Invited Review

The molecular basis of immune-based platelet disorders

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Abstract

Platelets have a predominant role in haemostasis, the maintenance of blood volume and emerging roles as innate immune cells, in wound healing and in inflammatory responses. Platelets express receptors that are important for platelet adhesion, aggregation, participation in inflammatory responses, and for triggering degranulation and enhancing thrombin generation. They carry a cargo of granules bearing enzymes, adhesion molecules, growth factors and cytokines, and have the ability to generate reactive oxygen species. The platelet is at the frontline of a host of cellular responses to invading pathogens, injury, and infection. Perhaps because of this intrinsic responsibility of a platelet to rapidly respond to thrombotic, pathological, and immunological factors as part of their infantry role, platelets are susceptible to targeted attack by the adaptive immune system. Such attacks are often transitory but result in aberrant platelet activation as well as significant loss of platelet numbers and platelet function, paradoxically leading to elevated risks of both thrombosis and bleeding. Here we discuss the main molecular events underlying immune-based platelet disorders with specific focus on events occurring at the platelet surface leading to activation and clearance.

Introduction

Platelets are anucleate blood cells produced by megakaryocytes resident in bone marrow and possibly the lung. They are approximately 2 μm in diameter with a specialised role in haemostasis (maintenance of blood volume) and important roles in the innate immune system (1-4). Platelets circulate in the bloodstream at concentrations ranging from 150-400 x 10^9 platelets per litre of blood and approximately one billion new platelets are produced every day (5). Platelets are released from the bone marrow, replete with a full complement of pro-adhesive and immunoreceptors and a host of storage granules containing calcium and adenosine diphosphate (ADP) as well as an arsenal of enzymes, growth factors and cytokines. They contain ribonucleic acid and all the cytoplasmic components necessary to perform protein synthesis *de novo* including mitochondria, ribosomes, endoplasmic reticulum and Golgi apparatus (6). They can also rapidly synthesise reactive oxygen species in response to engagement of receptors by ligands (7, 8).

Platelets normally circulate for 7-10 days before being cleared by reticuloendothelial systems in the liver and the spleen unless they have already been consumed in haemostatic processes (5, 9). Unless engaged, platelets circulate in a quiescent form and slowly undergo morphological and structural changes including reduction in levels of surface receptors and their glycosylation (10). Platelet production and life span as well as a host of physiological platelet functions, are tightly controlled by integrated mechanisms mediated by receptor-ligand interactions, molecular feedback loops and intracellular protein signalling cascades (5). Disruption of platelet function either through congenital deficiency or exposure to therapeutics with platelet-binding properties, can result in ablation of platelet function and a significantly elevated risk of bleeding. Further, reduction in platelet numbers (thrombocytopenia) can also elevate bleeding propensity. Thrombocytopenia can result from a decrease in platelet production, enhanced platelet clearance (11), increased consumption of platelets due to prothrombotic pathologies (12) or genetic mutations that disturb expression of surface receptors, granules and proteins essential for platelet function (5, 13-15) (Figure 1). Nonetheless, whilst

thrombocytopenia is accompanied by an increased risk of bleeding, the platelet count in isolation is a poor predictor of bleeding risk (16-18).

The regular checks and balances around thrombopoiesis and megakaryopoiesis are still being deciphered (19), however both platelet count and volume ("platelet mass") are maintained within tight numerical ranges in healthy donors (20). Megakaryocytic maturation from haematopoietic stem cells requires thrombopoietin (TPO) a key hormone produced constitutively in the liver, which binds to the c-MPL receptor on megakaryocytes and platelets. Severely reduced production of TPO, for example when the liver is diseased or during viral infection, can trigger thrombocytopenia. Equally, TPO mimetics such as eltrombopag, romiplostim and avatrombopag have been shown to be highly effective at increasing the platelet count in people with thrombocytopenia with or without antiplatelet autoantibodies (21).

The diagnosis of immune-based platelet disorders relies on history, clinical findings and on immediately available laboratory data. When a specific test is not readily available, clinical interpretation is used to make a presumptive diagnosis and to initiate treatment (22, 23). It is not always possible to differentiate these disorders at the time of presentation and the diagnosis is often challenging due to over-lapping features. Typically, a multitude of possibilities are considered together and a general approach towards management is used, largely based on prioritising safety by using the clinical acumen of the treating physician (24). Poor access to specialized diagnostic modalities can impair timely clinical decision making. Hence, diagnostic reclassification is not uncommon, and retrospectively it becomes clearer that some patients may have received unnecessary medical or surgical interventions (25-28).

Removal of the offending agent causing platelet activation (drugs, pathogens or antiplatelet antibodies) and elevation of the platelet count to avoid critical bleeding is the main aim of treatment for immune-based thrombocytopenia's (23, 29-31). Platelet transfusion is commonly reserved for

patients with severe uncontrolled or life-threatening bleeding and is not indicated in chronic stable patients (32).

Corticosteroids are generally given as the first line of treatment, alone or as an adjuvant for all newly suspected patients with immune thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP) or foetal and neonatal alloimmune thrombocytopenia (FNAIT) (31, 33, 34). Insights into molecular mechanisms of immune-based platelet disorders may not only translate in providing better diagnostic certainty, but can also play an important role in guiding specific treatment regimens. For instance, recently an immunoglobulin fragment targeting the A1-domain of von Willebrand factor (VWF), caplacizumab, was approved for adults with acquired TTP in combination with plasma exchange and immunosuppressive therapy (33). Targeted therapies like caplacizumab have inspired a new focussed approach to the management of immune-based platelet disorders.

