



Platelet lipidomics and *de novo* lipogenesis: impact on health and disease

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Purpose of review

Lipids play vital roles in platelet structure, signaling, and metabolism. In addition to capturing exogenous lipids, platelets possess the capacity for *de novo* lipogenesis, regulated by acetyl-coA carboxylase 1 (ACC1). This review aims to cover the critical roles of platelet *de novo* lipogenesis and lipidome in platelet production, function, and diseases.

Recent findings

Upon platelet activation, approximately 20% of the platelet lipidome undergoes significant modifications, primarily affecting arachidonic acid-containing species. Multiple studies emphasize the impact of *de novo* lipogenesis, with ACC1 as key player, on platelet functions. Mouse models suggest the importance of the AMPK-ACC1 axis in regulating platelet membrane arachidonic acid content, associated with TXA₂ secretion, and thrombus formation. In human platelets, ACC1 inhibition leads to reduced platelet reactivity. Remodeling of the platelet lipidome, alongside with *de novo* lipogenesis, is also crucial for platelet biogenesis. Disruptions in the platelet lipidome are observed in various pathological conditions, including cardiovascular and inflammatory diseases, with associations between these alterations and shifts in platelet reactivity highlighted.

Summary

The platelet lipidome, partially regulated by ACC-driven *de novo* lipogenesis, is indispensable for platelet production and function. It is implicated in various pathological conditions involving platelets.

Keywords

acetyl-coa carboxylase, *de novo* lipogenesis, lipidome, megakaryocyte, platelet

INTRODUCTION

Originating from megakaryocytes, platelets are small, anucleate blood cells that circulate for approximately 8–10 days [1,2]. Their significance lies in their pivotal roles as regulators of hemostasis and thrombosis. When vascular injury occurs, platelets promptly adhere to the newly exposed extracellular matrix, triggering their activation and aggregation, which, in turn, facilitates plug formation. Notably, hyperactivated platelets contribute to the pathological formation of occlusive arterial or venous thrombi, emphasizing their importance as potential targets for preventive interventions [2,3]. Beyond their established functions in hemostasis and thrombosis, a growing body of research has underscored the involvement of platelets in various physiological and pathological processes. These include angiogenesis, wound healing, fibrosis, atherogenesis, as well as antimicrobial defense and inflammation [2,4–9]. Recent advancements in mass-spectrometry analysis of lipids have significantly enhanced our understanding of the role of

lipids in platelet biology. Lipids serve as indispensable structural components and play central roles in metabolism and signaling within platelets [10¹¹]. Alterations in platelet lipid profiles have

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KEY POINTS

- Platelet lipids play crucial roles in structural, signaling and metabolic functions, they can originate from exogenous sources and are also synthesized *de novo*, a process tightly regulated by ACC1.
- The lipid composition of platelets is indispensable for platelet function, consequently influencing thrombus formation.
- Lipidome remodeling, along with *de novo* lipogenesis and ACC1, is pivotal for megakaryocyte maturation and subsequent platelet production.
- Alterations in platelet lipid content observed in various pathological conditions may impact platelet reactivity, investigating the relative importance of *de novo* lipogenesis in these changes could provide valuable insights into disease mechanisms.

been extensively documented in numerous platelet-related diseases, often correlating with changes in platelet reactivity and function. [12[•],13–16]. Remarkably, platelets are capable of *de novo* lipogenesis (DNL), a process tightly regulated by acetyl-coA carboxylase (ACC). Perturbations in DNL have been associated with modifications in the platelet lipidome, and subsequently in platelet production and function [17^{••},18–20]. This review aims to comprehensively cover the current literature on the significance of DNL and the platelet lipidome in regulating platelet functions, biogenesis, and their implications in pathological conditions.

