REVIEW ARTICLE

The Role of Platelets in Malarial Acute Lung Injury and Acute Respiratory Distress Syndrome: A World of Possibilities

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ABSTRACT
In recent decades our understanding of platelets' role in immune response has increased. Traditionally platelets were considered as bleeding-stopping and thrombosis-causing cells. In recent years the platelets' role in malarial innate and adaptive immune responses is being recognized. Platelets play critical role in pathogenesis of malaria infection leading to variety of outcomes. It is being realized that platelets play dual role in case of malaria (i) by preventing early stage exponential growth of parasitemia (ii) promoting exaggerated immune responses later. Platelets role in pathogenesis of severe and cerebral malaria has been widely studied. However their role in malaria related acute lung injury and respiratory distress has gained less attention. Recently the presence of active megakaryocytes and proplatelets have been explained in human lungs. Simultaneously, the platelets role in pathogenesis of acute lung injury and respiratory distress (ALI/ARDS) was also recognized. This gives a hint that there is a possible association of platelets with malaria related respiratory diseases as well. ALI/ARDS are characterized by lung edema due to increased permeability of the alveolar-capillary barrier and subsequent impairment of arterial oxygenation. In this review we have attempted to establish the importance of role of platelets in malaria related acute lungs injury and malaria acute respiratory distress syndrome and try to explain the underlying mechanism of this process. In ALI/ARDS, including those caused by malaria, platelets participate sequestration to the vascular bundle facilitating the recruitment of immune cells viz. neutrophils. Additionally, they secrete or induce the secretion of chemokines that result into vascular damage.

Keywords: Acute Lung Injury, Cerebral Malaria, Platelets, Neutrophils, Platelet Factor 4

PLATELETS AND IMMUNITY

Platelets are first line of defense against the damage to the vascular integrity. They also play important role in immune response, thrombosis and other pathogenesis. Platelets play a vital role in immune responses in infectious diseases such as malaria, viral encephalitis, dengue, meningitis, bacterial sepsis and some fungal infections.[1] Platelets contain three types of storage granules alpha, dense and lysosomal granules. These granules contain agents participating in events such as clotting, coagulation, endocrine, metabolic processes and immune response. In recent decades the platelets role in immunological response is being widely accepted, possibly making them highest in number of immune cells present in human blood. Platelets participation in physiological diseases such as diabetes, arthritis, gestational complications and cancer has been explained and are the target for therapy. In nearly all of these diseases platelets elicit inflammatory and thrombogenic function. Our group had first demonstrated that platelets are important for antigen presentation and transplant rejection serving as complete immune cell equivalent to macrophages and lymphocytes.[1]

CLINICAL ALI/ARDS

In critical care and trauma patients, acute lung injury and acute respiratory distress syndrome (ALI/ARDS) is a common and lethal form of pulmonary condition. Inflammation plays an important role in the pathogenesis of ALI/ARDS. Studies suggest that ALI/ARDS generally requires two important pathological steps (i) neutrophil activation and infiltration (ii) pulmonary capillary inflammation combined with endothelial permeability increase.[2] It is also associated with monocytes infiltration, pro-inflammatory markers including cytokines, proteases, free radicals and pro-coagulant factors. Evidences suggest that platelets play an important role in neutrophil mediated lung injury in non-malaria type ALI/ARDS.[3] The human lung is a reservoir of platelets, pro-platelets and megakaryocytes. In lung platelets and pro-platelets serve to prevent the pulmonary vascular integrity and may provide local immunity to alveoli. It is suggested that lungs itself is not the sites for megakaryocyte production and therefore the active platelets synthesis. However, a minute population megakaryocytes can escape from the bone

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marrow and deposit at the distant organ such as lung.[4,5] Therefore, platelets role in ALI/ARDS becomes object of interest due to its abundance, proximity and activity in lung. Studies demonstrate that activated coagulation and impaired fibrinolysis are also associated with ALI adding to a body of evidence supporting this hypothesis.[6] Platelets association with the pathogenesis and progression of ALI/ARDS has been previously reviewed. In this review, we want to advocate the direct participation of platelets in MALI/MARDS based on already existing, although scattered, evidences.

