Crosstalk between platelets and the complement system in immune protection and disease

Admar Verschoor; Harald F. Langer

1Institute for Medical Microbiology, Immunology and Hygiene, Technische Universität München, Munich, Germany; 2Medizinische Klinik III, Klinik für Kardiologie und Kreislauferkrankungen, Eberhard Karls-Universität Tübingen, Tübingen, Germany

1. Introduction

1.1 Platelet function in health and disease

The classical function of platelets is to cover and close endothelial and tissue wounds (1, 2). In addition to this temporary wound closure, which is followed by stable thrombus formation, platelets contribute to long-term healing and regenerative mechanisms (3–5). However, if platelet activation occurs without proper regulation or at unfavourable locations, the intended platelet function to form a thrombus can result in life-threatening events such as myocardial infarction, stroke, or when vulnerable atherosclerotic plaques rupture, and arteries to the brain occlude (6–8).

The process of platelet thrombus formation is a rather well understood and characterised process with distinct and strictly regulated steps (9–11). It involves initial loose contact between the platelet and the injured vessel wall, firm adhesion, spreading and finally thrombus formation (12, 13). The initial loose contact of platelets with the subendothelial matrix is mediated by platelet glycoprotein (GP) Ib–V–IX with von Willebrand Factor (vWF) (14, 15). Then, the glycoprotein receptor GPVI mediates interaction of the platelet with collagen and, indeed, anti-GPVI monoclonal antibodies or blockade with soluble GPVI attenuates arterial thrombosis in vivo (16, 17). GPVI can directly promote adhesion of platelets to subendothelial collagen and activate further platelet adhesion receptors including GPIIb-IIIa (αIIbβ3) and GPla-Ia (α2β1) (11). α2β1 represents a second collagen receptor while αIIbβ3 mediates irreversible adhesion to vWF (6). Subsequent inside-out signalling mediates further platelet activation, and the resulting shape change and pseudopodia formation allow for effective coverage of the injured vessel wall. Secondary mediators such as thromboxane A2 (TxA2) or adenosine diphosphate (ADP) provide an amplification loop that initiates and reinforces further platelet aggregation (12). The latter is achieved through fibrinogen-mediated contacts between activated platelet receptors on individual platelets (15, 18, 19). Figure 1 summarises the process of platelet thrombus formation.

During the last decades it has become increasingly evident that the relevance of platelets is not restricted to wound healing or thrombus formation, but that non-classical platelet functions contribute to inflammation and infection. Early insights into the pro-
motion of inflammation by platelets came from studies that recognised that atherosclerosis is in essence an inflammatory disease (20, 21). Platelet adhesion to endothelial cells was found to be crucial to the initiation of atherosclerosis, even before the actual plaque has formed (21). It was reported that platelets release chemokines such as CCL5 or CXCL4 which contribute to atherosclerosis, through a P-selectin-dependent process (20). A number of subsequent studies confirmed the early hypothesis that platelets contribute to vascular inflammation, e.g. by interacting with leukocytes (22-25). Moreover, interacting receptor / ligand pairs on platelets and leukocytes were identified (26-28). For instance, P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes mediates binding to platelet P-selectin (28), while leukocyte beta2-integrin Mac-1 (CD18/CD11b, CR3) promotes interaction with at least two platelet receptors, GPIb and the junctional adhesion molecule-C (23, 29-31). Platelet GPIIb/IIa recruits leukocytes via formation of fibrinogen bridges with leukocyte Mac-1, an interaction triggered by platelet activating factor (32). For a schematic overview of leukocyte-platelet interactions, see the article by Langer and Chavakis in this Theme Issue (124). A further prominent mechanism by which activated platelets contribute to inflammation is the release of active biomolecules, such as interleukin (IL)-1beta, platelet factor 4 or Rantes from platelet granules (33, 34). Recent research draws renewed attention to some of these processes, which were previously considered exclusively in the context of thrombus formation of classical cardiovascular diseases such as stroke or myocardial infarction, but are now being revisited in the context of infection (35), multiple sclerosis (36) or rheumatoid arthritis (37). Studies of prothrombotic or thrombocytopenic diseases such as idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) likewise led to a deeper understanding of platelet physiology, particularly their interaction with the complement system (38, 39).

