We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 3

Platelet Bacterial Interactions in the Pathogenesis of Infective Endocarditis — Part II: The Staphylococcus

Steven W. Kerrigan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55911

1. Introduction

Infective Endocarditis is a microbial infection characterised by the presence of septic vegetations on the surface of the endocardium (Moreillon and Que, 2004). Infection most commonly occurs on the heart valves that has been damaged by congenital defects such as previous disease or trauma (Durack, 1995). As a result these sites have the ability to generate turbulent blood flow which in turn can cause damage to inner most lining of the blood vessels, the endothelium, which causes surface damage leading to exposure of underlying matrix protein (Ruggeri, 2009). Once exposed this highly thrombogenic surface leads to rapid platelet deposition and the formation of a fibrin network. Circulating bacteria from a transient bacteremia in turn binds to this sterile platelet fibrin nidus which allows a secondary accumulation of platelets that encase the bacteria leading to stable thrombus formation (Moreillon and Que, 2004).

Despite improvements in medical and surgical therapy, invasive staphylococcal disease causing infective endocarditis is still associated with a severe prognosis and remains a significant therapeutic challenge. Once a disease primarily affecting younger patients presenting with rheumatic heart disease, modern times see a significant increase in newer 'at risk' categories including patients with long term indwelling central venous catheters, patients undergoing haemodialysis and invasive intravascular procedures such as arthroplasty, immunocompromized patients and intraveneous drug abusers (Thuny et al., 2012). Treatment of infective endocarditis usually requires a multidisciplinary approach involving specialists in infectious disease, cardiologists and cardiac surgeons. Current treatment regimes consist of aggressive prolonged antibiotic therapy, frequently combined with surgery (Prendergast and Tornos, 2010, Wilson et al., 2007). Prolonged antibiotic use is often less than successful as 40% of patients relapse within 2 months of finishing clinically effective therapy.

INTECH
open science | open minds

© 2013 Kerrigan; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Furthermore, prolonged exposure to antibiotics leads to a greater risk of adding to the global problem of multiple antibiotic resistant strains of bacteria. Surgery is a costly and risky alternative, however necessary in up to 47% of patients (Castillo et al., 2000, Murdoch et al., 2009). In many cases surgery is not preferable due to risks associated with cardiac failure, further spread of infection leading to persistent sepsis due to surgical removal of an infected thrombus and/or life threatening embolisation (Jault et al., 1997, Heiro et al., 2000, Thuny et al., 2012, Remadi et al., 2007).

2. The Staphylococcus

Staphylococcus aureus is a gram positive pathogen that continues to cause a significant number of community-acquired and nosocomial infections. It is a normal commensal of the human body and usually lives in harmony with its host without causing symptoms. Its primary habitat is the anterior nares in 20% of the population and is transiently associated with the rest (Foster, 2009). The success of *S. aureus* as an opportunistic pathogen is due in part to its expression of a wide array of microbial surface components recognising adhesive matrix molecules (MSCRAMM's) (Patti et al., 1994). Using these MSCRAMM's *S. aureus* uses a multitude of mechanisms to attach either directly or indirectly to host cells including platelets (O'Brien et al., 2002, Kerrigan et al., 2008, Miajlovic et al., 2010, Fitzgerald et al., 2006, Pawar et al., 2004, George et al., 2006). It is for this reason that *S. aureus* is now the most common and most virulent etiologic pathogen in infective endocarditis.

3. Platelets play a critical role in thrombosis and haemostasis

Platelets are small anucleate cell fragments of the larger haematopoietic precursor cell, the megakaryocyte (Thon and Italiano, 2010) and are crucial mediators of haemostasis. Platelets have no control over gene expression as they do not possess a nucleus however they have got limited capabilities in translational protein synthesis (Lindemann et al., 2001b). The primary role of platelets in haemostasis is to police the integrity of the endothelium to prevent blood loss (Nieswandt et al., 2009). Platelets circulate close to the endothelial cell surface at high shear as individual entities that ordinarily do not interact with any other cell types. A transition from this resting state to an activated state can be rapidly initiated if platelets are exposed to an appropriate stimulus. Disruption of the endothelial cell lining due to trauma or injury to the vascular endothelium platelets rapidly accumulate at the site of injury (Gawaz et al., 2005). Recruitment is a highly controlled event that is initiated by the adhesive interaction between the exposed extracellular matrix proteins in damaged endothelium and specific membrane receptors on the platelet (Tabuchi and Kuebler, 2008). Collagen (Santoro and Zutter, 1995), vonWillebrand factor (vWf) (Ruggeri, 1999), fibronectin (Savage et al., 1998, Kasirer-Friede et al., 2007) and thrombospondin (Jurk et al., 2003) constitute the exposed matrix proteins at the site of injury. Athough plasma proteins such as fibrinogen/fibrin and vitronectin are not

http://dx.doi.org/10.5772/55911

synthesized by endothelial cells they can bind to exposed matrix proteins and increase adhesiveness at the damaged site (Ruggeri et al., 2006, Ruggeri and Mendolicchio, 2007).