MALARIA AND RESPIRATORY DISTRESS

Malaria, TB and HIV are major cause of health concern world-wide and has massive mortality rate.[7] However, malaria alone is a serious cause of public health nuisance, affecting each year between 250-350 million patients, hampering their longevity, physical ability and economic status. While *Plasmodium falciparum* is one of the deadliest causative agent, other malaria parasites such as *P. vivax*, *P. ovale* and *P. knowlesi* also have health burden. In western world their is low prevalence of malaria, but other mosquito borne diseases are still present. However, people traveling to the endemic zone from malaria-free zone such as tourists, business travelers, volunteers, army, religious and sports personnel often suffer from malaria. This is primarily due to the absence of any form of acquired immunity against this disease. If untreated malaria can progress into morbid stage known as severe malaria, which is categorized by anemia, acidosis, renal failure, cerebral malaria (CM) and respiratory distress. Respiratory manifestation of severe malaria is known as malaria acute lungs syndrome and malaria acute respiratory distress syndrome (MALI/MARDS). While CM is mostly caused by the *P. falciparum* infection, MALI/MARDS can result from any type of parasite mentioned above.[8] As studied in case of *P. falciparum*, ARDS effects 5% to 25% in adults and up to 29% in pregnant women. However MALI/MARDS is not common in young children. This is in contrast to the CM which mostly afflicts the younger patients often less than 5 years of age. Therefore, species independence, lack of correlation to the therapeutic status, increasing prevalence and high mortality has brought MALI/MARDS into the type of condition that needs serious attention. MALI/MARDS patients show symptoms such as cough with expectoration, dyspnoea, pulmonary edema and pneumonia, impaired blood gas exchange followed by total respiratory failure. It is also witnessed by arterial hypoxemia as a result of pulmonary edematic fluid formation, resulting into impaired blood gas exchange. It is a consequence of increased alveolar permeability resulting in intra-vascular fluid loss into the lung. These symptoms are similar to the non-malaria related ALI/ARDS and emerges independent of the parasite load in patients. ALI/ARDS is fast becoming a common outcome in acute and severe *P. falciparum*, *P. vivax* and *P. ovale* infection and is reported nearly in all the endemic zone.[9] However, among these *P. vivax* is considered as relatively benign. However, recent reports on *P. vivax* have indicated the increased number of onset of MALI/MARDS as compared to *P. falciparum*.[10] This is probably is due to the important differences between *P. falciparum* and *P vivax* at the level of life cycle, infectivity, hemozoin formation and host immune response.

Both host and parasite factors contribute to the disease severity of malaria infection. The genetic events responsible for the disease and the host-parasite interactions involved in chemokine release is only recently being understood.[11] Several reports suggest that MALI/MARDS may develop either due to toxicity caused by parasite hemozoin, hospital ventilation injury, pre-existing respiratory conditions or co-infection with gram negative bacteria.[12] However, delay in treatment of infection and host genetic factors may also play significant role in progression of MALI/MARDS. In general, nearly all forms of malaria are accompanied by changes to the endothelial cells in affected organs. Therefore, a distinct immunological step may differentiate MALI from other pathogenesis viz. engagement and activation of neutrophil. Mouse model show enhanced neutrophil activity in ALI similar to the human. Age, gender, physiological status and genetic predisposition can affect the outcomes in malaria. Timely treatment of malaria ameliorates most of the malaria related complications e.g. anemia, cerebral malaria. However the MALI/MARDS complication can still develop post-therapy and discharge of the patients from the hospital.[10] It is also noticeable that the immunological response including the one mediated by platelets (just like hemostatic response) from different human population may vary. Thus travelers from non-endemic zone may develop MALI earlier and at a worse magnitude.[13] This leads to the increased need to perform the systematic investigation using experiments with experimental MALI/MARDS model from platelet perspective. These studies should emphasize to further understand the vascular inflammation, molecular pathogenesis, genetic susceptibility and therapeutic strategy in this highly neglected version of malaria.

