

P-Selectin and Platelet–Monocyte Interaction in Inflammation: Mechanisms, Hypothesis, and Open Questions

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Abstract: This review provides an integrated overview of how P-selectin-mediated platelet–monocyte interactions orchestrate key inflammatory processes in sterile and non-sterile pathological contexts. Inflammation presents a paradox: although it is a fundamental physiological process, uncontrolled activation can progress to a chronic state, contributing to the development of various inflammatory diseases. Platelets, previously considered to play a role exclusively in hemostasis, are now recognized as important immunomodulatory effectors capable of releasing inflammatory mediators and interact with leukocytes upon activation. The interaction between platelet P-selectin and monocyte PSGL-1 promotes the formation of platelet–monocyte aggregates, that together exert broad and profound inflammatory effects. These aggregates have been implicated in multiple pathological contexts, both sterile, such as atherosclerosis, obesity, autoimmune diseases, and hypertension, and non-sterile, such as sepsis and viral infections, highlighting their role as a common axis of immune and inflammatory regulation. This review integrates shared but contextualized mechanistic pathways and outlines current hypotheses regarding how platelet–monocyte interactions may operate in sterile and pathogen-induced inflammation. We further discuss emerging evidence connecting P-selectin signaling to metabolic reprogramming, vascular dysfunction, and immunothrombosis, as well as its possible influence on monocyte activation and phenotype in diverse inflammatory settings, discussing open questions, perspectives, and challenges in the field. By integrating interdisciplinary findings, this review highlights P-selectin-dependent platelet–leukocyte interactions as central axis in inflammation and promising therapeutic targets.

Keywords: P-selectin, platelet activation, platelet–monocyte aggregates, thromboinflammation, coagulation

Introduction

Inflammation is a fundamental physiological process and one of the body's most effective defense mechanisms against infection, injury, and exposure to foreign particles or stress.¹ Inflammation can be triggered by infectious agents (non-sterile inflammation)² or by disruptions in cellular and tissue homeostasis, such as injury or metabolic stress (sterile inflammation).^{3,4} Traditionally viewed as a crucial protective response, acute inflammation mobilizes specialized cell types, such as neutrophils and monocytes, from the circulation to the site of injury. This response is vital for host defense, orchestrating a cascade of events that leads to the eradication of invasive pathogens and facilitates tissue repair.⁵ Therefore, inflammation is a vital mechanism of homeostasis; however, uncontrolled inflammation can become chronic, contributing to a variety of diseases. This inflammation paradox highlights the complexity of the immune system and the need to differentiate between pathological and protective inflammatory responses.^{6,7} In both physiological and pathological contexts, inflammation can intersect with coagulation in a process known as thromboinflammation, which describes the interplay between coagulation and immune activation particularly within the vasculature. Thromboinflammation is driven by both humoral and cellular elements of the coagulation and immune continuum, including leukocytes, endothelial cells, and platelets, potentially leading to microvascular thrombosis and organ dysfunction.^{8–10}

For a long time, platelets were recognized solely by their roles in hemostasis and pathological thrombosis. However, mounting evidence now positions them as active immunomodulatory and “sentinel” cells within the innate immune system.^{11–15} Upon activation by various inflammatory or procoagulant stimuli, platelets release a wide range of stored and newly-synthesized factors, interacting in complex ways with other cells, especially leukocytes.^{16–19} Monocytes, along with their macrophage derivatives, are central components of the inflammatory response, acting in both host defense and pathogenesis. The interaction between platelets and monocytes has been reported to regulate monocyte responses, being indispensable in both hemostasis and inflammation.^{20,21} Circulating human monocytes subdivide into three main subsets according to the expression of CD14 and CD16.^{21,22} Classical monocytes (CD14^{high}CD16[−]) represent more than 90% of circulating monocytes and are characterized by strong phagocytic capacity, high expression of scavenger and pattern-recognition receptors, and robust inflammatory responses.^{23,24} Intermediate monocytes (CD14^{high}CD16⁺) display enhanced antigen-presenting capacity and are potent inducers of T cells.^{24,25} Non-classical monocytes (CD14^{low}CD16⁺), in contrast, are specialized in endothelial patrolling and surveillance, exhibit increased migratory potential and regulation of vascular inflammation.^{23,26,27} Such functional heterogeneity is particularly relevant in the context of platelet–monocyte aggregate (PMA) formation, as the composition and downstream consequences of PMAs may differ depending on the monocyte subset engaged, thereby influencing inflammatory amplification, endothelial dysfunction, and thromboinflammatory outcomes.

Selectins are calcium-dependent vascular adhesion molecules composed of three known members, namely E-selectin (CD62E), P-selectin (CD62P), and L-selectin (CD62L). CD62E is mainly expressed on endothelial cells, while CD62L is expressed in leukocytes and CD62P in both endothelial cells and platelets.²⁸ The main role of selectins is to regulate leukocyte recruitment to sites of inflammation. The initial tethering and rolling of monocytes over the vascular endothelium are dependent on interactions between selectins and their corresponding glycosylated ligands and are imperative for extravasation into inflammatory lesions.^{29,30} Importantly, selectin binding not only tethers the cells together but signals gene expression, regulating inflammation. Selectins, particularly CD62P, have been shown to contribute to many inflammatory diseases.^{31,32}

Like many platelet granular contents, CD62P is stored in α -granules after being synthesized by parent megakaryocytes and upon procoagulant, inflammatory or pathogen-derived stimuli is rapidly translocated to platelet surface alongside α -granule releasate.²⁸ Its surface and/or soluble (sCD62P) forms serve as markers of platelet activation. Platelet CD62P binding to its ligand P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes is the dominant molecular event in platelet–leukocyte interactions, with significant inflammatory consequences across a wide range of diseases. Patients with inflammatory disorders typically have higher levels of activated platelets and endothelial cells displaying CD62P, which subsequently increases platelet–leukocyte aggregation and leukocyte–endothelium adhesion, rolling, and infiltration.^{33–35}

In this review, we discuss the central role of P-selectin in mediating platelet–monocyte interactions through a spectrum of inflammatory diseases, addressing common mechanisms and specific characteristics in different pathological contexts, from infectious to sterile inflammation. Our focus is to discuss the effects of PMA on disease mechanisms and outcomes. The review is structured into two major sections: sterile inflammatory conditions and infectious diseases. Within each section, we highlight shared and disease-specific mechanisms of P-selectin-mediated platelet–monocyte responses and their roles in diseases’ pathogenesis. Finally, therapeutic implications and future research directions are addressed in the concluding section.

P-Selectin-Mediated Interaction in Sterile Inflammatory Diseases

Obesity

Abdominal obesity, one of the most prevalent metabolic disorders of the 21st century, has reached epidemic proportions worldwide and is now recognized as a chronic disease by the World Health Organization (WHO).^{36,37} Obesity is associated with reduced life expectancy and higher risk of several comorbidities, many of which are components of metabolic syndrome, a cluster of interrelated cardiometabolic risk factors that significantly increase susceptibility to cardiovascular disease (CVD) and type 2 diabetes (T2DM).^{38–40} Obesity independently increases the risk for adverse cardiovascular outcomes, which remains the main cause of obesity-related morbidity and mortality.^{41,42} Chronic low-grade inflammation and a prothrombotic state are hallmarks of obesity, further amplifying the risk for thrombotic events

even after procedures like percutaneous coronary intervention.^{43,44} This condition stems from enhanced platelet response, a state of hypercoagulability and hypofibrinolysis,⁴⁵ and enhanced platelet–monocyte interactions.^{46–48}

Dysfunctional adipose tissue, combined with systemic immune activation, promotes chronic inflammation, monocyte, and macrophage activation, and increased tissue factor (TF) expression, enhancing thrombin generation, and coagulopathy in obesity.^{44,49,50} Clinical evidence shows elevated sCD62P levels in obesity, likely reflecting platelet and endothelial activation.⁵¹ PMA formation is also increased in obesity,^{49,52} a phenomenon that correlates with elevated TF expression in monocytes.⁴⁹ Bariatric surgery induces significant weight loss and reverses many of these thromboinflammatory alterations, improving insulin sensitivity, systemic inflammation, and metabolic syndrome characteristics.⁵³ Platelet transcriptomic analyses reveal normalization of inflammatory signaling and reduced platelet hyperreactivity one year after surgery.⁵³ Likewise, a significant decrease in PMA formation has been reported after surgery,⁵⁴ highlighting the reversibility of obesity-associated platelet and monocyte dysregulation.

Studies in experimental models of obesity (ob/ob mice and diet-induced obesity) demonstrate that visceral adipose tissue is an active focus of inflammation, marked by increased leukocyte rolling and adhesion, platelet aggregation, and elevated expression of CD62P, CD62E, and ICAM-1 on the endothelium. Platelet activation occurs primarily within the adipose tissue itself, where platelets exhibit high surface CD62P and form PMA via PSGL-1, favoring macrophage recruitment and activation. These findings show that visceral obesity promotes intensified interactions between endothelium, platelets, and leukocytes, sustaining local inflammation.⁵⁵

Recently, we showed increased platelet activation and PMA formation in obesity, which formed especially among CD16- and TF-expressing monocytes. Ex vivo mechanistic experiments demonstrated that platelet adhesion mainly through CD62P promotes reciprocal platelet and monocyte activation and secretion of inflammatory mediators.⁵² Platelets from obese patients induced TF and IL-1 β expression in monocytes partially depending on CD62P, CD40L, and integrin α IIB/ β 3 signaling, while secreted IL-1 amplified inflammation by activating endothelial cells.⁵² These findings indicate a platelet-driven amplification of inflammation in obesity.