Platelets express a vast array of membrane receptors that play a critical role in recognition of matrix proteins. The initial interaction of platelets with the injured vessel wall occurs between GPIbα and immobilised vonWillebrand factor (Chesterman and Berndt, 1986). This interaction initiates the tethering of circulating platelets to the vessel wall. Platelets typically 'roll' over the vWf in the direction of flow driven by shear forces experienced by the vasculature (Ruggeri, 2009). A loss of interaction between GPIb and vWf on one side of the platelet leads to the formation of another GPIb-vWf interaction on the other side of the platelet which gives rise to a rolling phenomenon. This rolling mechanism is critical to slowing down the platelet long enough for a second interaction that anchors the platelet to the damaged site. This firm adhesion can be mediated by several membrane receptors, some of which will have become activated as a result of platelet rolling and others who are expressed on the platelet surface as a result platelet activation (Jackson et al., 2009). Once firmly adhered, the platelets rearrange cytoskeletal components which results in filopodia and llamelipodia extension leading to flattening or spreading of the platelet. Platelet spreading is critical following firm adhesion as it firstly allows the platelet withstand the shear forces experienced in the vasculature and secondly it increases the platelet surface area thus covering more of the damaged site.

Following attachment, platelets undergo a series of highly controlled intracellular signalling events that lead to the release reaction where platelets release the contents of its stored intracellular granules. Alpha granules contain proteins such as P-selectin which mediates adhesion of platelets to monocytes, neutrophils and lymphocytes, resulting in the formation of platelet leukocyte complexes (Diacovo et al., 1996a, Diacovo et al., 1996b, Larsen et al., 1989). These granules also contain many chemotactic agents which lead to the recruitment of various inflammatory cells; platelet derived growth factor (PDGF) and 12-hydroxyeicosatetraenoic acid (12-HETE) which recruit neutrophils (Herd and Page, 1994, Mannaioni et al., 1997); platelet factor 4 and platelet derived histamine releasing factor (PDHRF) which recruit eosinophils in airway disease (Brindley et al., 1983, Frigas and Gleich, 1986); PDGF and transforming growth factor β (TGF-β) which recruit monocytes and macrophages and TGF-β which recruits fibroblasts (Deuel et al., 1982, Tzeng et al., 1985, Wahl et al., 1987). Platelet granules also contain several mediators of tissue damage such as oxygen free radicals and hydrolytic enzymes. Dense granules release cationic proteins that initiate vascular permeability and mediators that enhance aggregate formation such as adenosine diphosphate (ADP) and serotonin (5-HT) (Rendu and Brohard-Bohn, 2001). Bioactive amines are also secreted from platelets following activation including Thromboxane A_2 (TxA2) and platelet activating factor (PAF) (McIntyre et al., 2003, Patrono et al., 2001).More recently it has been shown that platelet granules contain many antimicrobial peptides such as beta-lysin, platelet microbial protein (PMP), neutrophil activating peptide (NAP-2), released upon activation normal T-cell expressed and secreted (RANTES) and fibrinopeptides A and B (Johnson and Donaldson, 1968, Donaldson and Tew, 1977, Kameyoshi et al., 1992, Yeaman et al., 1997, Krijgsveld et al., 2000).

Once activation is complete the platelet forms a new surface for additional platelets to adhere, predominantly through GPIIb/IIIa crosslinking adjacent platelets through a fibrinogen bridge,

resulting in aggregate formation. The final step sees and effective plug at the site of injury that is reinforced by the conversion of fibrinogen to fibrin through the coagulation cascade (Ruggeri et al., 2006).