1.2 The complement system

The complement system is a largely blood-borne cascade of proteins with its evolutionary roots in innate immune defence and homeostasis. Its activation is controlled by zymogens, proteolytically activated enzyme precursors, which set in motion an expanding and self-sustaining array of effector molecules that have the potential to induce inflammation, tag (opsonise) targets for phagocytosis or directly lyse cells. The complement system’s ability to mark targets for destruction and removal plays not only a role in the combat of invading microbes, but also in maintaining homeostasis, for instance via the controlled clearance of dead and dying cells.

The biological effects of complement activation are broad, reaching into adaptive immunity, and are mediated in part via specific receptors for complement activation products (complement receptors [CR]), and in part directly by the activation products themselves. Several complement activation pathways are recognised, differing in their modes of initiation, progression and molecules involved. These are briefly reviewed and schematically represented in ▶ Figure 2 to provide a frame of reference. For a further in depth description of the complement system, the reader is referred to (40).

- The Alternative Pathway (AP) may be the most fundamental and anciently preserved cascade of the complement system. It functions as a self-sustaining loop of activation, initiated by spontaneous conversion of the reactive internal thioester within the central component C3. Generally, this reactivity is quickly neutralised in the aqueous environment of the blood,
resulting in an inactive form of C3. However, if a suitable hydroxyl or amine acceptor group is present within close proximity of the reactive thioester, the resulting reaction can form a covalent bond that effectively tags the target with activated C3 (C3b). The self-sustaining nature of the AP stems from the fact that C3b becomes part of its own conversion complex (convertase) causing focussed activation of ever-more C3 molecules around the site of initial deposition. Obviously, hydroxyl or amine acceptor groups are not unique to foreign substances or microbes and equally occur in self molecules and on host cells. Therefore, the expression of complement regulatory molecules (CRM; also commonly referred to as complement regulatory proteins) limit activation on self-surfaces, while allowing unrestricted complement activation on non-protected foreign or altered-self substances.

- The Classical Pathway (CP) forms a functional interface between the complement system and antibodies of adaptive immunity, thus providing the innate complement system with a mode of antigen specific activation. Once bound to its cognate antigen target, slight conformational changes in the antibody Fc-portion allow complement C1q to bind it. C1q can also bind selected targets directly or via intermediates including C-reactive protein (CRP), serum amyloid protein (SAP) or pentraxins without the need for antibody. Bound C1q proteolytically activates serine proteases C1r and C1s which in turn (and analogous to the activation of C3) convert C4 to C4b. Together with activated C2, C4b now forms the classical C3 convertase. Once C3 becomes activated and deposited by this convertase, it can feed into the AP, which further amplifies complement activation.

Figure 2: Schematic overview of the complement system. Classical, Lectin and Alternative Pathways (CP, LP, and AP, respectively) commence from the left side of the diagram, leading to the converging point of C3-activation (top right). At each step of the cascade, new additions to the antigen (Ag) complex are shown in blue, their position taken within the complex shown in red, and released small proteolytic products are shown in green. With the convergence of the three initiation pathways at the level of C3 activation (top right), a C3 Amplification Loop is generated via the AP. Furthermore, at this point, also the Terminal Pathway is initiated with the formation of a C5 convertase, leading to the assembly of the membrane attack complex (MAC). The MAC ultimately interferes with the target cell’s structural integrity by penetrating its membrane (bottom right), while opsonisation with C3 activation products provides complement receptor-expressing immune cells with a ligand to interact with the Ag. Several of the small proteolytic products (green) function as anaphylatoxins in the recruitment and activation of a broad range of immune defence mechanisms, including platelet activation. MBL (mannose binding lectin); MASP (MBL-associated serine proteases).
The Lectin Pathway (LP) follows much the same principle of activation as the CP, short of its initiation, which in the LP is mediated via a distinct set of zymogens which take the place of the C1 complex. To initiate the LP, mannose binding lectin (MBL) or ficolins must bind their target (typically specific sugar residues) to activate MBL associated serine proteases (MASPs). Structurally, the LP initiation complex shows great similarity to the C1 complex of the CP; and also further complement activation progresses via C4 and C2 as in the CP.