MOUSE MODEL OF MALI/MARDS

In contrast to the other severe malaria conditions such as cerebral malaria, placental malaria or anemia, MALI/MARDS so far has lacked an intense investigation. This lack of attention has mostly been due to the absence

of consensus on animal model of MALI/MARDS. In recent years, few parasite-host relation specific model has emerged that are being used for the MALI/MARDS study. The general strategy for mouse model selection must be to choose combination of mouse and parasite type that avoids development of cerebral malaria (CM). For example in our hand introduction of 0.5-1 million *P. berghei* ANKA i.p. develops CM in mice by 5-6 days.[14] Higher dose exhibits other type of pathogenesis including pulmonary distress and not the CM. In several studies, C57Bl6 mice with *P. berghei* NK65 has been used at a high introductory parasitemia i.p and study histology of harvested lung.[15] This model again did not develop CM, instead results into 90% of incidence of respiratory distress with a high degree of similarity to the human MALI/MARDS. Some studies have used DBA/2 mice infected with *P. berghei* ANKA. Lungs harvested from these mice were subject to electron microscopy.[16] The results from lungs ultrastructure reveal sequestration of infected red blood cell to endothelium contact, swollen endothelium with distended cytoplasmic extensions and thickening of basement membrane. These results were similar to what has been described in *post-mortem* electron microscopy studies of lungs from human infected with *P. falciparum*. Just like human pathogenesis, mouse model of MALI/MARDS is independent of parasite type and largely depend upon the host-parasite relationship. In our opinion, any systematic study must employ atleast two such model for to rule out any differences based on parasite and mouse type. As usual, caution must be exercised while extrapolating the data from the mouse into the human because of the dissimilarity at the level of immune response. Mouse malaria model usually has exaggerated immune response as compared to the human.[17]

IMMUNE RESPONSE AND PLATELETS IN MALI/MARDS

Progression of non-malaria related ALI/ARDS is dependent upon two steps (i) the neutrophil entrapment and infiltration and (ii) pulmonary vascular inflammation leading to increased permeability changes leading to edema formation.[2] Similarly, MALI/MARDS is also dependent upon neutrophil sequestration and infiltration. In either form, leukocytes sequestration to vascular bundle is a critical step. Vascular events such as endothelial cell damage, infiltration, sequestration and barrier breakdown in MALI makes it equivalent to CM in pathogenesis. In recent decades our understanding in molecular and cellular pathology in CM has advanced and shows its high dependence on platelets. It is clear that platelets are critical agent for CM pathogenesis and progression. Therefore, it is prudent to draw a similarity between CM and ALI from the vascular and platelets perspective. Platelets can contribute to the MALI/MARDS complications in two ways: (i) Platelet may get physically attached to the neutrophils and guide their infiltration to the lungs. (ii) Platelet get activated in all type of malarial infections, and release inflammatory cytokines. These cytokines therefore can activate neutrophils, monocytes and macrophages and cause the pulmonary microvessel endothelial damage. These steps may lead to the increased attachment/infiltration into the lungs equivalent to the blood brain barrier breakdown in CM. Platelets can adhere to endothelial cells via von-Willebrand Factor (vWF) independent of tissue type.[18] As a matter of fact, experimental ALI was reversed by blocking the platelet and neutrophil aggregate formation.[19] In this study the thromboxane A2 (TXA2) was identified as an important molecule released by platelet-neutrophil aggregates for neutrophil sequestration and infiltration. TXA2 as an important mediator of organ failure in malaria is well accepted.[20]

In experimental ALI, P-selectin mediates the initial recruitment of the platelets to the leukocytes and (and hence neutrophil) to endothelial cells. Platelet alpha granule store P-selectin which can express on its surface and bind to P-selectin glycoprotein ligand (PSGL-1)[21,22] and perhaps additional unexplained ligand.[23] As a matter of fact, P-selectin blocking by antibody did reduce the experimental ALI.[24] The attachment step can be followed by consolidation step, mediated by binding of the leukocyte integrin αMβ2 (CD11b, Mac-1)[25,26] to GPIb on platelets.[27] Fibrinogen bound to activated platelet integrins αvβ3 or αIIbβ3 can form a bridge to leukocyte Mac-1[28] and ICAM-2 on platelets and integrin αLβ2 on neutrophils can also participate in adhesion.[29] In fact leukocyte integrin αMβ2 (Mac-1, CD11b/CD18) and integrin αLβ2 participate in ALI. Irrespective of the adhesion mechanism, platelets-leukocyte attachments can result into the activation of leukocytes. Blocking this attachments can be an important therapeutic strategy in ALI. It is therefore important to study the reversal of MALI/MARDS, using antibody blocking platelet-leukocyte attachment.