4. The growing role of platelets in infection and immunity

Platelets are poorly recognised for their role in infection and immunity even though just like professional phagocytes (neutrophils, macrophages and dendritic cells) platelets are derived from the same haematopoietic stem cell, undergo chemotaxis (Clemetson et al., 2000), phagocytose foreign particles (Youssefian et al., 2002), and secrete a multitude of products including inflammatory mediators (Kameyoshi et al., 1992), cytokines (Lindemann et al., 2001a, Antczak et al., 2010) and antimicrobial peptides (Tang et al., 2002, Mercier et al., 2004), all while directing and recruiting several members of the innate immune system to the infected area (Cox et al., 2011, Semple and Freedman, 2010). In addition, toll like receptors (TLR) which are a family of pattern recognition receptors expressed by several professional phagocytes recognise conserved molecular motifs expressed on different classes of infectious agent (Janeway and Medzhitov, 2002, Armant and Fenton, 2002). To date at least 13 TLRs have been described in various immune and nonimmune cells in both human and mice. Recently human platelet have been shown to express TLR1,2,4,6,8 and 9, reinforcing their role as primitive immune cells in host defence (Cognasse et al., 2005, Shiraki et al., 2004, Aslam et al., 2006, Zhang et al., 2009, Garraud and Cognasse, 2010, Andonegui et al., 2005, Keane et al., 2010). More recent studies have also demonstrated that TLRs are also responsible for lipopolysaccharide (LPS)-induced thrombocytopenia (Andonegui et al., 2005, Aslam et al., 2006).

5. Mechanisms of interaction

Bacteria can interact with platelet in two ways, they can either support platelet adhesion or they can induce platelet aggregation. Platelet adhesion to immobilised bacteria is a measure of the strength of the interaction, whereas platelet aggregation induced by bacteria is a measure of the quality of the interaction. In contrast to typical platelet aggregation induced by physiological agonists such as adenosine diphosphate (ADP), collagen or thrombin, bacteria induce an all or nothing response. This means that the bacteria either induce a maximal aggregation or they don't induce platelet aggregation at all, there is no intermediate response. Another unique feature of bacteria induced platelet aggregation is a distinct pause in time before aggregation takes place. This is typically called the lag time. Increasing the concentration of bacteria shortens the lag time but never eliminates it. The average lag time to platelet aggregation following addition of Staphylococci is between 5-12 minutes. This is in contrast to the lag time observed upon the addition of typical platelet agonists ADP or thrombin which have a lag time less than 10 seconds.

There are 3 main interactions between bacteria and platelets. In the first interaction bacteria express proteins that can directly interact with a surface receptor on the platelet. In this case

http://dx.doi.org/10.5772/55911

the bacterial protein express ligand mimetic domains that act as agonists on the platelet receptor thus triggering an intracellular signal that culminates in platelet activation. In the second interaction bacterial proteins bind a plasma protein that is a natural ligand for a platelet receptor. For example, bacteria can bind antibody which in turn bridges the bacteria to the antibody receptor (FcγRIIa) expressed on the platelet. Once engaged the receptor results in the generation of an intracellular signal leading to platelet activation. Finally bacteria may have the ability to secrete products or toxins that in turn activate platelets. Engagement of the product or toxin with a platelet receptor results in activation. These different mechanisms of interaction may help explain the lag time to platelet aggregation. For example, the lag time could be representative of the time taken to trigger a response or bind a plasma protein. A major challenge in studying platelet bacterial interactions is that most bacteria can interact with platelets using multiple mechanisms. This makes it incredibly difficult to identify either the platelet receptors or the bacterial proteins involved in triggering thrombus formation. Moreover not only are the interactions species specific but strain specific as well.

6. Staphylococci interactions with platelets

6.1. Indirect interaction (Released products)

Staphylococcus aureus was one of the first bacteria isolated from patients with acute endocarditis. Despite improvements in medical and surgical therapy, invasive staphylococcal disease causing infective endocarditis is still the most frequent etiologic microorganism found in patients (Rasmussen et al., 2011). Studies investigating the mechanism through which *S. aureus* contributes to endocarditis dates back as far as the early 1900's. By the mid 1900's significant attention had been placed on the involvement of *S. aureus* alpha (α)-toxin in contributing to IE. Alpha-toxin is produced by almost all strains of *S. aureus*. Typically α-toxin disrupts the cell membrane by binding to the lipid bilayer of platelets, erythrocytes and some leukocytes, forming an oligomeric structure that forms a water filled transmembrane pore. In 1964 Siegel and Cohen made two critical observations; first, addition of α-toxin led to the loss of single platelets as evidenced by turbidimetric aggregometry and second that addition of α-toxin to human platelets resulted in leakage of intracellular ions; NAD+, K+ and ATP but interestingly not protein, suggesting that α-toxin was not lysing the platelets (Siegel and Cohen, 1964). Further studies by Bernheimer and Schwartz confirmed these reports and demonstrated by electron microscopy that following exposure to α-toxin platelets swelled but did not show signs of lysis (Bernheimer, 1965). These early studies suggested that α-toxin may have the ability to generate a signal upon binding to the platelet. Focusing on this Arvand and colleagues demonstrated that α-toxin did indeed trigger a platelet signal upon binding and most importantly one that leads to secretion of intracellular contents including procoagulant mediators, platelet factor 4 and factor V. Secreted factor V in turn associates with the platelet membrane leading to assembly of the prothrombinase complex (Arvand et al., 1990). This explains the major pathway responsible for the procoagulatory effects of α-toxin. In contrast to these early findings Bayer et al. demonstrated that α-toxin did cause platelet lysis and this led to the release of platelet microbial proteins (PMP's) which was bactericidal to *S. aureus*.

