Journal of
Clinical & Medical Surgery

www.jclinmedsurgery.com

ISSN 2833-5465
Open Access
Volume 5

Review Article

Platelet-neutrophil aggregates: Perspectives for the treatment of postsurgical hemostatic disorders

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Article Information

Received: Apr 22, 2025
Accepted: May 21, 2025
Published: May 28, 2025
Archived: www.jclinmedsurgery.com

Abstract

Pathological interplay between inflammation and thrombosis, induced by surgery, triggers abnormal procoagulant and proinflammatory responses. This dynamic crosstalk leads to the formation of platelet-neutrophil aggregates, which act as mobile thrombotic platforms, obstructing microvascular blood flow, causing tissue damage, and exacerbating inflammation during or shortly after surgical procedures. Surgical intervention causes rapidly accumulation of neutrophils at sites of local inflammation, inducing and amplifying platelet activation (and vice-verse). This uncontrolled cascade of clotting and inflammation irreversibly disrupts hemostatic balance, contributing to wide spectrum of postsurgical complications. Identifying novel therapeutic targets to mitigate platelet-dependent adverse effects and improve hemostatic outcomes remains a critical challenge. This review focuses on the characterization of platelet-neutrophil aggregates as potential therapeutic targets for managing and preventing hemostatic imbalance. Furthermore, exploring the regulatory mechanisms underlying neutrophil interactions with aggregating and procoagulant platelets may streamline the search for effective inhibitors to block platelet-neutrophil aggregation, offering promising avenues for therapeutic intervention.

Keywords: Platelet-neutrophil aggregates; Postsurgical hemostatic disorders; Platelet subpopulations; Therapeutic molecular targets.

Introduction

Surgery is known to be a major risk factor for thromboembolic complications, including acute atherothrombotic events, deep vein Thrombosis (VTE) and pulmonary embolism as a main cause of postoperative morbidity and mortality. Surgical tissue injury may also induce local and systemic inflammatory responses, which may give rise to immunothrombosis or/and thromboinflammation [1,2]. To prevent life-threatening disorders, current postoperative therapy usually includes anticoagulant and antiaggregant drugs. Heparins and direct inhibitors of factors Xa and IIa (thrombin) are commonly used to avoid hypercoagulability, while platelet inhibitors such as aspirin, $P2Y_{12}$ inhibitors, Glycoprotein (GP) IIb/IIIa inhibitors may be added to prevent excessive platelet aggregation. Despite the wide range of anticoagulant and antiplatelet agents, their use to date remains associated with bleeding risks or thromboinflammation. Besides, antithrombotic therapy is not always successful depending on the type of surgery [3] and even can provoke thrombotic complications (which are known as paradoxical thrombosis). As an example, the most well-known manifestation of this phenomenon is Heparin-Induced Thrombocytopenia (HIT), a complex of side effects (from hypercoagulable state to thrombocytopenia) caused by therapeutic doses of unfractionated or low molecular weight heparins which occurs in about 5% of surgical heparin-treated patients [4]. Even the combination of heparins with non-heparin potent anticoagulants (argatroban or lepirudin) did not always mitigate the devastating clinical outcomes in patients with HIT [5]. The pathogenesis of HIT is known to be mediated by IgG autoantibodies that recognize complexes formed by Platelet Factor 4 (PF4) and heparin.

Citation: Patalakh I, Drobotko T, Tykhomyrov A. Platelet-neutrophil aggregates: Perspectives for the treatment of postsurgical hemostatic disorders. J Clin Med Surgery. 2025; 5(1): 1192.

These autoimmune complexes are able to activate platelets, monocytes, neutrophils and endotheliocytes through FcγRIIa receptors [6,7], resulting in mutual interaction of platelets and leukocytes. Besides HIT, platelet-leukocyte interaction is an important pathogenetic event for many other inflammatory-related diseases, such as atherothrombosis, atherosclerosis, stroke, deep vein thrombosis, heart failure, sepsis, transfusion-related acute lung injury [7]. Humoral factors and proteins released into the blood during surgical tissue damage, rapidly activate blood leukocytes and platelets and attract them to the site of injury. Together with cells of the damaged endothelium, leukocytes and platelets contribute to the pathogenesis of thrombosis. Moreover, for HIT, VTE and arterial thrombosis, activated neutrophils and monocytes (rather than platelets) have been shown to be the main triggers of pathogenic events [8]. As the most abundant leukocyte subset, activated neutrophils considerably recruit platelets from the circulation via adhesion molecules expressed in response to stimulation by inflammatory cytokines. The initial interaction of platelets and neutrophils facilitates their reciprocal activation, which in turn enhances the expression of adhesion receptors and promotes the formation of Platelet-Neutrophil Aggregates (PNA). PNA can act as mobile platforms for thrombi generation, obstructing blood flow in the microvasculature, leading to tissue damage and escalation of inflammation. Thus, PNA triggers thromboinflammatory reactions that can worsen the patient's post-surgical condition.