Platelets, therefore, can physically interact with neutrophils and other immune cells in mechanism explained above, and hence accelerate their entry into the lungs. Platelets are highly active in malaria and they also form increased binding to the monocytes.[30] Platelet Factor 4 (PF4 or CXCL4) is a platelet specific chemokine released upon platelet activation. PF4 level is highly elevated in malaria infection both in mouse and human. PF4 can activate the immune cells such as monocytes, macrophages and lymphocytes, which can later invade the alveoli. PF4 heterodimerizes with interleukin IL-8 and binds to the surface receptor to activate the neutrophils. Activation can also be individually

carried out by PF4[31,32] Knockout and depletion studies have indicated that IL8 and its receptor CXCR2 are crucial for ALI progression[33] The studies suggest that PF4 may be an important mediator in neutrophil-platelet interactions and the induction of acute inflammation especially at sites of platelet microthrombi where the concentration of PF4 would be elevated.[34,35] PF4 can individually promote neutrophils attachment to the endothelium in physiological or pathological conditions.[36] Together, these studies indicate that activated platelet in malaria can release PF4 a powerful chemo-attractant, which can incite neutrophil activation and attachment to endothelium via or independent of IL-8. While the level of IL-8 in malaria infection may or may not change depending upon type of parasite and immune response of patients, it can still interact with suddenly elevated level of PF4 causing pathogenesis.[37] Therefore, as done in the case of CM studies, experimental MALI/MARDS studies using PF4 knockout mice can specifically reveal the role of PF4.

PF4 binds to its target cells using a CXC-class chemokine receptor CXCR3. Our and other group's studies have previously shown that PF4 activates the target immune cells by binding to the CXCR3 receptors.[14] Studies engaging knock-out mice demonstrate that CXCR3 strictly regulates the ALI progression when studied using other pathogen induced ALI model.[38] These studies also suggested that neutrophils may express the CXCR3 receptors and respond to variety of chemokine agonists.[38]It is therefore possible that PF4 mediated pathogenesis in MALI is mediated by CXCR3 receptors. This serves as another reason why PF4 might be a prudent therapeutic target in MALI.

Platelets express a high level of CD36 which is involved in platelet activation and thrombus formation.[39] CD36, also known as scavenger receptor, has important role in immune response by adhering to the surface of immune cells.[40] Role of CD36 has been highly appreciated in malaria pathogenesis.[41] Our results using *in vitro* model indicates that platelets CD36 is responsible for cyto-adherence to the infected red blood cells (iRBCs) and consequently for the activation of platelets. In this study incubation of platelets with fAb-fragments of CD36 antibody completely blocked PF4 release upon interaction with iRBCs.[14] *P berghei* ANKA mice studies have shown that CD36-/- mice had reduced sequestration of iRBC to the tissue blood vessels.[42] These mice were not only protected from CM but also the incidence of ALI. It is therefore, possible that platelet CD36 binding is upstream to the events responsible for the platelets mediated ALI damage. Platelets CD36 may help in sequestering iRBC or immune cells to the pulmonary microvessel endothelium and transport them across the barrier.

There is increased expression of chemokine IL-1β in platelets from patients with dengue or after platelet exposure *in vitro* to dengue virus.[43] This activates NLRP3 inflammasomes and caspases pathways which then results into the increased vascular permeability. NLRP3 inflammasomes and caspases activation has been directly implicated in ALI/ARDS pathogenesis.[44] Growing body of evidence suggest that NLRP/caspase pathway are activated in malaria infection and coinfection that leads to MALI.[45] Further study is needed to understand the NLRP activation in MALI/MARDS and dependence of platelets for this pathway. Also, platelets secreted inflammatory agents such as PF4, can activate the Toll like receptor (TLRs) in target cells.[46] ALI/ARDS progression caused by both malaria and other diseases are highly dependent upon TLRs.[47] TLR activation is target of therapeutics development in several diseases.