Using an animal model of endocarditis the authors demonstrated that different strains of *S. aureus* differed in the expression of functional versus mutant forms of α-toxin. Under these conditions, the *S. aureus* strains producing either minimal or no α-toxin were less virulent *in vivo* than wild-type strains (Bayer et al., 1997). Wild-type *S. aureus* strains or indeed an isogenic strain engineered to over-express α-toxin were associated with increased release of PMP from platelets. These results suggest that when *S. aureus* releases α-toxin, platelets release PMP's therefore leading to a protective role for the host by destroying *S. aureus*.

Lipoteichoic acid (LTA) is an essential component of the cell wall of *S. aureus* and plays a key role in host-pathogen interactions (Morath et al., 2005). LTA is anchored to the cell wall via diacylglycerol, however following bacteriolysis induced by cationic proteins from leukocytes or antibiotic treatment with certain antibiotics, LTA is released from the cell wall (Lotz et al., 2006). LTA is a very potent stimulator of cells expressing the pattern recognition receptor, toll like receptor 2 (TLR2) (Kawai and Akira, 2010). Functional TLR2 is expressed on a number of immune cells including platelets (Blair et al., 2009, Keane et al., 2010, Ward et al., 2005). Work by Sheu et al, demonstrated that LTA from *S. aureus* inhibited platelet aggregation, calcium mobilisation and cyclic AMP in human platelets (Sheu et al., 2000a, Sheu et al., 2000b). It remains to be seen whether TLR2 is mediating this inhibition of platelet signalling.

6.2. Indirect interaction (Cell wall proteins)

There are numerous cell wall proteins expressed on the surface of *S. aureus* that have been demonstrated to bind to platelets and trigger platelet activation. The majority of these cell wall proteins have been found to bind plasma proteins and bridge to a platelet receptor. Staphylococcal protein A is a widely expressed protein found on greater than 90% of *S. aureus* strains. In 1979, Hawiger et al., demonstrated that protein A is capable of binding to immunoglobulin G (IgG) which in turn bridges to the platelet antibody receptor, FcγRIIa. This interaction results in platelet signal generation, GPIIbIIIa dependent platelet aggregation and serotonin release from the platelet dense granules. Interestingly purified protein A failed to cause measureable platelet aggregation and release of serotonin was significantly reduced (Hawiger et al., 1979). Recent studies have demonstrated that protein A can bind to the A1 domain of the major plasma protein vonWillebrand factor with high affinity (low nM range) (O'Seaghdha et al., 2006) which serves as a receptor for GPIbα expressed on platelets (Andrews et al., 2003). More recent studies have investigated this interaction under fluid shear conditions and demonstrated that preincubating platelet rich plasma with a vonWillebrand Factor antibody or indeed blocking the platelet GPIbα receptor with an inhibitory monoclonal antibody partially inhibited the platelet-*S. aureus* interaction. Furthermore using a strain of *S. aureus* that is deficient in protein A expression reduced its interactions with platelets (Pawar et al., 2004).These results suggest that protein A plays a role in triggering platelet activation.

More recent studies demonstrated that multiple cell wall proteins expressed on *S. aureus* are capable of interacting with and triggering platelet aggregation (O'Brien et al., 2002). Among the cell wall proteins identified, clumping factor A (ClfA) and clumping factor B (ClfB) are possibly the most extensively studied. ClfA and ClfB has been shown to bind a number of plasma proteins including fibrinogen, IgG and complement, which in turn bridge the bacteria

