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Authors
Vulliamy, Paul
Kornblith, Lucy Z
Kutcher, Matthew E
et al.

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Alterations in platelet behavior after major trauma: adaptive or maladaptive?

Paul Vulliamy[1], **Lucy Z. Kornblith**[2], **Matthew E. Kutcher**[3], **Mitchell J. Cohen**[4,5], **Karim Brohi**[1], **Matthew D. Neal**[6,*]

[1]Centre for Trauma Sciences, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, E1 2AT, United Kingdom

[2]Department of Surgery, Zuckerberg San Francisco General Hospital and the University of California, San Francisco, San Francisco, California

[3]Division of Trauma, Critical Care, and Acute Care Surgery, University of Mississippi Medical Center, Jackson, Mississippi

[4]Department of Surgery, University of Colorado, Aurora, Colorado

[5]Ernest E Moore Shock Trauma Center at Denver Health, Denver, Colorado

[6]Division of Trauma and Acute Care Surgery, Department of Surgery, University of Pittsburgh, Pittsburgh, PA

Summary

Platelets are damage sentinels of the intravascular compartment, initiating and coordinating the primary response to tissue injury. Severe trauma and hemorrhage induce profound alterations in platelet behavior. During the acute post-injury phase, platelets develop a state of impaired *ex vivo* agonist responsiveness independent of platelet count, associated with systemic coagulopathy and mortality risk. In patients surviving the initial insult, platelets become hyper-responsive, associated with increased risk of thrombotic events. Beyond coagulation, platelets constitute part of a sterile inflammatory response to injury: both directly through release of immunomodulatory molecules, and indirectly through modifying behavior of innate leukocytes. Both procoagulant and proinflammatory aspects have implications for secondary organ injury and multiple-organ dysfunction syndromes. This review details our current understanding of adaptive and maladaptive alterations in platelet biology induced by severe trauma, mechanisms underlying these alterations, potential platelet-focused therapies, and existing knowledge gaps and their research implications.

Introduction

Injury is a leading cause of global death and disability [1]. Uncontrolled hemorrhage accounts for the majority of preventable mortality [2] and is frequently accompanied by an acquired impairment in hemostatic competence termed trauma-induced coagulopathy (TIC)

*Corresponding author: nealm2@upmc.edu.

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[3] that drives increased transfusion requirements, resource utilization, and death [4, 5]. Patients who survive the initial insult are at high risk of secondary organ dysfunction and thromboembolic events, which are major contributors to subsequent morbidity and mortality [6–9]. These conditions are thought to emerge from dysfunctional or exaggerated responses to major tissue damage and shock, exacerbated by iatrogenic factors such as transfusion and surgical intervention [10–12].

The principal adaptive functions of platelets after injury are to recognize tissue damage and to influence hemostatic and innate immune responses. First, they express a wide array of cell surface receptors at high density, enabling rapid responses to a range of stimuli [13] including local extravascular matrix components exposed by injury as well as circulating intravascular damage-associated molecular patterns (DAMPs) released by injured tissues [14]. Second, their small size relative to other intravascular cells results in margination to the edge of flowing blood, ensuring close endothelial contact. Third, they possess a diverse toolkit of molecular effectors which can be deployed rapidly and simultaneously [15, 16]. Control of hemostasis is the most widely recognized effector function of platelets; however, as sentinel innate immune cells, platelets are also key regulators of inflammation. This dual regulation of inflammation and thrombosis, known as immunothrombosis, is critical to understanding the response to injury [17]. This review describes platelet involvement in the response to tissue damage and hemorrhage, summarizes current understandings of how alterations in platelet behavior modulate coagulation and inflammation during recovery, and discusses focuses for future research and innovation.

Platelet behavior after major injury

Despite well-mapped roles in normal hemostasis, TIC-induced changes in platelet behavior are an active area of investigation [18]. Platelets undergo a number of behavioral changes after major trauma and hemorrhage (Table 1), both quantitative and qualitative.