The Terminal Pathway (TP). The aforementioned initiation pathways merge with the formation of their respective C3 convertases, and the pathways now progress into the formation of the membrane attack complex (MAC), a molecular structure that effectively forms a pore into the target membrane. The complex is initiated by the activation of C5 via the C5 convertase (a further modification of the C3 convertases), which recruits C6, C7, C8 and multiple copies of C9, which ultimately forms the pore, preventing the target cell to maintain osmotic pressure and functionality.

The unique modes of pathway initiation (i.e. microbe-specific antibody mediated or microbe-specific sugar residue-specific) provide the complement system with a degree of specificity towards its targets. Still, complement activation in the fluid phase creates potential for diffusion of activated products and non-intentional collateral damage to bystander targets, such as neighboring self-cells. To limit such damage to the host, and to focus the destructive capacity of the complement system on the intended target, the system is tightly controlled via CRM which are present in the serum as well as on all host cells. CRM operate on various levels of complement activation, varying from destabilisation of the convertases to preventing the formation of a MAC on self-cells.

Apart from its functions in marking targets for phagocytosis via complement opsonisation and lysis via the MAC, the complement system alerts and supports other areas of the immune system. Phagocytic cells such as granulocytes, monocyte/macrophages and dendritic cells express high levels of phagocytic CR3 (CD11b) and CR4 (CD11c) with specificity for iC3b (the opsonising but inactivated form of C3b). Also the B cell co-receptor complex includes a CR, CR2 (CD21), with specificity for iC3b and its further proteolytic products C3d and C3dg), lowering the B cell activation threshold to antigen several orders of magnitude (41), with crucial effects during the response to infection (42, 43). Thus, opsonisation of a particular target with the proteolytic products of C3 enables a more effective antibody response than to the non-opsonised target alone, in part also due to the expression of CR2 on follicular dendritic cells, which direct and orchestrate the B cell response (44). Activation of C3 or C5 generates small peptide-like split products, C3a and C5a respectively, also known as anaphylatoxins. They have been shown to influence processes as diverse as angiogenesis (45) or asthma (46), histamine release or vasoconstriction (47), and generally mediate leukocyte activation and recruitment (48). C3a and C5a are recognised by C3aR and C5aR receptors on granulocytes, mast cells and monocyte/macrophages.

1.3 Modes of interactions between the complement system and platelets

Complement and platelets share several levels of interaction. That after years of targeted research new points of interaction are regularly being discovered may in part be due to the fact that the systems are typically addressed by separate groups of scientists and clinicians. The complexity of the cascades and their mechanisms of activation or regulation complicate the understanding further. However, it is clear that platelets do maintain a range of CR, as well as CRM, hinting at the importance of the complement system for their function and physiology. Moreover, it has been demonstrated that not only receptors, but also various complement factors can be detected on the platelet surface (49) and that thrombin activated platelets initiate the complement cascade (50). Engagement of CR2 (receptor for iC3b C3d and C3dg) was reported to activate human platelets (51), while the iC3b receptor CR3 promotes arachadonic acid-induced platelet aggregation (52). Expression of iC3b receptor CR4 has also been reported (53), but its physiological role remains unclear. Not only C3-fragment receptors have been described on platelets, also C1q-receptor expression has been documented, specifically gC1qR/p33 and cC1qR with affinity for the C1q globular heads and its collagenous tail, respectively, mediating platelet aggregating and activating effects (54-56). There are also strong indications that anaphylatoxin C3a and C5a receptors are present on human platelets, and C3a and its derivative C3adesArg induce platelet activation and aggregation in vitro, whereas in vivo data are not available to date (57, 58). Interaction between platelets and complement may also occur via receptors not typically regarded as CR, such as P-selectin (57). Del Conde et al. could demonstrate that P-selectin binds C3b and this interaction resulted in both C3a generation and C5b-9 MAC complex formation (59).

