

Role of Platelets in Abdominal Aortic Aneurysm Formation and Progression: New Aspects from Experimental and Clinical Approaches

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Abstract

Abdominal aortic aneurysm (AAA) is a vascular disease with an atherosclerotic background resulting in progressive abdominal aortic dilation. The mechanisms of AAA progression include chronic inflammation within the aneurysm segment, reinforcing extracellular matrix degradation, and weakening of the aortic vessel wall. Platelets are essential mediators of hemostasis and play a dominant role in cardiovascular disease. Recent data suggest a pivotal role of platelets in AAA formation and progression by dysregulated platelet activation. These findings include a potential crosstalk of platelets with different cell types such as macrophages and fibroblasts, which amplifies the inflammatory response within the aortic tissue and promotes aortic wall stiffening. Experimental studies provided evidence for platelets to directly contribute to AAA formation and progression via the collagen receptor glycoprotein VI by promoting vascular inflammation, as well as aortic wall remodeling. Moreover, platelet and red blood cell interactions via the TSP-1–CD36 axis reinforces aneurysm formation via elevated procoagulant activity of both cells in experimental mice and AAA patients. Therefore, platelets and a platelet-mediated cellular crosstalk play a crucial role in AAA by promoting the development and progression of AAA. To date, no therapeutic treatment is available and surgical repair is the only option to prevent patients from aortic rupture. Thus, there is a strong need for an effective therapy to attenuate AAA progression. This review highlights the mechanisms of platelet activation and the relevance for the identification of new platelet-derived targets to develop a drug-based therapy for AAA patients.

Keywords

- ▶ platelets
- ▶ abdominal aortic aneurysm
- ▶ inflammation
- ▶ ECM remodeling

Introduction

Platelets are central mediators of hemostasis, preventing excessive blood loss at sites of vascular injury.^{1,2} Beyond their pivotal role in hemostasis, platelets directly modulate different physiological processes such as thrombosis, angio-

genesis, cell survival, tissue regeneration, wound healing, and inflammation.^{2,3} Dysregulated platelet function has been implicated in a range of pathological conditions, including thrombotic disorders, cancer progression, fibrosis, chronic inflammation, and Alzheimer's disease.^{3,4} Moreover, platelet hyperactivity and reactivity contribute to the onset and progression of major cardiovascular diseases (CVDs), such as atherosclerosis, stroke, and myocardial infarction.^{5–9}

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Experimental and clinical data strongly indicate that dysregulated platelet activation and function are key drivers for the initiation and progression of abdominal aortic aneurysms (AAA).^{10–12} AAA is an atherosclerosis-associated vascular disease, which is predominantly characterized by an ongoing increase in the diameter of the abdominal aorta. The underlying mechanisms of AAA progression are mainly driven by a chronic inflammation within the aneurysm segment, reinforcing extracellular matrix (ECM) degradation, structural remodeling, and weakening of the aortic vessel wall. In addition, a further hallmark of AAA disease is the generation of a platelet-rich intraluminal thrombus (ILT), which occurs in 75% of all patients.^{13–17}

In this review, we first provide an overview of the role of platelets in cardiovascular disease followed by an extensive analysis of their contribution to AAA formation and progression, discussing the underlying pathophysiological mechanisms and the evidence for platelet activation and procoagulant activity as a key modulator of AAA development. Subsequently, we elaborate how platelet-derived mediators modulate inflammatory responses within the aneurysmal segment and contribute to the progressive ECM remodeling in AAA pathology. In addition, we highlight two major signaling pathways—glycoprotein (GP) VI-mediated platelet activation and the TSP-1–CD36 axis—that reinforce vascular inflammation, platelet–cell interactions, and aortic wall degeneration. Finally, we focus on the translational relevance of these findings and discuss their clinical implications for therapeutic strategies to restrict aneurysm growth and prevent aortic rupture in AAA patients.

Platelets and Their Impact in Cardiovascular Disease

Platelet Function and Physiology

Platelets are small, anucleated, discoid cells derived from megakaryocytes that circulate throughout the bloodstream and serve as central mediators of hemostasis, thrombus formation, and vascular repair. In addition to these classical hemostatic functions, platelets actively participate in cellular processes such as inflammation and tissue regeneration, highlighting their multifunctional nature.¹⁸ Platelet activation is mediated by a complex repertoire of surface receptors, which detect vascular injury and trigger intracellular signaling cascades. Following vascular injury, the GPIb–IX–V complex binds immobilized Von Willebrand factor (vWF), initiating the first contact between circulating platelets and the exposed subendothelium.¹⁹ This initial tethering enables firm platelet adhesion to the collagen bound vWF via the GPVI receptor. Subsequent GPVI activation triggers intracellular signaling cascades that amplify platelet activation, stimulate the release of second wave mediators, and induce integrin activation being important for platelet adhesion and aggregation. The platelet surface exposes various integrins, including $\alpha_{IIb}\beta_3$ (fibrinogen), $\alpha_v\beta_3$ (vitronectin), $\alpha_2\beta_1$ (collagen), $\alpha_5\beta_1$ (fibronectin), and $\alpha_6\beta_1$ (laminin), which collectively coordinate adhesion and thrombus formation. Among these, integrin $\alpha_{IIb}\beta_3$ is the most abundant receptor.