Thrombocytopenia

Adequate platelet number is required for hemostasis, and early thrombocytopenia even within normal ranges is associated with increased risk of death after injury, and at later timepoints is associated with bleeding, progression of brain injury, and mortality [19, 20]. In particular, thrombocytopenia after traumatic brain injury is associated with a nine-fold increased adjusted odds of death [21]. Decline in platelet count after injury has been attributed to both consumptive processes and dilutional effects. While inadequate platelet contribution to hemostasis is intuitive in thrombocytopenia, several of these studies suggest that significant platelet impairment can exist despite a normal platelet count [22, 23]

Activation and aggregation

Circulating platelets from trauma patients exhibit impaired responses to *ex vivo* agonist stimulation in aggregometry assays [22–25], persisting after injury and more pronounced in non-survivors [22, 23]. These observations have been replicated in porcine and non-human primate models of trauma hemorrhage and brain injury, demonstrating impaired aggregation within 15 minutes of injury [26, 27]. However, mechanisms responsible for this apparent

functional impairment are poorly defined. An early prospective study correlated surface markers of activation with impaired *ex vivo* aggregation in brain-injured patients [22], hypothesizing that systemic activation renders platelets inert to subsequent stimulation - referred to as 'platelet exhaustion' [28]. In contrast to earlier studies in which 'exhausted' platelets displayed increased activation markers, a recent study found that platelets harvested from injured patients had resting activation profiles similar to uninjured volunteers, but significantly impaired calcium mobilization and activation marker expression when stimulated; this 'exhaustion' phenotype could be reproduced in healthy volunteer platelets by *in vitro* exposure to injured patient-derived plasma, suggesting as-yet undefined soluble factors as potential mediators of 'exhaustion' [29].

Beyond aggregation, adhesion and other mechanochemical aspects of platelet hemostatic function have received relatively less attention. One study assessed platelet adhesion to collagen using a microfluidic whole blood assay, with the majority of patients exhibiting loss of function compared to healthy volunteers [30]. A subsequent larger study identified impaired platelet contractile force in an *in vitro* microfluidic model of TIC, and correlated impaired contractile force on arrival with later transfusion requirements in injured patients [31]. Importantly, these studies describe a qualitative defect in platelet behavior beyond quantitative platelet number. Each of the above-detailed studies found platelet counts within the normal range during the early postinjury period, suggesting that trauma-induced alterations in platelet activity are distinct from disseminated intravascular coagulation (DIC), in which thrombocytopenia is an almost universal feature [32].

The clinical significance of *ex vivo* platelet aggregation assays has been questioned. One large cohort study of 'platelet-mapping' thromboelastography (PM-TEG) showed that significant impairment in *ex vivo* platelet agonist responsiveness was common even after minor injury, but did not correlate with outcomes [33]; a second showed that impaired PM-TEG parameters correlated with adverse outcomes but did not add predictive power to standard TEG or platelet count [34]. This highlights the lack of correlation between viscoelastic and aggregometry-based measures of platelet function in coagulopathic trauma patients [35, 36]. Some investigators suggest that this indicates a normal adaptive response to injury rather than a manifestation of TIC [37], citing contradictory biologic patterns of increased platelet activation but decreased aggregation after injury [22]. Achieving clarity is complicated by the absence of a 'gold standard' for platelet function – outside of perhaps bleeding time, which is appealing for its directness but not easily applicable clinically [38]. Conceptually, all *ex vivo* measures of platelet function are limited by the absence of endothelium and flow conditions, as well as variability related to platelet count and hematocrit [39]. Strategies to measure specific, clinically relevant aspects of platelet behavior are a matter of active investigation.