LIPIDS IN PLATELETS

Upon exposure to prothrombotic stimuli, platelet activation necessitates the involvement of not only proteins but also lipids [21,22[•]]. Lipids are abundantly present in platelets, with Slatter *et al.* [23] estimating a total of more than 5000 unique species in human platelets. These species are comprised into eight categories established by the LIPID MAPS consortium: fatty acyls, glycerolipids, (glycerol)phospholipids, sphingolipids, sterol lipids, prenol lipids, saccharolipids, and polyketides [23,24]. Lipids serve three primary functions in platelets. In addition to being the structural components of plasma and organelle membranes, they play crucial roles in signaling and energy metabolism [10^{••},11] (Fig. 1).

Lipids as signaling mediators

Upon activation, approximately 20% of the platelet lipidome undergoes a two-fold alteration, primarily

affecting lipids containing arachidonic acid [21]. This observation is not surprising, given that arachidonic acid notably serves as the precursor of thromboxane A₂ (TXA₂), a potent stimulator of further platelet activation and aggregation [21,25]. Platelet functional activation also relies on intracellular signaling mediated by lipids. Mediators such as diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃), generated by phospholipase C (PLC), trigger protein kinase C activation and calcium mobilization, ultimately leading to integrin αIIbβ3 activation [26,27]. Another example of signaling lipids involves the exposure of aminophospholipids, such as phosphatidylserine and phosphatidylethanolamine, on the outer leaflet of the plasma membrane of highly activated platelets. These negatively charged phospholipids serve as cellular scaffold for the formation of coagulation cascade complexes, thus defining the platelets as procoagulant [22[•],27–29]. In addition to their hemostatic functions, recent findings have highlighted the role of platelets as immune and inflammatory actors [4,30]. This latter function is notably mediated by their ability to secrete pro or anti-inflammatory lipid mediators. Alongside TXA₂, platelets produce prostaglandins (PGE₂ and PGD₂) and 12-hydroxyeicosatetraenoic acid (12-HETE), which notably regulate neutrophil and monocyte functions [31].

Lipids as players in platelet metabolism

Platelets, despite their apparent simplicity, are high energy-consuming cells. Even at rest, they require significant ATP levels for maintaining calcium homeostasis, and plasma membrane asymmetry [23,32]. The metabolic pathways required to meet this ATP demand have been extensively studied using the Seahorse metabolic flux assay. These studies reveal that in quiescent platelets, glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) contribute 40 and 60%, respectively, to ATP production, with lipidic substrates predominantly fueling OXPHOS [33,34,35[•]].

Platelet activation is characterized by significant shape changes, degranulation, and aggregation. This process necessitates a rise in ATP production, which is enabled by increased uptake of glucose and glutamine, breakdown of glycogen, and cleavage of fatty acids [33,35[•],36]. Debate persists regarding the relative contributions of glycolysis and OXPHOS to ATP production [33,35[•],37^{••}]. However, studies suggest a preferential shift towards aerobic glycolysis as the administration of glucose metabolism inhibitors, such as 2-deoxy-D-glucose (2DG), alters thrombin-mediated platelet activation and aggregation [33,34,35[•],38]. The significance of glucose uptake