The complement system plays a vital role in innate immune response against infectious agents. Uncontrolled complement activation can result into tissue injury including alveoli and pulmonary capillary damage. Compliment activation via C3a and C5a can result into neutrophil activation increasing lung permeability and ALI.[48] Platelets possess the machinery to interact with and trigger both classical and alternative pathways of complement activation. Platelet participate in complement activation by significantly increasing soluble inflammatory mediators such as C3a and C5a.[49] Other group have also shown that complement system is active in human malaria, indicating possible role of platelet mediated compliment activation in ALI/ARDS.[50] Similarly, our lab has also explained the contribution of platelet mediated acute phase response in malaria involving proteins such as SAA and CRP.[51] While this response is intended to reduce parasite burden in the host, the tissue injury, especially in lung, can be an important after effect of this process.

OTHER POSSIBLE EVENTS IN MALI/MARDS INVOLVING PLATELETS

Scores of studies have associated the presence of microparticles in blood to the ALI.[52] These studies have shown presence microparticles and correlated it to the severity of ALI. Microparticles are released by both physiological and pathological activation of platelets. More interestingly the studies have specifically indicated that platelet derived microparticles are responsible the acute lung injury.[53] More studies would reveal the microparticles role in platelets mediated MALI/MARDS. It would not be surprising to find that platelets shed microparticles in malaria that lead to MALI/MARDS. Increasing number of studies have implicated VEGF and its receptor to be responsible for the pathogenesis of ALI/ARDS.[15] Platelets