Platelet-endothelial interactions

Trauma-induced alterations in platelet biology may also be driven by endothelial injury, and our understanding of this remains limited and controversial [22, 24, 25, 40]. Circulating biomarkers of endothelial injury are elevated following trauma [41–43], and endothelial damage is a driver of organ failure in other clinical settings [44–46] as well as in animal

models of combined injury and hemorrhagic shock [47, 48]. Some have hypothesized that endothelial disruption following trauma catalyzes functional platelet ‘exhaustion’[28], and injuries with significant tissue and endothelial damage have the strongest associations with impaired platelet aggregation [22–25]. One candidate mechanism identified *ex vivo* impairment of platelet aggregation in response to ristocetin in brain-injured patients [49], consistent with decreased functional circulating von Willebrand Factor (vWF). Further, brain injured patients had increased circulating coagulation factor VIII, consistent with decreased vWF carrying capacity [50]. Ongoing assessments of vWF quantity and function, as well as other endothelial biomarkers, will further clarify endothelial mechanisms of platelet modulation after injury [49, 51]. Conversely, platelets regulate endothelial integrity through release of several intracellular signaling molecules that bind endothelial receptors and stabilize intercellular junctions [52]. Our current understanding of this limb of bidirectional platelet-endothelial interactions is even more limited.

Platelet-leukocyte interactions

In addition to endothelial cells, platelets interact bidirectionally with circulating leukocytes [53] and platelet binding induces a number of important cellular changes (Table 2) [54–58]. The overall effect is a phenotypic switch towards a proadhesive, proinflammatory phenotype in leukocytes upon binding of activated platelets, facilitating entry into damaged tissues and priming leukocytes for antimicrobial or tissue reparative functions. In a murine model of thermal liver injury, platelets facilitate neutrophil entry into the lesion site, and platelet depletion resulted in delayed tissue clearance and prolonged healing [59]. This suggests that platelet-mediated leukocyte recruitment is important to injury recovery, although the generalizability of this observation is debatable. Conversely, platelet-leukocyte interactions appear detrimental to the host in other models of sterile tissue damage by exacerbating inflammation and secondary organ injury [60]. An example of this is activated platelet induction of extracellular trap (ET) elaboration by macrophages and neutrophils [57]. These structures are involved in bacterial trapping but also result in endothelial damage [56], acute kidney injury secondary to rhabdomyolysis, and transfusion-associated lung injury [57, 61]. Pharmacologic blockade of platelet-neutrophil interactions, depletion of platelets, and inhibition of platelet activation all attenuate organ damage in these models [62]. Platelet-T-cell conjugates are also implicated in the pathobiology of several disease states, including HIV infection and rheumatoid arthritis [63, 64]. Platelet binding to T-cells appears to modulate their activation and differentiation [65], but the functional significance of this in trauma patients has not been evaluated.

Platelets also modulate leukocyte and endothelial cell behavior by releasing soluble mediators during activation. This was first described in relation to CD40L, which is stored in platelet α-granules, upregulated on the platelet surface, and released in soluble form (sCD40L) upon platelet activation [66]. CD40L on activated platelets activates endothelial cell adhesion molecule expression and chemokine release, localizing leukocyte recruitment to sites of injury. Trauma patients have elevated levels of circulating sCD40L, which correlate with markers of tissue damage, systemic hypoperfusion, endothelial injury and TIC [67]. Other immunomodulatory molecules stored in platelet α-granules are also increased within two hours of injury, and are similarly associated with injury burden [68].

Platelet ballooning and extracellular vesicle release

In addition to soluble signaling aspects, platelets undergo major structural changes during traumatic hemorrhage. A subpopulation of circulating platelets demonstrate a 'ballooned' morphology early after injury in proportion to injury severity [69], which is associated with elevated thrombin generation and impaired platelet aggregation [70]. Extracellular histones, archetypal DAMPs which reach high concentrations in the bloodstream of trauma patients [71–73], are detectable on the surface of these ballooned platelets and appear to drive this phenotypic switch *in vitro*. The process of platelet ballooning results in extracellular vesicle (EV) production [74, 75].