The platelet homo-and heteroaggregates appears to serve as an important interface where postoperative inflammation as an immune response to surgical trauma is rapidly complemented by a hemostatic response. Apparently, the established ideas about platelets as a key regulator of hemostatic balance have led to many years of attempts to obtain an effective antiplatelet drug that combines anticoagulant, antiaggregant and anti-inflammatory effects. As regrettably noted in [9], huge investments in the development of new effective drugs for the treatment of thromboinflammatory complications have not yet produced the desired effect. However, although the current results are not very successful, they allow us to adjust the further direction of research. Inhibition of intercellular contacts in the PNA may be explored as an alternative approach to the prevention of postoperative thrombosis and possible reduction of the risk of hemorrhagic complications. This review discusses recent data on platelet-mediated neutrophil binding, which may be a promising target for novel drugs that can prevent thromboinflammation and treat thrombosis without compromising hemostasis.

Inappropriate interplay of the immune and hemostatic systems

Both hemostasis and inflammation are evolutionarily developed, dynamically balanced mechanisms of protection and restoration of the body's health. Their dysregulation can cause thromboinflammation. Any disruption of tissue integrity triggers reactions of inflammation, coagulation and the formation of platelet microthrombi. Thromboinflammation is a pathological condition in which inflammation and thrombosis influence one another, triggering abnormal pro-coagulant and pro-inflammatory events. For clarity, this can be illustrated with a diagram that helps to imagine how the physiological interaction between coagulation and immunity is enhanced, which can lead to serious pathologies of hemostasis or sepsis (Figure 1). This bidirectional positive feedback is due in part to cell-cell interaction between platelets, which are responsible for thrombosis, and leukocytes, which regulate inflammation [10-12]. Appearing in the systemic circulation, platelet-leukocyte aggregates can act as mobile platforms for thrombi generation that may obstruct blood flow in the microvasculature, leading to tissue damage and escalation of inflammation. The interaction of platelets with neutrophils leads not only to physical binding, but also modulates the cellular immunological functions of neutrophils through subsequent integrin-mediated outside-in signaling, stimulating the release of chemokines, NETs and ROS by activated neutrophils [13,14]. The uncontrolled amplification of clotting/inflammation irreversibly shifts the hemostatic balance, contributing to the development of coagulopathy/gypercoagulation, thrombocytopenia, thrombosis, systemic inflammation and multiple organ failure [13,15].

