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The Role of Platelets in Central Hubs of Inflammation Regulation

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Abstract. When receptors were found, the study of platelets turned to the signaling pathway. When platelets in the progression of some disease could provide valuable clues, the study of platelets turned to the relationship between platelets granules, platelet morphology and inflammatory immune responses. And even some geneticists through the analysis of genes tried to encode the secret of platelets and inflammation. We reviewed the study of platelets and found the substance released by platelets could perform complex functions. The formation of immunothrombosis was central to immunological platelet function. And it could lead to the release of platelets granules, thus initiating a cascade of inflammatory immune responses, which played a central role in adaptive and innate immune. And we found platelets induced epilepsy immune by S100b. In this review, we focused on sterile inflammation, pathogen infection immunity, tumor immunity and provided the latest evidence. Hoping in the future development, platelets shed new light on pathogens infection.

Keywords: platelets, infection immune, epilepsy immune, sterile inflammation

1. Introduction

Numerous studies have revealed the association between inflammation and hemostasis [1]. Platelet function was a source of granules in platelet. These granules were released by platelets ultimately leading to thrombus formation. Bactericidal protein in platelets granules released by platelets could be blind to bacteria leading to eliminate these bacteria [2]. Although studies showed the primary function of platelets was hemostasis, the number and morphology of platelets were altered in sterile inflammation especially autoinflammatory diseases [3]. It was not clear that platelets played a core role in different types of inflammation. We reviewed some researches of platelets and inflammation. We based by platelets granules described separately infectious and sterile inflammation, which indicated platelets had central regulation in different types inflammation.

2. Platelets granules

There are bluish-purple platelet granules in the central platelet, termed granulomere. There is a light blue heterogeneous zone in the surrounding platelet, termed hyalomere. There are 3 granule classes in granulomere: α-granules, β-granules, and lysosomes [4].

2.1. α Granules

αgranules included plasma protein, adhesion molecules, complement and complement activation

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regulator, complement binding protein, hemostatic factors, angiogenic factor, anti-angiogenesis factors, growth factors, protease, necrosis factor, cell factor, cationic protein sterilization etc. Plasma protein included coat protein such as clathrin, adaptor protein 1 (AP1), adaptor protein 2 (AP2), and protein required for vesicular transport such as the Neurexin/N-Ethylmaleimide-sensitive Factor (NSF), attachment protein receptor regulator (SNARE), Sec1/Munc18 protein, and GTPase such as Rabs [4], and IgG etc. Adhesion molecules could mediate innate immunity such as P-selectin, platelet endothelial cell adhesion molecule 1 (PECAM-1), CD9-integrin alphaIIbbeta3 (GPIIb-IIIa).

Cationic bactericidal protein mediated host immunity defense, including platelet factor 4 (CXCL4), thymosin-β4, CXCL7 derivatives, CCL5, thrombospondins 1, thrombospondins 2[5]. Regulators of complement activation (RCA), complement, and complement binding protein could enhance immune cell function, including C3, C3b and C1- inhibitor [5]. The cytokine modulated platelets-leukocytes interaction, including CXCL1 (GRO-α)、CXCL4、CXCL5 (ENA-78)、CXCL7 (PBP、β-TG、CTAP-III、NAP-2)、CXCL8 (IL-8)、 CXCL12 (SDF-1α)、CCL2 (MCP-1)、CCL3 (MIP-1α) and CCL5 (RANTES) [5].

Others are unable to make the classification of substances. For instance, hemostatic factors angiogenesis factors, anti-angiogenesis factors, growth factors, proteases and Necrosis factors. Hemostatic factors included V, von Willebrand factor (vWF), fibrinogen. Angiogenesis factor included angiogenin and VEGF. Anti-angiogenesis factors included vascular statin, PF4. Growth factors included PDGF、bFGF、SDF1α. Protease included MMP2、MMP9. Necrosis factors included TNFα、TNFβ.