http://dx.doi.org/10.5772/55911

to specific platelet receptors and trigger activation. Binding each plasma protein individually is not sufficient to trigger platelet aggregation. To trigger full platelet activation ClfA or ClfB must bind specific IgG along with either fibrinogen or complement, IgG being the key molecule. There are at least two distinct sites on each ClfA or ClfB that allows IgG and fibrinogen bind at the same time. Once this occurs, fibrinogen binds to platelet GPIIbIIIa, IgG binds to platelet FcγRIIa and together induces receptor clustering leading to activation of signal transduction pathways culminating in platelet aggregation (Loughman et al., 2005, Miajlovic et al., 2007). Deletion of the fibrinogen binding domain on ClfA or ClfB led to the discovery of another much slower platelet aggregation (8-20 minutes versus 2-4 minutes). Loughman et al initially demonstrated that complement must assemble on the *S. aureus* surface and then cross link to complement receptors expressed on platelets. Similar to before, IgG binds to FcγRIIa, complement proteins binds to complement receptors on platelets and together induces receptor clustering leading to activation of signal transduction pathways culminating in platelet aggregation (Loughman et al., 2005). Much controversy surrounds the existence of complement receptors on platelets however the most convincing evidence of a complement receptor is that demonstrated by Nyugen et al., who demonstrated the expression of gC1qR/p33 following platelet activation. This suggests that an initial interaction leads to platelet activation which in turn triggers expression of gC1qR/p33 on the platelet surface. Expression of this receptor post activation most likely serves to anchor the bacteria to the platelet.

A critical part of *S. aureus* survival in the host is the wide array of cell wall proteins it expresses at various growth phases of its cell cycle. For example, ClfA is weakly expressed during the exponential phase and strongly expressed during the stationary phase. In contrast to this fibronectin binding protein A (FnbpA) is strongly expressed during the exponential phase of growth and weakly expressed during the stationary phase of growth. FnbpA also plays a key role in inducing platelet aggregation. The mechanism through which FnbpA induces platelet aggregation is more or less identical to the mechanism that ClfA uses to induce platelet aggregation. Fnbp contain a specific immunoglobulin binding domain (A domain) and a separate fibronectin binding domain (BCD). FnBPA possesses two different but related mechanisms of engaging and activating platelets (Fitzgerald et al., 2006). In the first mechanism, fibrinogen can bind to the A domain which crosslinks to GPIIb/IIIa, and specific immunoglobulin must crosslink to FcγRIIa to trigger platelet activation and aggregation (Fitzgerald et al., 2006). In the second mechanism fibronectin can bind to *S. aureus* via the FnBPA BCD domain (Meenan et al., 2007, Raibaud et al., 2005). The signal to trigger platelet activation/aggregation is complete when specific immunoglobulin binds the A domain of FnBPA and cross links to platelet FcγRIIa inducing receptor clustering.

As discussed in chapter 2 serine rich proteins expressed by viridans streptococci play a critical role in inducing platelet aggregation. *S. aureus* also expresses a highly glycosylated serine rich protein called SraP on its surface (Siboo et al., 2005). Strain of *S. aureus* deficient in expression of SraP has been shown to have reduced virulence in a rabbit model of endocarditis. Regardless of the fact that SraP shares significant similarities with a number of other serine rich glyco-

proteins found in the streptococci that have been found to bind to platelet GPIbα (Kerrigan et al., 2007, Plummer et al., 2005), SraP does not appear to bind to this platelet receptor.

While all of these studies are critical to our understanding of the molecular mechanisms involved in aggregate formation, one must be aware of the relevance of these findings to physiological conditions experienced in the vasculature. For example, almost all of the studies carried out to date have been carried out under non-physiological stirring or using static adhesion assays, neither of which are representative of the conditions experienced in the vasculature. Many reports in the literature in recent times have clearly demonstrated that the local fluid environment in the circulation critically affects the molecular pathways of cell-cell interactions (Varki, 1994). To address this several attempts have been made to create an environment more representative of conditions experienced in the circulation. Rheology is a useful technique that can be employed to shear cells at physiological rates. Using a cone and plate viscometer, Pawar et al. demonstrated that when *S. aureus* is mixed with whole blood isolated from a healthy individual thrombus formation could be observed. Additional studies demonstrated that the thrombus formation was dependent on multiple *S. aureus* cell wall proteins including protein A, ClfA, SdrC, SdrD, SdrE (Pawar et al., 2004). A potential limitation to using a cone and plate viscometer is that is measures thrombus formation in a soluble setting and it is well established that thrombus formation on a heart valve in IE occurs under stable conditions. To address this Kerrigan et al. developed a parallel flow chamber to assess the interaction between *S. aureus* and platelets in whole blood. To do this *S. aureus* was immobilised on a glass slide (to mimic the focal infection on a heart valve) and whole blood was perfused over the bacteria at both arterial and venous shear rates. This method demonstrated that platelets perfused over immobilised *S. aureus* under arterial shear led to a very strong adhesion, followed by rapid aggregate formation. Deletion of ClfA (but not protein A or FnbpA) from *S. aureus* abolished adhesion and subsequent aggregate formation. Using a plasma-free system, fibrinogen led to single platelet adhesion but not aggregate formation. Specific immunoglobulin failed to have any effect on either platelet adhesion or aggregation. However, addition of fibrinogen and specific immunoglobulin together to the plasma-free system led to platelet adhesion followed by aggregate formation thus highlighting the importance of fibrinogen and IgG in aggregate formation. Interestingly platelets did not adhere to or induce aggregate formation under low shear conditions using the parallel flow chamber (Kerrigan et al., 2008).