Under resting conditions this receptor remains inactive. Upon platelet activation, the receptor undergoes a conformational change and is additionally translocated from α -granules to the plasma membrane. This ‘inside-out signaling’ increases the integrin $\alpha_{IIb}\beta_3$ surface expression and ligand affinity. By the increased ligand affinity ‘outside-in signaling’ and thus ligand binding to the receptor is triggered. This promotes platelet spreading, stabilizes platelet aggregates, and supports thrombus formation. Furthermore, collagen receptors (GPVI, $\alpha_2\beta_1$) and G protein-coupled receptors such as P2Y₁, P2Y₁₂, thromboxane A₂ (TXA₂), and PAR4, amplify these signaling pathways to sustain platelet activation and coordinate adhesion and aggregation.^{20,21} Upon activation, platelets undergo actin-dependent cytoskeletal reorganization, which facilitates firm adhesion to the vascular wall, aggregation, and the release of granule contents. They secrete primarily α - and δ -granules, which contain adhesion molecules, coagulation factors, and signaling mediators, while lysosomes provide additional degradative enzymes. Granule release not only delivers bioactive molecules and is necessary for the translocation of receptors to the platelet surface, but also reinforces intracellular signaling and receptor conformational changes, further amplifying platelet recruitment and aggregation.¹⁸ During primary hemostasis, platelets rapidly adhere to exposed subendothelial matrix proteins via the GPIb–IX–V complex and GPVI to form an initial hemostatic plug, with subsequent interaction of $\alpha_{IIb}\beta_3$ and fibrinogen promoting platelet aggregation.²² In secondary hemostasis, platelet phosphatidylserine (PS) exposure facilitates thrombin generation and fibrin formation, thereby strengthening and stabilizing the growing thrombus.^{23,24} Signaling through GPVI is not only important for degranulation, calcium mobilization, and integrin activation but also for the primary pathway driving the formation of procoagulant platelets. This process involves the externalization of Fas ligand (FasL) on the platelet membrane, which binds to Fas receptor (FasR) on red blood cells (RBCs), triggering PS exposure on both platelets and RBCs, thereby promoting thrombus formation under flow conditions.^{25,26}

Platelets in Cardiovascular Disease

In the last decades, platelets, originally recognized for their central role in hemostasis and thrombosis, have emerged as key regulators in the pathogenesis of CVDs. In addition, platelets actively participate in pathological processes such as atherosclerosis, vascular inflammation, arterial thrombus formation, and myocardial infarction.^{27,28} Their ability to detect vascular injury, respond to biochemical signals, and interact with immune and vascular cells positions them as key mediators in both tissue repair and pathological vascular remodeling.^{10,12,27} In atherosclerosis, platelets contribute to all stages of plaque development. Activated platelets adhere to dysfunctional endothelium via interactions between GPIb–IX–V, P-selectin, and vWF, releasing proinflammatory mediators such as CD40L, PF4, TXA₂ and RANTES. These molecules recruit leukocytes, enhance monocyte infiltration, and promote the differentiation of macrophages into foam cells.^{5,29} Additionally, platelet-derived growth factors and cytokines stimulate vascular smooth muscle cell (VSMC)

proliferation and migration, accelerating plaque formation and progression.²⁷ During vascular inflammation, platelets also play a pivotal role, acting as effector cells connecting the innate and adaptive immune responses. By binding to the activated endothelium at sites of vascular inflammation, platelets release chemokines, cytokines, and extracellular vesicles, and thereby being able to modulate leukocyte recruitment as mentioned previously. Following, the formation of platelet–leukocyte aggregates serves as potent amplifier of inflammation.^{30,31} In the context of thrombosis, platelet activation at sites of endothelial disruption leads to rapid aggregation, mediated by the interaction of integrin $\alpha_{IIb}\beta_3$ and fibrinogen. This process not only seals the injured vessel but, when dysregulated, also contributes to pathological thrombus formation.³² In myocardial infarction, platelet adhesion and aggregation are critical early events following plaque rupture. The exposition of subendothelial collagen and tissue factor triggers platelet activation, degranulation, and aggregation, resulting in coronary artery occlusion leading to myocardial infarction. Furthermore, platelets exacerbate ischemic injury by releasing proinflammatory mediators, promoting vasoconstriction, oxidative stress, and endothelial dysfunction.^{33,34} In particular, platelet-derived molecules such as PLD1/2 and the collagen receptor GPVI have been identified as key regulators of inflammation and remodeling after myocardial infarction.^{8,9} FasL, exposed at the platelet membrane, is able to induce cell apoptosis via the extrinsic pathway of FasR activation of target cells. Moreover, platelet FasL contributes to myocardial ischemia and reperfusion injury, suggesting that platelets contribute to tissue homeostasis after acute myocardial infarction.³⁵ Taken together, platelets act as multifunctional effectors in various CVDs by connecting processes such as coagulation, inflammation, and vascular remodeling.

The Role of Platelets in Abdominal Aneurysm Formation and Progression

Pathophysiological Mechanisms of Abdominal Aortic Aneurysm Formation and Progression

The AAA pathology is mainly characterized by the progressive and irreversible dilation of the abdominal aorta. Mechanistically, a pathophysiological hallmark for AAA formation is the recruitment of proinflammatory leukocytes into the aortic wall, accompanied by the activation of proteolytic enzymes that reinforce ECM degradation, thus compromising aortic wall integrity. Beyond, the formation of a platelet-rich ILT can be observed in many AAA patients and is considered to function as a critical modulator of AAA progression by directly affecting the inflammatory response within the aneurysm segment (**–Fig. 1**).^{13,15,36} Despite intensified research throughout the last years, the underlying mechanisms by which the ILT contributes to the AAA pathology remain controversial and are still object of ongoing research.^{14,37}

The progressive and irreversible remodeling of the aortic wall in AAA is defined by profound structural alterations of the ECM, which directly attenuate the integrity of the aortic vessel wall.^{38,39} Thereby, loss of VSMCs represents a crucial

event in the remodeling process of the aortic wall, accompanied by the proteolytic degradation of essential ECM components within the tunica media (especially elastin and collagen fibers), which normally preserve aortic strength and elasticity.^{40–42} Mechanistically, this proteolytic degradation is primarily driven by a reinforced matrix metalloproteinase (MMP) activity in the aneurysmal tissue, most prominently mediated by MMP-2, MMP-9, respectively, MMP-12.^{43–46} This excessive proteolytic activity is due to a pathological imbalance between MMPs and their endogenous tissue inhibitors (TIMPs), resulting in a compromised aortic wall integrity, thus promoting aortic diameter expansion and the risk of rupture (**–Fig. 1**).^{47,48}