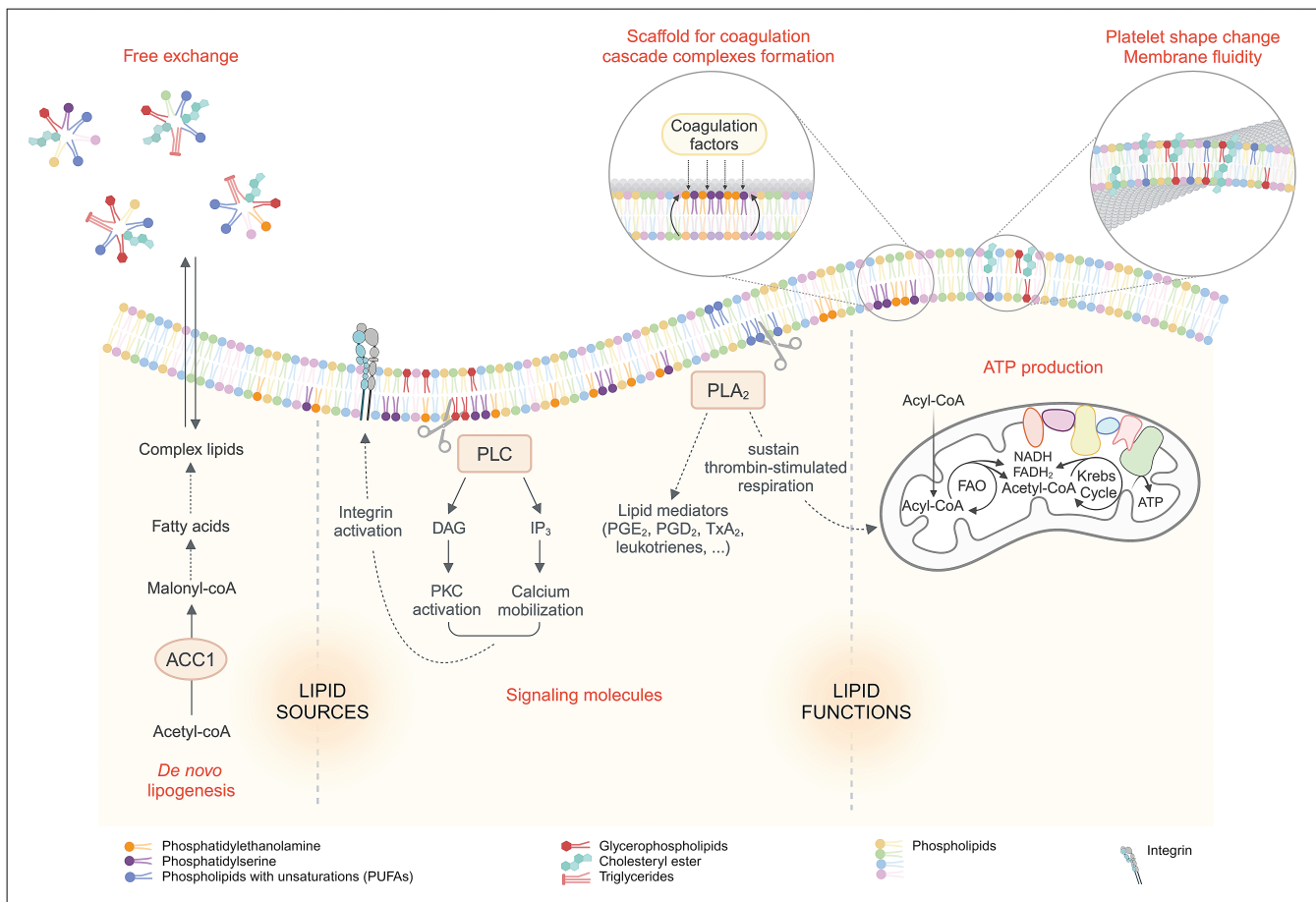


FIGURE 1. Lipid sources and functions in platelets. Lipids originate from exogenous sources or can be generated by *de novo* lipogenesis. They are mainly stored as (glycero)phospholipids. They can be liberated by phospholipases to act as signaling molecules or as a supply for mitochondrial FAO. Platelet activation involves lipid-mediated membrane changes, including exposure of phosphatidylserine and -ethanolamine on the outer leaflet of the plasma membrane, allowing the formation of coagulation factor complexes. ACC1, acetyl-CoA carboxylase 1; DAG, diacylglycerol; FAO, fatty-acid oxidation; IP₃, inositol triphosphate; PGD₂, prostaglandin D₂; PGE₂, prostaglandin E₂; PLC, phospholipase C; PKC, protein kinase C; TXA₂, thromboxane A₂. Original Figure created with a licensed version of BioRender.com.

