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Chapter 4

Platelet and Immunity in Transfusion Medicine

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Abstract

Platelets are classically used in the clinic to maintain hemostasis, while recent evidence has shown the important role for platelets in the host inflammatory and immune responses. In fact, platelets in vivo produce different mediators such as cytokines or chemokines, which may be involved in the course of disease treatment, thus platelets transfusion is often an effective therapy in many cases. It is well known that platelets can regulate neutrophils, lymphocytes and other immune cells behavior in immune response, thus directing these immune cells onto the damaged tissues, organs or infected sites. On the other hand, platelets can induce neutrophil extracellular traps release in response to bacterial or viral infection. All the characterized novel profile of platelet, if not all, at least in some situations, should be take into consideration when platelets have to be transfused into patients.

Keywords: platelets, inflammation, immunity, transfusion, infection

1. Introduction

Platelet is one of the visible components in mammalian blood and is shed from the cytoplasmic cleavage of megakaryocytes in bone marrow. Platelets are small and nucleuses cells with a diameter of 2–3 μm. There are 100–300 × 10^9/L platelets in human blood circulation system [1, 2]. It was first proposed as platelets by an Italian physician Giulio Bizzozero in 1862 after he found that platelets played an important role in the process of hemostasis after vascular injury [3]. Now, platelets are used to curing dysfunction of blood coagulation, thrombopenia and other diseases in hemostasis. As blood homeostasis greatly depends on platelets (PLT), platelets are routinely transfused and its consumption is enormous in worldwide. There approximately 393375 PLT components were administrated between 2010 and 2012 in the United States America [4], while the transfusion of PLT in China increases dramatically during past years.

To prevent activation *in vitro* before transfusion, platelets are conventionally being maintained at 22 ± 2°C within shaking incubators, and this strategy only can guarantee functional PLT available for 5–7 days. This storage temperature for PLT is a risk because of bacterial contamination. However, bacterial infections after platelet transfusion are rarely reported. There were only 39 transfusion-transmitted bacterial infected cases among the 790854 PLT transfusions [5]. We recorded that the adverse reaction after PLT transfusion was 1% between 2013 and 2015, and bacterial contamination was not observed at all. The main reason undoubtedly is restrictive PLT prepare and administrative procedures. However, the possibility that platelets may have the potency to inhibit bacteria growth is not excluded.

Now, there is gradually recognized that platelets not only participate in hemostasis but also play a role in immune response. Actually, platelets have been reported could help liver macrophages (known as Kuffer cells) to fight against *Bacillus cereus* and methicillin-resistant *Staphylococcus aureus* (MRSA) in mice and platelets were the first cells that contacted with bacteria in liver [6, 7]. Platelets were also identified to contain immune recognition receptors, such as Toll-like receptor 4 (TLR4). Platelets are shedding from megakaryocytes in bone marrow. Each megakaryocyte can produce about 2000 platelets. The content of mRNA is very low in platelet, but it possesses 1/3 transcripts of the whole human genome can encode [8, 9]. There are α, δ and λ particles in platelets, and it is well known that microbicidal proteins (PMPs) and antibacterial effect cytokines are contained in the α particles [10]. So it's no strange that platelets may have the functions similar to neutrophilic granulocyte, and behavior more like immune cells [11].

As methicillin-resistant *S. aureus* infection usually results in high mortality, it has been a serious threat to clinical patients and public health. Broad-spectrum antibiotics vancomycin, cefoxitin and tigecycline are used to control MRSA infection, but frequent use of antibiotics is easy to induce drug resistance. Thus the multidrug resistant "super bacterial" was produced. The "super bacterial" is a great threat to human health. Cunningham et al. found that the platelet-rich plasma (PRP) could significantly inhibit the growth of *E. coli* in vitro [12]. In vivo studies using rabbit endocarditis model have shown that platelet-rich plasma could distinctly relieve the early stage endocarditis induced by *S. aureus* [13]. These studies may reveal the antimicrobial effect of platelets, and platelets may be a potential therapeutical agent to retard the regeneration of "super bacterial".