Chronic inflammatory responses represent a further pathological hallmark of AAA formation that is characterized by the constant infiltration of immune cells into the aortic wall tissue and the ILT.⁴⁹ Upon recruitment, these immune cells act as key amplifiers of vascular injury by releasing proinflammatory cytokines such as IL-6, TNF- α , and IL-1 β , various chemokines, and reactive oxygen species, which collectively activate inflammation-related downstream signaling pathways.^{50–52} This is paralleled by the secretion of ECM-degrading enzymes, such as MMP-2 and MMP-9, as well as elastases, thus promoting the proteolysis of ECM components such as elastin and collagen (**–Fig. 1**).^{53–55} In this context, migrated innate immune cells—including macrophages, neutrophils, natural killer cells, mast cells, and dendritic cells—and adaptive immune cells such as T and B lymphocytes have been identified within the aneurysmal tissue.⁵⁶ Thereby, especially macrophages and neutrophils have been shown to reinforce proteolytic and oxidative stress within the aneurysm.^{12,56–59} During the last years, it became apparent that the migration of neutrophils and the subsequent release of neutrophil-derived elastase and MMPs represent major contributors for the proteolytic cleavage of ECM components.^{60–62} In addition, the formation of neutrophil extracellular traps (NETs) is enhanced in both, the aortic wall and within the ILT of patients diagnosed with AAA. This enhanced NET formation directly contributes to the proinflammatory environment within the aneurysmal tissue, thus facilitating the recruitment of further immune cells into the growing aneurysm.^{63,64}

These pathophysiological mechanisms are culminating into a proinflammatory and proteolytic environment that compromises structural integrity of the aortic wall, thereby facilitating aneurysm expansion and increasing the risk of fatal rupture. However, the key role of inflammatory pathways and ILT formation in AAA pathology strongly suggests that dysregulated platelet activation is a potential driver of AAA development and progression. This is consistent with growing evidence linking platelet activity to the progression of various cardiovascular diseases.^{5,65}

Intraluminal Thrombus Formation in Abdominal Aortic Aneurysm

General Mechanisms of Intraluminal Thrombus Formation in Abdominal Aortic Aneurysm

ILT formation represents a characteristic pathological hallmark of AAA pathology and is observed in approximately 75%

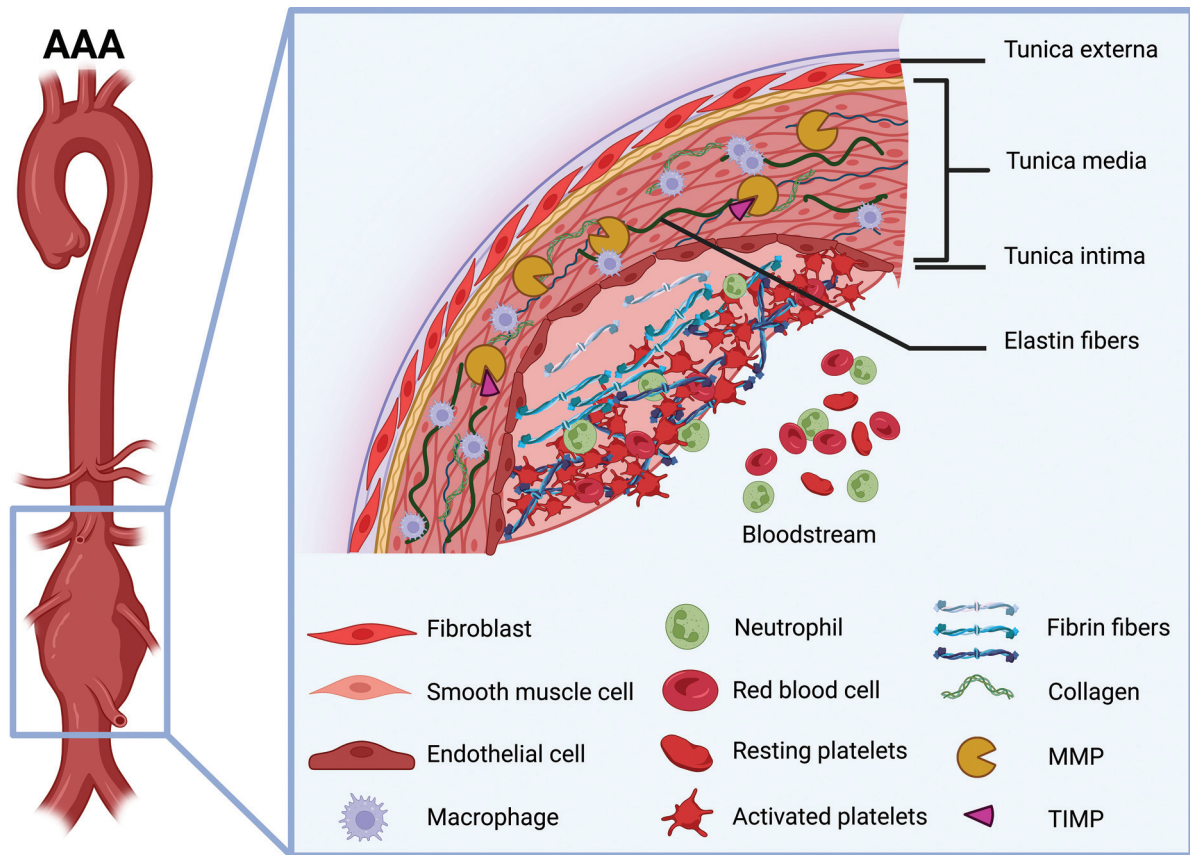


Fig. 1 Pathophysiological mechanisms of AAA formation and progression. AAA formation is primarily driven by three major pathophysiological hallmarks. First, the progressive remodeling of the aortic wall as mediated by increased MMP activity, resulting from dysregulated TIMPs. Proteolytic degradation of the ECM leads to elastin and collagen fragmentation, as well as VSMC loss, ultimately compromising aortic wall integrity. Second, chronic inflammation within the aneurysmal tissue. The recruitment of circulating inflammatory cells, including neutrophils and macrophages, to the site of aneurysm formation promotes leukocyte infiltration, which further enhances MMP activity, thus reinforcing the aortic wall degradation. Third, the formation of a platelet-rich ILT, contributing to the local inflammatory environment and promoting disease progression. AAA, abdominal aortic aneurysm; ECM, extracellular matrix; ILT, intraluminal thrombus; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of metalloproteinases; VSMC, vascular smooth muscle cells. Created with BioRender.com.