Formation of MAC-complexes further enhances the platelet and haemostatic response (60) and mice lacking C3 coincidentally show prolonged bleeding times (56). Combined, the general picture emerges in which engagement of complement-receptors on platelets may have a platelet-activating function.

The pro-thrombotic effect of complement may obviously have advantages to the host in times of vascular damage and possibly associated infection, when both immune and haemostatic systems are simultaneously called upon and cross-talk enhances the response. A recent and novel example of interplay between complement and platelets is reviewed in 4. Complement and platelets during systemic infection. This mechanism, involving complement C3 and platelet glycoprotein GPIb, was shown to have a strong enhancing effect on the immune response to systemic bacterial infection in vivo.

Nonetheless, pro-immune and pro-thrombotic interplay between complement and platelets needs to remain focused on vascular damage, insult or infection and is to be avoided under normal homeostatic conditions. Still, also under resting conditions platelets are continuously exposed to blood proteins, including complement, with the AP affording the complement system with a continuous, baseline-level of activation. This ever-present low-level complement activity requires a counter-balance on the pla-
Platelets and complement

Platelets: basic mechanisms and translational implications

Platelets are primary regulators of the haemostatic process, but they are also involved in the regulation of the complement system. To avoid complement-mediated platelet activation, aggregation or even MAC mediated lysis, this complement restraining action is provided by various CRM on human platelets, including C3b-inactivating and C3-convertase destabilising Factor H (bound via alphallbeta3 [61] and Thrombospondin-1 [62]). Furthermore, the same functions are mediated on platelets by membrane co-factor (MCP or CD46, C3b inactivation) (63), decay-accelerating factor (DAF or CD59, interfering with C3 convertase) (64) and CD59, which destabilises the MAC (65). Similar roles have been reported for CRM on mouse platelets, where Crry (a CR1-related murine CRM), DAF and factor H protect platelets from complement destruction (66). In Figure 3 we provide a schematic representation that summarises several modes of cross-talk between complement compounds and the platelet surface. In the following, we will review the current understanding and molecular underpinnings when an imbalance between the action of CRM-mediated protection and complement activation arises in persons with low expression of or mutations in CRM (see 2. Complement in diseases with a prothrombotic state), or in the presence of CP-activating autoantibodies to specific self-targets (see 3. Complement in immune thrombocytopenia).

2. Complement in diseases with a prothrombotic state

In HUS or PNH, involvement of the complement system and platelet activation have been firmly established. Two forms of HUS are recognised: HUS and atypical HUS (aHUS). Whereas HUS is caused by infection with bacterial strains such as Escherichia coli which produce cytotoxins (67), atypical HUS (aHUS) is a genetic or acquired disorder which is connected to a dysregulated complement system (68, 69). Still, both constitute diseases featuring microvascular thrombosis with subsequent thrombocytopenia, haemolytic anaemia and dysfunction of affected organs, accompanied by complement activation (38). For reasons of simplicity, we summarise both diseases as HUS.

Platelet function in HUS is modulated by various synergistic effects including endothelial cell activation, and complement activation shifts the disease phenotype from a "thromboresistant" state (preventing thrombosis on the endothelial monolayer) to a "prothrombotic" state (also see 1.3. Modes of interactions between the complement system and platelets) (68). The prothrombotic phenotype results from synergy between the release of P-selectin, vWF and Weibel-Pallade bodies (70) and the C3a or C5a-mediated upregulation of adhesion receptors and tissue factor on endothelial cells (71). Distinct mutations uncovered in recent years offer a mechanistic basis for the prothrombotic state of HUS patients. The net effect of aHUS-associated mutations is an increased susceptibility to uncontrolled activation of the AP on self-cell surfaces, reduced circulating C3 levels in a subset of patients, deposits of C3 and C5b-9 MAC on glomerular endothelium and on circulating platelets (38). When platelets are exposed to sera from aHUS patients with Factor H mutations C3 and C9 deposition on platelets associated with CD40L and P-selectin expression - markers of platelet activation -, aggregate formation, and generation of tissue fac-