Metabolic syndrome represents the convergence of obesity with comorbidities including insulin resistance, dyslipidemia, and hypertension. Patients with metabolic syndrome exhibit increased platelet activation, evidenced by greater fibrinogen binding (activated integrin α IIB/ β 3), CD62P translocation,⁵⁶ and greater aggregation under high shear.⁵⁷ Notably, platelet contact plays a key role in shaping monocyte phenotypes in metabolic syndrome. Patients with metabolic syndrome exhibit greater monocyte activation, with elevated CD11b (Mac-1) expression across all monocyte subsets.⁵⁶ PMA formation is higher in obese patients with metabolic syndrome and hypertension, accompanied by elevated TF expression on monocytes, while the shift from classical to intermediate and non-classical subsets associate with metabolic syndrome independently of diabetes or hypertension.⁵² Importantly, both platelet and monocyte activation correlate positively with the blood glucose levels.⁵⁶

Together, these findings indicate enhanced platelet activation and platelet–monocyte interactions in obesity, contributing to a prothrombotic state. These features are consistent with a broader thromboinflammatory environment that may extend beyond adipose tissue and influence vascular function. Whether targeted modulation of platelet–monocyte interactions can interrupt this thromboinflammatory loop and reduce cardiometabolic risk in obesity remains an open question.

Atherosclerosis and Coronary Arterial Disease

Atherosclerosis is a chronic inflammatory disease characterized by the progressive accumulation of lipid-rich and fibrous plaques in medium and large-sized arteries, driven by risk factors such as hyperlipidemia, hypertension, smoking, diabetes, and chronic inflammation.^{58,59} Atherosclerotic plaques are complex and dynamic structures characterized by the accumulation of lipids, particularly oxidized low-density lipoprotein (oxLDL), within the intima, in association with endothelial activation and an inflammatory microenvironment.^{60–64} These lesions contain multiple interacting cell types, including macrophages derived from recruited monocytes, lipid-laden foam cells, and vascular smooth muscle cells, which contribute to plaque organization and progression.^{65–69} Structurally, plaques typically exhibit a lipid-rich necrotic core covered by a fibrous cap formed by smooth muscle cells and extracellular matrix components.^{68,69} In addition, they display persistent inflammatory activity and extracellular matrix remodeling, which can compromise structural integrity and promote plaque instability, increasing susceptibility to rupture, thrombus formation, and vascular occlusion.^{70–75}

Consequently, plaque progression leads to varying degrees of arterial stenosis, which can impair blood flow and result in tissue hypoxia.^{70,76–78} Metabolic disturbances associated with obesity including insulin resistance, endothelial dysfunction, and chronic low-grade inflammation exacerbate these processes by promoting inflammatory signaling and monocyte recruitment within the vascular wall.^{79–83} Consistently, obesity is a major modifiable risk factor for atherosclerosis and cardiovascular diseases.^{84,85}

Platelet activation is a consistent feature of atherosclerosis, playing major pathological roles. During atherogenesis, high platelet CD62P surface expression supports PMA formation, preparing the environment for lipid accumulation and monocyte transformation into foam cells, which are strong predictors of cardiovascular risk (Figure 1).^{86,87} Activated platelets adhere to the inflamed endothelium enhancing leukocyte recruitment and extravasation through CD62P-dependent mechanisms (Figure 1a and b).^{88–91} Research with animal models demonstrates that CD62P-PSGL-1 interaction is crucial for monocyte accumulation. Activated platelets, when infused into mice, rapidly adhere to monocytes in a CD62P-dependent manner and transfer chemokines such as RANTES/CCL5 and PF4/CXCL4, amplifying leukocyte recruitment and accelerating the formation of atherosclerotic lesions (Figure 1b).⁸⁹ Ly6C-expressing monocytes depend on PSGL-1 for selective rolling and accumulation in the initial atherosclerotic endothelium (Figure 1c). Consistently, ApoE knockout mice (a model of atherosclerosis) with PSGL-1 deficiency exhibit reduced leukocyte infiltration and atherosclerotic progression.⁹² In vivo chimeric models (WT platelet transfusion into CD62P knockout),⁹³ together with ex vivo studies,⁹⁴ reinforce the predominance of platelet-derived CD62P over endothelial CD62P in mediating leukocyte adhesion.

Dyslipidemia intensifies these mechanisms by promoting chronic low-grade inflammation, platelet hyperactivity,⁸⁷ and PMA formation.⁹⁵ OxLDL, but not native LDL, induces platelet activation and CD62P exposure (Figure 1a),⁹⁶ which promotes PSGL-1 dependent PMA formation (Figure 1b), enhancing monocyte adhesion to the endothelium (Figure 1c) and differentiation into foam cells (Figure 1c and d).⁸⁹ Platelet adhesion increases OxLDL uptake by monocytes in a dose-dependent manner through mechanisms depending on CD62P. In murine models of atherosclerosis, platelet depletion reduces monocytes/macrophage accumulation within lesions, demonstrating that platelets accelerate monocyte infiltration and foam cell formation in vivo.⁸⁹ OxLDL-activated platelets also increase CD11b activation in monocytes, reinforcing their inflammatory and pro-migratory phenotype.⁹⁷

Pharmacological interventions further support the role of lipid-driven platelet activation in atherosclerosis pathogenesis. Lipid-lowering therapies, including statins and ezetimibe, have been shown to reduce platelet activation and CD62P expression.^{98,99} Similarly, monoclonal antibodies targeting the reduction of LDL by PCSK9 inhibition, such as evolocumab and alirocumab, also attenuate oxidative stress and platelet reactivity.^{100–102} Together, these findings indicate that modulation of lipid metabolism may indirectly limit platelet activation and its pathophysiological consequences. However, their relevance in reducing PMA formation remains to be fully established.

The cellular mechanisms underlying atherosclerosis translate clinically into coronary artery disease (CAD), characterized by narrowing or occlusion of the coronary arteries.¹⁰³ Increased levels of PMA have been consistently reported in patients with cardiovascular diseases, including myocardial infarction and other vascular complications.^{104–107} PMA formation has been suggested as reliable markers of early-stage cardiovascular disease.¹⁰⁵ Functionally, platelet–monocyte interactions are associated with changes in both cell types, including increased secretion of pro-coagulant mediators, which may contribute to angiopathy and thrombotic events.¹⁰⁷ Studies in human coronary arteries using intracoronary blood sampling show increased platelet CD62P and PMA in stenosed regions, with local monocyte and platelet activation specifically in the damaged area.¹⁰⁸ Animal models confirm that CD62P promotes inflammation and cardiac remodeling, since genetic ablation of CD62P reduces fibrosis and tissue inflammation.⁹³ Besides, transferring of wild-type platelets restores inflammatory and fibrotic responses.⁹³ These findings highlight the central role of platelet CD62P in aggregate formation,^{103,109} localized inflammation,¹⁰⁸ and tissue remodeling,⁹³ reinforcing its prognostic significance and its potential as a therapeutic target in cardiovascular diseases.¹¹⁰

Different clinical contexts rely on distinct cellular components of the CD62P-PSGL-1 axis to amplify thromboinflammation. In stable CAD, heightened platelet reactivity is reflected by circulating degranulated platelets and high levels of PMA,^{106,111,112} even without increased CD62P expression.¹⁰⁹ In acute coronary syndromes (ACS), however, plaque rupture triggers local activation of monocytes with upregulated PSGL-1 at the lesion site, promoting intense PMA formation and