2. Platelet is essential to coagulation

The physiological role of platelets is to aggregate, be activated to adhesion and initial the blood clot process on the wound site. Stimulating factors such as hormones, hypoxia, vascular endothelial injury and a variety of proinflammatory cytokines, granules can cause platelet activation. When the injury of blood vessel occurs, the structure of collagen located in vascular endothelium is changed to be easily combined with von Willebrand factor (vWF). Then the vWF/collagen complex is recognized by the glycoprotein Ib α (GPIbα), which is expressed on the surface of platelets, to recruit platelets to the injured site. Meanwhile, the collagen receptor glycoprotein VI (GPVI) on the platelets membrane is continuously expressed to make the

adhesion of platelets to the injury site more stable. After then, the activation of platelets will happen [14, 15]. Activation of platelets is the key step in the coagulation. This is all depended on the cascade amplification of platelets activation. Once the platelet is activated, its shape changes from discoid to pseudopodium. Meanwhile, the activated platelets release particles to the surrounding environment, thus concentration of adenosine diphosphate (ADP) and thromboxane A2 (TXA2) from the platelets particles get higher in the vicinity, and will combine with the adenonucleotide receptors P2X1 and P2Y12 on the adjacent platelets to induce activation [2, 10, 16]. CD62p (p-selectin) is a common marker for activated platelets, and can be acting as a bridge between platelets and immune cells that contain P-selecting Glycoprotein Ligand-1 (PSGL-1) [17].

Moreover, the number of platelets is negatively related to the severity of the disease. It is gradually clear that platelets will be activated and helpful to recruit immune cells like neutrophils to the infection sites. This illustrated that platelet may be not only simple enough to clot, but it also plays a role in the immune response.

3. Platelets express a variety of immune recognition receptors

Platelet cell surface contains a variety of pathogens pattern recognition receptors (pattern recognition receptors, PRRs), such as the Toll-like receptor (TLR) family [18], nucleotide-binding oligomerization domain-like receptor (NLR) family, formyl peptide receptor (FPR) (see in **Figure 1**). These PRRs are helpful to the immune system to resist infection.

TLR is classical of key molecules in human innate immune response to pathogens. Different TLRs could specifically recognize specific pathogens and induce immune cells to secrete different cytokines, resulting in varying degrees of host defense immune response. TLR4 is reported to be existed in both human and mice platelets [19, 20]. TLR4 can effectively recognize Gram-negative bacteria lipopolysaccharide (LPS) and then contribute to acquired immune response. LPS can induce rapid thrombocytopenia, hypotension, and sepsis. In the LPS-induced mouse endotoxemia model, the accumulative platelets in the lung only happened in TLR4 wild-type mice, not in TLR4 deficient animals. LPS could stimulate platelet secretion of dense and granules as indicated by ATP release and P-selectin expression, and thus enhance platelet activation [20, 21]. Platelets express TLR4, CD14, MD2, and MyD88 which are the LPS receptor-signaling complex, and the effect of LPS on platelet activation could be abolished by an anti-TLR4-blocking antibody or TLR4 gene knockout, suggesting that the effect of LPS on platelet aggregation depends on the TLR4 pathway [21]. Recent studies showed platelets TLR4 detected its ligands in blood and induced platelets binding to adherent neutrophils [22]. In addition to TLR4, TLR2 and TLR9 were also detected in platelets.

The NOD2 receptor is a cytoplasmic PRR, mainly recognizing the intracellular antigen and could effectively recognize the Gram-positive bacterial muramyl dipeptide (MDP) to help the body to play immune defense. The NOD2 receptor is mainly expressed in monocytes, macrophages, dendritic cells, intestinal epithelial cells, and paneth cells. But NOD2 receptor in human platelets was identified in recent [23]. The NOD2 receptor is necessary for platelet

