplasty | 107 |
| LTC4, LTD4, LTE4, LXA4, LXB4 | RP-HPLC-UV absorbance | GMSF primed neutrophils co-incubated with platelets in the presence of fMLP or thrombin | 99 |
| LTC4 | RP-HPLC-UV absorbance | fMLP and opsonized zymosan primed neutrophils co-incubated with platelets | 98 |
| 5-HETE, 12-diHETE, LTC4, LTD4, LTA4 | RP-HPLC-UV absorbance | Platelet and monocytes co-stimulated with calcium ionophore | 102 |
| LTC4, 12, 5-dihETE, total 5-LOX products (the sum of LTD4, 20-hydroxy-LTB<sub>4</sub>, trans-LTB<sub>4</sub> isomers, and 5-HETE) | HPLC and peak heights of each metabolite assessed with those of corresponding standards | GMCSF primed (or not), and fMLP challenged neutrophils co-incubated with thrombin activated platelets | 94 |
| Cyasoyl LTs (LTC4, LTD4, LTD4) | RP-HPLC-UV absorbance | Platelet and neutrophil coincubated in the presence of calcium ionophore | 95 |
| 5-LOX products (including LTB<sub>4</sub>,20-hydroxy-LTB<sub>4</sub>, 5-HETE), LTC4, 5,12-dihETE | RP-HPLC-UV absorbance | Time-dependent utilization of platelet AA by neutrophils in producing 5-LOX products | 92 |
| LxA<sub>4</sub>, LXB<sub>4</sub>, LTs | A comparison of different approaches RP-HPLC-UV absorbance GC/MS LC/MS/MS-ESI- scanning with UV/ VIS absorbance detector | Platelets and neutrophils coincubated in the presence of different stimuli | 96 |
| 12,20-diHETE | HPLC-UV absorbance with synthesized 12,20-diHETE as standard | Coincubation of thrombin activated platelets and unstimulated neutrophils | 100 |
| 12-HETE-1,2O-dioic acid (Dimethyl Ester) | TLC GC/MS | | |
group pioneered the comprehensive mapping of the platelet lipidome, showing >two-fold alteration of 900 lipids following thrombin stimulation, mostly featuring eicosanoids and oxPLs, accounting for 86% newly synthesized lipids. Moreover, the non-annotated lipids available in the public domain offers an opportunity for further discovery. Ahrends’ group explored the murine and human platelet lipidome showing PE, PC, SM, PS, and PI as the most abundant species and that only 15 lipids constitute 70% of the entire lipid mass. PCs, PEs, PGs, SM, and cardiolipin span a range of > two orders of magnitude; some ceramides and free-FAs reach > four orders of magnitude, while plasmaloyl/plasmalogen-PC are limited. This study claims that the platelet lipidome is altered <20% upon activation for 5 minutes. Another study demonstrates that collagen stimulation of murine platelets enhances free-FAs (31%), LPC (57%), LPE (38%), and DGs (21%). Besides, loss of the AMPK-ACC regulatory control over endogenous lipogenesis causes enrichment of PE-plasmalogens (28%), and increases the fraction of AA-PLs to substantiate TXA2 synthesis. Analysis of resting and ADP, thrombin, collagen stimulated human platelets, microvesicles (MVs) from activated platelets, and megakaryocytic DAMI cells showed PCs and SMs as the most abundant lipids. Thromboinflammatory LPCs are actively packaged in platelet-MVs released upon stimulation. The use of agonists, their concentration, and incubation period as employed in these studies vary considerably, which may differentially influence lipid enrichment relative to basal levels and should be taken into account. We established UHPLC-ESI-QTOF-MS/MS in DIA mode with SWATH for untargeted analysis of the platelet lipidome from CAD patients. SWATH acquires data comprehensively throughout an entire chromatogram over a defined m/z range providing an entire digital archive of the sample, allowing extended search for lipids of interest. Recently we detected 13 ± 7, 15 ± 9, and 0.6 ± 0.2 attomols/platelet of KHT, HHT, and TXB2, respectively, in targeted analysis of thrombin activated human platelet releasates, besides several oxylipins (12-HETE, 12-HEPE) and nonoxidized PUFAs in simultaneous untargeted profiling. Oxylin detection in targeted assays with QTRAP instruments in selected reaction monitoring (SRM) acquisition require a pre-assigned target list and SRM transitions programmed before data acquisition. Data independent acquisition with SWATH bridges the gap between sensitive targeted assays and comprehensive profiling. Annotation of lipids to molecular features can be done with software tools aiding automated lipid identification, eg, LipidView, LipidBlaster, LipidXplorer, and recently developed LipidFinder hosted on LipidMaps database as an LC/MS workflow. Spectral matching and annotation are still painstaking, often done manually to avoid false positives, particularly for untargeted analysis. We used MS-DIAL, which automatically identified 611 (31%) out of 1971 aligned molecular features, based on precursor mass accuracy, match of isotope pattern, and MS/MS spectra, showing TGs and PLs as the most abundant lipids with significant changes in CAD patients.

