

## Review (Narrative)

# Do Platelets Play Roles as An Immune Component?

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**SUMMARY**

Platelets are enucleate mobile fragments acknowledged for his or her important position in coagulation and vascular integrity. But, evidence is becoming more and clearer that platelets make contributions to various immunological strategies extending the past conventional view of platelets as fragmentary mediators of homeostasis and thrombosis. There may be current proof that platelets take part in: 1) intervention in opposition to microbial threats; 2) recruitment and promoting of innate effectors mobile capabilities; 3) modulating antigen presentation; and 4) enhancement of adaptive immune responses. In this way, platelets ought to be regarded as the underappreciated orchestrator of the immune system. This review will talk latest and ancient evidence regarding how platelets affect both innate and adaptive immune responses. As an instance, platelets have lately been proven to chemotaxis in response to specific stimuli and produce micro particles able to beginning each thrombosis and infection. The substantial role of platelets is a world still opens to exploration and could provide a non-stop source of amazement into the competencies of these anucleate cells.■

**KEYWORDS** Platelets; Immunity; Immunotherapy; Chemotaxis; Antigen presenting cells

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**T**HE classical function attributed to platelets has been inside the prevention of bleeding and the initiation of wound recovery. But, platelets in the interim are identified for their activities impartial of thrombosis. Platelets are the second one maximum great blood cell excellent outnumbered through manner of erythrocytes within the motion ( $\sim 1.5\text{-}4.0 \times 10^{11}$  platelets consistent with liter of blood in healthy individual people). In addition to their extraordinarily excessive numbers, they may be able to storing and releasing bioactive mediators and particular a huge style of realistic immunoreceptors. Platelets keep the ones bioactive molecules in 3 types of intracellular storage granules specifically dense ( $\delta$ -) granules, alpha ( $\alpha$ -) granules, and lysosomal ( $\lambda$ -) granules which can be released into the circulation or translocated to the surface upon platelet activation (1). It's is indicated that platelets package deal those numerous bioactive molecules discriminately into wonderful granule subpopulations and undergo differential styles of launch which will respond to remarkable types of tissue damage or threats in a selected and selective manner (2). Those are counseled to position platelets to play an important role in successfully speaking with and modulating the feature of different cells and to perform sentinel responsibilities in regulating immunity. Despite the fact that they contribute to various immunological methods, the immune functions of platelets were underappreciated. The characteristics of platelet cellularity and the recognition of platelets as "immune cells" were controversial. But, platelet immune functions have grow to be increasingly customary now that their molecular makeup supports viewing those "cells" as specific and vital additives of innate immunity (3, 4). Platelets have interaction the immune gadget by interacting with diverse immune cells and collaborating in each innate and adaptive immune response (5).

The potential of platelets to take part in innate immunity is largely because of their potential to release a myriad of inflammatory and bioactive molecules stored inside granules or synthesized upon activation. These mediators entice and modulate the effectors cells of the innate immune gadget. In addition, platelets themselves show direct effectors characteristic and therefore are seemed as effectors cells in innate immunity (6).

Platelets are the various first cells to discover endothelial injury and microbial pathogens as they advantage get entry to or invade the bloodstream or tissues. Injured endothelium exposes collagen and different mem-

brane proteins which allow platelets to adhere. Stable adhesion to collagen leads to platelet aggregation and promotes the release of such platelet against as ADP, thrombin, and VWF, main to activation and further platelet recruitment to the web sites of tissue damage and infection. This serves a two-fold purpose: 1) homeostasis where blood loss is best; and a couple of) frontline host protection against microbial infection. In addition, platelets specific CC and CXC chemokine receptors together with CCR1, CCR3, CCR4 and CXCR4 which discover indicators for all 4 types of chemokine (C, CC, CXC and CX3C) generated at websites of infection, ensuing in speedy accumulation of platelets to the website online of contamination (7). Platelets also explicit sample reputation receptors (PRRs) consisting of toll-like receptors (TLRs) which stumble on pathogen associated molecular patterns (PAMPs). The detection of PAMPs is an effective host defense characteristic of platelets to ensure a fast reaction to that specific danger (1, 8). It changed into proven that human platelet TLRs can recognize and discern diverse isoforms of bacterial LIP polysaccharide (LPs) through TLRs and respond differentially to distinct PAMP by way of releasing special cytokine profiles and effectors peptides.