2.2. Dense granules

Dense granules included non-protein molecules such as ADP, 5-TH [6], serotonin, polyphosphate [7], pyrophosphate, calcium ions, melanosomes, granule fusion [4], CD63 (LAMP 3) and LAMP 2, magnesium ions [8], which played an important role in expanding platelets.

2.3. Lysosomal

lysosomal included glycosidase and protein sterilization [9]. Peroxisome included 1 to 3 lysosomes such as beta aminocaproic glycosidase [4]. And there were cathepsin D, acid hydrolase, E100 and other protein in platelets lysosomal [8].

3. The role of platelets and leukocytes

3.1. The formation of immunothrombosis: neutrophils and platelets

The interaction of platelets and neutrophil besides the neutrophil death was promoted the formation of immunothrombosis [10] via neutrophil cell death, which could promote innate immune responses. Neutrophil extracellular traps (NETs) [11], DNA [12], histone, particulate components were favorable factor promoting the formation of immunothrombosis [13], which was considered overlapping mechanisms between the immune system signals and the coagulation signals. The risk of thrombosis increased when the innate immune induced by immune inflammatory thrombosis could hardly take control of serious infection.

Stuart Wallis et al showed that efb68-87 could blind directly to P-selectin and inhibits interactions of platelets with leukocytes that could lead to PLA and NETs formation [14]. Huilian Chen et al showed that fruitflow could inhibit platelet function by suppressing Akt/GSK3β, Syk/PLCγ2 and p38 MAPK phosphorylation in collagen-stimulated platelets [15]. Min Li et al reanalyzed the GSE45111 dataset of a spectrum of asthma and they showed that platelet activation could enhance the Th2 immune response and induce lung inflammation through δ, α, λ granule released by platelets [16]. Maximilian Mauler et al used two murine models of acute inflammation, and they showed that LPS challenge in Tph1−/− mice, prevented leukocyte recruitment and reduced platelet neutrophil complex (PNC) formation [17]. David M. Chesko et al found through 10 years of a retrospective study that platelet depletion enhanced the recruitment of T cells and macrophages. It was possible that in the absence of platelets, mediators produced by other cells could overcome the lack of platelet-derived mediators in thrombocytopenic mice

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[18]. Dimitra Gialamprinou et al thought that prostaglandin E1 (PGE1) synthesis modulated by platelets affected hypersensitive response (HR) [19].

4. The role of platelets in sterile inflammation

Cell injury probably induced sterile inflammation. Sterile inflammation had similar pathological progress. Atherosclerosis was common sterile inflammation [3]. Autoinflammatory Disease also induced sterile inflammation, such as chronic tophaceous gout. Cells injury activated Damage-Associated Molecular Patterns via monocyte/macrophage leading to the inflammatory response. Cells injury released some substances such as IL-1α、S100 protein、heat shock protein（HSPs）、dsDNA, which could activate some signal pathways, for example, MAP Kinase activation induced the role of NF-Kb [20]. Meanwhile, cells injury through dendritic cell activation released soluble platelet factors inducing inflammatory responses. However active platelets could induce the formation of neutrophil extracellular traps, thus activating inflammatory response [21]. Eithne Nic an Riogh et al suggested that an appropriate assay of platelet function could guide future therapy for patients with inflammatory arthritis [22]. Serena Bianchi et al proved that platelets in hemostasis, immune regulation and repair mechanism played a vital role [23]. H. ATLI1 et al found that neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) is related to the onset of proliferative diabetic retinopathy, and NLR could predict microvascular inflammation. Recep Yılmaz et al found that neutrophil/lymphocyte ratio but not platelet/lymphocyte ratio and mean platelet volume can be an indicator of subclinical inflammation in patients with Familial Mediterranean Fever [24]. Abderrahim Nemmar et al found via studying platelet activation by the neutrophil-released proteases cathepsin G and elastase that it potently activated platelets via an ADP-mediated mechanism, which potently enhanced a condition accompanied by local and systemic inflammation [25].