Molecular processes underpinning platelet function

To better understand the consequences of loss of platelet function it is important to have some familiarity with molecular processes that drive platelet function. Platelets circulate through the vasculature in an inactive 'resting' state. Upon detection of vascular injury or infection, in flowing blood, platelets are induced to move from the lumen of the blood vessel towards the vessel wall where they slow down, roll and then adhere at the site of endothelial cell perturbation (35, 36). Under vascular biorheological conditions, platelet rolling and adhesion requires coordinated interactions between platelet surface receptors and exposed sub-endothelial matrix proteins, primarily VWF and collagen (Figure 2) (37). The platelet receptors mediating initial interactions with VWF and collagen are the glycoprotein (GP) Ib-IX-V complex and GPVI. Importantly, GPVI and the GPIbα subunit of GPIb-IX-V are tightly co-associated on the surface of platelets and there is evidence of cooperation between these receptors (38). Engagement of both receptors, particularly under fluid shear stress (37) can

trigger intracellular signalling events, which lead to the upregulation of fibrinogen binding by the platelet specific integrin αIIbβ3.

The molecular pathways underpinning platelet activation steps are still being resolved however the major features have been reviewed extensively and involve contributions from a host of receptors (39-42). However, pathways stemming from engagement of one or both of GPIb-IX-V binding VWF or GPVI binding collagen are particularly important as these receptors are responsible for triggering the initial adhesive processes by cooperating under a range of blood rheological conditions (Figure 2). The ectodomains of these receptors are co-associated (38) and engagement of either GPIb-IX-V or GPVI by their respective ligands triggers detachment of calmodulin from juxtamembranous cytoplasmic tail binding sites (43), and activation of a series of phosphorylation events involving members of the Src family of kinases including Src, Fyn, Lyn and Syk (44, 45). This leads to activation of phosphoinositide (PI) 3-kinase and mobilisation of intracellular stores of ADP and Ca^{2+}, generation of thromboxanes and reactive oxygen species (8, 46), cytoskeletal rearrangement (47), membrane phosphatidylserine (PS) exposure and platelet degranulation (40, 48, 49). Ultimately the signalling pathways lead to modulating platelet integrin αIIbβ3 from a low- to a high-affinity receptor for fibrinogen as well as other matrix proteins (50).

Each fibrinogen molecule contains two αIIbβ3-binding arginine-glycine-aspartic acid (RGD) sequences which enables fibrinogen to simultaneously engage two αIIbβ3 molecules on adjacent platelets and form a molecular bridge. GPVI is linked via a transmembrane salt bridge to the fragment constant receptor (FcR) γ subunit which enables GPVI-collagen or GPVI-fibrin mediated immunoreceptor tyrosine-based activation motif (ITAM) signalling (51, 52). Activation of these pathways results in fibrinogen-linked platelet aggregates rapidly forming at local sites of blood vessel injury. A second integrin on platelets, α2β1 also contributes to stable platelet adhesion by binding exposed collagen.

Platelets involved in this process, become activated and are induced to degranulate, releasing a plethora of stored growth factors, cytokines and chemokines as well as stored calcium and ADP, which serve to amplify platelet activation and recruitment of additional platelets, and commence the process of wound repair. Architectural changes to the cytoskeleton and the membrane phospholipid bilayer ensue, causing platelet shape change and exposure of negatively charged PS molecules. This change in membrane electrostatic charge renders the surface of the adherent platelet highly procoagulant, which facilitates activation of coagulation pathways and the local generation of thrombin (53). Through this mechanism, a platelet aggregate can be stabilised as active thrombin cleaves fibrinogen to form insoluble fibrin, a principle component of a thrombus that provides structural integrity and protects from microbial invasion (54). However, certain bacteria most notably including members of the *Streptococcus* family produce enzymes such as streptokinase that directly activate the fibrinolytic pathway (55). This has the consequence of reducing the acute phase host response to bacterial infection which is centred on maintaining an anti-fibrinolytic state. Accelerating fibrinolysis by interfering with the contact pathway of coagulation further aids in bacterial dissemination by releasing trapped bacteria from fibrin clots produced by host defence mechanisms (56, 57). A wealth of data gained in animal models of sepsis supports the blockade of fibrinolytic pathways, however the transference of these insights to treatment of sepsis in humans is less profound (58) and requires further research.

Platelets contain a number of other receptors that once bound by ligand, are capable of activating platelets and controlling platelet responses. The receptors include C-type Lectin-like receptor (CLEC)-2, Trem-like Transcript (TLT)-1 and FcγRIIa a low affinity receptor for immunoglobulin (Ig) Fc regions (59-61). All of these receptors are able to activate signalling pathways upon ligand engagement however it is the ability of platelets to bind antibodies via engagement of FcγRIIa by the Fc portion of an antibody, that is important in the pathogenesis of several platelet-based autoimmune disorders (62, 63). Through both surface receptors and release of soluble mediators,

activated platelets are able to interact with other immune cells such as neutrophils. The interaction is mediated by platelet P-selectin binding neutrophil P-selectin glycoprotein ligand (PSGL)-1 along with platelet GPIbα engaging neutrophil integrin αMβ2 (also known as Mac-1). Whether these interactions are sufficient to generate signalling events leading to induction of neutrophil extracellular trap (NET) formation remains to be conclusively determined however platelets clearly contribute to NET formation observed during microbial and viral infection (64-66) and also in autoimmune inflammation (67, 68).

