Current Trauma Reports (2019) 5:202–209
https://doi.org/10.1007/s40719-019-00176-4

HEMOSTASIS AFTER TRAUMA (N SAILLANT, SECTION EDITOR)

Platelet Contributions to Trauma-Induced Coagulopathy: Updates in Post-injury Platelet Biology, Platelet Transfusions, and Emerging Platelet-Based Hemostatic Agents

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Published online: 5 November 2019

Abstract

Purpose The purpose of this review is to summarize the current understanding of the role of aberrant platelet biology in trauma-induced coagulopathy (TIC), discuss the evidence for platelet transfusions in the management of hemorrhaging trauma patients, and review emerging platelet-based hemostatic adjuncts.

Recent Findings Advances in the study of post-injury platelet biology have led to the discovery of pathways associated with altered platelet activation and aggregation observed in the context of TIC. Impaired platelet aggregation after injury has recently been associated with histone driven modifications in platelet structureand function, alterations in calcium signaling, and alterations in von Willebrand factor (vWF) platelet interactions. Furthermore, studies have identified several soluble factors in plasma which may play a role in inhibiting platelets after injury. Lastly, loss of the normal regulatory and bidirectional relationships of platelets with the endothelium and with fibrinolytic pathways may additionally play key roles in TIC. Importantly, the use of platelet transfusions as a treatment for hemorrhage control is not "one size fits all"—the benefit in several circumstances may be outweighed by risks, and there is a lack of demonstrated effectiveness for certain populations. Therefore, current efforts are underway to develop platelet based and platelet mimetic hemostatic agents, and to improve the effectiveness of platelet transfusions while mitigating the risks.

Summary Our understanding of how injury leads to altered platelet behavior contributing to TIC has grown substantially but remains incomplete. Decoding the complex biologic interface of platelets with the endothelium, fibrinolysis, and inflammatory pathways will lead to a more complete understanding of platelets and of TIC. Platelet transfusions remain the mainstay of treatment as part of balanced and goal-directed resuscitation, but through advancing knowledge of the underlying biology, safer, targeted, and more effective therapies may emerge.

Keywords Platelets · Trauma-induced coagulopathy · Platelet transfusions · Platelet biology · Platelet aggregation

Introduction

Although platelets have long been known to be central mediators of hemostasis [1], it is only recently that their importance in the development of disordered coagulation after trauma has been recognized, beyond the impact of low platelet counts [2–7]. Trauma-induced coagulopathy (TIC) is an acquired disorder characterized by alterations in multiple components of hemostasis, including impaired clot formation, dysregulated fibrinolysis, endothelial injury, and immunoregulatory dysfunction. Specific to platelet behavior in TIC, increased platelet activation, yet impaired platelet aggregation is present in vitro [5, 6, 8]. In this article, we will (1) highlight the role of altered post-injury platelet biology in TIC, (2) review diagnostic strategies to identify impairments in platelet function, (3) discuss the role for platelet transfusions in post-traumatic hemorrhage, with a focus on traumatic brain injury (TBI), and (4) provide an overview of synthetic platelet based therapies, which may have potential as future adjuncts or alternatives to transfusion.

This article is part of the Topical Collection on *Hemostasis after Trauma*

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Post-injury Platelet Biology in Trauma-Induced Coagulopathy

Overview of Platelet Functions: Mediators of Hemostasis, Regulators of Endothelium, and Immunomodulators

Platelets play essential roles in the hemostatic response to vessel injury, including formation of an initial platelet plug as well as their involvement as a cellular surface catalytic platform for procoagulant enzymatic machinery [1]. These functions lead to large scale thrombin generation and ultimately facilitate fibrin crosslinking and mature clot formation [1]. Furthermore, platelets have important regulatory roles in maintaining endothelial integrity and fibrinolysis [9–11]. Lastly, the function of platelets as immune signaling and effector cells is a previously under-appreciated, but important aspect of platelets that contributes to the sterile inflammatory response and to immune mediated thrombosis, which can be excessively activated by damage associated molecular patterns (DAMPS) released after massive tissue injury [6, 12, 13].