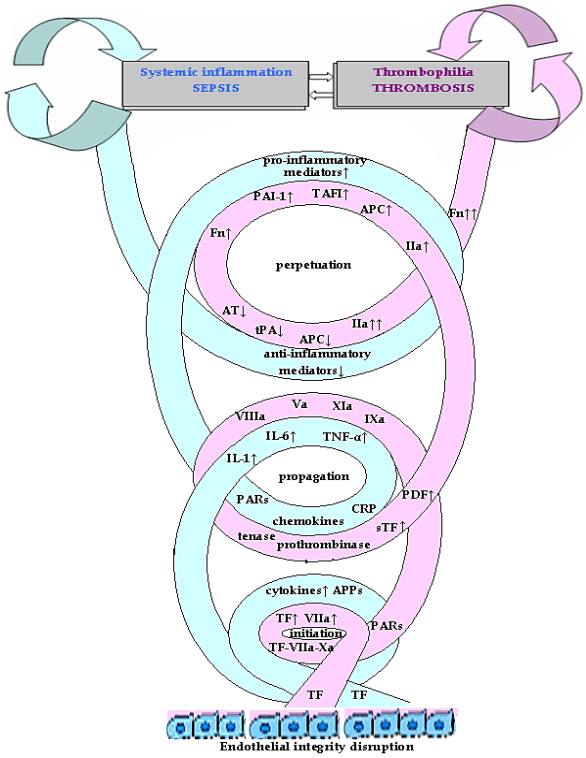

Figure 1: A simplified hypothetic model of pathophysiological interactions between inflammatory and hemostatic systems. Each spiral turn represents a potentially vicious cycle driven by excessive concentrations of some proteins (this is shown as arrows up) and/or insufficient concentrations of other proteins (as arrows down). Amplified activation of plasma hemostatic proteins in the initiation phase is achieved through interaction with components of the innate immune system, which in turn prolongs inflammation in the propagation phase. As a result, both processes, coagulation and inflammation, can come into perpetuation phase. These complex and reciprocal interactions can lead to life-threatening complications, such as thrombosis or sepsis.
Abbreviations: IIa, VIIa, IXa, Xa, and XIa indicate activated coagulation factors; Va and VIIIa – non enzymatic cofactors; Fn: Fibrin; TF: Tissue Factor; sTF: blood-borne (soluble) forms of Tissue Factor; PARs: Protease-Activated Receptors; IL: Interleukin; CRP: C-Reactive Protein; TNFα: Tumor Necrosis Factor Alpha; t-PA: Tissue Activator of Plasminogen; APC: Activated Protein C; AT: Antithrombin; PAI-1: Plasminogen Activator Inhibitor of Type 1; TAFI: Thrombin Activable Fibrinolytic Inhibitor. Copied with minor changes from [12].

Platelet-neutrophil interaction

Platelets are traditionally considered as to be cells dedicated to maintaining hemostasis and preventing traumatic blood loss. Indeed, activated platelets effectively enhance the coagulation cascade by supporting thrombin production and fibrin polymerization, and they also make physical contacts with other platelets, associating into homotypic aggregates to seal damaged endothelium. By now, there is accumulating evidence on the important role of platelets in the regulation of inflammation and immune response, in particular through interaction with leukocytes. As is known, platelets are capable of interacting with various groups of leukocytes, expressing various adhesion molecules. In particular, neutrophils, rapidly accumulating in areas of local inflammation, can cause and enhance platelet activation (Figure 2).

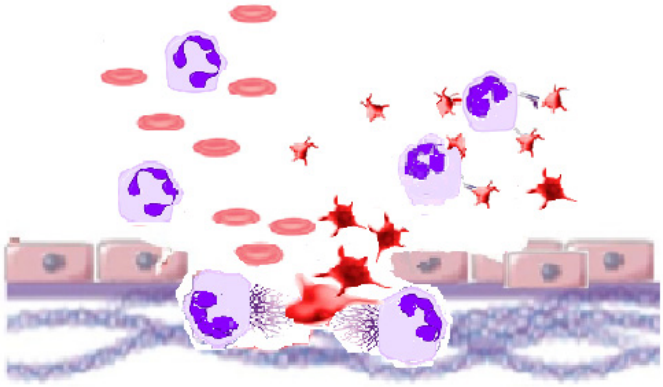

Figure 2: Endothelial injury triggers the release of proinflammatory and procoagulant molecules, which initially causes platelet activation and neutrophil priming. By attaching to the endothelium, activated platelets attract primed neutrophils, which become activated, can induce and amplify platelet activation. Upon mutual activation, platelets and neutrophils interact through adhesion molecules and soluble mediators and thereby form PNA. Adapted from [16].

Platelets participate in inflammatory processes via receptors and signaling pathways distinct from those involved in aggregation and procoagulant function. The molecular connectors used for physical linkage between platelets and neutrophils to form PNA are also distinct from those involved in platelet-platelet aggregation. This may explain why classical antiplatelet drugs have been insufficiently effective against thromboinflammation.

There are several mechanisms by which the platelet and neutrophil may directly and indirectly interact. Neutrophils upon contact with activated platelets express Mac-1 (CD11b/CD18), which is of particular importance for leukocyte-platelet aggregation. Mac-1 is a direct binding ligand for the platelet surface adhesion molecule GPIbα and also indirectly binds to the platelet receptor GPIIbIIIa (integrin $\alpha_{IIb}\beta_3$) via a fibrinogen bridge [17]. Activated platelets can directly modulate leukocyte activation, by expressing P-selectin. Among other, P-selectin (CD62P) and Platelet-Activating Factor (PAF) allow activated platelets to bind to activated leukocytes, enhancing intracellular signals and inducing expression of P-selectin/PAF receptors [18]. Remarkably, platelets synthesize PAF only when exposed to strong agonists such as thrombin and collagen [19].