Thrombocytopenia

Thrombocytopenia generally results from decreased production and/or increased destruction of platelets. Bone marrow failure syndromes such as aplastic anaemia, myelodysplastic syndromes, and chemotherapy-induced thrombocytopenia arise from a decrease in platelet production, whereas increased destruction is observed in conditions such as disseminated intravascular coagulation (DIC) and thrombotic microangiopathies. The molecular events governing megakaryocyte maturation and platelet production (thrombopoiesis) are intricate, highly controlled, and sensitive to bone marrow perturbations. In particular the maintenance of the niche environment is crucial for efficient platelet production, and oxidative stress, endothelial dysfunction and inadequate levels of factors such as nitric oxide may affect platelet production (69, 70). In this regard, changes to standard platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW) together with the reticulated (immature) platelet fraction may act as sentinels of bone marrow diseases that pre-empt the onset of thrombocytopenia (71, 72). Ideally these molecular reporters will help differentiate between thrombocytopenia due to immune-mediated platelet destruction versus bone marrow disorders or inherited macrothrombocytopenia (73, 74) and may also inform on responses to therapy (75). Autoantibody-mediated thrombocytopenia due to increased peripheral destruction has resulted in increases to PDW and MPV (76) whereas thrombocytopenia due to decreased production, or essential

thrombocythemia where there is a hyper-thrombopoiesis and elevated platelet counts, features platelets with lower MPV and PDW properties (76, 77).

Beyond the scope of this review, thrombocytopenia can also arise from platelet sequestration associated with splenomegaly or haemodilution. It is now well recognised that in many cases of thrombocytopenia, such as primary ITP (78), viral infection (79) and in sepsis (80), multiple co-incidental mechanisms may contribute to the development of thrombocytopenia. The remainder of this review will discuss molecular pathways involved in immune-based platelet disorders (Figure 3).

Immune-based thrombocytopenia

Platelet activation leading to thrombocytopenia is a common event in a number of autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome and anti-phospholipid syndrome (81-84), and is a signature event in platelet-based autoimmune diseases. This co-association with thrombocytopenia implies that immune system dysfunction contributes to the acquired thrombocytopenia. Immune-based disorders effecting platelet number generally manifest when the platelet surface is no longer recognised as autologous by the adaptive immune system, resulting in the generation of antibodies that target platelet surface receptors and megakaryocytes (85). The antibodies may recognise receptors directly or in combination with therapeutics that bind to receptors (drug-induced thrombocytopenia). The genetic and molecular triggers that lead to one or more platelet receptors becoming antigenic are not known, however immune-mediated thrombocytopenia is often coincident with other immune disorders or linked with acute viral exposure (86-89).

Primary Immune thrombocytopenia (ITP)

In ITP, a small number of B lymphocyte clones produce autoantibodies that target the platelet receptors GPIb-IX-V, αIIbβ3 as well as α2β1 and GPVI (90-93). Recently, GPV has been reported to be a major target for platelet autoantibodies whereby platelet bound anti-GPV antibodies were detected in 64.7%

of adult patients with suspected ITP (94). While it remains to be elucidated, the prevalence of platelet autoantibodies against these glycoprotein receptors (~70% anti-αIIbβ3, ~25% anti-GPIb-IX-V, ~5% anti-GPVI) may be driven by the density and/or post-translational modifications of these antigens (95). Aside from targeting platelets, these antibodies also compromise production of platelets by bone marrow megakaryocytes (96-98). There is no standard clinical test for diagnosis of ITP meaning ITP remains a diagnosis by exclusion and a major clinical challenge to diagnose and to treat (99, 100). Antiplatelet antibodies are often challenging to detect and assays to detect these antibodies, such as platelet flow cytometry and the monoclonal antibody-specific immobilization of platelet antigens (MAIPA) assay are not standardised or routinely performed (101, 102). Further, these assays have limited sensitivity and specificity.

Antiplatelet antibodies most commonly target one or both of the GPIb-IX-V complex and αIIbβ3 resulting in enhanced clearance of platelets (103). The clearance mechanism may involve Fc receptor activity resulting from opsonisation of the platelet surface by antiplatelet antibodies and binding by monocytes and macrophages bearing Fc receptors, leading to clearance by phagocytic cells (95). A second clearance mechanism which is independent of Fc receptors occurs when antiplatelet autoantibodies primarily targeting GPIbα, trigger the release of neuraminidase and cause loss of sialic acid residues (desialylation) from platelet surface glycans (104-107). This exposes galactose residues which are recognised and bound by Ashwell-Morell receptors on liver resident Kupffer macrophages and platelets are subsequently cleared (105). In ITP, whilst the platelet count does fall, patients tend not to incur serious bleeding (108). Further the platelet count nadir is generally not commensurate with the extent of bleeding observed in some ITP patients (109), suggesting that there is also a level of platelet dysfunction in ITP patients that contributes to the bleeding. This lesion remains to be fully elucidated however in a subset of ITP patients with anti-GPVI autoantibodies, where bleeding is commonly more severe than expected with the level of thrombocytopenia, investigations by light transmission aggregometry showed an isolated loss of response to collagen and flow cytometry