In recent human and murine studies of trauma-hemorrhage, platelet-derived extracellular vesicles (PEV) were shown to be markedly and persistently elevated immediately after major injury. Importantly, platelets appear to be the principle source of circulating EV release as measured in a large prospective cohort of injured patients [76]. Both ballooned platelets and PEVs have been shown to trigger thrombin generation, likely as part of the evolutionarily robust hemostatic response to severe injury. Interestingly, in both *in vitro* and *in vivo* models of vascular permeability, PEVs have been shown to decrease endothelial permeability and restore endothelial cell junctional integrity following thrombin challenge [77]. However, it appears early salutary hemostatic effects may be coupled with later detrimental consequences if trauma-induced PEV are either sustained in circulation or released beyond the early hemostatic period, as they are also linked to subsequent thromboembolic complications in murine models [78]. A better understanding of PEV biology remains critical given their potential as both biomarkers and novel hemostatic agents that could circumvent issues with platelet availability and storage.

Platelet-derived mediators of inflammation

Platelets are known effectors of both local and systemic inflammation, and express an array of immune-relevant receptors [79–82]. Specifically, the family of toll-like receptors (TLR) are expressed on platelets [83–85] and play multiple roles in inflammatory responses, including primary sensing of foreign molecules and DAMPs [81–85]. Platelets are known to express all 10 of the TLRs at least in transcript form and well as downstream signaling complexes [86], providing an immediate link between immunity and thrombosis. The best characterized TLRs in platelets with respect to thromboinflammatory phenotype are TLR2 and TLR4. In addition to binding microbial ligands, TLR2 on platelets has been shown to bind DAMPs and lipoproteins, with Pam3CSK4 being the best studied synthetic lipoprotein ligand. Pam3CSK4 has been shown to trigger aggregation, adhesion, and release of proinflammatory ligands in murine and human platelets [87, 88]. TLR2 activation has also been shown to regulate platelet-neutrophil interactions and NET production[89], a process well linked to the pathophysiology of acute injury. TLR4 has a role in hemorrhagic shock [90–94], and platelet-specific TLR4 has a role in inflammation downstream of lipopolysaccharide signaling [56, 95–97]. The contribution of platelet TLR4 to inflammation has been evaluated in a murine model of hemorrhagic shock, in which mice lacking TLR4 expression on platelets were protected from hemorrhage-induced lung and liver injury [98]. Transfusion of platelets lacking TLR4 into wild-type mice had a similar protective effect.

Subsequent work has implicated release of high-mobility group box 1 (HMGB1) from platelets as a mechanism explaining the dependence of these phenomena on this receptor [99]. Given that multiple other DAMPs implicated in post-traumatic inflammation signal through TLR4 [100], pharmacologic inhibition of TLR4 in trauma patients is an attractive potential therapeutic approach to mitigate TIC and attenuate post-injury inflammatory organ dysfunction.

Platelet-derived mediators of fibrinolysis

Alterations in fibrinolysis are known contributors to TIC, and platelets are intimately involved in control of both pro- and anti-fibrinolytic pathways. At one extreme, the combination of hemorrhagic shock and massive fibrinolytic activation confers an extremely high mortality [101]. Platelets harbor the fibrinolytic proteins single-chain urokinase-type [102] and tissue-type [103] plasminogen activators (uPA and tPA) on their surface, serving to modulate rates of clot lysis [104]. Conversely, reduced clot breakdown on viscoelastic testing is also associated with poor outcomes after injury [105]. Within developing thrombi, aggregated platelets augment fibrinogen binding and protect fibrin from plasmin-mediated lysis via clot retraction [106]. Activated platelets release α2-antiplasmin and plasminogen activator-inhibitor-1 (PAI-1), inhibiting plasmin-dependent clot breakdown and stabilizing nascent platelet plugs [107, 108]. Clinically, impaired platelet ADP responsiveness as measured by PM-TEG is associated with increased sensitivity to tPA-mediated fibrinolysis in trauma patients [109]. Other studies have identified similar associations between injury-induced impairment in platelet aggregation and fibrinolytic shutdown phenotypes [110–113].