of all affected individuals.¹⁷ The ILT is a biologically active and structurally heterogeneous entity that plays a central role in the progression and the pathophysiology of AAA. Most ILTs represent a characteristic multilayered organization composed of three distinct layers, the luminal, medial, and abluminal layer, each defined by unique structural and cellular characteristics.⁶⁶ The luminal layer is in direct contact with circulating blood and contains densely cross-linked fibrin fibers infiltrated by activated platelets, RBCs, and leukocytes, thus suggesting ongoing thrombotic activity.^{67–69} The medial layer exhibits partial fibrin degradation and progressing matrix degradation, whereas the abluminal layer, adjacent to the aneurysmal wall, is largely acellular and composed of loosely organized fibrin networks.⁶⁶ A continuous canalicular network traverses all layers, facilitating the infiltration of circulating cells such as macrophages and platelets and the diffusion of macromolecules, including proteolytic enzymes, toward the aortic wall, thereby promoting wall weakening and driving AAA progression.^{66,67,70} The mechanism of vascular injury leading to ILT formation is unknown. However, the loss of elastin leads to turbulent blood flow and abnormal wall stress by elongation of the

abdominal aorta, suggesting endothelial injury followed by platelet activation and the formation of a platelet-rich plug.⁶⁶ To date, the contribution of the ILT to AAA development and progression is not known and needs further investigations in near future. While the ILT can reduce local wall stress and provides transient biomechanical protection, evidence suggests that a high ILT burden paradoxically promotes rupture at smaller diameters, indicating that its wall-weakening effects outweigh any protective benefit.⁷¹

The Role of Platelets in Intraluminal Thrombus Formation

Platelets are key mediators of ILT formation, expansion, and proteolytic activity of the ILT.^{72,73} During the early stages of ILT formation, platelet adhesion to the injured endothelium initiates thrombus development, whereas in later phases, they accumulate on pre-existing platelet layers, aggregate, and contribute to the formation of a stable ILT.^{66,68} Within the luminal layer, activated platelets release procoagulant mediators and express surface receptors such as P-selectin, which promote the recruitment of neutrophils. Upon activation, neutrophils form NETs, which entrap enzymes including proteases, elastase, and pro-oxidases. These NETs are

gradually released, amplifying local inflammation and promoting ILT expansion.^{68,70} Retrospective studies investigating the effects of anticoagulant and antiplatelet therapies in patients with AAA have demonstrated that both treatments significantly reduce ILT volume; however, they do not prevent aneurysm progression. Nevertheless, anticoagulant therapy has been associated with more favorable outcomes, whereas antiplatelet therapy has been linked to greater aneurysmal growth and an increased need for surgical intervention.⁷⁴ These findings highlight the complex and context-dependent role of platelet activity within the ILT and underline the need for further mechanistic studies to analyze the dual hemostatic and pathophysiological functions of platelets in ILT formation and in AAA progression.

Platelet Activation in Abdominal Aortic Aneurysm

To investigate the mechanisms of AAA formation and progression, and to explore potential therapeutic targets, multiple murine models have been developed. The most widely used mouse models include the porcine pancreatic elastase (PPE) and the external PPE (ePPE), as well as the angiotensin II (AngII) infusion model. Each model reflects different key features of human AAA pathology, such as ECM degeneration, inflammation, and, in selected cases, ILT formation.^{75,76} In the PPE mouse model, Wagenhäuser et al recently demonstrated dynamic alterations in platelet activation during AAA development. While at early time points (days 3 and 10), only minimal changes in platelet activation have been observed, a significantly increase in P-selectin exposure, integrin $\alpha_{IIb}\beta_3$ activation, and procoagulant activity was detected at late stage (by day 28), particularly following GPVI stimulation. Importantly, procoagulant activity—as detected by PS exposure at the platelet surface—correlated with the aneurysm diameter, supporting its potential role in disease progression. Moreover, elevated levels of platelet–neutrophil aggregates at early stages suggest a contribution of platelet-mediated inflammatory responses to AAA pathophysiology.¹² In contrast to enhanced platelet activation observed in PPE mice, mice undergoing the AngII model exhibited decreased platelet activation, as presented by reduced P-selectin exposure and integrin $\alpha_{IIb}\beta_3$ activation following agonist stimulation at early time points. There were no significant differences detected during later stages of aneurysm development. Nevertheless, platelet depletion in both models showed reduced aneurysm progression one week after induction of experimental AAA supporting the crucial role of platelets in the pathogenesis of aneurysm formation.¹² Furthermore, Owens et al demonstrated that platelet inhibition provides protection against rupture in established AAAs in AngII-infused mice.⁷⁷ In the ePPE mouse model, only a dose-dependent increase in platelet degranulation in response to thrombin stimulation has been reported to date.⁷⁸ Beyond this observation, no further data on platelet activation or function in the ePPE model are available, highlighting the need for additional studies to analyze platelet-mediated mechanisms in experimental AAA. In general, a comprehensive investigation of platelet activation across different experimental mouse models of AAA is crucial for the

understanding of pathophysiological mechanisms in AAA to evaluate the translational relevance. In AAA patients, Wagenhäuser et al recently reported that platelets display a preactivated phenotype and increased sensitivity to agonist-induced platelet activation. This hyperreactivity of platelets is accompanied by reduced platelet counts. Immunohistological analysis further revealed that platelets accumulate within both, the ILT and the aortic wall, where they colocalize with the proinflammatory protein osteopontin (OPN), and different cells such as macrophages and fibroblasts. These spatial interactions point to a central role of platelets in mediating cellular crosstalk and maintaining local inflammation.¹² The clinical relevance of platelet activation in AAA is further supported by different studies demonstrating that patients with AAA exhibit lower platelet counts and higher mean platelet volume compared with healthy individuals. Recently, Feige et al published elevated plasma levels of soluble GPVI in patients with AAA, whereas the surface expression of GPVI on circulating platelets remained unchanged. Furthermore, fibrin, a key ligand of GPVI, was found to be increased systemically and within the ILT of AAA patients compared with arterial thrombi from other vascular pathologies.¹⁰ These results suggest enhanced platelet activation and turnover, as further evidenced by increased levels of soluble P-selectin in the plasma.¹¹ In contrast, Benson et al reported increased surface expression of GPVI on platelets from AAA patients. These contrary findings may be explained by variations in hemodynamic conditions such as shear stress across the patient cohorts analyzed in different respective studies.⁷⁹ Moreover, in 2022, transcriptomic profiling of platelets from AAA patients revealed upregulation of a signal transduction pathway shared with olfactory receptors, along with increased surface expression of the olfactory receptor OR2L13 at the platelet surface. These findings indicate that the olfactory receptor signaling modulates platelet activation and contributes to aneurysm progression.⁷⁸