Qualitative and Quantitative Platelet Deficits After Trauma

While this section will focus on qualitative platelet deficits, it should be noted that decreases in platelet number secondary to consumptive and dilutional processes do play an important role in critically ill trauma patients. Thrombocytopenia in a trauma patient is a poor prognostic sign—in fact, even within the accepted "normal" ranges, decreases in platelet counts are associated with worse outcomes and mortality in severely injured patients [14]. However, a number of key studies in the past two decades have characterized qualitative patterns of aberrant platelet biology, which are most pronounced in patients with severe injury and shock [2–4]. In fact, 45% of critically injured trauma patients with normal platelet counts have impaired measures of in vitro platelet aggregation, but increased biomarkers of platelet activation [2, 3]. This finding is concerning given many studies have identified that these patients have increased morbidity and mortality, independent of their platelet counts (Fig. 1) [2, 3].

Recent Advances in Mechanisms of Post-injury Qualitative Platelet Deficits

Several recent advances in the field of post-injury platelet biology highlight that changes in soluble factors in the plasma of trauma patients may be driving the observed alterations in platelet biological behavior. For example, after injuries characterized by extensive endothelial damage, such as TBI, an associated deficiency in functional von Willebrand factor (vWF) may play a role in mediating impaired platelet aggregation [15••]. Furthermore, in a mouse model of TBI, interactions between platelet derived microvesicles and vWF promote endothelial damage and coagulopathy [16].

Additionally, factors in the plasma of trauma patients may inhibit platelets in a microfluidics model [17••, 18••]. A recent study identified that soluble fibrin, which is markedly elevated in trauma patients [19], causes a defect in platelet glycoprotein VI signaling and, therefore, may provide an additional clue to the mechanisms of platelet impairments in TIC [18••]. Most recently, DAMPs such as histones, known to be toxic to cells, were shown by Vulliamy et al. to induce the development of procoagulant, but poorly aggregating platelet "balloon structures" visualized using electron microscopy [20••]. These procoagulant platelet structures are traditionally present only at sites of vascular damage; however, the authors postulate that massive histone release during trauma leads to diffuse "platelet balloon" formation, and subsequent disintegration into microparticles which were shown to coat leukocytes. Supporting this hypothesis, they found that the ballooning platelets observed in trauma patients were decorated with histone H4, and exposure of healthy platelets to histone H4 replicated the same morphological and functional changes [20••]. Additional work in this area is needed continue to characterize pathophysiology driving altered, and presumably pathologic post-injury platelet biology to identify novel therapeutic targets.

Interpreting Current In Vitro Assays of Platelet Function

While the associations between in vitro measures of platelet aggregation and poor clinical outcomes have been identified, alterations in platelet biology have also been found in minorly injured populations as well [21]. This dichotomy raises questions about the behavior of platelets in vivo in the setting of TIC. Furthermore, it remains a challenge to interpret platelet aggregometry data in an injury state due to the following: (1) trauma leads to systemic platelet activation and therefore a potential inability to further activate platelet in in vitro assays ("functional exhaustion"), and (2) impaired aggregometry may in part reflect that "functional" platelets are used in local clot formation and therefore are not well sampled in blood draws [2, 6, 22].

Despite these potential drawbacks to whole blood aggregometry, other methodologies incorporating shear stress and flow environments corroborate these significant impairments in platelet aggregation and platelet

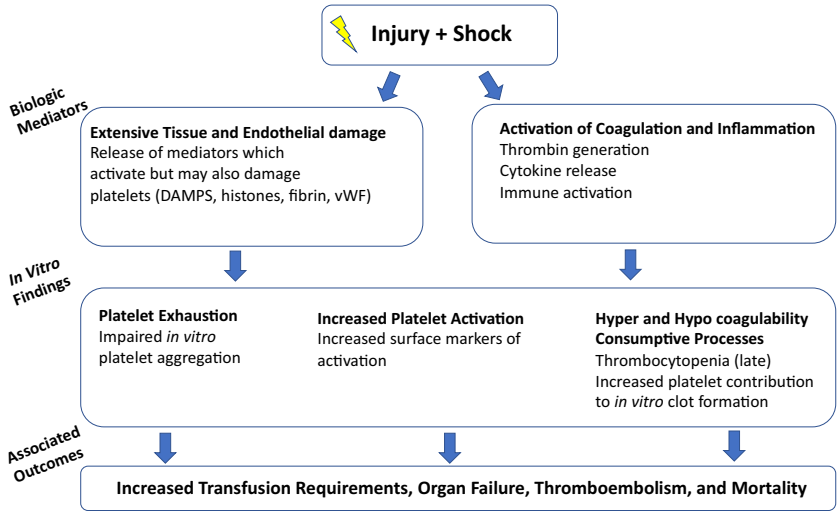

Fig. 1 Proposed pathways of altered platelet biology and associated clinical outcomes in trauma-induced coagulopathy (TIC). The combination of injury and shock has been shown to be the most critical factor which drives TIC and associated impairments in platelet behavior. Tissue injury and endothelial damage release mediators which activate platelets and may be responsible for functional impairments as well. These platelets are unable to be further stimulated to aggregate in vitro (platelet "exhaustion"), manifesting as impaired aggregation. Activation of immune and inflammatory responses also contribute to hypercoagulability, consumptive processes, thrombocytopenia (usually a late phenomenon, ~ 24–48 h after injury), organ failure, thromboembolic complications, and death. DAMPS, damage associated molecular patterns; vWF, von Willebrand factor