Platelet-derived mediators of thrombosis

Trauma patients are at high risk for thromboembolic complications during and after hospitalization [114, 115]. Following severe injury in patients and murine models, platelets release HMGB1 [116] as well as other pro-thrombotic mediators, including P-selectin. The release of HMGB1 from platelets, which signals in a paracrine fashion on platelets [116], neutrophils [117–120], and mononuclear cells [99], contributes to thrombosis following injury. Specifically, the disulfide form of HMGB1 released from platelets has been implicated in deep vein thrombosis in mice [118] in a neutrophil ET formation-dependent fashion, as ET inhibitors and DNAse reversed the prothrombotic effect of HMGB1 [121]. These data identify HMGB1 as an example pro-inflammatory ligand involved in reducing localized bleeding following injury [116] while also driving remote microvascular [116] and macrovascular [118, 121] thrombosis. The emergence of platelet HMGB1 as a functional component of other sterile inflammatory conditions, such as systemic sclerosis [119, 122, 123], suggests a conserved role in innate immune activation that may become excessive and pathologic, leading to thrombotic complications following the overwhelming inflammatory activation associated with severe injury and hemorrhage. As noted above, the release of PEV from ballooned platelets has similarly been implicated in the development of post-injury thromboembolic events [78], suggesting another example of platelets as controllers of the balance between localized hemostasis and systemic thrombosis.

Platelet transfusion after major injury

Transfusion of platelets seems an intuitive strategy to augment hemostasis after injury, as platelet count is inversely proportional to overall survival [19] and progression of intracranial hemorrhage [21]. Current standard-of-care in post-injury hemorrhage is empiric transfusion of platelets in balanced ratios with red blood cells and plasma until goal-directed therapy can be initiated, regardless of platelet count [124–126]. Two recent large multicenter prospective studies [127, 128] of over 1500 injured patients requiring early transfusion identified that increasing ratios of platelets to red blood cells were associated with improved early survival. A substudy of the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial [129] evaluated specific effects of early platelet transfusion (based on randomization to initial transfusion packs that either did or did not contain platelets), identifying decreased adjusted mortality, more frequent hemostasis, and less common exsanguination in the group receiving early platelets [130]. Importantly, these results are not generalizable to all patients: the effects of empiric platelet transfusion in nonmassively transfused trauma patients [131] and in massively transfused pediatric trauma patients [132] are unclear.

Despite these clinical observations, it is not clear that platelet transfusion improves platelet hemostatic function. Platelet storage leads to a number of important effects on platelet function (Table 3) [133–136] with wide inter-donor variability in the severity of these storage lesions [137, 138]. Further, although not traditionally administered in type-specific fashion, platelets do express ABO antigens, and ABO non-matched platelet transfusions have been linked with reduced hemostatic potential and adverse effects [139, 140]. At the patient level, platelet responsiveness to different agonists differs markedly in traumatic brain injury [22, 141] and in shock [23]. Platelet transfusion has not consistently been associated with improvement in aggregation, outcomes, or reversal of antiplatelet effects, specifically in patients with traumatic brain injury [40, 142–144]. The absence of improvement in platelet aggregation measures may be related to intrinsic platelet storage effects, circulating factors related to patient and injury characteristics, and/or variability of diagnostic measures used to assess platelet function. Additionally, whether platelet transfusion corrects [145] or even worsens [146] injury-associated platelet hemostatic function varies by the modality used to assess platelet function [36, 147, 148], and significant heterogeneity exists even between studies using the same modality [143, 149]. Finally, the timing of platelet transfusion also appears critical, as transfusion later in the clinical course has a greater impact on platelet aggregation compared to transfusion within the first 24 hours. Delineating this period of resistance to platelet transfusion on an individual basis would enable tailored resuscitation and improve utilization of this scarce resource [150]. Recent studies suggest that mechanisms other than primary platelet hemostatic function may explain the clinical benefit of platelet transfusion seen in large trials. One recent study demonstrated that while platelet transfusion did not alter platelet aggregation, it increased PAI-1, decreased tPA, and decreased viscoelastic measures of fibrinolysis [151]; this is consistent with *in vitro* observations that platelet-associated factors attenuate tPA-dependent fibrinolysis [152]. which has been linked with mortality benefits in observational studies [101].