Impact of Platelets on Inflammatory Responses in Abdominal Aortic Aneurysm Pathology

Recently, Wagenhäuser et al analyzed the contribution of platelets in inflammatory processes in AAA. Using the PPE mouse model, they demonstrated that platelet depletion markedly attenuated aneurysm development. This effect is accompanied by reduced recruitment of platelets and macrophages into the aneurysmal wall, indicating a potential role of platelets in modulating the inflammatory response during experimental AAA. In line, transcriptomic analyses of AAA tissue samples revealed an early downregulation of key inflammatory genes in platelet-depleted mice including *Il-1B*, *Il-6*, *Il-8*, *Il-10*, and *Il-12B*, underlining their role as regulators of cytokine-mediated pathways in vascular inflammation.¹² Consistent with these changes, the proinflammatory mediator OPN (*Spp1*) was significantly downregulated in both, aortic tissue and plasma of platelet-depleted mice. In the context of AAA, reduced OPN levels have been associated with decreased infiltration of macrophages and other immune cells as well as downregulation of

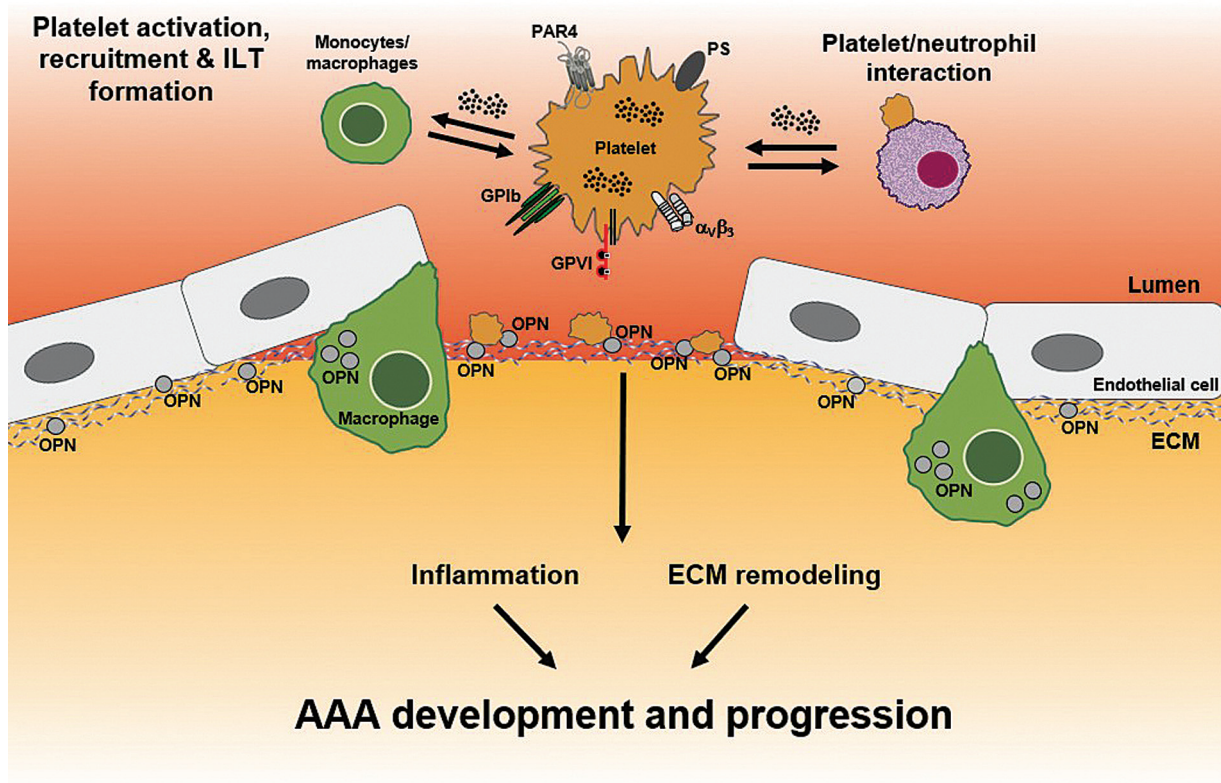


Fig. 2 The role of platelets in AAA formation and progression. Platelets play a pivotal role in AAA progression by modulating inflammatory responses and the degradation of the ECM. Thereby, platelets induce the upregulation of *SPP1* (osteopontin, OPN) gene expression in macrophages and aortic tissue, thus driving inflammation and vascular remodeling, as well as facilitating platelet adhesion and migration into the abdominal aortic wall and the ILT. Moreover, increased platelet activation and procoagulant activity are associated with elevated expression of various cytokines, *MMP9*, and *COL1A1* in macrophages, and of *IL-6* and *MMP9* in fibroblasts. AAA, abdominal aortic aneurysm; ECM, extracellular matrix; IL, interleukin; MMP, matrix metalloproteinase; OPN, osteopontin. Reproduced from Wagenhäuser et al 2024.¹²

matrix-degrading enzymes such as MMPs (→ Fig. 2).¹² Similarly, in the AngII mouse model of AAA, Liu et al showed that inhibition of platelets with clopidogrel markedly reduced inflammation represented by decreased macrophage infiltration and inflammatory cytokine expression.⁸⁰ Mechanistically, Wagenhäuser et al provided evidence for a direct contribution of platelets to AAA progression through paracrine interactions with vascular and immune cells. Platelet releasates from ADP- or GPVI-activated platelets induce proinflammatory (*IL-6*, *IL-12B*, *IL-1B*, *SPP1*) gene expression in macrophages, supporting a platelet-macrophage crosstalk that drives aneurysm initiation and growth. Taken together, these findings highlight a central role of platelets in coordinating inflammation, and cellular crosstalk that supports AAA progression.¹²