Figure 3: Modes of crosstalk between complement components and the platelet surface and potential relevance for disease. Under homeostatic conditions, complement regulatory molecules (CRM) prevent excessive complement deposition and activation on the platelet surface. Under pathological conditions, uncontrolled complement activation on platelets or insufficient counterbalance by CRM results in platelet damage, thrombosis and disease progression.
tor-expressing microparticles can be observed (72). In contrast, complement deposition and platelet activation were reduced when unmutated Factor H was preincubated with platelets and minimal when normal serum was used (72). Most of the mutations of Factor H are located in the exons coding for the C-terminal region of the protein (73), which is responsible for binding to the cell surface or surface-associated C3b (74). Mutant Factor H (75) as well as factor H neutralised by HUS-associated autoantibodies (76, 77) cannot exert functions preventing complement activation. On platelets, C-terminal bound factor H prevents complement activation, as treatment of platelets with mutated factor H resulted in complement propagation with subsequent platelet activation (72). Specifically, for the FH-E1198 Stop mutation within short consensus repeats of the C-terminal region a reduced binding to platelets and, thus, lack of complement inhibition on the cell surface could be demonstrated (72). Also mutations unrelated to the FH-E1198 Stop mutation but resulting in dysfunctional factor H or reduced factor H serum levels led to increased platelet activation (72). Besides factor H mutations, MCP mutations which affect extracellular domain involved in complement regulation, can cause aHUS and result in reduced MCP expression or decreased binding to C3b and reduced cofactor activity (78). Moreover, mutations in complement factor I located in the protease domain are relevant for defective C3b inactivation (79). Gain-of-function mutations in C3 or complement factor B (80, 81) can produce hyperactive regulation-resistant C3-convertase leading to HUS. Also, mutants affecting the complement inhibitory molecule thrombospondulin have diminished capacity to inactivate C3b via complement factor H and complement factor I (82). The collective evidence points towards a model in which mutations in CRM that down-modulate complement activity or, vice versa, complement mutations that resist down-modulation lead to dysregulation of normal platelet activation, resulting in a hyperactive and pro-thrombotic state.

Similar to HUS, PNH is also characterised by a prothrombotic state. PNH is a rare, acquired stem cell disorder, which becomes clinically apparent with haemolytic anaemia, bone marrow failure and thrombophila with high probability of thrombosis (39). The manifestations of thrombosis include visceral thrombosis (e.g. of hepatic veins and mesenteric veins), cerebrovascular thrombosis and pulmonary embolism (83). PNH is caused by a lack of several proteins on the blood cell surface (84-86) due to a mutation in the X-linked phosphatidylinositol glycan class A (PIGA) gene (87, 88), which is necessary for the biosynthesis of the glycosyl phosphatidylinositol (GPI) anchor (89, 90). This mutation results in a lack of complement regulators DAF (91, 92) and CD59 (93, 94) anchoring to the platelet surface. Absence of these CRM is are also closely associated with haemolytic anaemia (39). It was demonstrated that PNH platelets differ from normal platelets in their interaction with activated complement components (95). After alternative complement activation, greater amounts of C3 are present on the platelet surface and, in contrast to wild type platelets, PNH platelets show release of serotonin after C3 fixation (95). Moreover, upon exposure to MAC, PNH platelets lacking CD59 have more expression of coagulation factor Va, present more catalytic surface for the thrombinase complex (VaXa) and have increased prothrombinase activity compared to healthy platelets (96). Such observations closely link to the observed increased thrombosis in many PNH patients. In contrast, some PNH patients present with reduced platelet counts and their platelets reveal reduced reactivity regarding central functions such as clot formation, adhesion and aggregation. Considering prothrombotic nature of PNH, it may be concluded that this platelet hyporeactivity may be due to reactive down-regulation of function in response to chronic hyperstimulation, a form of “platelet exhaustion” (97).

A study with 187 PNH patients treated with Eculizumab (Soliris, Alexion Pharmaceuticals), a humanised monoclonal antibody which inhibits cleavage of C5 into C5a and C5b and preventing MAC-mediated cell damage, revealed clearly reduced thrombosis. The study showed a 85% reduction in thrombosis incidence using Eculizumab (98), but could not establish at what level (C5a, C5b or MAC) Eculizumab exerts its effect on platelet activation and thrombosis (39). Future studies will have to clarify exactly how complement influences platelet function and activation in HUS and PNH.