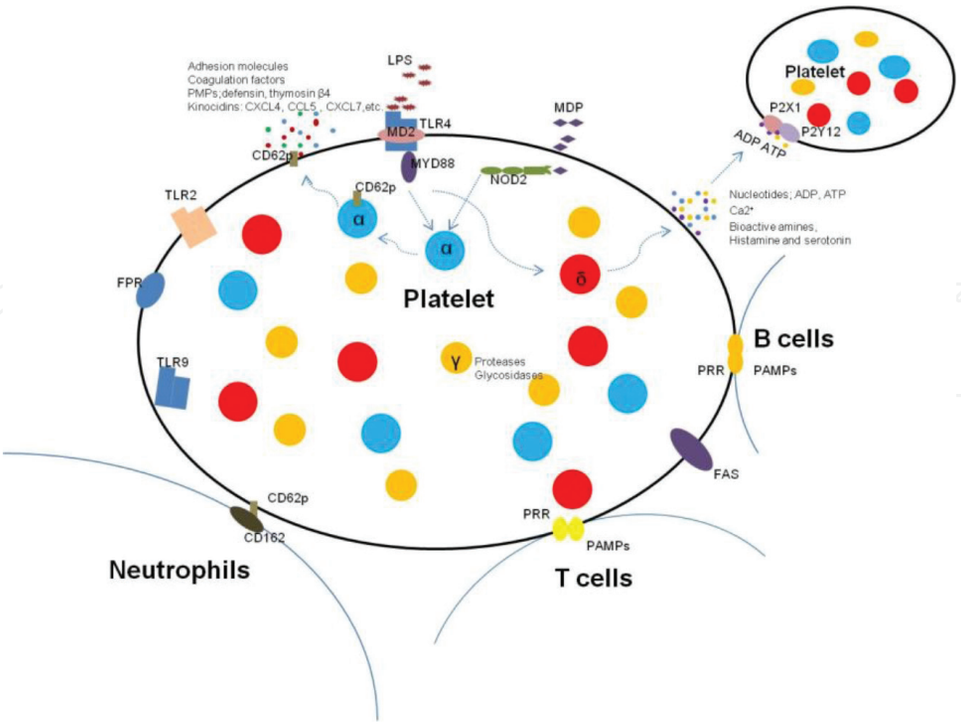

Figure 1. The immune receptors and factors in platelets.

aggregation and dense granule release induced by MDP, and the RIP2/MAPK pathway is involved. Different from the NOD2 receptor, there is no NOD1 receptor in the platelets.

In addition to TLR4 and NOD2 receptor, platelet membrane surface also exists formyl peptide receptor (FPR) [24], which plays important role in antimicrobial defense and an apoptosis-related FAS pathway surface receptors exists in platelets too [25]. These immune recognition receptors provide the possibility for the platelet to participate in immune response, which suggests that platelets have the similar function to other immune cells.

4. Platelet granules contain special antimicrobial peptide

The platelet granule contains many molecules. Among the three type (α, δ, λ) of granules, nucleotides (such as ADP, ATP, and GTP), bioactive amines (histamine and serotonin) and bioactive ions Ca^{2+} are stored in the δ granules; Enzymes such as proteases and glycosidases are stored in the λ granules; The α granules contain the abundant molecular for hemostasis (for example, adhesion molecules, coagulation factors), the proteins and cytokines for antibacterial activity (see in **Figure 1**). The α granules also have molecules such as mitogenic factors and protease inhibitors [26]. The molecules in platelets with antibacterial activity now have been classified as platelet microbicidal proteins (PMPs) and kinocidins [27]. There are kinocidins CXC chemokine ligand 4 (CXCL4; also known as PF-4), CCL5 (also known as RANTES) and CXCL7, and PMPs such as a human defensin, thymosin β4, and fibrinolytic products (FP-A, FP-1) isolated and identified with antibacterial activity [28]. Structural analysis showed that a cationic carboxy-terminal α-helix, which is consistent with peptides that

exert direct microbicidal activity. These modular N- and C-terminal regions are an antiparallel β-sheet domain containing the γ-core motif, which is characteristic of all cysteine-stabilized host defense polypeptides in CXCL4 [29]. CCL5 and CXCL4 were detected with high secretion after HIV infection [30]. Human β-defensins displayed classic antimicrobial activity and played a key role in the process of neutrophil extracellular trap formation [31].

Recognition of bacteria by the surface receptor on platelets can activate the platelets effectively and specifically, and induce the release of molecules from platelets granules. Then activation of different types of downstream immune cells indirectly promotes platelets to be involved in immune defense. Studies showed that platelets secrete different type and different doses of molecules when stimulated by different bacteria. When *Escherichia coli* and Salmonella contacted with platelets, the secretion of CCL5 and PDGF were at different levels, while the level of CD62p and CXCL4 were no significant difference. This diversity also exists when peripheral blood mononuclear cells (PBMCs) exposed to the supernatant of platelets contacted with Minnesota Salmonella-induced secrete IL-6, IL-8, and TNFα, while the supernatant of *E. coli* stimulated platelets could not do that [32].

There are many cytokines stored in platelets granules, which the role is not clear yet in hemostasis. For example, transforming growth factor-β (TGF-β), which plays unique and potent immunoregulatory properties, is the most stored in platelets α granules compared to that produced by each leukocyte lineage, including lymphocytes, macrophages, and dendritic cells. The content of TGFβ-1 in platelet is 40-100 times higher than those in other tissues [33, 34]. Increased levels of TGFβ-1 in circulation are usually associated with a wide range of dysfunctional disorders. The level of TGFβ-1 in circulation is always elevated in Marfan syndrome (MFS), coronary heart disease, aortic stenosis and malignancy [35–39]. In contrast, in patients with autoimmune thrombocytopenia, the level of TGFβ-1 in circulation was drastically reduced and increased after treatment [40]. This observation indicates that TGFβ-1 from platelets plays an important role in the immune regulation in diseases. So the role of TGFβ-1 may be helping participate in immune activities, whether TGFβ-1 has an impact on bacteria inhibition is not known yet.