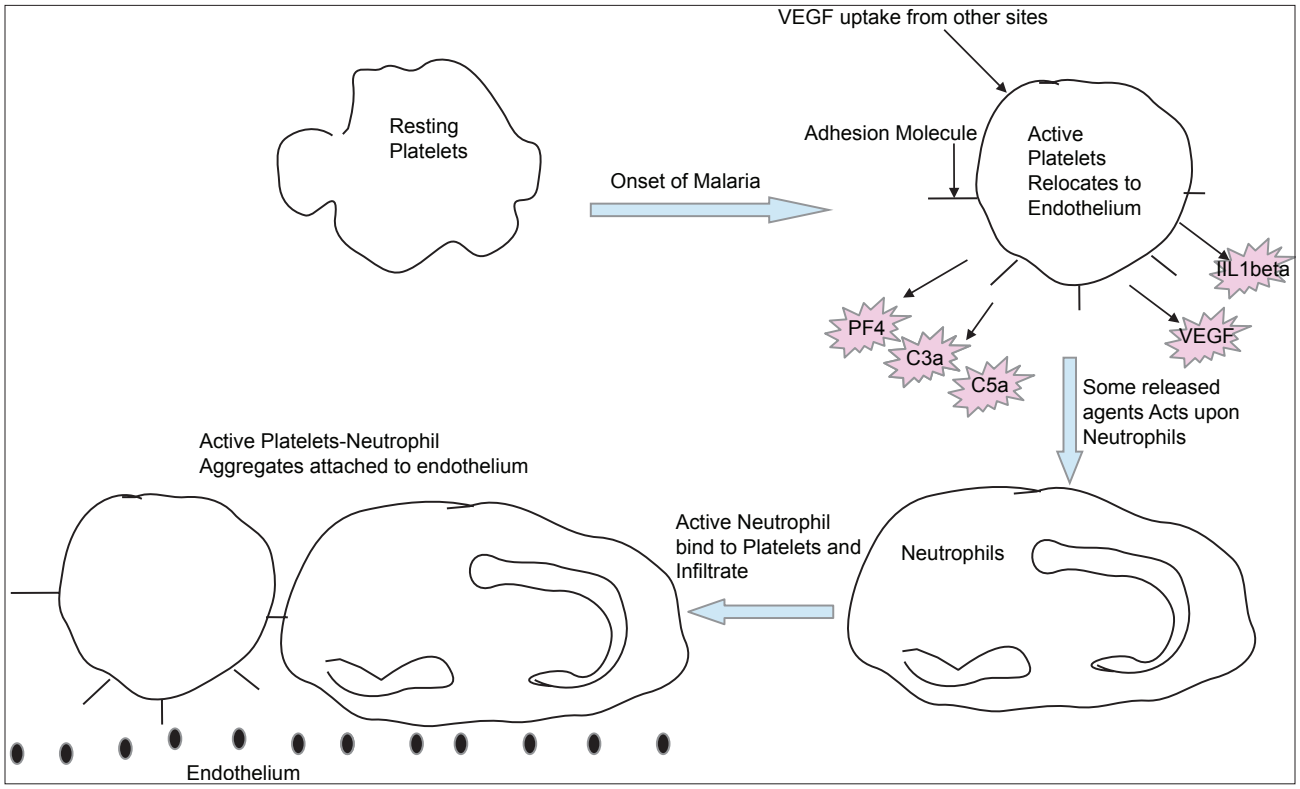

Figure 1: Malaria causes platelets activation which releases chemokine and other inflammatory agents. These agents than cause neutrophils activation and infiltration resulting into endothelial and alveolar damage in lungs.

under pathogenic conditions can serves as a transporter of VEGF.[54] VEGF and its receptors level is increased in *P. falciparum* infection and probably contributes to the pathogenesis of CM.[55] Therefore VEGF mediated pathogenesis in MALI/MARDS may involve platelets and must be studied closely.

CONCLUSION

With this review we have tried to draw attention towards the platelets role in malaria related ALI/ARDS. Most of the inferences were drawn using evidences from experimental or clinical ALI/ARDS. So far specific studies using mouse model of MALI/MARDS has not been performed to study the role of platelets. With new knowledge in platelets' role in experimental and clinical ALI/ARDS as well as malaria, it has become clear that platelets have critical role in MALI pathogenesis. What is important at this stage is to engage the platelets specific studies utilizing knockout mice such as PF4-/-, TPOR-/-, CD36-/-, CXCR3-/- mice and GpIb antibody platelet depleted mice to understand their role. These studies would help in understanding the role platelets in both malaria related and unrelated ALI/ARDS. However, caution must be taken while interpreting these data. Malaria is accompanied by thrombocytopenia in later stages, which discourages the use of anti-platelet therapy in these diseases. Also, reports indicate that platelets play important role in parasite clearance. Therefore, any therapeutic effort must target the platelets interaction with neutrophils and vascular bed and not the depletion of platelets. Also, the receptors on immune cells such as CXCR3, CCR5 and CCR1 are the very fascinating target. Advantage of targeting platelet-leukocyte interaction and platelets derived chemokine, is that this would simultaneously reduce the other risk such as CM.

REFERENCES

1. Morrell CN, Aggrey AA et al. Emerging roles for platelets as immune and inflammatory cells. Blood, 2014, May 1;123(18):2759-67.
2. Grommes J and Soehnlein O. Contribution of Neutrophils to Acute Lung Injury. Mol Med. 2011, Mar-Apr; 17(3-4): 293-307.
3. Matthay MA and Zemans RL. The Acute Respiratory Distress Syndrome: Pathogenesis and Treatment. Annual Review Pathology, 2011; 6: 147-163.
4. Zucker-Franklin D and Philipp CS. Platelet Production in the Pulmonary Capillary Bed New Ultrastructural Evidence for an Old Concept. Am J Pathol. Jul 2000; 157(1): 69-74.
5. Weyrich AS and Zimmerman GA. Platelets in lung biology. Annu Rev Physiol. 2013;75:569-91.
6. Ware LB, Camerer E, Welty-Wolf K et al. Bench to bedside: Targeting coagulation and fibrinolysis in acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2006; 291:L307-311.
7. Investigators team. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014 6(14)60844-8.