analysis indicated severely reduced levels of platelet GPVI (90, 110-113) and high levels of soluble (s)GPVI. By mixing healthy donor washed platelets with patient plasma, the loss of collagen responsiveness in ITP patients with an anti-GPVI autoantibody was demonstrated to occur via engagement of the Fc portion of the antibody with platelet FcγRIIa, triggering ITAM signalling and activation of metalloproteinase-mediated GPVI release. Whether this mechanism occurs *in vivo* and whether it could explain the bleeding out of step with the platelet count remains to be determined. Detecting antiplatelet autoantibodies remains a clinical challenge (101). However, it is worth noting that patients with detectable antiplatelet antibodies may achieve improved and sustained responses to ITP therapies (114-117) implying that ITP patients could be further subclassed and underscores the importance of developing and improving standardised assays to aid in clinical decisions around ITP.

Together with the aberrant B cell response, ITP patients may show impaired immune regulation manifested by increased proliferation of helper T lymphocytes, reduction in regulatory T cells and loss of control of cytotoxic T lymphocytes (118). Dysregulated control of T helper 1 (Th1) cell expansion for example via inadequate nitric oxide levels (119) may contribute to this pathology (70). Cytotoxic T cells are capable of attacking megakaryocytes and contributing to impaired platelet production (85). Exposure of platelet antigens to T cells results in triggering of B cell somatic hyper-mutation, formation of antiplatelet plasmocytes and enhanced production of antibodies (89). ITP patient immune responses have shown a bias towards a Th1 response resulting in increased serum levels of interferon (IFN) γ and interleukin (IL)-2 and enhanced stimulation of macrophages (89). A decrease in number and function of regulatory T cells along with a decrease in CD19+ regulatory B cells has also been shown in ITP patients indicating a loss of control of the adaptive immune response (78). As we improve our understanding of how to specifically modulate T cells in ITP patients, this is likely to lead to effective antigen-specific therapeutics.

Heparin-induced thrombocytopenia (HIT)

HIT is caused by antibodies, typically of the IgG class, recognising platelet factor (PF)-4, a cationic soluble factor released from activated platelets (120) in complex with polyanionic heparin (121). Not all antibodies produced against the PF4/heparin complex will be pathogenic. HIT pathogenicity occurs when platelet-activating antibodies form an immune complex with platelet-associated PF4/heparin aggregates in a precise stoichiometry (122, 123). The Fc portion of the HIT antibody engages platelet FcγRIIa, as wells as Fc receptors on monocytes (124, 125) and neutrophils (126, 127), and triggers platelet activation and aggregation via an ITAM-dependent signalling cascade, resulting in the paradoxical manifestation of both thrombocytopenia and thrombosis in a subset of patients. Complement-mediated activation of endothelial cells and release of extracellular traps by activated neutrophils may further contribute to a prothrombotic vascular environment (123, 128). HIT pathology requires anti-PF4/heparin antibodies and FcγRIIa expression as demonstrated in a transgenic mouse model (129). As such, FcγRIIa is regarded as the pathological HIT receptor. Among the cells involved in the pathogenesis of HIT, platelets form the largest pool of FcγRIIa (130).

HIT is the most common and potentially fatal, iatrogenic complication of heparin anticoagulation with an incidence rate of <0.1% to 7% among heparinised patients (131). Annually, heparin is administered to an estimated 12 million hospitalised patients in the United States alone (132). HIT prevalence is influenced by heparin preparation (unfractionated more so than low-molecular-weight heparin) (133), patient type (more prevalent among orthopaedic patients than cardiac patients) (134) and length of heparin administration (more prevalent among patients with longer heparin exposure) (135). Thrombotic complications, which may lead to limb amputation or death in patients with HIT, occur in 30-60% of cases (136). Clearly, HIT poses a significant clinical complication that warrants accurate and timely diagnosis.

Anti-PF4/heparin antibodies are extremely rare in healthy individuals with a prevalence of 0.3-0.5% as assessed in blood bank donors (137, 138). The use of unfractionated heparin and cardiac surgery have been significantly associated with the formation of anti-PF4/heparin antibodies.

However, there is a discrepancy between HIT antibody formation and the risk for HIT development. Up to 50% of cardiac patients were positive for HIT antibody compared to 14.1% among orthopaedic patients (134). However, among those with detectable anti-PF4/heparin antibodies, orthopaedic patients (52.6%) were more likely to develop HIT than cardiac patients (5%), suggesting a potential contribution from impaired mobility. This discord also suggests heterogeneity in the ability of anti-PF4/heparin antibodies to activate platelets and lead to the manifestation of the syndrome associated with HIT. Equally, HIT antibodies (but not necessarily HIT pathology) may be more prevalent in situations where there is intense platelet activation such as in intensive care and trauma units (139, 140).