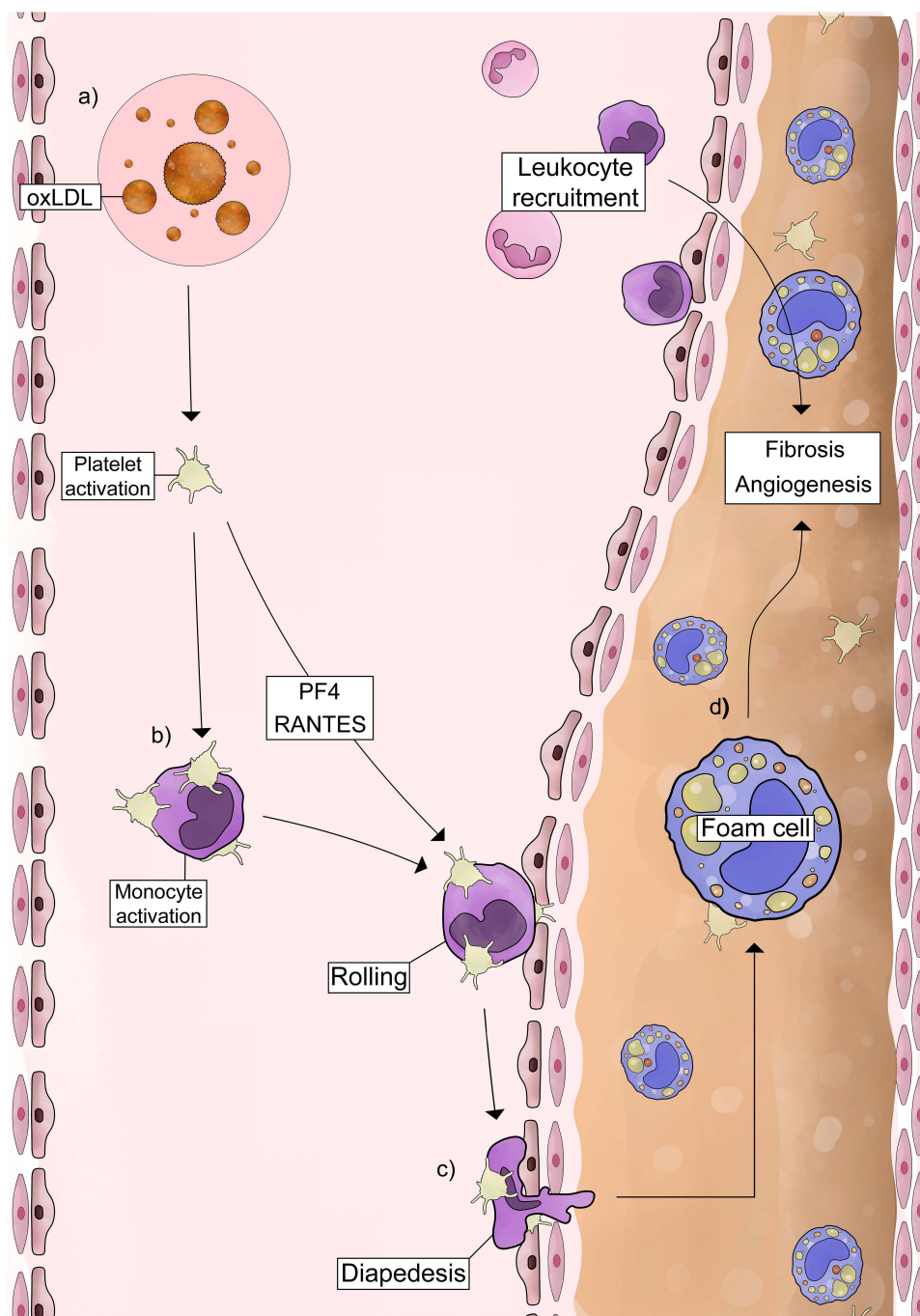


Figure 1 Mechanisms of platelet activation and platelet-mediated monocyte responses in atherosclerosis. Schematic representation of (a) OxLDL-driven platelet activation and CD62P exposure, which promote (b) chemokine secretion and PMA formation, (c) increase monocyte adhesion to the endothelium, and (d) support their differentiation into foam cells. See the text for details and references.

Abbreviations: OxLDL, oxidized LDL; CD62P, P-selectin; PMA, platelet-monocyte aggregates; ROS, reactive oxygen species; PSGL-1, selectin glycoprotein ligand-1.

fueling local inflammatory and thrombotic activation.¹¹³ Rather than representing a direct comparison between CAD and ACS, these observations illustrate how platelet-driven or monocyte-driven mechanisms may predominate depending on the pathological setting. Strategies that inhibit platelet activation or disrupt the CD62P-PSGL-1 interaction, such as the analog peptide IELLQAR, reduce monocyte recruitment and attenuate key steps in foam cell formation, offering potential to slow disease progression.^{88,114} These processes reinforce the central role of P-selectin-mediated platelet-monocyte interactions in coronary atherosclerosis and position them as promising therapeutic targets.^{115,116}

Importantly, P-selectin-mediated thromboinflammation is not confined to the coronary arteries. Structural alterations associated with arteriosclerosis and nephrosclerosis, including progressive intimal fibroelastosis, subendothelial hyalinosis, and intimal fibrosis in afferent arterioles, demonstrate that these mechanisms extend to multiple organs potentially contributing to hypertension and its associated vascular and renal complications (reviewed in¹¹⁷), as discussed in the next chapter.

Hypertension

Hypertension is a multifactorial disease influenced by genetic, endocrine, dietary, lifestyle, immune, and environmental factors.^{118,119} Vascular remodeling, including smooth muscle hypertrophy, endothelial injury, and immune cell infiltration, leads to extracellular matrix deposition and increased vascular stiffness.^{120,121} These structural and inflammatory alterations create a prothrombotic environment, with CD62P-mediated platelet–monocyte interactions amplifying vascular inflammation, endothelial dysfunction, and cardiac remodeling. Chronic platelet activation in hypertensive patients is reflected by elevated PMA formation in circulation, which correlates with tissue inflammation and early fibrosis in both experimental models and clinical studies.¹²²

Experimental⁹³ and clinical¹²³ evidence indicate that CD62P is a key mediator of vascular and organ damage associated with hypertension. In angiotensin II–induced hypertension models, wild-type mice develop cardiac inflammation, macrophage infiltration, and early fibrosis, while CD62P deficiency markedly attenuates these responses despite similar elevation in blood pressure.⁹³ CD62P-PSGL-1-facilitated PMA promote the recruitment of monocytes to cardiac tissue, where they differentiate into macrophages that secrete pro-inflammatory cytokines and induce fibrosis.⁹³ Consistently, clinical studies demonstrate that hypertensive patients exhibit increased platelet and endothelial activation, including elevated plasma and myocardial levels of CD62P.¹²³ Increased platelet activation, paralleled by low-grade inflammation, is more pronounced in individuals with signs of renal injury.¹²³ Furthermore, antiplatelet therapy with aspirin reduces surface and soluble CD62P levels, reinforcing the role of platelet and endothelial activation in cardiovascular and renal complications during hypertension.¹²⁴

These findings demonstrate that platelet activation and CD62P-mediated platelet–monocyte interaction represent key mechanisms of inflammation and tissue remodeling associated with hypertension.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) represents one of the most prevalent and clinically relevant consequences of overweight and obesity, as progressive weight gain is a major driver of metabolic dysfunction.¹²⁵ T2DM is characterized by insulin resistance, hyperglycemia, inflammation, and progressive β -cell dysfunction.^{126–129} Environmental factors and sustained nutrient excess induce epigenetic modifications that impair insulin signaling, reduce peripheral glucose uptake, increase hepatic glucose production, and elevate circulating free fatty acids.¹³⁰ Beyond metabolic dysregulation, T2DM is associated with chronic low-grade inflammation, which accelerates β -cell failure and disease progression.^{129,131}

T2DM patients exhibit a prothrombotic state associated with heightened platelet activation¹³² and PMA formation,⁹⁵ which directly correlate with poor glycemic control^{133,134} and to the presence of carotid plaques in patients.¹³⁵ The coexistence of T2DM and obesity further exacerbates platelet activation and hyperreactivity.¹³⁶ Increased PMA formation in T2DM is particularly higher among patients with higher adiposity.^{54,137–139} A positive correlation between PMA and the body mass index supports a role for excess adipose tissue in amplifying platelet–monocyte interactions. Similar associations are observed with other metabolic disorders, such as dyslipidemia.^{54,140} Mechanistically, initial CD62P-mediated platelet–monocyte interactions are subsequently stabilized by monocyte Mac-1 (CD11b/CD18), enhancing firm adhesion to the endothelium and promoting local inflammation.^{141,142} Notably, Mac-1 expression in monocytes increases rapidly in response to acute glucose excursions, further reinforcing the formation and stability of PMA under hyperglycemic conditions.¹⁴² This process initiated by increased CD62P on platelets, facilitates their interaction with leukocytes and rapid PMA formation,^{133,134} representing a central mechanism linking hyperglycemia, vascular inflammation, and atherothrombotic risk in T2DM.

Pharmacological strategies that reduce postprandial hyperglycemia, such as acarbose,¹⁴³ decrease platelet activation¹⁴⁴ and PMA formation¹⁴⁵ by mitigating acute glycemic fluctuations in patients with T2DM. These findings suggest that short-term glycemic excursions rather than long-term glycemic control are key drivers of thromboinflammation in T2DM.

Together, these observations suggest that different metabolic, inflammatory, and coagulation disturbances may converge to sustain platelet–monocyte interactions and thromboinflammation.

Fatty Liver Disease (Hepatic Steatosis)

Non-alcoholic Fatty Liver Disease (NAFLD) represents the hepatic manifestation of metabolic dysfunction, closely associated with obesity, insulin resistance, hypertension, and type 2 diabetes.^{146–149} During obesity, dietary energy surplus becomes a central driver of NAFLD development.^{150–152} When energy intake exceeds the adipose tissue expenditure capacity, excess lipids accumulate ectopically in organs such as the liver.^{153–155} Insulin normally exerts an antilipolytic effect and promotes triglyceride storage in adipose tissue, thus, insulin resistance plays a central pathogenic role by increasing free fatty acid flow to the liver and enhancing hepatic lipid accumulation.^{156–158} Within this spectrum, non-alcoholic steatohepatitis (NASH) represents a more severe form, characterized by steatosis accompanied by liver necro-inflammation and varying degrees of fibrosis, potentially progressing to cirrhosis, liver failure, and, in some cases, hepatocellular carcinoma.¹⁵⁹ The transition from metabolic dysfunction-associated steatotic liver disease to metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis involves a cascade of inflammatory and fibrogenic events.¹⁶⁰

NASH is associated with a chronic proinflammatory and prothrombotic state.¹⁶¹ Higher hepatic fat content positively correlates with increased coagulation activation,^{162,163} while the platelet and endothelial activation markers sICAM-1 and sCD62P are associated with markers of liver injury, such as aminotransferases enzymes.^{164,165} Similarly, patients with metabolic dysfunction-associated steatotic liver disease (MASLD) exhibit elevated serum thromboxane B2 (TxB2) and sCD62-P, which progressively increase from steatosis to steatohepatitis and cirrhosis, positively correlating with the stage of fibrosis.^{166,167} PMA formation also increases during NASH and correlates with platelet activation and plasma aminotransferases, while increased monocyte activation was associated with end-stage liver cirrhosis.¹⁶⁵ Within this context, platelet activation and PMA formation may link inflammation, coagulation, and fibrogenesis, contributing to both pro-inflammatory and pro-fibrotic responses that sustain hepatic injury.¹⁶⁰ Preclinical studies with genetic or pharmacological interventions targeting platelet activation or CD62P are still needed to better understand their role in NASH.