in the activated state of platelets has also been demonstrated *in vivo*, particularly through experiments involving mice with a platelet-specific deletion of both glucose transporter (GLUT) 1 and 3 (double knock-out or DKO) [37²²,38]. Despite an increase in mitochondrial OXPHOS of nonglycolytic substrates in DKO platelets, this failed to effectively compensate for glucose metabolism, resulting in impaired platelet activation [38]. Conversely, lipids also serve as crucial fuel suppliers during platelet activation [33,37²²,39,40²²]. Ravi *et al.* [33] demonstrated that simultaneous inhibition of glycolysis and fatty acid oxidation (FAO) had a greater effect on aggregation compared to glycolysis inhibition alone. Other studies reported that FAO inhibitors (e.g. etomoxir or trimetazidine) reduce platelet degranulation and aggregation [35²²,40²²]. Furthermore, mice treated with FAO

inhibitors were protected from ferric chloride induced mesenteric thrombosis, prompting the authors to consider them as a promising antiplatelet strategy [40²²]. These observations underscore the widely accepted consensus within the platelet scientific community regarding the multiplicity and flexibility of substrate utilization by platelets [33,35²²,37²²,40²²]. Another point of agreement concerns the endogenous origin of fatty acids used for OXPHOS. While platelets are capable of transporting fatty acids from the plasma, studies show that exogenous fatty acid supplementation does not significantly impact platelet respiration [33]. Accordingly, Slatter *et al.* [23] demonstrated that PLA₂, through the cleavage of fatty acids from platelet phospholipids, was responsible for the supply of endogenous fatty acids required to sustain thrombin-stimulated respiration.

ACETYL-COA CARBOXYLASE

The initial rate-limiting step in fatty acid biosynthesis is orchestrated by ACC, which converts acetyl-CoA into malonyl-CoA, the precursor of fatty acids [41]. ACC exists in two isoforms, ACC1 (265 kDa) and ACC2 (280 kDa), both catalyzing the same reaction but leading to malonyl-CoA with distinct functions. Malonyl-CoA generated by ACC1 serves as a substrate for DNL, while that generated by ACC2 regulates FAO by inhibiting mitochondrial CPT1. Consequently, ACC1 is predominantly cytosolic and expressed in lipogenic tissues such as fat and liver, whereas ACC2 is associated with the outer membrane of mitochondria and primarily found in oxidative tissues like skeletal muscle and heart [42]. Importantly, only the ACC1 isoform has been detected in both murine and human platelets [19,43].

The activity of ACC1 is regulated by both allosteric and covalent modifications. Allosteric modulation by citrate enhances ACC activity by promoting its polymerization. The enzyme dynamically shifts between its homodimeric form, characterized by low catalytic activity, and a polymeric state, which exhibits high enzymatic activity. On the other hand, binding of malonyl-CoA and fatty acyl-CoA decrease ACC catalytic activity [42,44]. Additionally, phosphorylation by AMP-activated protein kinase (AMPK) on residue Ser79 residue of ACC1 and Ser212 residue of ACC2 has been identified as the primary covalent inhibitory mechanism [41,45]. It is noteworthy that in both humans and mice, platelet stimulation with thrombin triggers a strong and sustained phosphorylation of ACC1 mediated by AMPK [46].

ACETYL-COA CARBOXYLASE AND PLATELET FUNCTIONS

The AMPK-ACC signaling pathway has been extensively explored in platelets (Fig. 2). Lepropre *et al.* [19] investigated the impact of ACC activity on platelet functions using ACC1-S79A and ACC2-S212A double knock-in (DKI) mice. These specific mutations prevent AMPK-induced ACC phosphorylation and subsequent inhibition [19,47]. Lipidomic analysis of platelets from DKI mice revealed a significant enrichment of phosphatidylethanolamine-plasmalogen containing arachidonic acid (PEP-ARA). This upregulation was associated with increased TXA₂ secretion following collagen stimulation and was interestingly correlated with enhanced primary hemostasis, as evidenced by a shorter bleeding time in ACC DKI mice compared to their control littermates. Additionally, ACC DKI mice exhibited increased thrombus formation, assessed both *ex vivo* using flow chamber assays, and *in vivo* via intra-vital microscopy [19].