contributions to clot formation. For example, microfluidic assays, which allow for assessment of platelet function under shear stress, support that there is in fact defective aggregation and impaired platelet-mediated clot growth in severely injured trauma patients compared to controls [23•]. Thromboelastography can also be modified to assess platelet dependent clot formation. Using the "platelet mapping" (TEG-PM™) technique, impairments in platelet dependent clot formation can be identified early after TBI, and are associated with mortality [24]. Importantly, many of the tests of platelet aggregation were designed for use outside of trauma (monitoring of anti-platelet therapy), and have yet to have a clear application in trauma patients outside of research settings. This is due to a multitude of reasons including conflicting data of clinical utility, highly specialized nature, and labor-intensive methods (flow cytometry, microfluidics, calcium mobilization assays, electron microscopy). Continuing to develop clinically valuable point of care tests remains an ongoing focus of the field to refine our understanding of the mechanisms of altered post-injury platelet behavior.

Platelet Transfusions in Trauma

Risks Versus Benefits

In the modern era of balanced resuscitation, it has become standard of care to transfuse platelets early in balanced 1:1:1 ratios with packed red blood cells and plasma with transition to goal-directed resuscitation for hemorrhaging trauma patients. The benefit of balanced transfusion ratios has been demonstrated in multiple observational studies [25–27]. Perhaps most notably, in the "Pragmatic, Randomized Optimal Platelet and Plasma Ratios" (PROPPR) randomized controlled trial, there were fewer deaths from exsanguination and increased rates of hemostasis in the group receiving 1:1:1 ratios of blood products [28••]. However, the evidence specific to platelet transfusions remains incomplete.

There continues to be debate regarding the optimal timing of platelet transfusion, and for which patients the benefits outweigh the risks. This is in part because compared with plasma and packed red blood cells, platelets have increased risks of both bacterial contamination (due to the room temperature current standard storage temperatures) as well as higher associated rates of other complications, such as acute respiratory distress syndrome even in non-massively transfused patients [29, 30]. In addition, the effectiveness of transfused platelets in trauma patients is further tempered by platelet storage defects and aforementioned factors in the plasma of trauma patients which may inhibit proper functioning of transfused platelets [18••, 29, 30]. While proposed guidelines recommend transfusions to greater than 50,000/μL platelet counts for hemorrhaging trauma patients, and to greater than 75,000/μL for traumatic intracranial hemorrhage, there is a lack of high quality evidence to broadly support these thresholds [31].

Importance of Timing

The appropriate timing of platelet transfusions may be critical, although there are some conflicting results in the literature. In the PROPPR trial, although there were statistically significant improvements in hemostasis and deaths from exsanguination, mortality was not different [28••]. However, in a secondary analysis of PROPPR by Cardenas and colleagues, early transfusion of platelets was associated with improved 24-h and 30-day mortality [32••]. Despite these findings, two studies have shown that early platelet transfusion may not improve impairments in aggregation or low platelet counts [33•, 34]. In an analysis by Kornblith and colleagues, it was shown that while early transfusions had little to negative impacts on platelet aggregation and minimal improvement on platelet counts, transfusions given at later timepoints (greater than 48 h after injury) led to improvements in aggregation and more significant responses in platelet count [33•]. More work is needed in order to understand how to incorporate this knowledge to best leverage the use of platelet transfusions in clinical practice for hemorrhaging trauma patients.

Special Populations: Traumatic Brain Injury and Patients on Anti-platelet Therapies

Some special populations to consider with respect to the role of platelet transfusions include patients with TBI, especially if they are taking anti-platelet agents. Patients with TBI on anti-platelet therapy are a vulnerable subpopulation with a three-fold risk of death compared with TBI patients not on anti-platelet therapy, but data guiding management in trauma patients is sparse and mixed [35] (see Table 1). Of two recent observational studies, one demonstrated improved outcomes and decreased neurosurgical interventions for patients with traumatic intracranial hemorrhage on P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) who received platelet transfusions [44], while another showed no associated improvements in outcomes, although platelet transfusions did ameliorate inhibition to both aspirin and plavix [43]. The authors also noted significant variability in transfusion practices between centers, and a lack of standardized protocols for the use of platelet transfusions in TBI in general.