Ulcerative Colitis

Ulcerative colitis (UC) and inflammatory bowel disease are characterized by inflammation of the colonic mucosa, in which genetic susceptibility, alterations in gut microbial composition and environmental factors collectively contribute to its development.¹⁶⁸ This persistent inflammatory environment leads to platelet activation, contributing to thromboembolic complications.¹⁶⁹ Patients in UC flare exhibit increased platelet activation and elevated CD62P expression,¹⁷⁰ which supports PMA formation primarily relying on CD62P-PSGL-1 interactions.¹⁷¹ In patients with severe endoscopic inflammation, PMAs were markedly increased and more abundant in regions of extensive mucosal damage. Moreover, PMA displayed higher CD16 expression compared to platelet-free monocytes, indicating preferential interaction with inflammatory monocytes.¹⁷² However, opposing data have been reported on whether PMA formation is associated with disease severity in UC by inducing or inhibiting inflammatory response.^{171–174} Zamora et al (2018) found reduced PMA formation in flare patients with endotoxemia, linked to decreased monocyte PSGL-1 expression.¹⁷¹ This finding was consistent with studies that lipopolysaccharide (LPS) downregulates PSGL-1, thereby impairing PMA formation.^{173,174} In a murine model of DSS-induced colitis, however, blocking either PF4/CXCL4 or CXCR3 expression alleviated inflammation.¹⁷⁵ Although the study did not specifically evaluate circulating PMA, it provides mechanistic insight into how platelet activation influence monocyte and macrophage response within the intestine, thereby amplifying local inflammation and contributing to disease progression. Despite ongoing debate regarding PMA dynamics, their association with severe mucosal damage supports the notion that they may contribute to local thromboinflammatory events in the colon.¹⁷⁵

Notably, therapeutic strategies targeting these interactions provide indirect clinical support for their pathogenic relevance. Adsorptive cytopheresis has been shown to significantly reduce circulating PMAs, with clinical response correlating with the magnitude of platelet depletion, reinforcing the concept that disrupting platelet–monocyte crosstalk may attenuate intestinal inflammation.¹⁷⁶ However, further studies are needed to determine whether PMA serve as reliable biomarkers of disease activity or prognosis and potential therapeutic targets in UC.

Autoimmune Diseases

Autoimmune diseases (ADs) are characterized by the presence of autoreactive immune cells, in which overactivation and recruitment of T and B lymphocytes result in immune-mediated damage.¹⁷⁷ Cardiovascular complications frequently contribute to increased mortality in ADs, with systemic lupus erythematosus (SLE) and type 1 diabetes mellitus (T1DM) ranking among those with the highest cardiovascular risk.¹⁷⁸ The increased risk of thrombotic events in patients with ADs is primarily driven by systemic inflammation, which promotes a hypercoagulable state associated with endothelial dysfunction and enhanced platelet activation.¹⁷⁹

In SLE, the immune system inappropriately targets nucleic acids-containing cellular components.¹⁸⁰ Among its various immunopathological processes, enhanced platelet activation and PMA formation have been identified as major players to vascular inflammation and thrombotic complications.¹⁸¹ PMAs consistently exhibit higher monocyte activation markers when compared to monocytes alone,¹⁸² and PMA formation is positively correlated to C-reactive protein levels,¹⁸³ indicating that PMA formation is associated with enhanced inflammatory activity in SLE. Elevated platelet activation and platelet–leukocyte interactions have been associated with enhanced TF-dependent coagulation activation in SLE.¹⁸⁴ Platelet–monocyte interactions are often described favoring inflammatory amplification, but PSGL-1/CD62P-mediated interactions can also contribute to tolerogenic responses.¹⁸⁵ Notably, PSGL-1 deficient mice develop a scleroderma-like syndrome, whereas the absence of its main ligand, CD62P, disrupts immune homeostasis and leads to a progressive lupus-like autoimmune disorder with many features observed in lupus-prone mice. Consistently, patients with cutaneous lupus exhibit reduced endothelial CD62P expression in dermal vessels, implying that decreased CD62P expression could play a role in disease development.^{186,187} Monocyte PSGL-1 expression is reduced in SLE patients despite increased PMA formation.¹⁸⁸ Monocyte CD40 and platelet CD40L may act as an alternative pathway mediating platelet–monocyte binding in SLE. Altogether, these findings emphasize the complexity and multifaceted nature of platelet–monocyte interactions in SLE. Understanding how these pathways cooperate, compensate, or become dysregulated may provide valuable insights for developing targeted therapies to mitigate loss of tolerance and thromboinflammatory complications in SLE.¹⁸⁸

T1DM is a chronic disorder characterized by autoimmune-mediated destruction of pancreatic islet β -cells leading to insulin deficiency and hyperglycemia.¹⁸⁹ Patients with T1DM often exhibit a hypercoagulable state, characterized by platelet hyperreactivity, elevated plasma coagulation factors, impaired fibrinolysis,¹³⁴ and increased PMA formation.⁹⁵ In individuals with T1DM who also develop insulin resistance, platelets shift toward a state of heightened reactivity while becoming less responsive to the inhibitory actions of prostacyclin (PGI₂). This combination of increased activation and reduced inhibitory sensitivity creates a platelet phenotype that is inherently harder to restrain, offering a clearer explanation for why these patients face an amplified risk of cardiovascular complications.¹⁹⁰ CD62P-positive platelets and PMA formation are associated with the degree of hyperglycemia and dyslipidemia in T1DM.¹⁹¹ Overall, this evidence indicates that persistent metabolic imbalance in T1DM enhances platelet activation and promotes the formation of PMA, amplifying thromboinflammation and contributing to a higher cardiovascular risk.

Sickle Cell Disease

Sickle cell disease (SCD) is a hereditary hemoglobinopathy caused by the substitution of glutamic acid for valine in the β -globin chain, characterized by chronic hemolysis, recurrent episodes of painful vaso-occlusive crises, multi-organ dysfunction, and premature death.¹⁹² These crises result from vaso-occlusive aggregates formed of sickle-shaped erythrocytes, activated platelets, and leukocytes to the endothelium, leading to tissue ischemia.¹⁹³ Platelet bind to erythrocytes, monocytes, and neutrophils, form multicellular aggregates that contribute to blood flow abnormalities and vascular inflammation.^{194–197} Monocytes from patients with SCD exhibit a highly activated phenotype, with increased expression of pro-inflammatory cytokines such as IL-1 β and TNF- α , promoting greater endothelial adhesion and further amplification of the inflammatory response.^{198,199}

In experimental SCD models, CD62P blocking or genetic deficiency significantly reduces leukocyte adhesion and protects mice from vaso-occlusion.^{196,200,201} Mice deficient in CD62P and CD62E exhibit markedly reduced leukocyte rolling and adhesion, a marked reduction in interactions between sickle cells and adherent leukocytes, preservation of

microvascular flow, and increased survival during the intravital experimental procedure, highlighting that selectin-dependent leukocyte recruitment is crucial for vaso-occlusion.^{196,201,202}

In humans, PMA are more abundant in patients with SCD than in healthy controls²⁰³ contributing to increased CD11b expression, inflammatory amplification, greater endothelial adhesion, and tissue damage.^{199,204} Circulating platelets remain chronically activated, showing higher levels of CD40L^{205,206} and CD62P,^{207,208} and TNFSF14,²⁰⁹ a cytokine associated with endothelial activation and inflammation. CD40L promotes the release of α and dense granules, intensifying platelet activation with increased CD62P exposure favoring the interaction with monocytes.²⁰⁶ In addition to the classic CD62P/PSGL-1 pathway, monocyte podoplanin binding to platelet CLEC-2 also contributes to platelet activation and the formation of PMA in patients with SCD, which was correlated with CD62P expression and disease severity, including hemolysis and coagulation activation markers, and history of vaso-occlusive crises.²⁰³

Those preclinical and translational findings provided the basis for therapeutic interventions targeting CD62P. Crizanlizumab, a humanized monoclonal antibody that blocks the CD62P-PSGL-1 interaction, significantly reduces the annual frequency of vaso-occlusive crises, prolongs the time between crises, and decreases hospital stays, without a relevant increase in adverse events.²¹⁰ These results directly demonstrate that CD62P inhibition can effectively modify disease outcomes in humans, showing that platelet–leukocyte interactions are not only essential mechanistic contributors but also actionable therapeutic targets that translate into significant clinical benefits. Building on this success, it will be valuable to explore whether CD62P blockade could provide similar benefits to other thromboinflammatory conditions where CD62P contributes to PMAs formation and poorer disease outcomes, representing a promising avenue for future investigation.

P-Selectin-Mediated Interaction in Infectious Diseases

Dengue Virus

Dengue viruses (DENV) are the most epidemiologically relevant arboviruses worldwide, responsible for approximately 400 million infections per year on the planet.²¹¹ Transmission occurs through the bite of blood-feeding mosquitoes of the genus *Aedes*, especially *Aedes aegypti*.²¹² Clinical manifestations range from self-limiting febrile illness to severe syndromes characterized by endothelial dysfunction and hemorrhage.²¹³ Among the most striking laboratory findings in severe forms are thrombocytopenia and cytokine storm, resulting in exacerbated systemic inflammation.²¹⁴ Platelet activation is evidenced by increased expression of classical markers such as CD62P, PAC-1, and phosphatidylserine,^{215–217} accompanied by secretion of inflammatory mediators including PF4/CXCL4, CCL5/RANTES²¹⁸ and nitric oxide.²¹⁹ This activation drives the formation of PMA, which are elevated in dengue patients^{220,221} and correlate with thrombocytopenia and increased vascular permeability in patients.^{215,216,219,221} Proteomic studies reinforce this profile, demonstrating higher expression of proteins associated with platelet activation and immunoregulation in platelets from infected patients.²²²

In vitro infection models demonstrate increased platelet activation^{215,216} and aggregation with monocytes²²³ resulting in the induction of inflammatory cytokines, chemokines and COX-2 expression, alongside monocyte metabolic reprogramming leading to lipid droplet-dependent PGE₂ production.²²³ Ex vivo studies corroborate these findings, demonstrating that platelets from dengue patients stimulates monocytes to produce inflammatory cytokines such as IL-8, IL-1 β , and IL-10 in a process depending on CD62P-mediated adhesion and phosphatidylserine recognition by the monocyte.²²¹ In addition to P-selectin-mediated adhesion, secreted mediators such as MIF also participate in monocyte reprogramming.²²³ Likewise, PF4-CXCR3 signaling has shown immunomodulatory proviral effects enhancing DENV replication in monocytes by reducing type I interferon while promoting proinflammatory cytokine production.²²⁴ Together, these in vitro and ex vivo data indicate that platelet activation drives PMA formation and modulates monocyte metabolic and inflammatory responses.