Platelet transfusion is not without risk. Although platelets comprise 10% of all transfused blood components, they account for more than 25% of reported adverse transfusion events [153]. Principal risks of platelet transfusion include hemolytic and non-hemolytic transfusion reactions, transfusion-related acute lung injury, and viral or bacterial pathogen transmission [154]. Beyond acute adverse events, platelet transfusion may have additional subclinical damaging effects on inflammation and endothelial integrity [155], although transfusion of higher volumes of platelets was not associated with an increased risk of secondary organ failure in a large multicenter randomized trial [129]. Although empiric platelet transfusion has not been studied as an isolated intervention in trauma, a recent randomized trial in non-traumatic intracranial hemorrhage associated with antiplatelet medications linked empiric platelet transfusion with a 2-fold higher odds of death or dependence at 3 months [156].

Finally, platelets are a scarce and difficult to store resource. Addressing challenges to scarcity, storage, and portability, alternatives to current standard practices of storage of platelets at 22°C for just 5–7 days are under investigation [153]. First, cold storage [157] and lyophilization [158] of platelets are appealing strategies to address logistical concerns. Storage of platelets at 4°C may extend their effective lifespan up to 14 days and lower risks of infectious complications. Prospective trials are underway to validate cold stored platelets in trauma, and lyophilized platelet-derived hemostatic products are now entering phase II trials as adjuncts to hemostasis [159]. Furthermore, non-component platelet administration as part of whole blood transfusion has shown clinical feasibility and potential benefit in both military [160] and civilian [161] settings. Platelet-derived extracellular vesicles have also been identified as feasible products for transfusion, as they show evidence of endothelial support and procoagulant effects *in vitro* and enhanced hemostasis *in vivo* [77, 162]. Beyond platelet transfusion, small studies suggest that pharmacologic agents such as desmopressin [163], tranexamic acid [164], and valproic acid [165] may augment existing platelet function. Finally, synthetic platelet particles have been developed that are shelf-stable, portable, and hemostatic both *in vitro* [166] and in animal models of hemorrhage [167, 168].

Adaptation or dysfunction?

It is an open question as to whether the changes in platelet behavior after trauma summarized in this review reflect adaptive or maladaptive responses. A prevailing view is that critically injured patients have sustained insults which would almost certainly have been fatal in the environments to which humans are evolutionarily adapted; hence, these post-injury platelet behaviors are unintended extensions of hemostasis, unregulated by natural selection, and only recently unmasked by modern medical practice. It is tempting to speculate that the alterations in trauma-induced platelet behavior described in this review represent ‘exhaustion’ of platelet hemostatic competence in the face of sustained, profound activation.

An alternative explanation is that these behaviors remain an adaptive response to major blood loss, and that survival bias leads us to label their associated side effects as ‘dysfunction’. For survival to occur after major injury, the low-flow state related to acute hypovolemia may be best managed by maintaining a relatively hypocoagulable state to

reduce the risk of microvascular thrombosis and maintain organ perfusion [169], potentially explaining the paradoxical phenomenon of reduced platelet aggregation during active hemorrhage. This argument is problematized by the switch to a relatively prothrombotic state later after injury.