8. Taylor WRJ, Hansen J et al. Respiratory manifestations of malaria. Chest. 2012;13:492–505.
9. Nayak KC, Mohini Kumar S et al. A study on pulmonary manifestations in patients with malaria from northwestern India (Bikaner). J Vector Borne Dis. 2011 Dec;48(4):219-23.
10. Lionel KK, Yacoub S et al. Acute lung injury and other serious complications of Plasmodium vivax malaria. The Lancet Infectious Diseases, 2008; 8(7) 449-454.
11. Pattaradilokrat S, Li J et al. Plasmodium genetic loci linked to host cytokine and chemokine responses. Genes Immun. 2014;15(3):145-52.
12. Mohan A, Sharma SK et al. Acute lung injury and acute respiratory distress syndrome in malaria. J Vector Borne Disease. 2008; 45(3) 179-193.
13. Tan LK *et al* Acute lung injury and other serious complications of Plasmodium vivax malaria Lancet Infect Dis. 2008;8(7):449-54.
14. Srivastava K, Cockburn IA et al. Platelet factor 4 mediates inflammation in experimental cerebral malaria. Cell Host Microbe. 2008;4(2):179-87.
15. Epiphanio S, Campos MG et al. VEGF promotes malaria-associated acute lung injury in mice. PLoS Pathog. 2010;6(5).
16. Aitken HE, Negri EM et al. Ultrastructure of the lung in a murine model of malaria-associated acute lung injury/acute respiratory distress syndrome Plasmodium falciparum. Malar J. 2014; 13: 230.
17. Wykes MN and Good MF. What have we learnt from mouse models for the study of malaria? Eur J Immunol. 2009;39(8):2004-7.
18. Ruggeri ZM. Von Willebrand factor. Curr Opin Hematol. 2003; 10:142-149.
19. Zarbock A, Singbartl K and Ley K. Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. J Clin Invest. 2006; 116:3211-3219.
20. Inyang AL, Sodeinde O, Okpako DT, Essien EM et al. Platelet reactions after interaction with cultured Plasmodium falciparum infected erythrocytes. Br J Haematol. 1987;66(3):375-8.
21. Yang J, Furie BC, Furie B. The biology of P-selectin glycoprotein ligand-1: its role as a selectin counter receptor in leukocyte-endothelial and leukocyte-platelet interaction. Thromb Haemost. 1999; 81:1-7.
22. Evangelista V, Manarini S et al. Platelet/polymorphonuclear leukocyte interaction: P-selectin triggers protein-tyrosine phosphorylation-dependent CD11b/CD18 adhesion: role of PSGL-1 as a signaling molecule. Blood. 1999; 93:876-885.
23. Ramos CL, McRae J et al. Functional characterization of L-selectin ligands on human neutrophils and leukemia cell lines: Evidence for mucin like ligand activity distinct from P-selectin glycoprotein ligand-1. Blood. 1998; 91:1067-75.
24. Doerschuk CM, Quinlan WM et al. The role of P-selectin and ICAM-1 in acute lung injury as determined using blocking antibodies and mutant mice.1996; J. Immunol. 157:4609-14.
25. Diacovo TG, Roth SJ et al. Neutrophil rolling, arrest, and transmigration across activated, surface-adherent platelets via sequential action of P-selectin and the beta 2-integrin CD11b/CD18. Blood. 1996; 88:146-157.
26. Evangelista V, Manarini S et al. Platelet/polymorphonuclear leukocyte interaction in dynamic conditions: evidence of adhesion cascade and cross talk between P-selectin and the beta 2 integrin CD11b/CD18. Blood. 1996; 88:4183-4194.
27. Simon DI, Zhiping C et al. Platelet GpIb alpha is a counter receptor for the leukocyte integrin Mac-1 (CD11b/CD18). J Exp Med. 2000; 192:193-204.
28. Weber C and Springer TA. Neutrophil accumulation on activated, surface-adherent platelets in flow is mediated by interaction of Mac-1 with fibrinogen bound to alphaIIbbeta3 and stimulated by platelet-activating factor. J Clin Invest. 1997; 100:2085-2093.
29. Diacovo TG, deFougerolles AR et al. A functional integrin ligand on the surface of platelets: intercellular adhesion molecule-2. J Clin Invest. 1994; 94:1243-1251.
30. Srivastava K, Field DJ et al. Platelet Factor 4 Regulation of Monocyte KLF4 in Experimental Cerebral Malaria. PLoS ONE 2010; 5(5).
31. Nesmelova IV, Sham Y et al. Platelet factor 4 and interleukin-8 CXC chemokine heterodimer formation modulates function at the quaternary structural level. J Biol Chem. 2005;280(6):4948-58.