6.3. Direct interaction (Cell wall proteins)

A growing concern about studies to date is the apparent lack of contrast with conditions experienced physiologically. *In vivo*, when *S. aureus* enters the blood stream it is in an environment where iron is sequestered in haem or haemoglobulin. The lack of iron available *in vivo* inactivates the Fur repressor in *S. aureus* that results in an up-regulation of a number of genes that typically wouldn't be expressed in when growing in normal laboratory bacterial growth media. A growing family of iron-regulated surface determinant proteins have been recently identified as expressed in *S. aureus* grown in iron limited conditions. Using surface plasmon resonance, Miajlovic et al. demonstrated that one family member, iron-regulated surface determinant B (IsdB), can bind directly (in the absence of plasma proteins) to the

http://dx.doi.org/10.5772/55911

purified platelet fibrinogen receptor GPIIb/IIIa. As a result of this binding subsequent studies demonstrated the ability of the wildtype *S. aureus* strain to support platelet adhesion and induce platelet aggregation. A. *S. aureus* strain defective in expression of IsdB displayed a reduce ability to adhere to or induce platelet aggregation (Miajlovic et al., 2010).

7. Final thoughts and future directions

Infective endocarditis is notoriously difficult to treat as antibiotics are incapable of penetrating the growing thrombus to reach the encased microorganisms. As a result of this the in-hospital mortality rate can be as high as 36% (Botelho-Nevers et al., 2009). Even with treatment, 40% of patients with infective endocarditis relapse within 2 months of finishing clinically effective therapy (Netzer et al., 2002). Furthermore, approximately 25% of patients with infective endocarditis eventually require surgery, usually within 2 years after completing therapy (Olaison and Pettersson, 2003). These statistics reflect the poor delivery and penetration of antibiotic into the growing thrombus. The costs associated with hospitalization (of which the average stay in hospital is 30 days), surgery and prolonged antibiotic treatment is extremely high placing a severe burden on already over-stretched healthcare systems though out the world. The danger of *S. aureus* invasive disease is also compounded by the rapidly increasing global widespread occurrence of multiple antibiotic resistant strains (MRSA and VRSA) which is directly attributed to prolong use of antibiotics. The greater the duration of exposure of an antibiotic to bacteria, the greater the risk of development of resistance and this is irrespective of the severity of the need for antibiotics. If this is not addressed soon, acquired resistance may produce a virtually untreatable pathogen. Therefore it is of the utmost importance that we understand the molecular interactions that lead to the development of thrombus formation on the heart valves. This will serve two purposes, first it may lead to the development of novel therapies that will prevent the formation of a thrombus on the heart valve and secondly as a result will overcome the problem associated with getting clinically effective concentrations of antibiotic to the site of infection on the heart valve.

Potential drug targets identified from studies over the years suggest that blocking the interaction between IgG and platelet FcγRIIa may indeed prevent platelet receptor clustering and thus inhibit thrombus formation. Blockade of the platelet FcγRIIa receptor has distinct advantages over other anti-platelet agents as inhibitors of FcγRIIa do not affect the platelet response to other agonist and therefore does not compromise essential platelet functions.

Author details

Steven W. Kerrigan

School of Pharmacy & Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland

References

[1] Andonegui, G, Kerfoot, S. M, Mcnagny, K, Ebbert, K. V, Patel, K. D, & Kubes, P. (2005). Platelets express functional Toll-like receptor-4. *Blood,* , 106, 2417-23.

[2] Andrews, R. K, Gardiner, E. E, Shen, Y, & Berndt, M. C. (2003). Structure-activity relationships of snake toxins targeting platelet receptors, glycoprotein Ib-IX-V and glycoprotein VI. *Curr Med Chem Cardiovasc Hematol Agents,* , 1, 143-9.

[3] Antczak, A. J, Singh, N, Gay, S. R, & Worth, R. G. (2010). IgG-complex stimulated platelets: a source of sCD40L and RANTES in initiation of inflammatory cascade. *Cell Immunol,* , 263, 129-33.