P-selectin is an adhesion protein which is stored in α-granules of resting platelets. When activated, platelets translocate P-selectin to the plasma membrane where it becomes available for interaction with its binding partner, e.g., PSGL-1 (also known as CD162), on neutrophils and monocytes. The interaction between platelet-bound CD62P and neutrophil PSGL1 provides the main contact for their physical binding, which is necessary to initiate the first interaction between platelets and neutrophils [14,20]. P-selectin-neutrophil PSGL-1 interaction promotes NETosis [21] which plays a significant role in thrombosis and hemostasis. PSGL-1 is also present on platelets, even though expressed 25- to 100-fold lower than on leukocytes [22]. Pharmacological blockade of CD62P or PSGL-1 was shown to suppress PNA and thromboinflammatory reactions, but can induce bleeding [23] Platelet P-selectin can also interact with its another ligand, platelet GPIb [21,22]. Additionally, PAF and P-selectin can participate in platelets recruitment promoting activation and aggregation of adjacent platelets [24,25]. Under physiological conditions, both, PAF and P-selectin promote platelet-neutrophil interaction during initiation of the innate inflammatory response and neutrophil extravasation [13]. However, PAF levels can increase due to extended periods of immune activation during the pathogenesis of numerous inflammatory processes including atherogenesis, asthma allergic, inflammatory skin, and multiple sclerosis [26]. Such dysregulated response to infection, accompanied by excessive platelet-leukocyte or platelet-platelet aggregation, triggers abnormal pro-coagulant and pro-inflammatory host responses. In this context, targeting the molecular players, that limit platelet–neutrophil interactions, might be an attractive therapeutic strategy supporting hemostatic balance and limiting inflammation.

In addition to their key role in hemostasis and thrombosis, platelets have been shown to play an important role in regulating the immune response. In particular, the platelet FcγRIIA receptor, in addition to heparin-induced thrombocytopenia and participation in the body's antimicrobial defense, has been found to be an important player in crosstalk with other immune cells [27]. Although the primary function of FcγRIIA is to recognize and immobilize immune complexes, it appears to be involved in hemostasis by amplifying aIIbb3-dependent outside-in signaling [27]. Two platelet chemokine receptors, CXCR4 and CXCR7, can mediate inflammatory signals and stimulate the expression of adhesion molecules on platelets during acute inflammation. Interestingly, inhibition of these platelet receptors suppressed PNC formation and diminished NETosis in the blood [28].

Platelet subpopulations

Recent findings on platelet heterogeneity may provide new ways to prevent and treat thromboinflammatory conditions. Heterogeneity refers to the division of platelets into subpopulations based on phenotypic diversity and functional specialization, which is primarily determined by the strength of the thromboinflammatory signal. It is now believed that at least 3 platelet subpopulations with different phenotypes can be differentiated due to their structural and functional heterogeneity [29]. The heterogeneity of the platelet population is easy to distinguish by comparing the platelets located inside the thrombus and on its periphery during its maturation. Platelets trapped in a thrombus differ in morphology, size, packing density, and the predominance of certain molecules exposed on the surface (Figure 3).

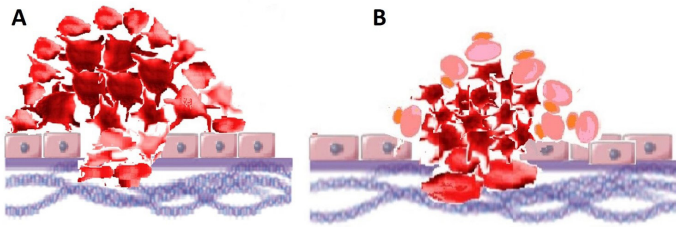

Figure 3: Phenotypic transformation of platelets at the initial **(A)** and late **(B)** stages of thrombus formation. Adapted from [30].

Non-activated (resting) platelets have a fixed discoid structure, little externalization of integrin receptors, an uncharged surface, and the presence of granules. Agonist-induced activation of quiescent platelets increases their heterogeneity in responsiveness, including secretion, exposure of active integrins and phosphatidylserine, changes in surface relief from uneven protrusion-like in some cells to balloon-like in others [30].