Opposite results were observed in a mouse model with specific invalidation of ACC1 in the megakaryocytic lineage (GPIb α Cre^{+/+}/ACC1^{flx/flx}). ACC1 deficiency occasioned a decrease in dense granule secretion, a platelet aggregation defect, and impaired thrombus growth. A consistent down-regulation of PEP-ARA was observed, along with a reduction in TXA₂ secretion (Octave & Piroton, personal communication).

In human platelets, it was demonstrated that modulating ACC activity with the pharmacological inhibitor named CP640.186 impairs aggregation [20]. The authors did not observe a significant impact of the treatment on the platelet lipidome, a difference attributed to the short period of incubation (2 h) with the ACC inhibitor. Instead, this aggregation defect was primarily related to an increase in α -tubulin acetylation levels upon thrombin stimulation [20]. Deacetylation of α -tubulin is indeed required for platelet spreading kinetics and aggregation [48,49].

DE NOVO LIPOGENESIS AND LIPIDS IN PLATELET PRODUCTION

De novo lipogenesis and platelet production

In addition to its role in regulating platelet functions, ACC has emerged as a crucial player in platelet biogenesis. Mice with specific platelet deletion of ACC1 displayed a reduction in platelet count, without any noticeable effect on platelet clearance (Octave & Piroton, personal communication). In human studies, Kelly *et al.* [18] observed a reduced platelet count in healthy volunteers treated with PF-05175157, a pharmacological ACC inhibitor. They reported that inhibiting ACC affects platelet production by impeding the synthesis of phospholipids required for the expansion of the demarcation membrane system (DMS) during megakaryocyte maturation. Importantly, the DMS supports the formation of protrusions known as proplatelets, from which platelets are released into the bloodstream via sinusoidal vessels. Notably, the authors primarily observed a reduction in phosphatidylcholine (PC) levels, with up to 30% of these PC species derived from DNL [18]. Their findings, along with those of others, underscore the importance of DNL in platelet production, as similar results were demonstrated with selective inhibitors of fatty acid synthase (FASN), another enzyme crucial for fatty acid generation [17^{''},18,50^{''}].

Lipidome remodeling in platelet production

The initial stage of megakaryocyte maturation involves significant remodeling of membrane