The practice of transfusing platelets to patients with TBI on antiplatelet therapy should be further cautioned given the findings of the PATCH trial, a well-executed randomized controlled study investigating platelet transfusions versus standard of care alone for patients on antiplatelet agents (primarily aspirin) suffering from non-traumatic hemorrhagic strokes [45]. Surprisingly, patients randomized to platelet transfusions had significantly higher odds of death or severe disability at 3 months, despite no clear major differences in baseline characteristics, or in rates of adverse events in the transfusion group. One possibility proposed for these findings may be related to the thrombogenicity of platelets—the authors suggest that transfused platelets could contribute to secondary ischemic insults around the region of infarct [45]. While the findings of this study may not be directly generalizable to TBI, they emphasize the need for larger, prospective observational, and randomized trials to evaluate the efficacy and safety of platelet transfusions in TBI patients on antiplatelet therapy.

More generally, for the broader population of patients with TBI, studies have suggested there may be clinical benefits to platelet transfusions, but again, timing plays a role and data is overall limited to observational studies (see Table 1). In a retrospective study by Naidech et al., the authors showed that early platelet transfusions (within 12 h) improved functional outcomes and were associated with decreased total volume of intracranial hemorrhage [46]. Using thromboelastography with platelet mapping (TEG PM™) as a point of care test, multiple groups have studied the impact of platelet transfusions on platelet inhibition to adenosine diphosphate (ADP) stimulation and clinical outcomes. Guillotte et al. found that while platelet inhibition measured on TEG PM™ was associated with severity of TBI, it was not associated with outcomes [41]. Furthermore, although platelet transfusions reversed this inhibition, they did not improve clinical outcomes [41]. A similar study with a pre-post design evaluated the impact of administering platelet transfusions to all patients with platelet inhibition (measured by TEG PM™) and severe TBI [40••]. In contrast, they found statistically significant reductions in mortality and associated improvements in platelet inhibition in the 35 patients that received transfusions according to this protocol, compared with their historical controls [40•].

Platelet Cold Storage and Other Advances in Platelet Transfusion Practices

As mentioned above, there are several limitations to current platelet transfusion practices, and overcoming these is the focus of novel therapeutic strategies. These challenges include short shelf lives due to the risks of bacterial contamination leading to infectious complications, as well decreases in the hemostatic capabilities of platelets the longer they are stored (platelet storage lesions) [29]. The current standard practices allow for storage of platelets at 22 °C for just 5–7 days [47]. Because of these issues, significant interest is vested in determining the effectiveness and feasibility of cold stored platelets and lyophilization processes [48, 49]. Storage of platelets at 4 °C rather than 22 °C may allow for usage for up to 14 days, provide platelets that are more hemostatic, and decrease the risk of infectious complications [48]. Cold stored platelets remain in circulation for shorter periods of time, although this may be less relevant in the setting of trauma than other conditions requiring platelet transfusions [48]. Prospective trials will work to validate the use of cold stored platelets in trauma.

Table 1 Summary of recent studies evaluating platelet transfusions in trauma patients

Study	Population	Key findings
Vulliamy et al. [36] 2017	All trauma	Platelet transfusions regulated fibrinolysis but did not improve platelet aggregation
Stettler et al. 2017 [37]	All trauma	Platelet inhibition on TEG PM™ was associated with the need for platelet transfusions, massive transfusion, and mortality, but was not a better predictor than conventional TEG and platelet counts
Cardenas et al. 2018 [32••]	All trauma	Sub-study of PROPPR trial [28••] which demonstrated that early platelet transfusion was associated with mortality benefits
Kornblith et al. 2019 [33•]	All trauma	Effects of platelet transfusion on aggregation improved when given later compared to early after injury
Kasotakis et al. 2019 [30]	Blunt trauma	Platelet transfusions increased the risk of ARDS in non-massively transfused blunt trauma patients
Kim et al. 2015 [38]	Blunt TBI	Neither platelet transfusion nor desmopressin administration impacted the progression of traumatic intracranial hemorrhage
Martin et al. 2018 [39]	TBI, blunt vs penetrating	Patients with penetrating TBI were more coagulopathic by TEG and platelet aggregometry, but TEG results did not correlate with aggregometry results
Furay et al. 2018 [40•]	TBI	Prepost study which showed improved mortality for TBI patients who were transfused platelets based on a protocol utilizing TEG PM™ to identify platelet inhibition
Guillotte et al. 2018 [41]	TBI	Platelet inhibition measured with TEG PM™ correlated to TBI severity, but was not significantly associated with outcomes, platelet transfusions, nor did transfusion improve outcomes
Briggs et al. 2015 [42]	TBI and anti-platelet therapy	Platelet transfusions improved aggregation responses to arachidonic acid but not to collagen, suggesting a reversal of Aspirin induced effects but not of trauma effects on platelets
Holzmacher et al. 2018 [43]	TBI and anti-platelet therapy	Platelet transfusion was not associated with improved outcomes in TBI patients on anti-platelet therapy, but did reverse platelet inhibition
Jehan et al. 2019 [44]	TBI and anti-platelet therapy	Platelet transfusions were shown to improve outcomes for those on P2Y12 inhibitors