[4] Armant, M. A, & Fenton, M. J. (2002). Toll-like receptors: a family of pattern-recognition receptors in mammals. *Genome Biol,* 3, REVIEWS3011.

[5] Arvand, M, Bhakdi, S, Dahlback, B, & Preissner, K. T. (1990). Staphylococcus aureus alpha-toxin attack on human platelets promotes assembly of the prothrombinase complex. *J Biol Chem,* , 265, 14377-81.

[6] Aslam, R, Speck, E. R, Kim, M, Crow, A. R, Bang, K. W, Nestel, F. P, Ni, H, Lazarus, A. H, Freedman, J, & Semple, J. W. (2006). Platelet Toll-like receptor expression modulates lipopolysaccharide-induced thrombocytopenia and tumor necrosis factor-alpha production in vivo. *Blood,* , 107, 637-41.

[7] Bayer, A. S, Ramos, M. D, Menzies, B. E, Yeaman, M. R, Shen, A. J, & Cheung, A. L. (1997). Hyperproduction of alpha-toxin by Staphylococcus aureus results in paradoxically reduced virulence in experimental endocarditis: a host defense role for platelet microbicidal proteins. *Infect Immun,* , 65, 4652-60.

[8] Bernheimer, A. W. (1965). Staphylococcal alpha toxin. *Ann N Y Acad Sci,* , 128, 112-23.

[9] Blair, P, Rex, S, Vitseva, O, Beaulieu, L, Tanriverdi, K, Chakrabarti, S, Hayashi, C, Genco, C. A, Iafrati, M, & Freedman, J. E. (2009). Stimulation of Toll-like receptor 2 in human platelets induces a thromboinflammatory response through activation of phosphoinositide 3-kinase. *Circ Res,* , 104, 346-54.

[10] Botelho-nevers, E, Thuny, F, Casalta, J. P, Richet, H, Gouriet, F, Collart, F, Riberi, A, Habib, G, & Raoult, D. (2009). Dramatic reduction in infective endocarditis-related mortality with a management-based approach. *Arch Intern Med,* , 169, 1290-8.

[11] Brindley, L. L, Sweet, J. M, & Goetzl, E. J. (1983). Stimulation of histamine release from human basophils by human platelet factor 4. *J Clin Invest,* , 72, 1218-23.

[12] Castillo, J. C, Anguita, M. P, Ramirez, A, Siles, J. R, Torres, F, Mesa, D, Franco, M, Munoz, I, Concha, M, & Valles, F. (2000). Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. *Heart,* , 83, 525-30.

[13] Chesterman, C. N, & Berndt, M. C. (1986). Platelet and vessel wall interaction and the genesis of atherosclerosis. *Clin Haematol*, , 15, 323-53.

[14] Clemetson, K. J, Clemetson, J. M, Proudfoot, A. E, Power, C. A, Baggiolini, M, & Wells, T. N. (2000). Functional expression of CCR1, CCR3, CCR4, and CXCR4 chemokine receptors on human platelets. *Blood*, , 96, 4046-54.

[15] Cognasse, F, Hamzeh, H, Chavarin, P, Acquart, S, Genin, C, & Garraud, O. (2005). Evidence of Toll-like receptor molecules on human platelets. *Immunol Cell Biol*, , 83, 196-8.

[16] Cox, D, Kerrigan, S. W, & Watson, S. P. (2011). Platelets and the innate immune system: mechanisms of bacterial-induced platelet activation. *J Thromb Haemost*, , 9, 1097-107.

[17] Deuel, T. F, Senior, R. M, Huang, J. S, & Griffin, G. L. (1982). Chemotaxis of monocytes and neutrophils to platelet-derived growth factor. *J Clin Invest*, , 69, 1046-9.

[18] Diacovo, T. G, Puri, K. D, Warnock, R. A, Springer, T. A, & Von Andrian, U. H. lymphocyte delivery to high endothelial venules. *Science*, , 273, 252-5.

[19] Diacovo, T. G, Roth, S. J, Buccola, J. M, Bainton, D. F, & Springer, T. A. (1996b). Neutrophil rolling, arrest, and transmigration across activated, surface-adherent platelets via sequential action of P-selectin and the beta 2-integrin CD11b/CD18. *Blood*, , 88, 146-57.

[20] Donaldson, D. M, & Tew, J. G. (1977). beta-Lysin of platelet origin. *Bacteriol Rev*, , 41, 501-13.

[21] Durack, D. T. (1995). Prevention of infective endocarditis. *N Engl J Med*, , 332, 38-44.