5. Antibacterial activity of platelet rich plasma

Platelet-rich plasma (PRP) is used to inhibit bacterium growth in vitro and in vivo [12]. Study of PRP on knee osteoarthritis displayed significant improvement in pain with an effect lasting for up to 6 months [41]. *E. coli* was significantly inhibited in a time-dependent manner when platelets co-cultured with platelet rich plasma (PRP) compared to the platelet poor plasma (PPP). The inhibitory effects increased after co-cultured for 0.5 and 2 h by addition of thrombin to pre-activate platelets in PRP [13]. Studies using rabbit endocarditis model induced by *S. aureus* indicated that platelet-rich plasma could distinctly relieve the early stage endocarditis. In a study of antimicrobial properties of autologous PRP in controlling *S. aureus* with pressure ulcers (PrUs), which is particularly to urine and feces, resulted in increased colonization of wounds, local application of autologous PRP changed the "biological milieu" of the PrUs by its antimicrobial properties, leading to the a reduction of bacterial colonization.

This must be a significant association between PrUs colonization and bacteria present in local environment [42]. An in vitro study of antibacterial properties of PRP on five bacteria (*E. coli, S. aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Streptococcus faecalis*), indicated that both PRP and PPP inhibited bacterial growth for up to 2 h of incubation. The antimicrobial effect of PRP was significantly higher than that of PPP, and the inoculation concentrations lower or higher, the incubation times longer or shorter are mainly depending on the different bacterial strain. It also indicated that PRP might supply an early protection against bacterial contaminations, because the inhibitory effect is already evident from the first hour of treatment, which may provided the possibility that physiological molecules in PRP might be important in the time interval required for the activation of the innate immune response [12]. As plasma contains antimicrobial peptides and other active substances, the inhibition effect are dependent on platelets or not, is not that clear yet.

6. Platelets are involved in inflammation and infection

Clinical studies have shown that bacterial infections, especially sepsis, frequently brought extensive platelet depletion, and the number of platelets is negatively correlated with the severity of the disease [43]. It is known that the sepsis caused by gram-positive bacterium such as *Staphylococcus aureus* often followed by the count reduction of platelets. And infection of gram-negative bacterium *Helicobacter pylori* can induce the immune-thrombopenia [44]. HIV patients are easily detected with drastic platelets number decrease, and this trend is more relevant to the stage of AIDS progress [45]. Similar to HIV infection, infection with Hepatitis C virus (HCV) also lead to the reduction of platelets [46]. It also reported platelets were involved in the fungal infections, such as Aspergillus, Candida, and Cryptococcus [47–50]. As platelets PMPs and kinocidins display sound antibacterial activity, more and more evidence showed that the function of platelets relates to inflammation or infection. Platelets help neutrophils to initial immune defense by secreting a variety of immune associated chemotactic factors, such as β-defensins [31]. Additionally, the link between platelets and neutrophils depends on the combination of CD62p with P-selectin glycoprotein ligand 1 (PSGL1; also known as CD162) molecular on neutrophils. When exposed to the foreign bacterium, platelets are quickly activated and adhere to the wrapped bacterium, while the platelet cell itself occurs intracellular and extracellular membrane rearrangement. Then the CD62p molecular, which rearranges to the platelet membrane surface during the activation of platelets, combines with its ligand PSGL1 to recruit neutrophils to reach the site of infection, and promote the formation of neutrophils extracellular network structure (NET) [51]. After that, it will release antimicrobial substances to kill the bacterium. Platelets can also recruit T cells or B cells (see in **Figure 1**) to reach the site of infection after the bacterial antigens presented by antigen-presenting cells (APCs) such as dendritic cells (DCs) [29, 52–54]. In addition, a recent study reported that there was stem-like megakaryocyte committed progenitors (SL-MkPs) from hematopoietic stem cells (HSCs). SL-MkPs share many features with multipotent HSCs and served as a lineage-restricted emergency pool inflammatory. During homeostasis, SL-MkPs are maintained in a primed but quiescent state, thus contributing little to the megakaryopoiesis in a steady state. Once the inflammation is triggered, SL-MkPs are

activated, resulting in megakaryocyte protein production from pre-existing transcripts, then the activated SL-MkPs mature into other megakaryocyte progenitors. This leads to an efficient replenishment of the reduced platelets during inflammatory challenge [55].