Crosslinking of FcγRIIa triggers ITAM signalling in platelets resulting in calcium mobilisation, integrin activation and release of pro-coagulant microparticles. FcγRIIa present on monocytes can also be engaged by HIT antibodies resulting in generation of tissue factor and thrombin (141) contributing to HIT pathology (123). Ultimately, thrombosis and thrombocytopenia ensue as platelets are consumed in thrombotic events or are cleared by splenic macrophages (123). FcγRIIa activation of platelets mediated by HIT antibodies can result in metalloproteolytic loss of the extracellular portion of GPVI (59, 142). This loss requires active ITAM signalling and it remains an open question as to whether the sGPVI ectodomain could report on the presence of pathogenic HIT antibodies in patients at risk of developing HIT. Due to the leading role for ITAM signalling in HIT antibody activation pathways, it may be possible to interfere with this pathway in people at risk of developing HIT by modulating ITAM signalling intermediaries (143, 144). Importantly, plasma sGPVI was associated with major bleeding in critically-ill patients with suspected HIT. sGPVI may be a novel biomarker to predict bleeding risk in patients with suspected HIT (145).

Thrombocytopenia related to pathogenic infections

Thrombocytopenia is a common complication of bacterial and viral infections, and its severity predicts the clinical outcome of critically ill patients (146). Due to their abundance in blood and the presence of virus-binding sialic acid residues, Toll-like receptors (TLR) as well as other receptors, platelets are amongst the first blood components to meet and ingest viral particles (11, 147-149). Platelets also bear a number of receptors that bacterial proteins are able to engage directly (150, 151). Pathogenic infections can often result in thrombocytopenia either directly by platelet activation followed by consumption and clearance, or by way of infection of megakaryocytes or haematopoietic stem cells in the bone marrow, acting to disrupt megakaryocyte maturation pathways and disturb platelet production (11). Some viruses directly impact liver function and interfere with TPO production which also results in thrombocytopenia (152).

In viral-associated thrombocytopenia, the underlying pathophysiology includes accelerated peripheral platelet destruction and ineffective production of platelets from infected megakaryocytes. A number of viruses are able to interfere with megakaryocyte biology. For example immature, but not mature megakaryocytes, express co-receptors such as CXCR4 and CD4 on their surface which human immunodeficiency virus (HIV) can use to mediate entry into the cell (153, 154). Experiments conducted *in vitro*, as well as mouse models *in vivo* have provided evidence that dengue virus is able to suppress several bone marrow populations including infection of megakaryocytes resulting in virus replication and decreased thrombopoiesis (155). Hepatitis C virus (HCV) has also been shown to suppress megakaryopoiesis in the bone marrow however the exact mechanism is unknown (87).

The damage caused to liver tissue by HCV has been shown to decrease liver TPO production and platelet numbers and TPO levels are typically restored after liver transplant (88). Interestingly, molecular mimicry has been proposed as a mechanism that can lead to thrombocytopenia and secondary ITP in patients with HCV, HIV as well as varicella zoster virus, Zika virus and *Helicobacter pylori* infections (78). Clinicians have speculated on an association between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the development of ITP, but thrombocytosis

and deleterious thrombosis are more frequently encountered (156, 157). Found in patients with a high HCV viral load, an epitope encompassing amino acids 49-66 of the β3 integrin subunit of αIIbβ3 with high sequence homology with several antigenic HCV core envelope peptides, was targeted by an antibody raised against the viral peptides leading to thrombocytopenia (158). Strong sequence identity between the platelet β3 integrin subunit and HIV glycoprotein 120 also has led to generation of cross-reactive antibodies that can trigger platelet clearance (159). Whilst reports of amino acid sequence homology between viral and platelet proteins are sporadic (89), situations where a viral antigen structure mimics a platelet protein, giving rise to cross-reactive antiplatelet autoantibodies, is likely to be an area of research that requires more attention. Further, some viruses can mediate direct entry into platelets via platelet surface receptors and therefore result in platelet activation and thrombocytopenia by consumption and clearance by macrophages. For example, dengue virus and influenza A can directly bind to FcγRIIa, cytomegalovirus can bind to TLRs and HIV-1 can bind to CLEC-2 (160).

Drug-induced thrombocytopenia (DITP)

Considered to be distinct from HIT because of the peculiarities in HIT pathogenesis, and cytotoxic chemotherapies to which megakaryopoiesis is acutely sensitive, DITP is an uncommon but severe side effect of a growing list of more than 300 medications, foods, nutritional supplements and herbal remedies. DITP can result in haematological dysfunction and major bleeding outcomes if not detected quickly (29, 161, 162). A dramatic drop in platelet count to levels below 20 x 10^9/L typically occurs within 2-3 days after exposure to the drug and the thrombocytopenia will usually resolve within days once the therapy has been cleared. Antibiotics including the sulphonamides, anticonvulsants and nonsteroidal anti-inflammatory drugs can cause DITP (29).