TBI traumatic brain injury; *TEG* thromboelastography; *TEG PM™* thromboelastography with platelet mapping; *ARDS* acute respiratory distress syndrome; P2Y12 inhibitors = Plavix, Prasugrel, Ticagrelor

While platelets do carry the aforementioned drawbacks, they remain a critical component of the resuscitation of trauma patients, particularly for those suffering from massive hemorrhage as part of damage control, and goal-directed 1:1:1 transfusion practices. Further research in this area should seek to continue to focus on improving platelet shelf lives, reducing the risk of transfusion-associated complications, and better understanding the clinical conditions in which platelets have the most benefit for the hemorrhaging trauma patient. While it is essential to improve the efficacy of platelet transfusions in the near term, longer term solutions include synthetic platelet based therapies which are discussed in the following section.

Novel Platelet–Based Hemostatic Agents

Platelet-based hemostatic agents may eventually offer an alternative to platelet transfusions, particularly in resource limited or even prehospital settings. These therapies include platelet derived extracellular vesicles and synthetic platelet analogs, which are not subject to the limitations of platelet transfusions such as storage defects, transfusion reactions, limited shelf life, pathogen contamination, and inactivation by plasma proteins.

Extracellular Vesicles

Platelet-derived extracellular vesicles are small, procoagulant, platelet-derived fragments abundantly found in the plasma of trauma patients which have multiple properties that make them appealing as a treatment for patients suffering from TIC. Platelet-derived extracellular vesicles promote hemostasis through expression of GPIIb/IIIa, tissue factor, and phosphatidylserine [50•]. In addition, they have been shown to regulate endothelial integrity in vitro and in vivo, and have the potential to be stored for long periods of time [50•, 51•]. Some of the concerns regarding the clinical use of platelet-derived extracellular vesicles include the potential for inducing pathologic thrombosis and the possibility that they may have proinflammatory properties [50•, 52•]. Other potential disadvantages of these and other platelet membrane based therapies include immunogenicity, high costs, and challenges with batch variation and stability [53].

Synthetic, Platelet-Based Agents

Synthetic, platelet mimetic micro- and nanoparticles have been designed as alternative hemostatic adjuncts which may avoid some of the challenges of platelet membrane-based systems [31, 53]. There are a range of products that have been developed and tested in vitro and in animal models, but none have yet reached clinical trials. The designs all involve some form of micro- or nanoparticle platforms coated with protein fragments that promote platelet activation, or mimic and enhance platelet aggregation. For example, in the late 1990s, albumin microspheres coated with fibrinogen (thrombospheres™) were shown to enhance platelet aggregation and decreased bleeding times and blood

loss in vivo in rabbit models [54, 55]. A similar technique was used to develop "Synthocytes", which are albumin "microcapsules" with embedded fibrinogen. These were tested by Levi et al. and showed improved bleeding times in thrombocytopenic rabbits and decreased bleeding from surgical wounds, without obvious systemic thrombotic complications [56]. Other techniques involve "decorating" latex beads or other polymeric particles with fibrinogen like peptides; however, one challenge of this strategy is the ability to cause aggregation of inactive platelets and recognition of other cells and extracellular matrices leading to off target effects and systemic thrombotic complications [57, 58]. Another key limitation of these earlier synthetic platelet mimetic particles is that they tended to only recapitulate one function of platelets (i.e., only their adhesive or aggregatory properties), and therefore had less hemostatic potency.