Experimental DENV infection of interferon-deficient (A129) mice also shows a robust increase in platelet activation and platelet–leukocyte aggregate formation alongside bone marrow hypocellularity and thrombocytopenia.²²⁵ P-selectin neutralization in vivo significantly recovered marrow cellularity and peripheral platelet counts. In addition, blocking P-selectin reduced platelet–monocyte and platelet–neutrophil aggregates formation, thereby mitigating chemokine levels and neutrophil infiltration to the lungs, reducing tissue damage. Together, these clinical and experimental evidence highlight the central role of CD62P in mediating thromboinflammation in dengue. Targeting these pathways may attenuate pathophysiological processes linked to vascular dysfunction, providing potential therapeutic insights.

COVID-19 and Post Acute Sequelae of COVID-19 (PASC)

Severe COVID-19 is a complication of SARS-CoV-2 pneumonia characterized by systemic thromboinflammation.^{226–230} Thromboembolic events are a major cause of mortality in severe COVID-19, with a growing body of evidence showing coagulation activation and platelet activation markers associated with poor outcomes.^{35,226,228,231–238} COVID-19 patients platelets exhibit a hyperactivated phenotype with increased CD62P surface expression, TXB₂ secretion, EV release, and heightened responsiveness to stimuli such as thrombin, collagen, and fibrinogen, besides platelet–leukocyte aggregates formation among neutrophils, monocytes, and T-cells.^{226,228,232,235,239–242} Notably, platelet activation and platelet-induced monocyte reprogramming correlate with disease severity, thrombosis, and mortality.^{226,243,244}

Although ACE2 and TMPRSS2 are central receptors for SARS-CoV-2 entry in multiple cell types,^{245,246} platelets internalize the virus via ACE2-independent mechanisms, as most studies did not detect ACE2 on platelets.^{239,245,246} Yet, the viral RNA is found within platelets from patients or in vitro infection models.^{239,247–251} Many alternative receptors have been proposed for SARS-CoV-2 binding on platelets, including CD42b, CD147, and CD26, although consensus on whether they are involved in viral entry was not reached.^{229,252–256} Recently, P-selectin was proposed as a target for SARS-CoV-2 binding on platelets under flow.^{229,256,257} Regardless of viral entry, SARS-CoV-2 or Spike protein binding to most of these receptors triggers signal transduction inducing platelet activation and PMA formation.^{229,252–256} New studies are still necessary to determine whether SARS-CoV-2 binding to Platelet P-selectin may play a role in infection and/or platelet-mediated responses during COVID-19.

Severe COVID-19 is marked by systemic inflammation with elevated circulating cytokines such as TNF- α , IL-1 β , and IL-6.^{226,228–230,258,259} Plasma from COVID-19 patients is sufficient to induce platelet activation, PMA formation, and TF expression independently of viral presence and depending on IL-6 receptor.²²⁸ The PMA phenotype induced in this model is similar to the one reported during severe COVID-19, involving majorly CD16+ monocyte subsets with higher TF and lower HLA-DR expression.^{12,35,229,241} These monocyte characteristics were related to disease severity and mortality in COVID-19 patients.^{226,260}

Mechanistic experiments with platelet–monocyte co-cultures using platelets from COVID-19 patients *ex vivo*, or SARS-CoV-2 infection *in vitro*, showed that platelets are determinant and sufficient to induce TF expression in monocytes depending on CD62P and integrin α IIB/ β 3.^{12,226} Neutralization of CD62P, but not integrin α IIB/ β 3, disrupted PMA formation, confirming P-selectin as the dominant adhesion molecule mediating platelet–monocyte binding, even though both adhesion molecules signal monocyte activation and TF expression.^{12,226} While platelets from COVID-19 patients induced monocyte inflammatory responses, monocytes from patients were also hyperresponsive to platelets and to immobilized CD62P or fibrinogen, producing higher levels of TNF- α and IL-1 β .¹² Consistently, platelets from COVID-19 patients trigger monocyte TNF- α and IL-1 β secretion.^{12,35} Similar results have been reported with *in vitro* models using SARS-CoV-2 Spike protein-induced platelet activation and PMA formation, promoting monocyte IL-1 β and IL-6 secretion through CD62P and CD40L signaling.²²⁹ Parallel neutralization of P-selectin, integrin α IIB/ β 3 and TF in both, *ex vivo* and *in vitro* experimental models, revealed a sequential mechanism of platelet-driven monocyte inflammatory amplification in COVID-19. P-selectin and integrin α IIB/ β 3 surface signaling induce the secretion of inflammatory cytokines and chemokines plus TF expression in the monocyte (Figure 2a). TF then amplifies the inflammatory signaling by triggering PAR-1 engagement in platelets and PAR-1 and PAR-2 in monocytes (Figure 2b). This reciprocal activation loop amplifies platelet degranulation and is responsible for monocyte CD16 expression and TNF- α and IL-1 β secretion (Figure 2c).^{12,35} This P-selectin-induced and TF-amplified signaling mechanism contributes to hyperinflammation and hypercoagulability in severe COVID-19 (Figure 2d).

Even though pre-clinical data described above may suggest a major role for P-selectin in inflammatory amplification during COVID-19, clinical evidence remains limited. A randomized, double-blind, placebo-controlled pilot trial investigating hospitalized COVID-19 patients treated with the anti-P-selectin monoclonal antibody crizanlizumab found no significant effects on inflammatory mediator levels or clinical outcomes.²⁶¹ However, given the small sample size, these findings should be interpreted with caution, and larger studies are required to determine whether targeting P-selectin or its downstream pathways, including TF, could provide clinical benefit.

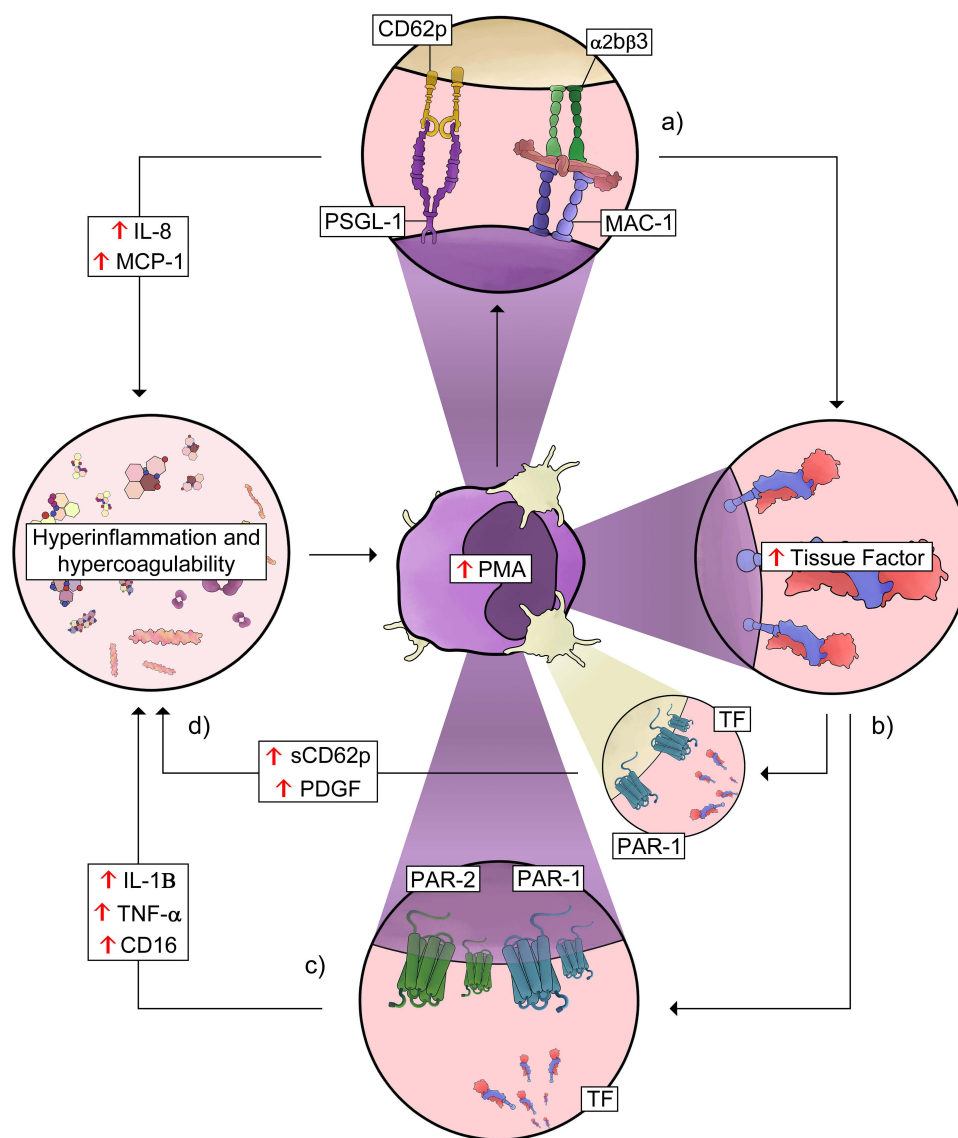


Figure 2 Platelet–monocyte interaction-driven thromboinflammatory loop in COVID-19. Schematic representation of thromboinflammatory amplification mediated by platelet–monocyte aggregates (PMA). (a) Activated platelets interact with monocytes mainly through P-selectin (CD62P)–PSGL-1 binding and additional integrin-mediated interactions, such as α IIb β 3 and MAC-1, promoting PMA formation. This interaction enhances the release of inflammatory mediators, including IL-8 and MCP-1, contributing to a hyperinflammatory and hypercoagulable state. (b) Platelet–monocyte interactions promote tissue factor (TF) expression in monocytes, increasing the procoagulant potential and contributing to thrombus formation. (c) TF-driven activation of the coagulation cascade leads to signaling through protease-activated receptors (PAR-1 and PAR-2) on platelets and monocytes, amplifying inflammatory responses and sustaining the thromboinflammatory loop, with increased levels of mediators such as IL-1 β , TNF- α , CD16, soluble P-selectin (sCD62P), and platelet-derived growth factor (PDGF). (d) Mediators from activated platelets and monocytes amplify inflammation and hypercoagulability in COVID-19. See the text for details and references.