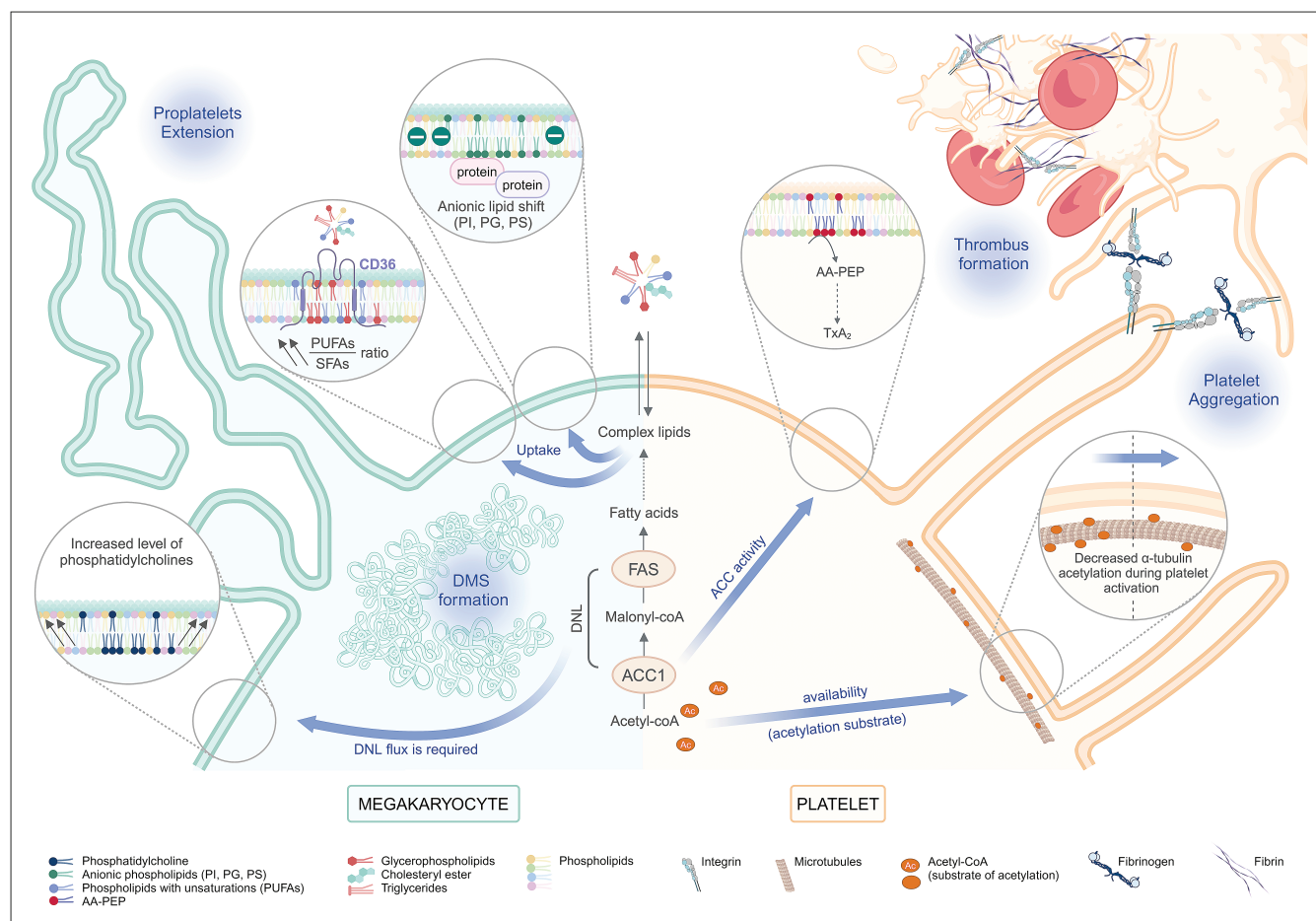


FIGURE 2. Impact of lipid biosynthesis and uptake on platelet production and function. Both DNL and lipid uptake are crucial for membrane phospholipid remodeling and DMS expansion, required for proplatelet formation. DNL, through ACC1 activity, modulates platelet reactivity via its influence on platelet PEP-ARA content and by regulating the acetylation of α -tubulin. ACC1, acetyl-CoA carboxylase 1; DNL, *de novo* lipogenesis; DMS, demarcation membrane system; PEP-ARA, phosphatidylethanolamine plasmalogen containing arachidonic acid; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids. Original Figure created with a licensed version of BioRender.com.

phospholipids. Anionic phospholipids like phosphatidylserine, phosphatidylinositol, and phosphatidylglycerol are increased, facilitating the relocation of specific proteins that regulate platelet biogenesis [17^{***}]. Moreover, Barrachina *et al.* [50^{***}] observed a notable decrease in saturated fatty acids (SFAs) as megakaryocytes mature, accompanied by an increase in polyunsaturated fatty acids (PUFAs)-containing phospholipids. Consequently, megakaryocytes supplemented with exogenous SFAs, such as palmitate, displayed an immature phenotype, with reduced capacity for proplatelet formation. In murine models, an elevated dietary ratio of SFAs to PUFAs resulted in a similar phenotype, coupled with a reduced platelet count. These findings underscore the critical role of membrane flexibility provided by PUFAs in facilitating DMS formation and proplatelet expansion [50^{***}]. In addition, alongside increased