32. Clark-Lewis I,Dewald B et al. Platelet factor 4 binds to interleukin 8 receptors and activates neutrophils when its N terminus is modified with Glu-Leu-Arg Proc. Natl.Acad.Sci.USA. 1993; 90(8): 3574-3577.
33. Strieter RM, Keane MP et al The role of CXCR2/CXCR2 ligands in acute lung injury. Curr Drug Targets Inflamm Allergy. 2005;4(3):299-303.
34. Bebawy ST, Gorks J et al. J Leukoc Biol. In vitro effects of platelet factor 4 on normal human neutrophil functions. 1986;39(4):423-34.
35. Deuel TF, Senior RM et al. Platelet factor 4 is chemotactic for neutrophils and monocytes. Proc Natl Acad Sci U S A. 1981;78(7):4584-7.
36. Kasper B, Brandt E et al. Neutrophil adhesion to endothelial cells induced by platelet factor 4 requires sequential activation of Ras, Syk, and JNK MAP kinases. Blood. 2006;107:1768-1775.
37. Boström S, Giusti P et al. Changes in the levels of cytokines, chemokines and malaria-specific antibodies in response to Plasmodium falciparum infection in children living in sympatry in Mali. Malaria Journal 2012, 11:109.
38. Ichikawa A, Kuba K et al. CXCL10-CXCR3 enhances the development of neutrophil-mediated fulminant lung injury of viral and non viral origin. Am J Respir Crit Care Med. 2013;187(1):65-77.
39. Nergiz-Unal R, Lamares MM et al. Signaling role of CD36 in platelet activation and thrombus formation on immobilized thrombospondin or oxidized low-density lipoprotein. J Thromb Haemost. 2011; 9(9):1835-46.
40. Silverstein RL and Febbraio M. CD36, a Scavenger Receptor Involved in Immunity, Metabolism, Angiogenesis, and Behavior Sci Signal. 2009; 2(72).
41. Cunha-Rodrigues M, Portugal S et al. Bone marrow chimeric mice reveal a dual role for CD36 in Plasmodium berghei ANKA infection. Malar J. 2007;6:32.
42. Lovegrove FE, Gharib SA et al. Parasite burden and CD36-mediated sequestration are determinants of acute lung injury in an experimental malaria model PLoS Pathog. 2008;4(5).
43. Hottz ED, Lopes JF et al. Platelets mediate increased endothelium permeability in dengue through NLRP3-inflammasome activation. Blood. 2013;122(20):3405-14.
44. Grailer JJ, Canning BA et al Critical role for the NLRP3 inflammasome during acute lung injury J Immunol. 2014;192(12):5974-83.
45. Ataide MA, Andrade WA et al. Malaria-induced NLRP12/NLRP3-dependent caspase-1 activation mediates inflammation and hypersensitivity to bacterial superinfection. PLoS Pathog. 2014;10(1).
46. Suvarna S, Qi R et al. Platelet factor 4-heparin complexes trigger immune responses independently of the MyD88 pathway. 2008; 142(4), 671-673.
47. Tolle LB and Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. J Pathol. 2013;229(2):145-56.
48. Bosmannand M and Ward PA. Role of C3, C5 and Anaphylatoxin Receptors in Acute Lung Injury and in Sepsis Adv Exp Med Biol. 2012; 946: 147-159.
49. Peerschke EI, Yin W and Ghebrehiwet B. Complement Activation on Platelets: Implications for Vascular Inflammation and Thrombosis Mol Immunol. 2010; 47(13): 2170-2175.

50. Korir JC, Nancy K et al Complement Activation by Merozoite Antigens of Plasmodium falciparum. PLoS One. 2014;9(8).
51. Aggrey AA, Srivastava K et al. Platelet induction of the acute-phase response is protective in murine experimental cerebral malaria J Immunol. 2013;190(9):4685-91.
52. Dengler V, Downey GP et al. Neutrophil intercellular communication in acute lung injury. Emerging roles of microparticles and gap junctions. Am J Respir Cell Mol Biol. 2013;49(1):1-5.
53. Xie RF, Hu P et al. The effect of platelet-derived microparticles in stored apheresis platelet concentrates on polymorphonuclear leukocyte respiratory burst. Vox Sang. 2014;106(3):234-41.
54. Verheul HM, Hoekman et al. Platelet: transporter of vascular endothelial growth factor. Clin Cancer Res. 1997;3(12 Pt 1):2187-90.
55. Furuta T, Kimura M and Watanabe M. Elevated levels of vascular endothelial growth factor (VEGF) and soluble vascular endothelial growth factor receptor 2 (VEGFR-2) in human malaria. Am J Trop Med Hyg. 2010;82(1):136-9

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