Platelets interact with bacteria, viruses, fungi and protozoa show anti-microbial capabilities. The mechanism of platelet-micro organism interactions are complex because of the range of platelet receptors concerned in the popularity of bacteria. Platelets specific a huge range of bacterial receptors, along with supplement receptors, FC $\gamma$ RIIA, TLRs, GPIIB-III A, and GPIB, and the interplay of platelets and bacteria is mediated via direct or indirect binding to those receptors (9). Upon touch with sure micro organism, platelets can become activated, aggregate and degranulate. Activated platelets launch over three hundred recognized secretory products which include anti-microbial merchandise (collectively referred to as platelet microbicidal proteins (PMPs)). Four households of PMPs were proven to be released from platelets which encompass kinocidins (CXCL4, CXCL7 and CCL5), defensins (human  $\beta$  defensin 2), thymosin  $\beta$ 4, and derivatives of PMPs (thrombocidins and fibrinopeptide A or B). Recently, a take a look at validated the expression of  $\beta$  defensin 1 in human platelets and its novel antibacterial interest (9, 10). It changed into observed that activated platelets surround *Staphylococcus aureus* and force the pathogens into clusters which reduce growth charge. Platelet-derived  $\beta$  defensin 1 not simplest impaired the increase

of *S. aureus*, however additionally brought about neutrophil extracellular trap (NET) formation. Interestingly, platelets launched  $\beta$  defensin 1 after being inspired with *S. aureus*  $\alpha$ -toxin, but not through agonists that set off granular secretion.

In addition to the anti-microbial mechanisms, platelets can internalize micro organism and viruses. Particularly, platelets had been shown to engulf *S. aureus* and human immunodeficiency virus (HIV) for this reason promoting pathogen clearance from blood stream and tissues. In reality, platelets are able to no longer most effective internalizing objectives but also the killing of diverse internalized bacterial species such as *Escherichia coli* and *S. aureus*. Whether or not this entitles platelets a capacity phagocytic function desires similarly research. Furthermore, platelets generate and launch hydrogen peroxide and other reactive oxygen species to mediate different anti-microbial outcomes in reaction to stimuli (10).

Platelets have the capacity to have an effect on immune responses and kill pathogens; but, pathogens have also advanced mechanisms to evade platelet immune sports. As an example, the gram-fine *S. aureus* is widely known to govern more than one elements of platelet activation (11). *S. aureus* expresses von Willebrand binding protein (VWBP) which binds von Willebrand factor (VWF) and also can set off prothrombin main to fibrin production resulting in clot formation. The micro organism can then use the formation of clots and publicity of VWF as an anchoring for colonization of tissue main to complications consisting of infective endocarditic. *S. aureus* also can make use of fibrinogen to crosslink platelets and reason their activation through the GPIIb-IIIa integrin making *S. aureus*/platelet/fibrin complexes leading to platelet activation (12).

Streptococcal species have also been extensively studied on the subject of platelet activation. In addition to *S. aureus*, *S. pyogenes* M1 protein can bind fibrinogen main to ligation and crosslinking of the GPIIb-IIIa integrin and subsequent platelet activation and aggregation. However, *S. pyogenes* does not create stable aggregates and it has been shown that the bacteria can then escape from the shaped mixture. *S. pneumoniae* can spark off platelets through TLR2 signaling, and different streptococcal species can immediately bind to the VWF receptor GPIbA. Platelet interactions with micro organism aren't restricted to gram high-quality species. In a version of *Klebsiella pneumoniae*, platelet depletion

caused multiplied mortality in mice; but, in the follow up article the authors found out that this become no longer due to loss of platelet TLR4 signaling (via exclusion of MYD88 signaling) (13).

In parallel to their interactions with and reaction to bacterial pathogens, platelets come upon protozoa, parasites, and viruses. Particular molecular and immune activities are brought about upon the encounter and in response to distinctive classes of pathogens. As an instance, after protozoal *leishmania* contamination in vertebrates, within one minute of blood contact, platelets adhere to *Leishmania promastigotes* which rapidly advanced into large leishmania-platelet aggregates and that is believed as a key mechanism to beautify their phagocytosis and clearance from blood. Off route, this is not a popular response mechanism that is not unusual to all protozoans. Human platelets kill *Toxoplasma gondii* via a mechanism that entails thromboxane A2 synthesis, some other instance of their protecting role in protozoal infections as well as their specific response to specific pathogens (14).

Earlier observations confirmed that human platelets inhibit the growth of the acknowledged malaria parasite, plasmodium falciparum, *in vitro* whereas a later observe stated that human platelets kill plasmodium in infected human red blood cells and mediate survival to infection. In either case, the consequences from both research suggested a protective characteristic for platelets only within the early tiers of erythrocytic contamination. Interestingly, this is wonderful from their position in cerebral malaria (CM) as platelets are recognized to have a negative function and considerably make contributions to the pathogenesis of CM (15). There are several reports demonstrating distinct mechanistic roles for platelets in using the pathology related to CM. Those contradictory unfavorable as opposed to defensive outcomes of platelets in cm and inside the early stages of malaria indicates the complexity of the implicated role of platelets in CM. However, a current observe attributed this complicated position to the timing of platelet activation at some point of infection. The results show that platelets are activated very early in experimental CM (ECM) and result in the extreme segment reaction to blood level contamination which in turn limits parasite increase early submit contamination and protect mice from ECM, whereas continued platelet activation because the disease progress contributes to ECM associated irritation (16).