DITP is most commonly characterized by severe thrombocytopenia due to clearance and/or destruction of platelets sensitized by a drug-dependent antibody. Quinine-type drug-dependent antibodies bind tightly to platelets only in the presence of the sensitizing drug and most often target

αIIbβ3 and GPIb-IX (29, 163). Hapten-dependent DITP occurs when a small molecule therapeutic (penicillin, cephalosporins) engages a platelet surface protein which then presents this molecule to the immune system. Drug-specific antibodies that target the drug when bound to the platelet surface are then produced, resulting in platelet opsonisation and clearance (29, 164). DITP can also occur when platelet inhibitors tirofiban or eptifibatide, bind to the fibrinogen-binding site of αIIbβ3 and cause a conformational change and exposure of a neoepitope (29, 165, 166)

Immune-based thrombocytopenias as a complication of pregnancy

FNAIT is a rare but severe disease with an incidence of approximately 1 per 1500 pregnancies with consequences ranging from sub-clinical moderate thrombocytopenia to life-threatening bleeding in the neonatal period, resulting in death or permanent neurological damage (167). FNAIT occurs when the foetus inherits a paternal platelet antigen genotype, most commonly human platelet antigen (HPA) 1a which causes allo-immunisation and production of IgG antibodies in the mother. These antibodies can cross the placenta and bind to neonatal platelets resulting in opsonisation and clearance (168). Alloantibodies have been shown to activate proapoptotic pathways and suppress megakaryopoiesis *in vitro*, and this may also contribute to the thrombocytopenia observed in FNAIT (169).

HPA-1a alloantigenicity is also a prime mediator of post transfusion purpura (PTP), a rare but life-threatening side effect of platelet transfusions, with an estimated incidence of around 1 in 24,000 up to 1 in 100,000 transfusions (170). Patients previously sensitized to platelet antigens through pregnancy or transfusion are re-sensitized to the same antigen(s), and produce potent platelet-reactive antibodies primarily against HPA-1a. It is most common in women who have had multiple pregnancies and presents 5-10 days after transfusion with severe thrombocytopenia (171). People who have been exposed to HPAs can develop PTP upon re-exposure. Interestingly, the alloantibodies not only target transfused platelets but are also able to target self-platelets, likely due to concomitant production of antiplatelet autoantibodies, resulting in severe thrombocytopenia (171-173).

Thrombotic thrombocytopenic purpura (TTP)

TTP is a rare but potentially lethal syndrome characterized by severe thrombocytopenia, microangiopathic haemolytic anaemia, and neurological symptoms. In TTP, intravascular platelet aggregation induces transient ischemia in organs and in the central nervous system (174). Congenital TTP (cTTP) is caused by an inherited deficiency in a disintegrin and metalloproteinase with thrombospondin type 1 motif member 13 (ADAMTS13), which is the enzyme responsible for cleaving high molecular weight multimers of VWF. Individuals with cTTP generally do not present until adulthood and presentation is often linked with pregnancy (175). The acquired or immune form of TTP results from the generation of autoantibodies that target ADAMTS13 and inhibit metalloproteinase activity (176). Whilst ADAMTS13 binds to circulating VWF, the proteolytic activity is controlled by the conformation of VWF, and shear-mediated changes to the secondary structure of VWF are essential for efficient cleavage. Binding of ADAMTS13 to VWF is mediated through several non-catalytic domains which are distant from the catalytic site, permitting a unique shear-responsive allosteric activation of the metalloproteinase (177). Whilst autoantibodies recognising epitopes within the whole of ADAMTS13 can be detected, people with TTP almost universally have antibodies that target the spacer region of ADAMTS13 (178), a region that is critical for VWF recognition and binding by ADAMTS13, and proteolysis of VWF multimers (179). The trigger of the autoimmune response observed in TTP remains unclear, but pregnancy, recent infection and surgery are common elements (180-182).

The molecular mechanism underlying both forms of TTP is the loss of functional ADAMTS13 in plasma and ability to manage and process VWF multimers. VWF is secreted as ultralarge multimers from endothelial cells, which are then cleaved by ADAMTS13 in flowing blood generally under high shear conditions (183, 184). Ultralarge VWF multimers preferentially bind to platelets via the GPIb-IX-V complex as part of a normal haemostatic response. However, if left unregulated, excessive amounts of ultralarge VWF multimers will cause the formation of microthrombi and thrombocytopenia

that are signature events of TTP, which can lead to multi-organ damage (182). TTP can be clinically challenging to differentiate from the systemic inflammatory disorder, haemolytic uremic syndrome (HUS), a microangiopathy characterised by haemolysis of red blood cells, thrombocytopenia and microthrombi formation (185).

Concluding remarks

Although excellent progress towards understanding the pathophysiology of immune-based thrombocytopenias has been made, the immunopathogenesis of these diseases remains elusive. Antiplatelet autoantibodies can be detected only sometimes, and development of approaches to readily identify imbalances in the adaptive immune system and the key immune cells that trigger the production of antiplatelet autoantibodies are essential. It is crucial to understand in more detail the mechanisms leading to the loss and re-establishment of self-tolerance of the immune system towards platelets, including consideration of predisposing genetic factors, and modifying factors such as ethnicity, gender, the contribution of sex hormones and co-occurrence of other autoimmune diseases. Future studies should explore why these identified genetic risk factors are frequently found in the healthy population, even though the incidence of immune-mediated thrombocytopenia is extremely low.

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Figure legends

Figure 1 Hallmarks of thrombocytopenia – impacts on haemostasis. Thrombocytopenia can result from an increase in platelet destruction and clearance by macrophages in the spleen and liver; a decrease in platelet production from megakaryocytes; sequestration in the spleen or a haemostatic disruption that causes large amounts of platelets to be consumed in thrombotic or bleeding events. Platelet function can also be impaired due to loss of functional receptors on the surface or lack of granules required to release bioactive molecules and secondary activators of platelets.