Platelets and Their Role in Extracellular Matrix Remodeling

Beyond platelet-induced inflammatory responses in AAA, platelets also contribute to ECM remodeling within the aneurysmal wall. Using the PPE mouse model, Wagenhäuser et al found that platelet depletion markedly decreased structural degeneration in the experimental AAA mouse model, as evidenced by reduced intima-media thickness and elastin fragmentation. These morphological changes

were accompanied by reduced expression of ECM-related genes, including *Mmp9* and *Col1a1*. Since MMP9 is known as one of the major enzymes responsible for elastin degradation, and collagen I is a key structural component ensuring the mechanical stability of the aortic wall, the reduced expression of these genes strongly suggests that platelets play a critical role in ECM remodeling and vessel wall destabilization in AAA. In vitro, platelet releasates stimulate *IL-6* and *MMP9* expression in aortic fibroblasts, thereby amplifying monocyte recruitment and ECM remodeling (→ Fig. 2).¹² Consistent with these findings, Liu et al demonstrated that platelet inhibition with clopidogrel significantly suppressed elastic lamina degradation and MMP production, thereby attenuating ECM remodeling using the AngII-infused mouse model of AAA.⁸⁰

Furthermore, platelets not only induce the upregulation of OPN in macrophages, the primary cellular source for OPN, but also adhere under flow conditions to both, full-length and cleaved OPN via the integrin $\alpha_v\beta_3$ receptor. These observations provide first evidence for a role of OPN in recruiting platelets to the aortic wall and the ILT in AAA. This indicates a self-perpetuating loop, in which platelet-mediated upregulation of OPN in plasma and the vascular wall promotes further platelet migration into the aortic tissue, thereby amplifying AAA pathophysiology.¹²

Procoagulant Activity as Key Driver of Abdominal Aortic Aneurysm Progression

Platelet activation, followed by thrombin generation and coagulation, are essential for the formation of stable arterial thrombi. Platelets play a central role in these processes by providing a procoagulant surface through the externalization of PS, which facilitates the assembly of coagulation complexes on their plasma membrane.⁸¹ Recently, increased platelet reactivity accompanied with elevated procoagulant activity was shown in AAA patients and PPE-operated mice. In detail, at early time points (day 3 and day 10) post-PPE surgery, PS exposure at the surface of platelets was unaltered, while at day 28 procoagulant activity was significantly increased compared with sham-operated controls. Determination of the Spearman's correlation coefficients between aneurysm diameter and annexin V-binding to platelets in PPE mice revealed a strong correlation between aortic diameter enlargement and increased procoagulant activity, highlighting the contribution of platelet PS exposure to the pathogenesis of AAA. In line with the results from experimentally induced AAA formation, increased procoagulant activity of platelets in AAA patient was detected. In combination with platelet hyperactivity and reactivity, this may lead to the prothrombotic phenotype in AAA patients.¹²

In addition to PS exposure at the platelet surface, recent evidence indicates that mature RBCs are able to externalize PS on their membrane, thereby facilitating the assembly of the prothrombinase complex and contributing to thrombin generation.^{82–84} Moreover, Krott et al demonstrated that platelet–RBC interactions include CD36 and TSP-1-mediated signaling, which is important for the externalization of PS at the RBC and platelet membrane. This points to a direct contribution of RBCs and platelets in thrombin generation and ILT formation in thrombosis and AAA.⁸⁵

Glycoprotein VI–Mediated Platelet Activation Promotes Inflammation and Aortic Wall Remodeling in Abdominal Aortic Aneurysm

GPVI represents the main platelet collagen receptor and is a central regulator of thrombus formation at sites of vascular injury. Apart from this, GPVI orchestrates key thromboinflammatory processes underlying CVDs. Thereby, elevated GPVI expression in patients with acute coronary syndromes has been linked to an enhanced thrombotic risk, underscoring the potential of GPVI as a biomarker for patient risk stratification in other atherosclerosis-related diseases such as myocardial infarction or ischemic stroke.^{86–89} Therefore, GPVI represents a promising therapeutic target, as selective inhibition may attenuate thrombus formation and thromboinflammatory effects without impairing hemostasis. Notably, pharmacological targeting of GPVI signaling via glenzocimab or revacept demonstrated beneficial effects for ischemic stroke and symptomatic carotid stenosis in phase II clinical trials, highlighting the translational potential of GPVI targeting as an antithrombotic strategy for different CVDs.^{87,90,91}

In AAA, first mechanistical evidence for platelets to directly contribute to AAA formation and progression by GPVI signaling has been identified in experimental studies.^{10,79} Genetically induced GPVI deficiency offered protection against aneurysm formation and progression in two different mouse models of experimental AAA (the PPE and ePPE mouse model). Mechanistically, the absence of GPVI resulted in an improved aortic wall remodeling, cumulating in an attenuated degradation of aortic wall components, and thus preserving aortic wall integrity. In detail, loss of GPVI leads to reduced levels of circulating MMP-2 and MMP-9, resulting in less elastin fragmentation within the aortic vessel wall. This was accompanied by significantly reduced apoptosis of VSMCs. Consequently, GPVI-deficient mice revealed a significantly lower incidence of experimentally induced aneurysm formation (–Fig. 3).¹⁰

However, platelet GPVI has not only emerged as a key modulator of vascular integrity but also to promote different inflammatory responses, including the recruitment and activation of leukocytes to sites of vascular inflammation.⁹² In AAA, it was demonstrated for the first time that platelet GPVI directly facilitates vascular inflammation at sites of aneurysm formation by fostering neutrophil activation, migration, as well as NET formation in mice (–Fig. 3).¹⁰ These findings are supported by Burkard et al who reported that GPVI critically mediates neutrophil activation, driving their recruitment and promoting NET formation in a model for acute lung injury, highlighting the relevance of GPVI signaling for neutrophil-mediated inflammatory responses in disease.⁹³