A significant advancement in their design now includes particles that have both proadhesive and proaggregatory effects. For example, Synthoplate™ consists of a lipid vesicle platform coated with synthetic vWF-binding peptides, collagen-binding peptides, and active GPIIb/IIIa–binding fibrinogen-mimetic peptides (see Fig. 2) [60]. The effectiveness of Synthoplate™ has recently been evaluated in animal studies, including a mouse model of liver injury and a porcine model of arterial hemorrhage [59, 61•]. Both studies showed promising reductions in bleeding, with the mice being pretreated with Synthoplate™ infusion prior to injury, while in the porcine model it was given after injury [59, 61•]. Ongoing research efforts are needed to further define the effectiveness for these products and establish their safety for their potential clinical use in trauma patients.

Conclusions and Future Directions

Platelets are key players in hemostasis with significant roles in the development of TIC. The past two decades of research have underscored the importance of altered post-injury platelet biology, yet our understanding of the mechanisms involved are still in large part undefined. Of the many available in vitro assays which test various platelet functions, there is a need to further establish their clinical utility for trauma patients. Platelet transfusions remain standard of care as part of balanced, hemostatic, and goal-directed resuscitation for traumatic hemorrhage, but continuing to improve our knowledge of how to best use platelet transfusions as well as improving their effectiveness and shelf life is an ongoing effort. Lastly, platelet-based analogs have been under development for some time, and recent advances in their design show promise as potential hemostatic therapies, but have yet to be tested clinically.

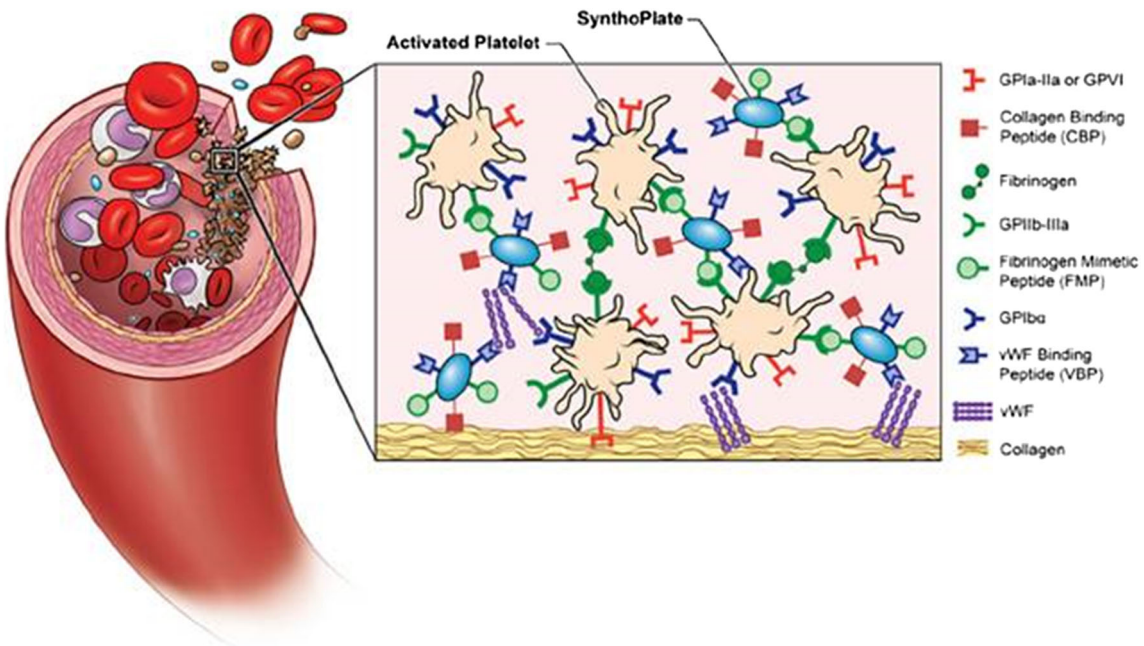

Fig. 2 Schematic representation of SynthoPlate design and mechanism. Nano-constructs are heteromultivalently decorated with von Willebrand factor (vWF)-binding peptide (VBP), collagen-binding peptide (CBP) and fibrinogen mimetic peptide (FMP) motifs to render platelet-mimetic interactions with vWF, collagen and active platelet integrin GPIIb/IIIa respectively, and thus amplify platelet-mediated primary hemostatic mechanisms at the injury site. Figure and caption reproduced with permission from Hickman et al. [59]

Compliance with Ethical Standards

Conflict of Interest Dr. Kornblith and Dr. Matthay have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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