Figure 2 Haemostatic function of platelets in response to endothelial injury. Upon injury to a vessel wall sub-endothelial collagen and VWF are exposed and allow tethering of platelets to the site of injury, principally by the VWF A1-domain binding GPIbα of the GPIb-IX-V complex and collagen binding GPVI and integrin α2β1. Activated adherent platelets undergo cytoskeletal rearrangement and intracellular signalling resulting in calcium mobilisation from intracellular stores, generation of thromboxane, exposure of membrane phosphatidylserine and release of proteins and soluble platelet mediators from granules. These changes make the platelet surface highly procoagulant, and triggers integrin activation via inside-out signalling. This serves to accelerate coagulation and recruit additional platelets and other cells to the site of injury. Plasma fibrinogen binds to activated αIIbβ3 to form an aggregate, and local thrombin generation results in formation of fibrin to stabilise the thrombus, seal the vessel and commence tissue repair. VWF = von Willebrand Factor, FXa = active factor X, Ca^{2+} = calcium, C = calmodulin, TXA_2 = thromboxane A_2, ADP = adenosine diphosphate, PF4 = platelet factor 4, GPO = glycine-proline-hydroxyproline, RGD = arginine-glycine-aspartate, orange phospholipid = phosphatidylserine.

Figure 3 Molecular basis of immune-based platelet disorders. In immune-based platelet disorders autoantibodies and CD8+ T cells may interfere with multiple aspects of the platelet life cycle, including

platelet production, lifespan and clearance resulting in thrombocytopenia. The triggers leading to loss of self-recognition of platelets are not known but can include strong viremia, or exposure to certain drugs (HIT, DITP). Indirect mechanisms of thrombocytopenia include viral mimicry and disruption of TPO production, antibody-mediated loss of ADAMTS13 activity or generation of anti-HPA alloantibodies via transfusion or pregnancy. See text for details. MK = megakaryocytes, HPA = human platelet antigen, PF4 = platelet factor 4, TPO = thrombopoietin, VWF = von Willebrand factor, ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13.