The Thrombospondin-1–CD36 Axis Promotes Abdominal Aortic Aneurysm Formation by Mediating Platelet–Red Blood Cell Crosstalk

The thrombospondin-1 (TSP-1)–CD36 axis has recently been identified as a key mediator of platelet–RBC interactions that plays a role in arterial thrombosis but also contributes to AAA formation and progression. TSP-1 is a multifunctional matricellular GP released from α -granules upon platelet activation. Beyond its autocrine effects on platelets by enforcing the recruitment of further platelets into the growing thrombus, platelet-derived TSP-1 interacts with other cells including RBCs by binding to CD36.^{85,94–97} Mechanistically, TSP-1–CD36-mediated platelet–RBC interactions reinforce PS exposure on both cell types, support local thrombin generation, and thus foster AAA formation. Krott et al demonstrated that the genetic loss of either TSP-1 or the erythroid CD36 receptor provides protection against experimentally induced aneurysm formation (PPE and ePPE mouse model). In detail, genetic deletion of TSP-1 markedly attenuated aortic diameter expansion, accompanied by reduced platelet activation, as indicated by lower integrin $\alpha_{IIb}\beta_3$ activity and diminished procoagulant activity of platelets. Similarly, CD36 deficiency restricted to RBCs displayed a protective effect as well. In contrast, platelet-specific CD36 deficiency did not influence aneurysm

Impact of platelet GPVI on inflammation and aortic wall remodelling in AAA formation and progression

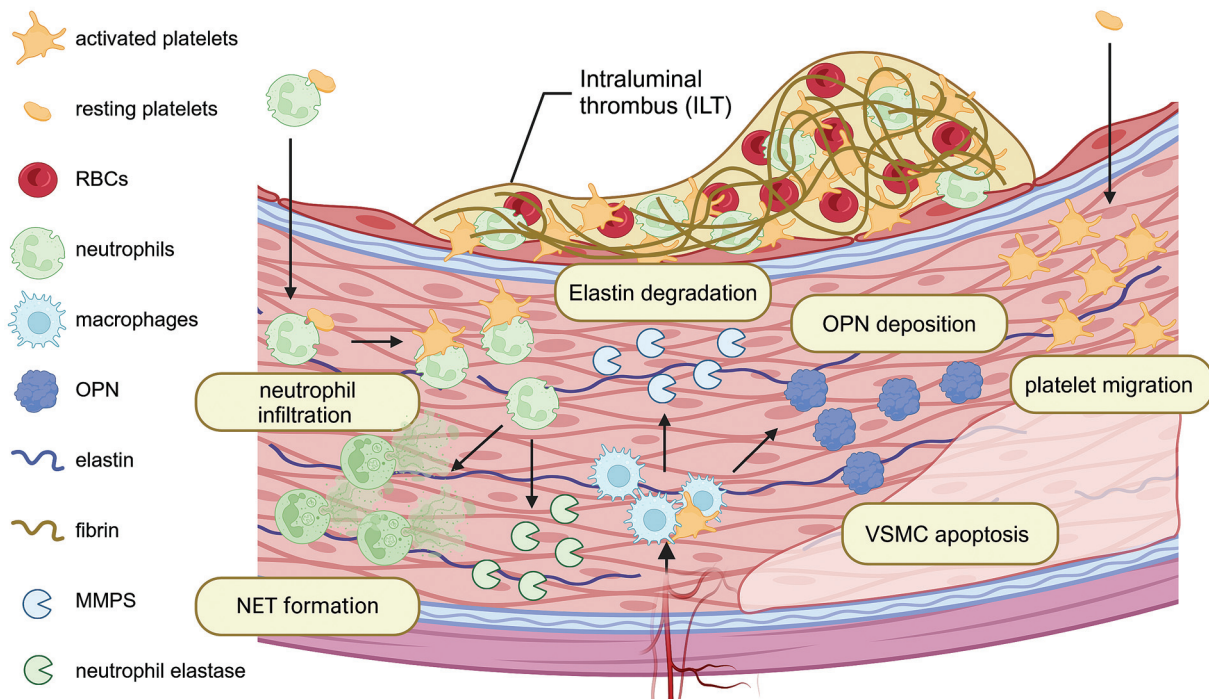


Fig. 3 Impact of platelet GPVI in inflammation and aortic wall remodeling in AAA formation and progression. GPVI contributes to the AAA pathophysiology by modulation of neutrophil and platelet migration into the aortic wall in early AAA formation. In addition, GPVI promotes elastin fragmentation, as well as VSMC apoptosis within the aortic media, contributing to aortic wall remodeling and progressive abdominal aortic expansion. Moreover, deposition of the inflammation and remodelling associated cytokine OPN is elevated in a GPVI dependent manner. AAA, abdominal aortic aneurysm; ECM, extracellular matrix; MMP, matrix metalloproteinase; OPN, osteopontin; RBC, red blood cell; VSMC, vascular smooth muscle cells. Reproduced from Feige et al 2024.¹⁰

progression, highlighting the predominant contribution of erythroid CD36 in mediating these pathological processes.⁸⁵ Additionally, TSP-1 also critically regulates the migration and adhesion of mononuclear cells in experimentally induced AAA, thereby promoting vascular inflammation during AAA progression.⁹⁸ Moreover, myeloid-derived TSP-1 promotes aneurysm development by suppressing TIMP-1, linking immune cell-mediated inflammation to ECM remodeling in both, AAA patients and mice.⁹⁹

In patients with AAA, a novel mechanism by which platelet–RBC interactions induce procoagulant activity through the release of TSP-1 from platelets was identified. Thereby, TSP-1 binds to platelets (autocrine) and RBCs (paracrine) via CD36. Flow cytometric analyses revealed elevated surface expression of the scavenger receptor CD36 in AAA and increased binding of platelet-released TSP-1 to platelets and RBCs. Moreover, plasma concentrations of soluble CD36 and TSP-1 were significantly higher in AAA patients. The plasma concentrations of soluble CD36 were positively correlated with the increased aneurysm diameter, suggesting shear stress-induced activation and elevated activity of the CD36–TSP-1 axis in AAA pathology.⁸⁵ Histological analysis further demonstrated accumulation of platelets, RBCs, and TSP-1 within the aortic wall and the ILT of AAA patients. Under turbulent flow conditions inside the

aneurysm, platelets displayed increased activation and degranulation, as well as platelet–RBC aggregate formation, further reinforcing a prothrombotic microenvironment in AAA patients. The accumulation of platelets, RBCs, and TSP-1 in the ILT and the aortic wall of AAA patients together with elevated surface expression of CD36 suggest active recruitment of platelet–RBC aggregates into the growing ILT via the CD36–TSP-1 axis.