Damaged endothelium and exposed collagen induce initial platelet activation via the collagen receptor GPVI. The GPIb-IX-V receptor anchors platelets to collagen via the Von Willebrand Factor (VWF). Disrupted endothelial cells expose Tissue Factor (TF), triggering TF-dependent thrombin production, recruitment of additional platelets, and their aggregation. Aggregating platelets form pseudopods, undergo secretion, and bind fibrinogen [30]. Platelet aggregation occurs due to the formation of fibrinogen bridges between adjacent cells by bivalent binding of active integrin receptors $\alpha_{IIb}\beta_3$ (CD41/CD61) at their surfaces. Functionally, they form the primary hemostatic plug and also have a role in fibrin clot retraction, which implies that they bind fibrin [30].

The GPIb-IX-V receptor and the collagen receptor GPVI are the main mediators that amplify platelet activation by thrombin, which promotes the appearance of procoagulant platelets. Procoagulant platelets (or highly activated platelets) have a rounded structure, surface-exposed Phosphatidylserine (PS^-), prolonged cytosolic Ca^{2+} - rises and do not expose activated $\alpha_{IIb}\beta_3$ [30,31]. Externalization of negatively charged phospholipids such as PS as well as internalization of $\alpha_{IIb}\beta_3$ are the main features of procoagulant platelets. Their predominant function is to stimulate thrombin generation. These platelets also actively form fibrin [30,31]. They are often referred to as COAT platelets because of their mode of activation (i.e., induced by Collagen and Thrombin, COAT) [30]. It is not known exactly, but it seems that affinity of fibrin remains the same as that of fibrinogen, but binding avidity is also used. Most likely, fibrin binds to the surface through multiple contacts with the collagen and fibrinogen receptor Glycoprotein VI (GPVI) and the integrin $\alpha_{IIb}\beta_3$ [32]. Fibrinogen is known to contain an epitope in the D-domain that is involved in binding to leukocytes via the MAC-1 receptor. However, it is cryptic in the fibrinogen molecule and therefore has a weak affinity for MAC-1. When fibrinogen polymerizes to form fibrin D-dimers, this epitope is exposed, so fibrin's affinity for MAC-1 is much higher [32-34]. Perhaps, using the repertoire of currently existing inhibitors of blood cell adhesion and migration, it will be possible to identify those that will selectively inactivate PNA without affecting aggregation.

At high (sub-maximal) concentrations of thrombin/collagen, the level of COAT platelets can be up to 30% of the total population. Such dual agonistic activation resulted in the binding on PS-exposing platelets of a number of proteins released by α-granules [30]. COAT proteins are characterized by an unusually strong binding affinity for the surface of platelets. It is probably due to the catalytic activity of transglutaminases, such as factor XIIIa, which is externalized by a receptor-signaling dependent mechanism on the membrane of procoagulant COAT platelets [30,35]. Platelets bind FXIIIa via $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ [30,31]. Interestingly, PMN leukocytes are involved in the inactivation of FXIIIa and prevent cross-linking of α-granule proteins on the cell surface [32,36].

The generation of procoagulant platelets, as a cause of division into two subpopulations with different PS expression, requires the activation of one of three receptors: GPVI, PAR-1, or PAR-4 [31]. However, it seems that the obligatory action of thrombin (rather than its synthetic analogs) should be a prerequisite for the formation of COAT platelet. It is believed that the activating effect of thrombin, leading to appearance of COAT platelets is mediated by an effect on PAR-1, but not on another thrombin receptor, PAR-4 (however, GPIb may be ancillary involved) [33].

Conclusion

This review does not pretend to cover in depth the role of PNA in the development of pathological thromboinflammation. It was not intended to reflect the complexity of interactions between leukocytes and platelets, aggravated by their heterogeneity. We have simply proposed to move away from the beaten path, where for several decades scientists have been trying to find a way to suppress aggregation and limit the procoagulant properties of platelets in order to control blood clotting. Such attempts are still not very successful, since they are limited by the risk of bleeding or systemic inflammation. Perhaps the solution lies at the crossroads where platelets are involved in immune reactions and leukocytes are able to affect hemostasis. Several such target points at the level of receptor-ligand interactions of platelets and neutrophils are proposed here for discussion.

Declarations

Acknowledgments: This review was prepared as part of the project supported by German Research Foundation (die Deutsche Forschungsgemeinschaft, DFG). Project number is 537809747, principal grant recipient - P.I.

Authorship contribution: P.I. and T.A. cowrote and reviewed the manuscript, and D.T. prepared the figures.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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