5. The role of platelets in inflammation of the pathogen

5.1. The role of platelets with bacteria

The interaction of platelets with bacteria activated platelets and formatted immune thrombosis to prevent a spreading bacterium [26] and meanwhile proinflammatory mediator released by platelets could play a great role in bacterial infections immunity. For instance, streptococcus pyogenes are first snared by fibrinogen and then combined with GPIIb/IIIa signals from platelets, thus platelets activation [2]. When platelets activation, platelet volume expansion induced the aggregation of platelets leading to the capture of bacteria and next releasing inflammatory mediators in platelets granulomere could activate leukocytes to accomplish bacterial infection immunity. These inflammatory mediators included regulated upon activation of normal T cell expressed and secreted factor (RANTES), PF4, soluble CD40-ligand (sCD40L), soluble P-selectin, PDGF and ADP [27];[28].

5.2. The role of platelets with fungus

Platelets could be blind to a fungus-associated substance [29];[30] to play a great role in fungus infection immunity. For example, protease-activated receptors (PARs) and toll-like receptors (TLRs) [31] could identify β-1,3 glucan or β-galactomannan leading signaling cascade. Meanwhile, β-glucan and α-glucan could protect the human body against aspergillus infection [32]. Bactericidal substance released by platelets such as 5-HT was considered antibacterial peptides to exert immune function.

5.3. The role of platelets with virus

Platelets mediated virus infection immunity via the regulation of Toll-like receptor pathway [33]. Platelets activated Toll-like receptors through the phagocytosis of the virus. Thrombocytopenia after severe viral infections was the manifestation of antiviral immunity function decline [34]. Especially, platelets phagocytosis response was probably affected by the integrin receptor [35]. Participating in human immunodeficiency virus research revealed that platelets could be controlled in a slow decline of viral load, and virus particles were found in platelets cytoplasm, which confirmed platelets phagocytosis

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response [36]. Sokratis A. Apostolidis et al blocking the signaling of the FcgRIIa-Syk and C5a-C5aR pathways on platelets revealed a key role in platelet-mediated immunothrombosis [37]. Li Tianyang et al showed that patelets could mediate inflammatory monocyte activation by SARS-CoV-2 spike protein [38]. Ana Kasirer-Friede et al showed that platelet SHARPIN could regulate platelet adhesion and inflammatory responses through associations with αIIbβ3 and LUBAC [39]. Ana Paletta et al showed that platelets could modulate CD4+ T-cell function in COVID-19 through a PD-L1 dependent mechanism [40]. To further investigate platelet reactivity in COVID -19, Alexey A. Martyanov et al analyzed 46 COVID - 19 patients' data, and they showed that coagulation dysfunction of COVID-19 associated with intravascular coagulation-induced refractoriness [41].

5.4. The role of platelets with parasite

Participating in malaria research revealed that platelets via the release of platelet plasmodial factor, platelet factor 4 (PF4) [42] and the red cell-expressed Duffy-antigen [43] molecule could mediate parasite immunology.

First platelets were blinded with infection erythrocytes [44] and inducing the interaction of plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) and scavenger receptor CD36, and then this infection protein markers transferred to erythrocyte surface leading identification and elimination [45].

5.5. Platelets and complement

Consumption of little complement-related substance during the uptake of plasma by platelets could induce platelets associated with complement pathway. And the formation of C3b, C3a and C5b-9 activated complement pathway, which was induced by platelets activation and P-Selectin [46]. Meanwhile chondroitin sulfate released by platelets could activate complement pathway [47]. However, gC1qR expressed by platelets could activate classical complement pathway [48]. The interaction of platelets with complement greatly promoted pathogen immune killing by platelets.