Taken together, these findings identify the TSP-1–CD36 pathway as a key mediator of a thromboinflammatory platelet–RBC crosstalk driving AAA progression, thus highlighting this mechanistic pathway as a potential therapeutic target for the treatment of AAA patients.⁸⁵

Translational Relevance and Clinical Implications

Targeting Platelet Activation in Abdominal Aortic Aneurysm: Current Knowledge

Experimental studies in animal models have demonstrated that antiplatelet drugs significantly attenuate AAA formation and growth. The integrin $\alpha_{IIb}\beta_3$ inhibitor Abciximab has been shown to attenuate thrombus area and to prevent aortic enlargement in a rat xenograft model of aneurysm formation.¹⁰⁰ Clopidogrel, which irreversibly inhibits the ADP

receptor P2Y₁₂, reduced AAA progression and rupture in mice as shown by reduced aortic diameter expansion, leukocyte infiltration, MMP9 expression, and elastic fiber degradation.⁸⁰ Thus, experimental data strongly suggest that platelet activation is a key element in AAA formation and progression. Antiplatelet therapy, particularly low-dose aspirin (ASA), is routinely prescribed in AAA patients as secondary prevention against thrombotic complications. However, in AAA patients, no consistent results have been shown clinically to date. Thompson and colleagues analyzed drug modulation of AAA and found that ASA therapy has no impact on aneurysm growth in patients.¹⁰¹ In contrast, small clinical trials demonstrated that platelet activation contributes to AAA development and progression, because antiplatelet medication with low-dose ASA has been beneficial for patients with small size aneurysms as indicated by decreased aneurysm size.¹⁰² In another patient study, the impact of ASA therapy on the progression of thoracic and AAA revealed that the effectiveness of aspirin varies by sex and potentially by aneurysm size.¹⁰³ Interestingly, nationwide inpatient sample data for 3.8 million patients over 7 years identified antiplatelet drugs as an independent predictor of protection from AAA, aortic dissection, and aortic rupture by multivariate regression.¹⁰⁴ This is in line with a retrospective single-center cohort study with 3,435 patients, providing evidence for ASA to be associated with slower progression of AAA.¹⁰⁵ Other clinical trials indicate that antiplatelet agents may have no efficacy or even increase the risk of bleeding.¹¹ These divergent results suggest that potential benefits may occur in selected patient groups. This is also true for the treatment of AAA patients with an ADP receptor blocker. While one clinical trial found reduced rupture and dissection in AAA patients treated with P2Y₁₂ blocker or ASA,⁷⁷ no reduction in the growth of small AAA has been detected in patients treated with ticagrelor.¹⁰⁶

In summary, although evidence regarding the efficacy of antiplatelet therapy in human AAA progression remains unclear, results from clinical trials and molecular studies highlight the multifaceted role of platelets in AAA pathophysiology, suggesting that further evaluation of antiplatelet therapy and its benefit for AAA patients are needed. This complex disease may require precision medicine approaches using different patient subgroups, differentiated by sex and aneurysm size and growth rate.

Therapeutic Potential of Glycoprotein VI as Novel Antiplatelet Therapy in Abdominal Aortic Aneurysm

As no pharmacological treatment for AAA has been implemented in clinical practice to date, preclinical evaluation of novel potent therapeutic targets that effectively attenuate aneurysm growth remains of great importance.^{66,107} Recently, different translational approaches targeting GPVI in mice reported beneficial effects on aortic diameter progression upon intervention with anti-GPVI antibodies.^{10,79} Thereby, preventive treatment with a GPVI-blocking antibody (Fab Y020347) of mice that underwent experimental AAA using the ePPE mouse model revealed an attenuated aneurysm growth.¹⁰ In addition, Benson et al demonstrated that

therapeutic treatment with the GPVI-neutralizing antibody JAQ1 was capable to significantly reduce aneurysm growth in mice that already exhibited an established AAA (experimental mouse models of AngII and ePPE) prior to the intervention.⁷⁹ These data indicate that targeting GPVI-signaling sufficiently reduces aneurysm growth in different preclinical settings. Therefore, GPVI represents a promising target for the development of novel antiplatelet therapies to effectively attenuate AAA progression, thus preventing patients from fatal aortic rupture and death. This is strengthened by the fact that different GPVI targeting drugs such as glenzocimab (ACT017) or revacept showed beneficial effects in patients with different CVDs such as stroke or symptomatic carotid stenosis as investigated in different clinical trials.^{90,91,108}

Beside its potential for antiplatelet therapy, GPVI might be beneficial as biomarker in AAA because soluble GPVI is upregulated in the plasma of AAA patients and predicts AAA growth rate.^{10,79}

Conclusion and Future Directions

Platelet activation including procoagulant activity represents a major contributor to vascular wall inflammation and ECM remodeling in AAA formation and progression. Increasing evidence indicates that platelet-specific signaling cascades, particularly those mediated via GPVI and the TSP-1-CD36 axis, constitute central components of the pathological axis driving aneurysm formation and progression. These signaling pathways orchestrate complex interactions between platelets and inflammatory mediators, thereby promoting proteolytic degradation, and aortic wall weakening. Consequently, targeting platelet activation and function—either by inhibition of GPVI, respectively TSP-1-mediated signaling or by other antiplatelet therapies—emerges as a promising therapeutic approach to attenuate AAA growth and reduce the risk of aortic rupture in patients.

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Conflict of Interest

The author declare that they have no conflict of interest.

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