Beside HUS and PNH there are other diseases where interplay between complement and thrombotic responses may be relevant, such as systemic lupus erythematoses (SLE) and TTP. Based on the increasing mechanistic understanding, there is ongoing discussion if TTP and HUS should be combined under the term “thrombotic microangiopathies” (38). The same is true for ITP (see 3. Complement in immune thrombocytopenia), which shares mechanistic features with TTP and HUS, including complement-induced platelet alterations with consequences for blood homeostasis. ITP and TTP, however, also have features that are decidedly distinct from HUS: ITP and TTP are autoantibody mediated autoimmune diseases that coincide with other clinical constellation such as HIV-infection or systemic lupus erythematoses. Both are characterised by thrombocytopenia and both present with abrupt onset of manifestation (99). Still, whereas ITP is associated with platelet lysis, TTP links to functional platelet alterations. Moreover, TTP patients have, in contrast to ITP patients, measurable activation of platelets and endothelial cells (99). Therefore, further research is needed to classify the diseases in detail and to provide new evidence-based avenues for targeted, differential and effective treatment. For reasons of brevity, we refer for further reading on SLE and TTP to (100, 101).

3. Complement in immune thrombocytopenia

ITP, also known as immune thrombocytopenia, is a condition characterised by low platelet counts in the presence of autoantibodies directed to platelet antigens. Patients present with a tendency for bleedings, most obviously detected as bruises of the skin, known as purpura, due to spontaneously occurring intracutaneous bleeding (102). There are clear indications that complement activation is involved in the disappearance of platelets from the circulation of patients with ITP (103). Under normal conditions in healthy persons, ever-present low level AP complement activation and deposition is controlled and sufficiently counteracted by CRM

© Schattauer 2013

Thrombosis and Haemostasis 110.5/2013
present in the circulation as well as associated with the cell membrane (see 1.3. Modes of interactions between the complement system and platelets) and indeed, CRM deregulation is associated with thrombotic diseases (see 2. Complement in diseases with a prothrombotic state). However, in the presence of autoantibodies (typically IgG isotypes) that specifically target platelet epitopes and can activate complement via the CP (see 1.2. The complement system) (104), it appears that these protective mechanisms become over-stretched. As a result, more complement is deposited on the platelet than under usual conditions, and the presence of complement and antibody on the platelet surface promotes their uptake by phagocytic cells, especially those located in the reticuloendothelial system such as hepatic Kupffer cells and splenic macrophages. Indeed, ITP patients with a high degree of complement fixation onto their platelets benefit significantly from splenectomy, and subsequently show increased numbers of circulating platelets (105). In addition to phagocytosis, also direct damage inflicted by the accumulation of MAC onto platelet and megakaryocyte membranes is thought to contribute to the low platelet numbers in ITP patients (106). Short of splenectomy, which is not considered a first line treatment, currently approved treatment options aim to replenish platelets via transfusion or stimulation of thrombopoiesis (Eltrombopag, Romiplostim) (107), or to interfere with their consumption via immunomodulation therapies that utilise transfusion of pooled immunoglobulins (IVIG), general immune suppression via glucocorticoids, or interfere with the source of the anti-platelet antibodies by depletion of peripheral B cells (Rituximab) (108). Combined clinical and laboratory data suggest that therapies, which target complement deposition and MAC formation (eculizumab), could be effective in ITP, but no clinical trial data are available to date.

4. Complement and platelets during systemic infection

Infections of the blood stream provide ample opportunity for interactions between microbes, platelets and the complement system. Systemic infections become particularly apparent when they result in acute clinical disease, for instance during disseminated intravascular coagulation (DIC) or bacterial sepsis (“blood poisoning”). The vast majority of sepsis cases are associated with bacterial infection (109). Especially people and patients with generally weakened defences to infection are vulnerable to developing this condition. Sepsis has remained notoriously difficult to control clinically, with mortality rates reaching 50% in cases of septic shock (109). Factors closely associated with a bad prognosis for septic patients are the occurrence of DIC (110) and high levels of complement activation (111). The mechanisms of sepsis are complex, and ultimately result in the deterioration of the normal balance between initiation and resolution of haemostasis, a combination of coagulation and platelet aggregation. To make matters worse, haemostasis factors may simultaneously contribute to exacerbation of sepsis via the generation of anaphylatoxins (112) from an already overheated complement system (111).