6. The role of platelets in tumor

Adhesive proteins modulated platelet-tumor interaction. For example, active platelets were covered on tumor cells surface. This formation of platelets-tumor micro-thrombocytosis could be conducive to protecting tumor cells against the mechanical shear of the blood's circulation [49]. Meanwhile, tumor cells by dynein uptake platelets CD42a, thus obtaining all metabolism substances by the phagocytosis of platelets in platelets cytoplasm [50]. Podoplanin (PDPN) was a sialylated membrane glycoprotein. And it could bind to C-type lectin-like receptor 2 on platelets, which mediated platelet activation. PDPN is expressed on cancer cells. PDPN's expression on cancer cells was involved in metastasis [51]. The Low Molecular Weight Protein Tyrosine Phosphatase (LMWPTP) at the cell level affected tumor-platelets interaction. Upregulating LMWPTP at the cell level could promote tumor cells proliferation. Interesting, tumor cells proliferation upregulated LMWPTP at the cell level via positive feedback which mediated enhancement of tumor invasion and chemotherapy resistance. In addition, protein tyrosine kinases could be a potential therapeutic target. Xiaowei Liu et al showed that platelet protects angiotensin II-driven abdominal aortic aneurysm formation through inhibition of inflammation [52]. Dina Ali Hamad et al combined blood indexes of systemic inflammation as a mirror to admission to the intensive care unit in COVID-19 patients and found that SIRI was associated with clinical result, which predicted survival rates of breast cancer and gastric cancer. SIRI was defined in the following formula: SIRI = N × P/L, where N could represent neutrophils, P—platelets and L—lymphocytes. Interestingly, this effective parameter fully reflected the balance between host immune and inflammatory status [53].

7. The role of platelets in epilepsy immune

The presence of the lymphatics in the brain received very little attention. Because of the tight junction and non-fenestrated capillaries, blood brain barrier (BBB) could prevent passage of mostly substance of blood, especially immune cells, which construct an immuno-isolation membrane. Thus, lymphatics

in the brain was important structures in the brain region immune [54]. When epilepsy occurred, local electrical activity of brain cells was abnormal. And dysregulation of brain-electric activity homeostasis would have an adverse impact on the brain tissue, such as cells membrane damage and cells damage. When brain tissue damaged especially BBB, those substances that were absent from brain tissue, were released by BBB. At that moment, those substances could activate platelets in order to BBB repair, thus via TLR leading to limit the substances to movement, which could abstract innate immune cells to eliminate those substances. There were usually astrocytes cells, microglial cells, mast cells in this special immune response. Interesting, those immune cells could release a lot of S100b [55]. Those S100b also via super pathway activate neuroimmune response. For example, TRAAF6 activated TLR7/8 or 9 to induce NFκB and MAP kinase leading to amplify immune responses [56]. Continuous immune response could cause inflammatory immune infiltration, which damaged brain tissue again especially endothelial cells of BBB and the extent of the damage was variable. Injuryed BBB reduced the protective effect, which caused out-brain substances entered in the brain area leading chronic injure immune. Surprisingly, gamma globulin levels remained high in blood, it could alleviate this destruction of BBB [55]. If BBB was repaired by gamma globulin at this time, how was quenched the immune injury reaction in brain area? We predicted that compared with out-brain immune system, the local immune response of brain area lymphatics could have higher dominance rank, which caused the local immune response of brain area lymphatics to eliminate out-brain substances. And brain area immune homeostasis restored again.

8. Conclusion

Platelets played a core role in developing an immunologic inflammatory response. Formation of immunothrombosis by the capture of targets activated platelets leading the release of signals to accomplish immune clearance. In addition, platelet itself could release complement and bactericidal protein. Platelets could induce pathogens' death. On the other hand, platelets could initiate the complement pathway. More interesting, platelets via DAMPS activated immunological inflammation. Meanwhile platelets via S100b could induce epilepsy immune. All in all, platelets widely attended all kinds of immunological inflammation. And platelets could reflect immunity. Therefore, platelets could keep a range of the special level beneficial for stabilization of immunity function.

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