Platelets also make contributions to antiviral immunity. They come upon and interact with viruses as confirmed by using experimental and clinical models of viral infections from *HIV*, influenza virus, dengue virus and hepatitis C virus. Platelets display an immediate interaction with *HIV-1* through different mechanisms together with binding, engulfment, and internalization, all of which play a position in host defense during *HIV-1* infection, by using proscribing viral spread and probably by means of inactivating viral debris (17). It became shown that supernatants from activated platelets suppressed *HIV-1* infection of t cells and that the inhibitory hobby was attributed to platelet-derived *cxcl4* suggesting that the granule content may exert antiviral pastime. In a murine model of lymphocytic choriomeningitis virus (LCMV) infection, platelets avoided lethal hemorrhage with the aid of selling cytotoxic T lymphocyte (CTL)-dependent clearance of the virus (18). Animals depleted of platelets had reduced viral clearance and impaired virus-unique CTL response. The protecting immune response of platelets to *lcmv* was additionally tested through stopping splenic necrosis. Some interactions alter morphology and hemostatic properties of platelets main to immune-pathological results together with thrombocytopenia as seen in dengue contamination. In the example of dengue virus (DENV) contamination in vitro, now not most effective do platelets bind to DENV directly; in addition they release energetic virions indicating that they are able to actively spread the contamination. This illustrates that the stumble upon of viruses via platelets are complicated and that both host defense and damage can result (19). This complexity in platelet-pathogen interactions that result in pathogen clearance or host harm depend upon the biologic context and platelet interactions with other host immune effectors cells.

Even though platelets are in general placed intravascular, they can greatly affect leukocyte recruitment to areas of inflammation in lots of tissues, but we limit our dialogue to lung, pores and skin and kidney as examples with many overlapping mechanisms. Platelet-leukocyte interactions were extensively studied within the lung, especially throughout each sterile and non-sterile irritation. Importantly, studies overwhelmingly display that platelets appear to play an essential position in regulation of lung damage due to granulocyte infiltration (20). For instance, in a murine model of ovalbumin (OVA)-inspired lung infection, depletion of platelets the usage of both the busulfan approach and anti-platelet

serum significantly decreased eosinophil and leukocyte recruitment to the lung tissue. Furthermore, this effect was determined to be due to loss of p-selection on platelets and no longer on endothelial cells. Thrombocytopenia abrogated eosinophil recruitment and it turned into handiest restored when mice had been transfused with platelets that have been dealt with thrombin after which fixed with 1% paraformaldehyde. No longer best is the floor receptor p-selection worried in allergic inflammation, however the purinergic P2Y1 (no longer P2Y12) receptor has additionally recently been implicated in recruitment of leukocytes in allergic infection (21). Using precise inhibitors to all purinergic receptors on the platelet floor, inhibition of leukocyte and granulocyte recruitment changed into most effective found with P2Y1 antagonists, displaying specificity and feasible goals for intervention. Importantly, during allergic infection in each rodents and sufferers, there was a boom in circulating platelet-leukocyte complexes which could lead to elevated infiltration to the lung due to platelets binding the infected endothelium main to leukocyte binding and extravasation. Not handiest do platelets have an effect on granulocytes in allergic irritation; they induce activation of dendritic cells at some point of allergic infection and probable make contributions to antigen presentation by using professional antigen supplying cells (APCs) (22).

In sufferers with atopic dermatitis, a type of allergic infection that results in formation of purple patches at the skin mediated by IgE, markers of platelet activation (PF4, soluble p-selection) are appreciably expanded in the blood. Once the skin lesions have cleared, platelet interest returns to ordinary degrees. Further, in patients with psoriasis, a persistent immune-mediated inflammatory situation of the pores and skin, platelet aggregation in reaction to agonist is amplified and extended plasma p-selection ranges had been said (23). The use of murine fashions of acute and continual pores and skin inflammation, it's clear that platelets play a position in recruitment of leukocytes main to increased severity of those conditions, because of mechanisms regarding p-selection. In atopic dermatitis platelet depletion showed a lower in leukocyte recruitment to the epidermis which leads to much less severity of the disease. In fashions of touch dermatitis, a situation involving an inflammatory reaction to a chemical allergen immediately at the pores and skin, platelets are also liable for law of hemorrhage and edema via inflicting leukocyte infiltration. In both of those allergic skin fashions of infection

platelet p-selection seems to be the maximum important issue (24). The findings are similar with cutaneous arthus response mediated by using immune complexes, which also showed that platelet p-selection performs a primary function in leukocyte recruitment.