7. PLT transfusion refractory and immune-related factors

Platelet transfusion is used in cases of very low platelet counts or coagulation dysfunction. The count of platelets is usually performed by a blood cell counter, while thromboela-stogram (TEG) is used for the test of blood clotting function. It has been defined as thrombocytopenia when platelet counts are lower than 150×10^9/L. Thrombocytopathy appears if a patient has functionally abnormal platelets. Both thrombocytopenia and thrombocytopathy can result in bleeding. Platelet transfusion is suitable for and treatment of thrombocytopenia or platelet dysfunction in patients after or before bleeding, and has become a variety of hematological with chemotherapy and effective supportive therapy for cancer of leukemia patients [56]. But patients in multiple blood transfusion (whole blood, erythrocyte, platelets), pregnancy and organ transplantation, easily produce platelet-related antibodies, resulting in platelet transfusion refractory (PTR). Invalid platelet transfusion refers to the patient in the transfusion of platelets after the platelet count did not effectively improve and the clinical bleeding symptoms did not improve, either. It is generally believed that patients who have received at least two consecutive randomized ABO blood type matched platelets have not achieved a suitable post-transfusion platelet count correction index (CCI) value are considered to be ineffective in platelet transfusion (PTR). At present, the clinical judgment of PTR is mainly the percentage of platelet recovery (PPR or PR%) and CCI [57].

The main causes of PTR can be divided into two categories, non-immune factors, and immune factors. Most PTRs are caused by nonimmunogenic factors, such as the quality of platelet products, hypersplenism, disseminated intravascular coagulation, fever, and antibiotic use. Immune factors include ABO blood type incompatibility, anti-HLA, HPA antibodies, autoantibodies, drug antibodies, allogeneic immune factors. Platelet homologous immunity is equivalent to several times the frequency of erythrocyte antibodies. Antibodies against platelet surface antigens, especially HLA, are the main cause of PTR [57–59]. Platelet-borne antigens can be divided into two major categories: one is the platelet-associated antigen, including HLA class I antigen, as well as ABH, MN, lewis, etc; the other is platelet-specific antigen (HPA), which has a unique type specificity and forms part of the platelet membrane structure. HLA class I antibodies are the most common immune factors that cause PTR, accounting for 80% of all immune factors and 11.7% of all etiologies. PTR caused by HPA antibodies accounts for about 1.7% of all etiologies. Among the HPA types, HPA 1a antigen frequency is > 99.9% in the Chinese population [60, 61], and HPA 2b, 5b, 4b, 3a is not high [62], suggesting that may be the same kind of immune factors lead to the main impact on PTR antigen system.

The current clinical platelet transfusion is a mainly preventive infusion, which become an important means of treatment for thrombocytopenia patients, significantly reducing the mortality of patients with hematological and tumor disorders. However, the pre-procedure platelet transfusion was reported with a high risk of thrombosis and death. In a study of

more than 350 hospitalized patients undergoing an invasive procedure, the rate of thrombosis and death increased. Another study of pre-procedure platelet transfusions in a single facility of 376 patients, 19 thrombotic events were appeared up to 5%, this was 21 times greater than the thrombosis rate reported by the Centers of Disease Control and Prevention. So platelets transfusion triggers may need to be reevaluated in non-bleeding patients with available platelet counts [63].

8. Summary

Platelets are key factors to maintain hemostasis. Since platelets are involved in infection and inflammation, the immunologic and antimicrobial functions of platelets cannot be ignored when transfused in the clinic. The abundant molecules involved in immune recognition on the platelets surface, such as TLRs, NOD2, CD62p, provide the basis for platelets functional diversity. The functions of bacteria inhibition and performances of anti-infective defense are being more and more recognized. The PMPs and kinocidins from platelets are more potential to be acting as anti-infective agents due to the remarkable immune capability. These natural molecules are safer for the disease control compared to antibiotics, since antibiotics are easily developed into drug-resistance. Moreover, a better understanding of platelets function is helpful to use in diseases therapy. There are also many molecules produced by platelets are unknown, which are deserved to study in the future. In short, the impact of platelets biology on the clinic is profound, and deeply understanding of platelets function will undoubtedly benefit the transfusion medicine.

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