Abbreviations: PMA, platelet–monocyte aggregates; PSGL-1, P-selectin glycoprotein ligand-1; MAC-1, macrophage-1 antigen (CD11b/CD18); CD62P, P-selectin; α IIb β 3, integrin alpha-IIb/beta-3 (glycoprotein IIb/IIIa); sCD62P, soluble P-selectin; PDGF, platelet-derived growth factor; MCP-1, monocyte chemoattractant protein-1; PAR-1, protease-activated receptor-1; PAR-2, protease-activated receptor-2.

Beyond the immune alterations observed during acute COVID-19, a subset of individuals develops a syndrome known as PASC or long COVID, defined by the persistence of symptoms for more than 12 weeks after acute SARS-CoV-2 infection. This post-acute condition involves immunological and inflammatory mechanisms that, although distinct, arise from the dysregulated response triggered during the initial infection. Clinical presentations include fatigue, post-exertional malaise, cognitive impairment, dyspnea, and arthralgia.^{262,263} The most relevant manifestations result from pulmonary involvement with dyspnea, chest pain, and fatigue associated with tissue remodeling and infiltration observed in computed tomography scans.^{264,265}

Chronic low-grade inflammation in PASC sustains a persistently activated platelet phenotype, marked by increased expression of P-selectin, α IIb β 3 activation, and platelet aggregation in individuals who have had severe COVID-19.^{266,267} Persistent platelet activation is observed months after infection, accompanied by elevated platelet–leukocyte aggregates and coagulation markers such as D-dimer.^{268–270} Platelet–monocyte and platelet–granulocyte aggregates formed in PASC express higher TF levels and correlate to the extent of lung parenchymal damage, linking platelet hyperactivation to common PASC symptoms, including fatigue, breathlessness, and persistent pulmonary inflammation.^{265,270} The PASC inflammatory milieu is sufficient to drive platelet activation, as plasma from PASC patients induces platelet activation and platelet–leukocyte aggregates formation through mechanisms depending on Fc γ -R and IL-6R, but independent of PAR-1 signaling.^{268,270} Future studies should further examine the CD62P/PSGL-1 axis to elucidate how CD62P-mediated signaling shapes monocyte function in PASC. The enrichment of PMA and the heightened procoagulant phenotype of monocytes in PASC raise the possibility that sustained platelet-driven reprogramming may represent a key mechanism underlying chronic thromboinflammation in long COVID.

Influenza Virus

Influenza is one of the most prevalent respiratory infections in humans, occurring both as occasional pandemic outbreaks and recurrent seasonal epidemics, resulting in substantial morbidity and a significant number of deaths. Its pathogenesis is multifaceted, involving virological and host immune system determinants.^{271–273} In severe cases, dysregulated inflammation contributes to lung injury,^{274–276} a process largely orchestrated by the vascular endothelium, whose activation and dysfunction promote platelet adhesion and leukocyte recruitment.²⁷⁷ Clinical research confirms in vivo platelet activation in critically ill H1N1 patients, including enhanced PMA formation.²⁷⁸

In vitro studies have confirmed the relationship between Influenza A Virus (IAV) strains and platelet/endothelial activation, possibly impacting strain-dependent lung pathology. The highly pathogenic IAV strain H5N1 induces pulmonary microvascular endothelial cells to express selectins, including CD62P and CD62E, whereas seasonal strains such as H1N1 and H3N2 did not.^{279–281} Even though, seasonal H3N2 promotes platelet-endothelium adhesion in vitro through mechanisms independent of CD62P but dependent on α_v/β_1 integrin.²⁸¹ These findings highlight the capacity for platelets and endothelial cells to recognize viral subtypes, influencing adhesion-mediated responses.

In murine models of lethal influenza infection, increased sCD62P in bronchoalveolar lavage fluid indicates platelet activation in the pulmonary microenvironment. Additional approaches, including direct platelet counting and immunohistochemistry, demonstrated platelet migration into the airways and lung tissue, associated with congestion, infiltration of monocytes and neutrophils, interstitial and alveolar hemorrhages, and thrombosis.²⁸² Murine models infected with H5N1 show increased macrophage and neutrophil infiltration in the lungs.²⁸³ Antiplatelet pharmacological interventions, including aspirin or the GPIIb/IIIa antagonist eptifibatid, reduced CD62P activation and prevented lung injury, highlighting the functional role of platelets in pulmonary pathogenesis during influenza.^{281,282}

Influenza vaccination is widely used as a controlled model of systemic inflammation to investigate platelet–monocyte interactions. Following vaccination, increased PSGL-1 expression and PMA formation were observed, particularly within the intermediate monocyte subset. This subset was more sensitive to interactions with activated platelets, correlating positively with platelet activation and systemic inflammatory markers.^{284–286} Co-culture studies demonstrated that PMA formation and increased CD16 expression in monocytes depended directly on CD62P/PSGL-1-mediated interactions exhibiting enhanced cytokine production and adhesion with platelets and endothelial cells. In contrast, the addition of platelet releasate or recombinant sCD62P does not fully reproduce this phenotype, indicating that physical contact with activated platelets is essential for functional modulation. COX-2 inhibition abolished CD16 upregulation but did not affect PMA formation, suggesting that specific intracellular pathways, such as COX-2/PGE2, modulate distinct aspects of the monocytic phenotype during PMA formation.^{223,287}

Further studies are needed to understand how platelet CD62P-mediated leukocyte recruitment contributes to pulmonary pathogenesis during severe influenza infection, and whether PMA formation amplifies inflammation and exacerbates tissue injury. Investigating these mechanisms may reveal novel strategies to modulate inflammatory responses without compromising antiviral immunity.

HIV Infection

Human immunodeficiency virus 1 (HIV-1) is the most prevalent retrovirus in the world, being highly transmissible and widely distributed.²⁸⁸ Acute infection progresses with high viremia and CD4+ T-cell depletion, followed by chronic viral replication and progressive immune deterioration. Acquired immunodeficiency syndrome (AIDS) is characterized by severe immunosuppression and occurrence of opportunistic infections.^{289,290} However, with the introduction of antiretroviral therapy (ART), the epidemiology of HIV infection underwent an important transition, from high mortality due to opportunistic infections in AIDS to the predominance of long-term non-infectious comorbidities among chronically infected individuals.^{291,292} With sustained virological control by ART, people living with HIV (PLHIV) now live longer, but remain susceptible to long-term comorbidities including hypertension, metabolic syndrome, dyslipidemia, cardiovascular disease, neurocognitive disorders, and non-AIDS-related cancers.^{290,293–303}

In untreated HIV, or AIDS patients, viral replication and systemic inflammation promote intense platelet activation with CD62P and CD40L surface expression,³⁰⁴ which correlates with increased TF in monocytes.³⁰⁴ Untreated HIV patients exhibit increased PMA formation, especially within CD16+ monocytes, and show elevated levels of sCD163 and sCD14, indicating increased monocyte activation.³⁰⁵ Both, platelet activation and PMA formation correlate positively with the viral load and negatively with CD4+ T-cell count, supporting a role in AIDS pathophysiology (Figure 3a).^{305–307} In addition, platelets from AIDS patients become exhausted, secreting lower levels of chemokines when stimulated *ex vivo*. Complementing these observations, studies in non-human primate models infected with SIV show increased platelet activation, with CD62P and CD40L favoring PMA formation primarily with CD16+ monocytes and correlating with thrombocytopenia.³⁰⁸ These data suggest that platelet activation and PMA formation may be related to viral replication in AIDS. However, recent studies have shown residual platelet activation in PLHIV under ART, with increased CD62P and sCD40L persisting for months to years after virological suppression.^{306,309–316} Additional analyses of PLHIV on stable ART show persistent platelet exhaustion evidencing chronic platelet activation,³⁰⁹ and elevated levels of sCD163,³¹⁷ indicating that platelet and monocyte activation involves other mechanisms besides viremia. Like HIV, SIV-infected primate models receiving ART exhibit persistent monocyte and macrophage activation.³¹⁸ These findings indicate that, despite viral suppression achieved through ART, several mechanisms continue to contribute to a persistent inflammatory state in PLHIV (Figure 3b). Among these mechanisms, viral persistence and latency, as well as microbial translocation, with continuous activation of Pattern Recognition Receptors in the innate immunity are probably involved.³¹⁸

In addition to the peripheral blood, platelet activation and PMA formation have functional effects in target tissues, including the brain, potentially amplifying local and systemic inflammatory responses, with implications for long-term comorbidities in PLHIV.³¹⁹ Particularly relevant for neurological pathogenesis, studies in animal models and human tissues indicate PMA adhesion and infiltration to the brain.^{319,320} *In vitro* experiments using brain microvascular endothelial cell monolayers showed that monocytes within PMAs exhibit increased CCR2, PSGL-1, and CD40 expression, along with enhanced adhesion and trans-endothelial migration in a CD62P-dependent manner.³²⁰ Studies showed that platelet-derived sCD40L increases blood–brain barrier permeability and promotes monocyte adhesion and migration into the brain.³¹⁹ Clinical studies have shown that the expansion of non-classical monocytes was correlated with poor cognitive performance in PLHIV with neurological disorder, highlighting an association between monocyte activation and HIV-associated cognitive impairment.³¹⁴ Corroborating these findings, post-mortem brain tissues from patients with HIV-associated encephalitis exhibited higher numbers of PMAs marginated along post-capillary venule walls compared with HIV-negative individuals, suggesting that platelet activation and PMA formation directly contribute to HIV-associated neuroinflammation (Figure 3c).³²⁰ These data indicate that, even under ART, HIV-1 infection induces residual platelet activation and PMA formation, contributing to monocyte infiltration into the brain and neuroinflammation, but potentially contributing to other long-term comorbidities involving other target tissues.