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Figure 1

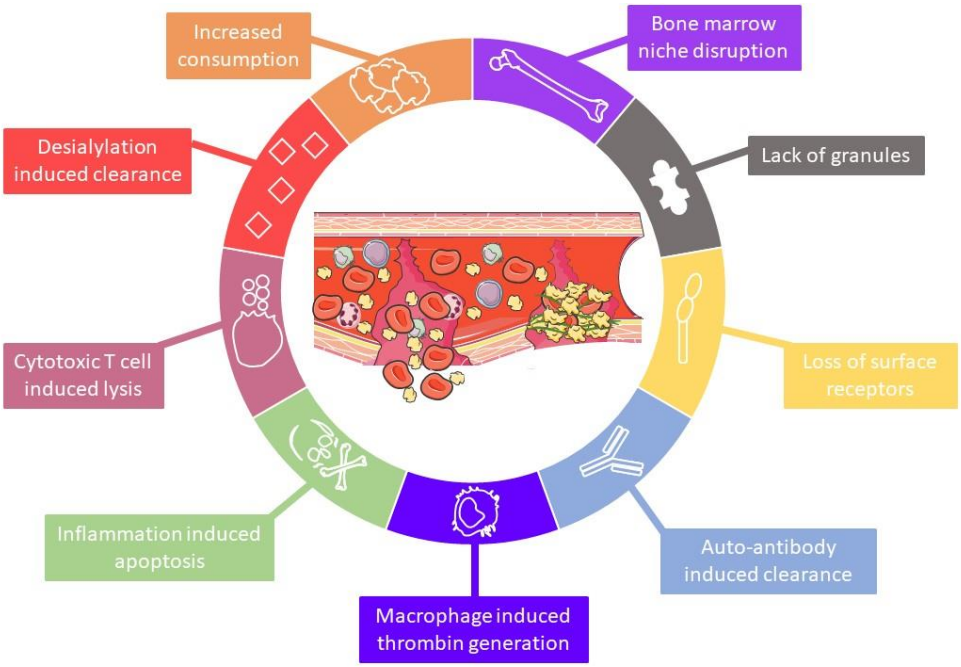


Figure 2

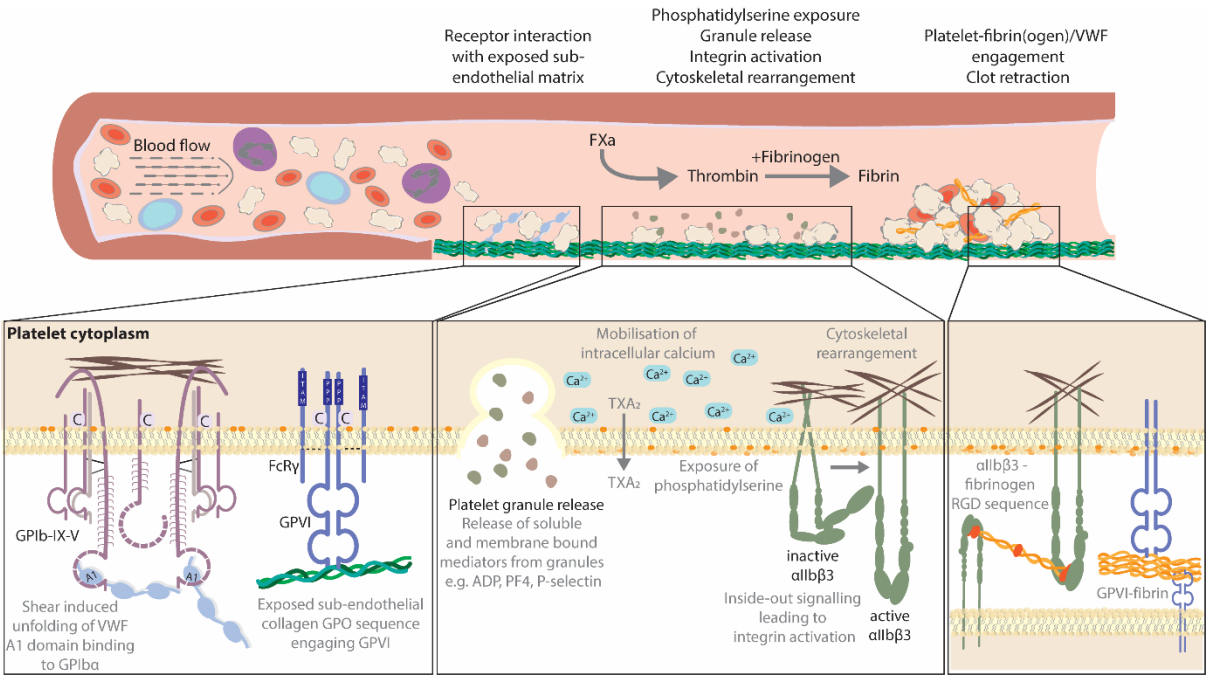
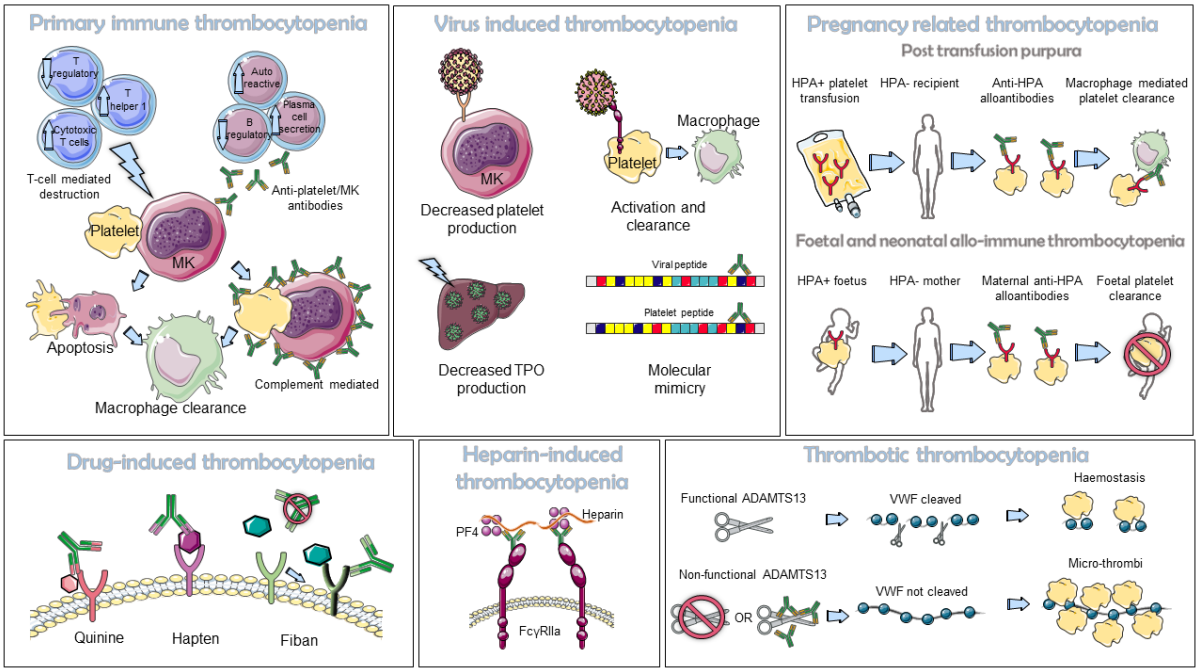


Figure 3


Primary immune thrombocytopenia
T regulatory
T helper 1
Cytotoxic T cells
Auto reactive
B regulator
Plasma cell secretion
T-cell mediated destruction
Anti-platelet/MK antibodies
Platelet
MK
Apoptosis
Complement mediated
Macrophage clearance
Virus induced thrombocytopenia
MK
Decreased platelet production
Macrophage
Platelet
Activation and clearance
Decreased TPO production
Viral peptide
Platelet peptide
Molecular mimicry
Pregnancy related thrombocytopenia
Post transfusion purpura
HPA+ platelet transfusion
HPA- recipient
Anti-HPA alloantibodies
Macrophage mediated platelet clearance
Foetal and neonatal allo-immune thrombocytopenia
HPA+ foetus
HPA- mother
Maternal anti-HPA alloantibodies
Foetal platelet clearance
Drug-induced thrombocytopenia
Quinine
Hapten
Fiban
Heparin-induced thrombocytopenia
PF4
Heparin
FcγRIIa
Thrombotic thrombocytopenia
Functional ADAMTS13
VWF cleaved
Haemostasis
Non-functional ADAMTS13
OR
VWF not cleaved
Micro-thrombi