Similarly, it is not clear whether platelet contributions to post-traumatic inflammation are detrimental or beneficial. As discussed, platelets are important in danger recognition, damage response, and wound healing. It seems clear, however, that in some circumstances platelets contribute to excessive systemic inflammation resulting in secondary injury to remote tissues. One potential explanation is that platelets responses are appropriate for localized responses to minor injuries, but that these responses become untethered, dysregulated, or excessive in the context of major tissue damage and hemorrhagic shock. In all likelihood, classifying platelet responses as adaptive or maladaptive is an over-simplification.

Future Directions

There is a pressing need for further investigations into platelet behavior beyond conventional aggregometry. It should be recognized that most point-of-care platelet function assays used in trauma were designed to detect antiplatelet medication efficacy for agents such as aspirin or clopidogrel [149, 170], and have only secondarily been generalized to injury states. The use of exogenous agonists to stimulate platelet activation *in vitro* relies on the principle that platelets are in an inactivated state and will only aggregate when stimulated; this may not hold true when investigating platelet responses in severely injured patients. Broadening the assessment of platelet function in the setting of injury to include flow and endothelial environments via high-throughput microfluidics measurements, structural assessments via microscopy, mitochondrial respiration measures, and expanded panels of biomarkers of platelet activation and platelet-endothelial interactions are needed as important next steps [30, 43, 136, 171, 172].

Soluble mediators present in plasma of patients with TIC are able to induce impaired platelet responsiveness[29] - identifying these mediators is a promising research target to open the door to novel therapeutics targeting such mediators as HMGB1 or histone H4. Examination of individual receptors involved in specific agonist responses - such as GPVI and GPIbα in the response to collagen, or PAR receptors in response to thrombin - could also inform new treatment approaches [173]. Modulation of platelet structure and mitochondrial function are also potential targets [174]. Molecular regulation at the single platelet level also holds promise, as recent studies suggest that a pool of resident immature ribonucleic acids undergo splicing modifications contributing to individual platelet behaviors [175, 176]. Given the complexity of the intravascular milieu in the critically injured patient, it is likely that multiple mechanisms act in concert to produce the phenotypic changes described in this review.

In the short term, improvements in patient selection for platelet transfusion in trauma and hemorrhage could improve targeted delivery of this resource-limited intervention. In the longer-term, insights into the specific functional mediators of platelet transfusion and effects

of storage may stimulate the replacement of allogeneic blood products with novel synthetic therapies or purified platelet-derived mediators. This process has already begun with the development of functional synthetic platelet-mimicking particles [177], and is likely to be a major focus for research and innovation in years to come.

Conclusion

Platelets are increasingly recognized as sentinel damage-recognition agents with diverse roles in hemostasis, thrombosis and inflammation. Recent advances in our understanding of platelet biology have led to reevaluation of and renewed interest in their roles in the response to major trauma. Work is ongoing to further delineate the contribution of platelets to trauma-induced coagulopathy, immunothrombosis, and post-traumatic organ dysfunction. Novel therapeutic strategies are already emerging as a consequence of these investigations, and there is great potential to translate increasing understanding of platelet biology after injury into improved clinical outcomes in this important patient population.

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Table 1:

Summary of alterations in platelet behavior after major trauma.

Increased	Reduced
Basal markers of activation	Aggregation on *ex vivo* stimulation
Ballooning platelets	Responsiveness to Ristocetin
Extracellular vesicles	Adhesion under flow
Platelet-leukocyte interactions	Calcium mobilisation
Platelet HMGB-1 release	
Circulating sCD40L	

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Table 2:

Cellular changes in leukocytes induced by platelets

Integrin activation
Release of granular contents
Production of DNA-containing extracellular traps
Transcellular biosynthesis of lipid mediators
Induction of inflammatory gene expression via NFkB

Table 3:

Storage-induced alterations in platelet structure and function

Impaired response to stimulation
Mitochondrial dysfunction
Reduced support of endothelial integrity
Loss of surface receptors
Release of granular content
Phosphatidylserine exposure