Bacterial Infection/Sepsis

Sepsis is characterized by a dysregulated immune response to infection that can progress to multiple organ dysfunction, septic shock, and death.³²¹ Although it may arise from bacterial, viral, or fungal pathogens, Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* are among the most frequently associated with sepsis.³²²

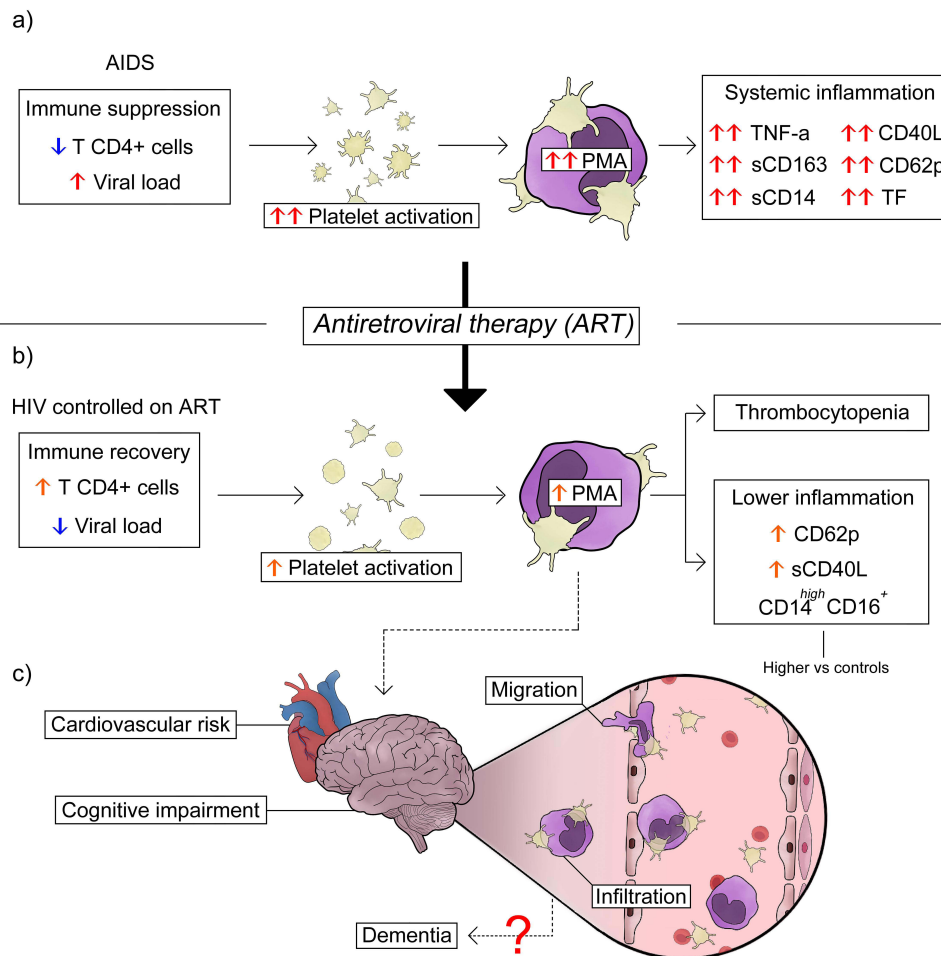


Figure 3 PMAs in HIV-associated inflammation. (a) HIV-infected untreated AIDS patients exhibit increased platelet activation and PMA formation in association with viral load and immunosuppression. (b) Platelet activation and PMA formation in individuals living with HIV under ART-induced virological control. ART partially reduces platelet activation and PMA formation, resulting in decreased inflammatory markers and improved immune recovery. (c) Despite this improvement, residual activation persists contributing to PMA infiltration into the parenchyma of target organs, such as the brain, which is associated with increased neuroinflammation. See the text for details and references.

Abbreviations: AIDS, immunodeficiency syndrome; PMA, platelet-monocyte aggregates; CD62P, P-selectin; CD40L, CD40 ligand; TF, tissue factor; sCD163, soluble CD163; sCD14, soluble CD14; ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Platelets recognize bacterial structures through many receptors such as Toll-like receptors, GPIb, and GPIIb/IIIa, among others.³²³ In addition, bacteria release soluble products capable of stimulating platelets,³²⁴ or proteins that associate with plasma proteins, such as vWF and fibrinogen, forming molecular bridges that indirectly activate platelets.³²⁵ Once activated, platelets promote immune cell activation and drive the formation of PMAs, playing central roles in sepsis by contributing to microvascular thrombosis and organ dysfunction.^{326–328}

Transcriptomic analysis of Peripheral Blood Mononuclear Cells from patients with sepsis revealed that platelets and monocytes are the cell types exhibiting the most pronounced transcriptional disturbances associated with inflammation and coagulation during the transition from high risk to clinical sepsis.³²⁹ This pattern indicates a coordinated immune response between platelets and monocytes that potentially contributes to disease progression. Clinical studies further support the importance of platelet–monocyte interactions in sepsis. Gram-positive sepsis is associated with higher platelet activation, platelet hyperreactivity, and increased PMA formation compared with sepsis caused by common Gram-negative pathogens.³¹¹ In elderly septic patients, PMA formation was associated with mortality, a relationship not observed in younger individuals.³³⁰ Another recent study examined PMAs in septic patients who developed respiratory distress syndrome (ARDS), showing that PMA levels were significantly elevated in ARDS group compared with sepsis alone, and positively correlated with APACHE II severity scores.³³¹

Experimental sepsis reinforces the central role of platelet–monocyte interactions. In a murine model of peritoneal sepsis, early and robust upregulation of CD62P was accompanied by a marked increase in PMA formation within hours after abdominal sepsis.³³² The functional importance of this pathway is demonstrated in CD62P-deficient mice, which show reduced PMA formation, impaired bacterial clearance, dysregulated inflammatory responses, and significantly

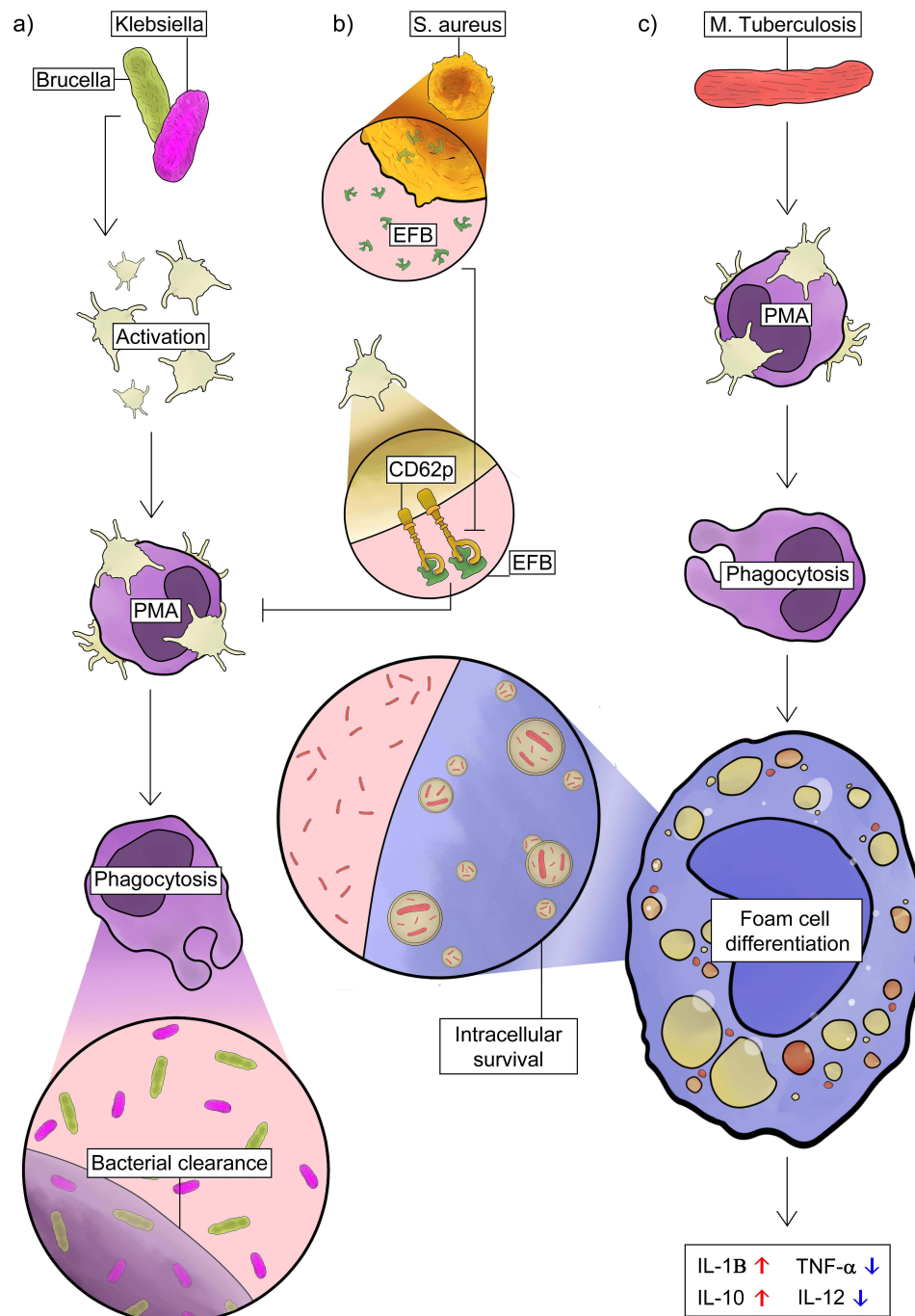


Figure 4 Platelet–monocyte interactions in bacterial infections. (a) During infection with *Klebsiella pneumoniae* and *Brucella abortus*, platelets interact with monocytes promoting their activation, enhancing phagocytosis and cytokine production, which contributes to bacterial clearance. (b) In *Staphylococcus aureus* infection, the bacterial protein Efb interferes with CD62P-PSGL-1 interactions, impairing platelet–leukocyte aggregate formation and favoring bacterial persistence and survival. (c) In active pulmonary tuberculosis caused by *Mycobacterium tuberculosis*, increased levels of platelet–monocyte aggregates (PMAs) promote monocyte differentiation into foam cells, a phenotype associated with high lipid load, increased IL-1 β and IL-10 production, and reduced TNF- α and IL-12, which favors pathogen intracellular survival. See the text for details and references.