### 5.1 Platelet lipidome: Clinical prospects and challenges

The Platelet lipidomic landscape might be considered a treasure-trove of diagnostic and prognostic biomarkers for CVD, as shown for plasma ceramides. Platelet lipidome in CAD patients shows increased levels of TG, CE, SM, oxPLs, acylcarnitines, also ceramides corresponding to those in plasma having significant prognostic impact in ACS. However, causative mechanisms linking signature metabolites to the clinical manifestation of CAD remains to be ascertained. Lipidomic profile also changes with platelet storage lesions demonstrating a 10% decrease in platelet lipids and a corresponding 5% increase in plasma. Platelet storage increases ceramide (69%), LPC (32%), cholate (49%), and decreases free-cholesterol (10%). In addition to AA containing PE and PS, both proinflammatory and proresolving lipid mediators are elevated in platelet concentrates and platelet derived extracellular vesicles during storage without significant alteration to the levels of AA-derived pro-inflammatory lipid mediators. Platelet storage lesion also leads to shedding of platelet-extracellular vesicles (EV). Several glycerophospholipids, cholesterol, sphingolipids are transferred to newly formed platelet-EVs, which exhibit lipid enrichment by 30% during shedding of platelet-extracellular vesicles (EV).

### Table 1 (Continued)

| Lipids of interest | Lipidomics approach | Platelet source and or conditions | Ref. |
|--------------------|---------------------|----------------------------------|------|
| Senescence during platelet storage | ESI-MS/MS; direct flow injection on a triple-quadrupole mass spectrometer | Platelet and plasma lipids in platelet apheresis samples during a storage of 5 days | 118 |
| PE, PE-pl, PG, PI, PS, LPC, Cer, free cholesterol and CE | LC-MS/MS | Lipid profile of platelets, plasma, platelet-EVs during a storage of 5 days | 120 |

#### LipidMaps database as an LC/MS workflow.

Spectral matching and annotation are still painstaking, often done manually to avoid false positives, particularly for untargeted analysis. We used MS-DIAL, which automatically identified 611 (31%) out of 1971 aligned molecular features, based on precursor mass accuracy, match of isotope pattern, and MS/MS spectra, showing TGs and PLs as the most abundant lipids with significant changes in CAD patients.
were aspirin naïve. Acute aspirin administration in AMI patients increased sphingosine-1-phosphate levels by >40%, but decreased PPP levels, because aspirin counteracts TXA2 triggered sphingosine-1-phosphate release from platelets. Low-dose (75 mg/d) aspirin intake by healthy individuals downregulates thrombin-induced ex vivo changes to the platelet lipidome by 45%. In aspirin exacerbated respiratory disease (AERD), a chronic inflammatory condition, platelet-monocyte/neutrophil aggregates in peripheral blood and nasal polyps engage in transcellular lipid metabolism and generate cysLT causing elevated urinary LTE4 levels. Therefore, thrombo-inflammatory potential of platelets may remain unaffected by aspirin and the choice or combination of antiplatelet therapy to check not only platelet hyper-reactivity but thromboinflammation requires reconsideration. Ticagrelor regulates levels and distribution of cholesterol and sphingomyelin in lipid rafts, which may also influence response to agonists in the extracellular microenvironment and thereby thromboinflammatory functions. Results from larger clinical cohorts are expected to reveal the impact of antiplatelet (mono versus dual), anticoagulant approaches, and lipid-lowering strategies on the platelet lipidome. The time of blood sampling (eg, before and after PCI) has to be considered following ethical guidelines to ensure unbiased characterization at baseline. In addition, confounders, cardiovascular risk factors should be taken into account to fully appreciate implications as a diagnostic/prognostic tool. Ideally, with the advent of high-throughput methods, platelet lipidomics might be introduced as routine analysis in the future. Such lipidomic profiles may also reveal the endogenous balance of prothrombotic AA-derived oxylipins versus antithrombotic DGLA derivatives (Figure 3), which can be corrected by dietary supplementation of PUFAs recommended for their cardio-protective benefits, possibly attributed to their antithrombotic effects.