DNL, the upregulation of the platelet scavenger receptor CD36, capable of capturing fatty acids released from adipocytes, contributes to the augmentation of PUFAs [50^{***},51]. Supporting these observations, it was noted that CD36 gene deletion in mice, as well as human familial CD36 loss-of-function mutations, were associated with thrombocytopenia [50^{***}]. In summary, both DNL and exogenous capture of phospholipids are pivotal in ensuring proper megakaryocyte maturation and subsequent platelet production (Fig. 2).

PLATELET ACETYL-COA CARBOXYLASE AND LIPIDS IN PATHOLOGIES

The field of lipidomics, driven by its ambition to identify, quantify, and comprehend the functions of all lipid species, has expanded to encompass clinical

applications. Clinical lipidomics seeks to integrate lipids with genomic, proteomic, and clinical data, to discover new diagnostic and prognostic biomarkers, foster personalized medicine, and improve therapy monitoring [10²²,11,52]. With platelets playing a pivotal role in numerous pathologies, including cardiovascular diseases, immune disorders, and inflammatory conditions, recent attention has been drawn to their lipid landscape [10²²]. Alterations in specific platelet lipid pathways have been associated with inherited pathologies such as Scott syndrome, which arises from mutations in the *TMEM16F* scramblase gene, resulting in impaired phosphatidylserine exposure and subsequent loss of procoagulant functions [29]. Similarly, platelet hyporeactivity and thrombi instability result from decreased expression of PLC- β 2 [53,54].

Beyond genetic-related diseases, acquired changes in lipid composition can lead to platelet dysfunction. Studies have shown that modifications in the platelet lipidome of patients with acute coronary syndrome (ACS) or with COVID-19 significantly correlate with alterations in platelet reactivity [12²,14,16]. Furthermore, alterations in the platelet lipidome have been observed across various conditions, including obesity [55], liver diseases [13], and malignant diseases [56].

While the impact of DNL on these lipid alterations has not been extensively studied to date, it is noteworthy that it appears to be influenced by coronary artery disease (CAD). AMPK-mediated phosphorylation of ACC has been proposed as a potential risk stratification marker, given its observed increase in the platelets of CAD patients and strong association with acute coronary events [57].

CONCLUSION

Traditionally confined for their roles in hemostasis and thrombosis, platelets currently emerge as key players in a multitude of other physiological processes. The composition of their lipidome holds significant importance, as lipids serve crucial structural, signaling and metabolic functions within platelets. Consequently, it is not surprising that alterations in the platelet lipidome are observed in various platelet-related diseases, including atherosclerosis, CAD, and inflammatory conditions such as COVID-19. Recent advancements in lipidomic technology have revolutionized our understanding of the platelet lipidome, leading to the identification of novel diagnostic and prognostic biomarkers. Moreover, certain lipid species not only serve as biomarkers but actively contribute to the pathological processes underlying these diseases. Thus, their

identification presents a promising avenue for the development of novel pharmaceutical targets. Platelet ACC, the enzyme responsible for DNL, emerges as a particularly intriguing target for clinical scrutiny in the context of thrombotic diseases. Studies in murine models reveal that its constitutive activation leads to alterations in the platelet phospholipidome, resulting in heightened thrombus formation. Correspondingly, *in vitro* studies on human platelets treated with specific ACC inhibitors demonstrate decreased activation. Furthermore, the central role of DNL in platelet production has garnered increasing attention. With a plethora of pharmaceutical inhibitors targeting ACC currently available, it presents an enticing direction for future research and therapeutic development.

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Conflicts of interest

None.

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