To prevent aforementioned conditions from arising, it is a principle task of our immune system to remove blood-borne bacteria from the circulation. Blood clearance is achieved through the active capture, uptake and killing of bacteria by professional phagocytes. Large populations of these cells, particularly macrophages, reside in spleen and liver, organs with a great capacity for filtering and clearing the circulation (113, 114). The complement system plays not only a role in direct lysis of microbes via MAC, but also a central role in the acquisition and retention of bacterially derived “antigen”, as is evident from the expression of a broad palette of complement receptors (115) and/or ligands (42, 43, 116) by all phagocyte populations (see also 1.2 The complement system). Indeed, complement is vital for the proper function of the immune response to bacteria, as complement deficiencies are associated with recurrent bacterial infections, including bacteraemia and sepsis (117, 118).

Various blood-borne systems, including those traditionally associated with haemostasis, participate in (immune) protective mechanisms. Indeed, platelets contain a broad array of substances that are not primarily associated with haemostasis but rather with immune defence, in some species even compounds that are directly bactericidal (119). Moreover, platelets induce neutrophils to extrude web-like structures, appropriately known as neutrophil extracellular traps (NETs) that can entrap bacteria (120). The close biochemical similarities between the complement, coagulation and fibrinolytic cascades, all principally blood-borne systems, create for more areas of interaction than previously realised (121).

While controlling the ongoing blood infection via phagocytic clearance is the first goal, the immune system is laid out to “learn” from this experience and to “remember” so it can protect more efficiently against re-infection in the future. It has been shown that platelets may interact with dendritic cells mediated by adhesion molecules JAM-C on platelets and Mac-1 on dendritic cells (122). Recent work reveals a novel mechanism in which complement and platelets aid T-cell responses to bacteria in the blood stream (123). In this mechanism, interaction between bacteria and platelets via complement C3 is needed to efficiently shuttle the bacteria into antigen presenting DC. In turn, better targeting of bacteria to DC results in more efficient induction of T-cell immunity. The complement and haemostatic systems are linked via GPIIb, a receptor on platelets for von vWF, and bacterial adhesion to platelets tip the clearance balance from macrophages towards DC, thus boosting the generation of effective anti-microbial T-cell responses. Importantly, and in contrast to DC and macrophages, T cells “remember” their encounters with microbes, and their ability to form “memory” improves their effectiveness during a reinfection. Thus, this novel mechanism of platelet- and complement-directed clearance provides a blueprint that can aid the rational design of novel strategies to exploit the immunity-boosting capacity of platelets and complement during systemic infection.
5. Summarisation

In conclusion, complement activation and platelet thrombus formation occur in close spatiotemporal proximity in various homeostatic and pathophysiological contexts, such as during the resolution of vascular wounds, infections of the blood stream, or several diseases with prothrombotic state. Taking both complement and haemostatic systems into consideration, integrating them in research efforts as well as clinical practice, may foster new insights into mechanisms of disease and generate novel targets for drug development and diagnosis.

Acknowledgements

H. F. L. is supported by the Volkswagen Foundation (Lichtenberg program), the Tuebingen Platelet Investigative Consortium (TuePIC) and the Clinical research unit 274 supported by the German Research Foundation, and the Wilhelm Sander Foundation. A.V. is supported by the Collaborative Research Centre SFB 914 ( Trafficking of Immune Cells in Inflammation, Development and Disease, Project B4) from the German Research Foundation.

Conflicts of interest

None declared.

References


© Schattauer 2013

Thrombosis and Haemostasis 110.5/2013

Verschoor, Langer: Platelets and complement
Platelets: basic mechanisms and translational implications