Acute kidney injury (AKI) can arise from a couple of mechanisms starting from ischemic injury to injury from infection. AKI has a high mortality charge, and is characterized by using platelet-based neutrophil infiltration leading to harm to the organ. Platelet p-selection is once more implicated within the recruitment of neutrophils to the inflamed kidney. Apparently, it was additionally proven that neutrophils are required for platelet recruitment to inflamed glomeruli. Activated platelets can release soluble CD40L and are responsible for about ninety 5% of the SCD40L in flow. CD40L is an essential cytokine that leads to activation of an extensive spectrum of immune cells. Importantly, the receptor for CD40L, CD40, exhibits multiplied expression inside the injured or infected kidney. It has been shown that the interaction of CD40L and CD40 inside the kidney is an essential factor in mediating both acute and chronic kidney damage (25).

Platelets are acknowledged to persuade the innate immune response through law of each the maturation and activation of such innate immune cells as macrophages, neutrophils, and dendritic cells. First proven in vitro using co-culture studies, platelets can set off maturation of monocytes into macrophages. In addition research has elaborated on specific platelet additives that are accountable for differentiation of monocytes to macrophages (26). Even though platelet cytokines inclusive of RANTES and IL-1 $\beta$  have been proven to prompt monocytes, the chemokine CXCL4 plays a first-rate role on this differentiation manner from monocyte to macrophage. While platelets are activated or undergo apoptosis they release platelet micro particles (PMPs) which could have an effect on macrophage differentiation and neutrophil activities.

Platelets have also been implicated within the maturation and activation of dendritic cells (DCs), indicating platelets can help bridge the innate and adaptive immune structures. Platelets have already been shown to recruit DCs through JAM-C/MAC-1 interaction main to dc activation (26, 27). Platelets can also result in activation of naïve DCs through SCD40L after stimulation with thrombin. Curiously, another document described that platelets want now not be in contact with immature DCs to prompt them and that SCD40L from plate-

lets was not causative of activation. DCs are taken into consideration expert phagocytes and are important in bridging the innate and adaptive immune structures (28). Maturation and activation of DCs cause presentation of antigen to t cells and induction of the adaptive immune response.

The position of platelets in innate immune responses has been recognized for at the least four a long time. But, the function of platelets in adaptive immune response is emerging and has now not been surely elucidated. Developing proof shows that platelets and their derived merchandise affect adaptive immunity and play enormous roles in shaping the immune response (29). As an instance, it showed that platelets express purposeful CD154 (CD40L), a molecule vital to the modulation of the adaptive immune reaction.

Platelets no longer only play a function in antigen presentation, but also affect T cell responses. The capability of platelets to participate in T mobile immunity turned into investigated upon the invention that activated platelets express purposeful CD40L as mentioned above. An early study showed that platelets through CD40L augmented CD8 T cellular responses and enhanced protective secondary immune responses towards viral contamination. Similarly, platelets promote cytotoxic T lymphocyte (CTL) hobby and appear to have interaction with CD8 T cells to facilitate the targeting of virally inflamed host cells required for viral reservoir clearance. Within the absence of platelets at some point of viral hepatitis, liver irritation is decreased but viral titers are elevated because of lack of CD8 cells (29). In the presence of platelets, liver irritation is increased due to CD8 mobile infiltration however viral titers are decreased. In this acute viral hepatitis mouse model, transfusion of everyday platelets into platelet-depleted mice restored CTL accumulation and targeting of virally inflamed hepatic cells.

Platelets also modulate B cell adaptive responses to microbial pathogens. As mentioned above, it's miles properly mounted that CD40L on activated CD4 T cells trigger B cellular CD40 supplying the second signal necessary for T-cellular-based b lymphocyte activation, next isotype switching, and B cell differentiation and proliferation. This position of platelets in mobilizing B cellular humoral immune responses become clearly observed through the usage of the murine CD40L<sup>-/-</sup> mouse model. On this model, transfusion of activated wild-kind platelets, however now not CD40L<sup>-/-</sup> platelets, become sufficient to set off B cellular isotype switching.

This study also established that depletion of platelets in wild-kind mice compromised their capability to mount an efficient IgG response (30). A next record also demonstrated that adaptively transferred wild-type CD4 T cells alone into CD40L<sup>-/-</sup> mice failed to generate green B cell germinal center and antibody responses to adenovirus, but were able to significantly increase germinal middle formation and IgG production upon transfusion together with wild-kind platelets. These consequences

had been discovered beneath proscribing conditions of CD4 T cells or antigen dose which resemble the physiological putting at the time of a preliminary antigen encounter. But, platelets did no longer add to the mounted reaction to high dose adenovirus or upon the transfusion of high quantity of CD4 T cells (31, 32). Together, those results may also advise that platelets increase T cell-based B cell responses through linking T movement and B movement interaction via CD40-CD40L. ■

## ARTICLE INFORMATION

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