Abbreviations: PMAs, platelet-monocyte aggregates; Efb, fibrinogen-binding protein; CD62P, P-selectin.

worse clinical outcomes, including increased mortality, during pneumosepsis.^{333,334} These findings support that CD62P-mediated platelet–monocyte interactions are not only biomarkers of disease severity but actively contribute to host defense mechanisms in sepsis.

The importance of platelet–monocyte interactions for bacterial clearance has also been demonstrated in in vitro models of *Klebsiella pneumoniae* and *Brucella abortus* infection, where platelets enhance phagocytosis, activation, and cytokine production (Figure 4a).^{335,336} However, certain pathogens have evolved mechanisms to counteract this host defense strategy. *Staphylococcus aureus*, for instance, secretes the extracellular fibrinogen-binding protein (Efb), which blocks interaction between CD62P and PSGL-1, thereby inhibiting the formation of platelet–leukocyte complexes (Figure 4b).³³⁷ This evasion mechanism highlights the importance of PMA formation in antibacterial immunity, as bacteria capable of disrupting these interactions can effectively dampen inflammatory responses and improve their survival within the host.

Increasing evidence indicates that platelets play an active role during *Mycobacterium tuberculosis* (M.tb) infection, contributing to inflammatory and tissue-damage processes that exacerbate tuberculosis pathogenesis. Tuberculosis primarily affects the lungs and is characterized by an intense immune response, extensive tissue remodeling, and frequent pulmonary cavitation.³³⁸ Patients with active pulmonary TB show significantly elevated levels of circulating PMAs.³³⁹ In the presence of platelets, human monocytes differentiate into large epithelioid-like multinucleated foam cells resembling those found in tuberculous granulomas.³⁴⁰ This process requires platelet phagocytosis by monocyte and results in the formation of foam cells with a distinctly immunoregulatory phenotype, characterized by increased IL-10 and IL-1 β alongside reduced TNF- α and IL-12 release. Together, these changes indicate platelet-driven monocyte differentiation towards permissive macrophage subsets during mycobacterial infection which in turn contributes to increased intracellular bacterial viability (Figure 4c).^{341,342} Furthermore, monocytes co-stimulated with platelets and M.tb showed higher expression of matrix metalloproteinases MMP-1, enzyme strongly linked to collagen degradation and pulmonary tissue destruction in TB.³⁴² These studies demonstrate that platelets can modulate monocyte responses and may contribute to granuloma organization and potentially to the balance between pathogen control and immune regulation in tuberculosis.

Thus, platelet–monocyte interactions in bacterial infections occupy a central and paradoxical position, acting as essential components of host defense while also driving pathological inflammation, promoting tissue remodeling, and even facilitating pathogen survival within monocytes.

Conclusion

CD62P-mediated platelet–monocyte interactions represent a central axis of inflammation across diverse pathological conditions. These interactions contribute to multiple pathophysiological processes including leukocyte recruitment, chemokine transfer, monocyte activation, and foam cell formation, contributing to vascular remodeling, fibrosis, and tissue injury. PMA formation is primarily driven by platelet activation and P-selectin-PSGL-1 interactions, in both sterile and non-sterile inflammatory conditions, leading to monocyte activation and amplification of thromboinflammatory responses that contribute to inflammation and organ dysfunction. However, the upstream triggers and functional outcomes differ significantly. Sterile inflammation is driven by damage-associated molecular patterns, such as oxidized lipids and metabolic stress signals, leading to sustained formation of PMAs. These aggregates are often associated with endothelial dysfunction and proatherogenic processes. In non-sterile inflammation, pathogen-associated molecular patterns directly activate innate immune and platelet receptors, resulting in an acute and robust inflammatory response with enhanced PMA formation. In bacterial infections, PMAs may also contribute to host defense by enhancing pathogen recognition, promoting monocyte activation, and facilitating bacterial clearance. Thus, while the core mechanisms of PMA formation are shared, their regulation and pathological consequences are highly context dependent.

Likewise, therapeutic strategies targeting CD62P, including PSGL-1 analogs and anti-P-selectin antibodies, have also shown context-dependent efficacy. Clinical benefit has been demonstrated primarily in SCD,²¹⁰ in which crizanlizumab supports the mechanistic relevance of CD62P-mediated platelet–leukocyte interactions. However, similar benefits have not been consistently observed in other thromboinflammatory diseases, many of which CD62P-targeted therapies have not yet been clinically evaluated. In hospitalized COVID-19 patients, a randomized, placebo-controlled pilot trial of the

crizanlizumab showed no significant effects on inflammatory markers or clinical outcomes,²⁶¹ suggesting that CD62P blockade alone may be insufficient to modulate inflammation in certain contexts. Larger, adequately powered trials are needed to determine whether targeting P-selectin or its downstream pathways, such as TF, may provide clinical benefit. Therefore, while effective in SCD, CD62P-targeted strategies likely depend on disease-specific inflammatory drivers and the relative contribution of CD62P-mediated pathways, requiring further evaluation across diverse conditions with consideration for combination therapies and patient stratification.

Pharmacological approaches targeting platelet–monocyte interactions through anticoagulation also exhibit context-dependent effects. While anticoagulant treatment has been associated with a reduction in PMA formation in conditions, such as dyslipidemia, this effect appears limited or insignificant in type 1 and type 2 diabetes mellitus.⁹⁵ These observations suggest that in metabolic diseases characterized by chronic inflammation and hyperglycemia, additional mechanisms beyond coagulation may sustain platelet–monocyte interactions. Antidiabetic¹⁵⁵ and lipid lowering agents⁹⁹ have been shown to reduce platelet activation and PMA formation. Therefore, even though isolated P-selectin-based or anti-platelet therapeutic approaches may be insufficient to effectively modulate PMA formation, combined strategies, including glucose-lowering or hypolipidemic agents emerge as promising alternatives to reduce PMA formation and its pathological consequences. Thus, an integrated view of these mechanisms not only broadens the understanding of the pathophysiology involved but also points towards the development of more targeted and effective therapeutic interventions.

Despite these advances, important gaps remain in the understanding of CD62P-mediated platelet–leukocyte interactions. Most studies have focused on platelet–neutrophil aggregates,^{204,343–351} and the specific contributions of PMA to human pathophysiology remains incompletely defined, particularly across heterogeneous inflammatory and infectious diseases. Future research should address these gaps at multiple levels. At the mechanistic level, further studies are needed to elucidate the signaling pathways and cell-specific contributions underlying PMA formation and function. At the clinical level, improved characterization of patient heterogeneity and disease-specific inflammatory profiles will be essential to better define the contexts in which PMA are most relevant. At the therapeutic level, the development of combination strategies and targeted interventions should be prioritized to overcome the limited efficacy observed with CD62P blockade alone.

In summary, CD62P-dependent platelet–monocyte interactions are key mechanisms in sterile and non-sterile inflammation. Integrating mechanistic, translational, and clinical research will be essential for developing novel therapeutic strategies aimed at mitigating thromboinflammatory complications and improving patient outcomes. This holistic perspective reinforces research and clinical significance of PMAs and highlights critical avenues for future investigation. Understanding these pathways will be essential for developing new therapeutical approaches and improving clinical outcomes.

Abbreviations

CD62E, E-selectin; CD62P, P-selectin; CD62L, L-selectin; PSGL-1, P-selectin glycoprotein ligand-1; PMA, platelet–monocyte aggregates; sCD62P, soluble P-selectin; OxLDL, oxidized LDL; CAD, coronary artery disease; ACS, acute coronary syndromes; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; TF, tissue factor; NASH, Nonalcoholic Fatty Liver Disease; MASH, metabolic dysfunction-associated steatohepatitis; vWF, von Willebrand factor; SCD, sickle cell disease; PDPN, Podoplanin; ADs, autoimmune diseases; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; UC, ulcerative colitis; LPS, lipopolysaccharide; DENV, dengue viruses; PS, phosphatidylserine; LD, lipid droplet; TxB2, thromboxane B2; PASC, Post-Acute Sequelae of COVID-19; hPMEC, human pulmonary microvascular endothelial cells; HIV, human immunodeficiency virus; AIDS, immunodeficiency syndrome; ART, anti-retroviral therapy; PLHIV, people living with HIV; SIV, simian immunodeficiency virus; ARDS, respiratory distress syndrome; Efb, fibrinogen-binding protein; M.tb, *Mycobacterium tuberculosis*; TB, tuberculosis.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analyzed in this study.

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Author Contributions

MKCF, MMLdP, RTR, JPRSdS, and MCBM: Writing – original draft. MKCF and EDH: Writing – review and editing. EDH: Conceptualization, funding acquisition, project administration, resources, and supervision. All authors discussed the concepts.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, literature search, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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