5.2 | Antiplatelet lipids

The antiaggregatory effect of DGLA came into focus in the 1970s. Only recently has its molecular mechanism been delineated by Holinstat group. Dihomo-γ-linolenic acid derived 12-HETE acts on a Gsα coupled IP receptor, leads to activation of adenylyl cyclase, generation of cAMP, and PKA activity culminating in vasodilator-stimulated phosho-protein (VASP) phosphorylation, a well-characterized platelet inhibitory track otherwise employed by endothelial PGI2. Therefore, DGLA or 12-HETE supplementation checks aggregation in vitro, and retards platelet accumulation at the injured cremaster arterioles and carotid artery in vivo. Platelet 12-LOX simultaneously metabolizes AA and DGLA, but AA being more abundant, 12-HETE generation exceeds that of 12-HETrE. Dihomo-γ-linolenic acid is also converted to PGD1 and PGE1 by COX-1 oxygenation, while AA generates PGI2. However, the DGLA-12-HETE antithrombotic axis operates independently of COX-1, is not influenced by aspirin, and does not compromise primary hemostasis, making it a promising antiplatelet strategy. Limited amounts of DGLA in platelet membrane might be enhanced by dietary supplementation without altering levels of thrombogenic lipids.

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**FIGURE 3** Pro- (in red) and anti-thrombotic (in green) lipid derivatives of AA, DPA, DHA, EPA and DGLA generated in platelets through the enzymatic actions of COX-1 and 12-LOX. CYP450 derived metabolites have been shown in platelets; those from other cellular sources like endothelial cells mostly show antiplatelet properties.
12-LOX (12-HETE) or COX-1 (TXA2) derivatives. It would be interesting to validate how antiplatelet therapies might influence the endogenous levels of antiplatelet lipids in CVD patients. Specialized proresolving mediators (SPMs) comprising resolvins, lipoxins, maresins, and protectins, derived from dietary ω-3/ω-6-PUFAs are also being explored as antiplatelet effectors. Platelets express SPM receptors Chem23 (resolvin E1), GRP18 (resolvin D1), GRP32 (resolvin D2), and ALX (resolvin D2 and lipoxin A4). But, the effects of specific SPMs vary with platelet stimulus (eg, ADP, thrombin, or collagen), and functional response (eg, aggregation, spreading, pro-/anti-inflammatory release). The overall objective of SPMs is to resolve inflammation at a later stage without interfering with hemostatic “plug” formation essential during initial phases of healing.

5.3 Future perspectives

The platelet lipidome remains a vastly unchartered territory inviting researchers to decrypt the molecular machinery generating thrombotic and thromboinflammatory mediators; to interpret lipid flux through the bioenergetic drive, particularly in metabolic disorders which enhance the risk of CVD; to monitor pathological alterations, unmasking noninvasive biomarkers; and offer much needed therapeutic alternatives. Therefore, platelet lipidomics will indisputably keep our interest alive for the next decades to come.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

AUTHOR CONTRIBUTIONS

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