[22] Fitzgerald, J. R, Loughman, A, Keane, F, Brennan, M, Knobel, M, Higgins, J, Visai, L, Speziale, P, Cox, D, & Foster, T. J. (2006). Fibronectin-binding proteins of Staphylococcus aureus mediate activation of human platelets via fibrinogen and fibronectin bridges to integrin GPIIb/IIIa and IgG binding to the FcgammaRIIa receptor. *Mol Microbiol*, , 59, 212-30.

[23] Foster, T. J. (2009). Colonization and infection of the human host by staphylococci: adhesion, survival and immune evasion. *Vet Dermatol*, , 20, 456-70.

[24] Frigas, E, & Gleich, G. J. (1986). The eosinophil and the pathophysiology of asthma. *J Allergy Clin Immunol*, , 77, 527-37.

[25] Garraud, O, & Cognasse, F. (2010). Platelet Toll-like receptor expression: the link between "danger" ligands and inflammation. *Inflamm Allergy Drug Targets*, , 9, 322-33.

[26] Gawaz, M, Langer, H, & May, A. E. (2005). Platelets in inflammation and atherogenesis. *J Clin Invest*, , 115, 3378-84.

[27] George, N. P, Wei, Q, Shin, P. K, Konstantopoulos, K, & Ross, J. M. (2006). Staphylococcus aureus adhesion via Spa, ClfA, and SdrCDE to immobilized platelets demonstrates shear-dependent behavior. *Arterioscler Thromb Vasc Biol,* , 26, 2394-400.

[28] Hawiger, J, Steckley, S, Hammond, D, Cheng, C, Timmons, S, & Glick, A. D. Des Prez, R. M. (1979). Staphylococci-induced human platelet injury mediated by protein A and immunoglobulin G Fc fragment receptor. *J Clin Invest,* , 64, 931-7.

[29] Heiro, M, Nikoskelainen, J, Engblom, E, Kotilainen, E, Marttila, R, & Kotilainen, P. (2000). Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. *Arch Intern Med,* , 160, 2781-7.

[30] Herd, C. M, & Page, C. P. (1994). Pulmonary immune cells in health and disease: platelets. *Eur Respir J,* , 7, 1145-60.

[31] Jackson, S. P, Nesbitt, W. S, & Westein, E. (2009). Dynamics of platelet thrombus formation. *J Thromb Haemost,* 7 Suppl , 1, 17-20.

[32] Janeway, C. A. Jr. & Medzhitov, R. (2002). Innate immune recognition. *Annu Rev Immunol,* , 20, 197-216.

[33] Jault, F, Gandjbakhch, I, Rama, A, Nectoux, M, Bors, V, Vaissier, E, Nataf, P, Pavie, A, & Cabrol, C. (1997). Active native valve endocarditis: determinants of operative death and late mortality. *Ann Thorac Surg,* , 63, 1737-41.

[34] Johnson, F. B, & Donaldson, D. M. (1968). Purification of staphylocidal beta-lysin from rabbit serum. *J Bacteriol,* , 96, 589-95.

[35] Jurk, K, Clemetson, K. J, De Groot, P. G, Brodde, M. F, Steiner, M, Savion, N, Varon, D, Sixma, J. J, Van Aken, H, & Kehrel, B. E. (2003). Thrombospondin-1 mediates platelet adhesion at high shear via glycoprotein Ib (GPIb): an alternative/backup mechanism to von Willebrand factor. *FASEB J,* , 17, 1490-2.

[36] Kameyoshi, Y, Dorschner, A, Mallet, A. I, Christophers, E, & Schroder, J. M. (1992). Cytokine RANTES released by thrombin-stimulated platelets is a potent attractant for human eosinophils. *J Exp Med,* , 176, 587-92.

[37] Kasirer-friede, A, Kahn, M. L, & Shattil, S. J. (2007). Platelet integrins and immunoreceptors. *Immunol Rev,* , 218, 247-64.

[38] Kawai, T, & Akira, S. (2010). The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol,* , 11, 373-84.

[39] Keane, C, Tilley, D, Cunningham, A, Smolenski, A, Kadioglu, A, Cox, D, Jenkinson, H. F, & Kerrigan, S. W. (2010). Invasive Streptococcus pneumoniae trigger platelet activation via Toll-like receptor 2. *J Thromb Haemost,* , 8, 2757-65.

[40] Kerrigan, S. W, Clarke, N, Loughman, A, Meade, G, Foster, T. J, & Cox, D. (2008). Molecular basis for Staphylococcus aureus-mediated platelet aggregate formation under arterial shear in vitro. *Arterioscler Thromb Vasc Biol,* , 28, 335-40.

[41] Kerrigan, S. W, Jakubovics, N. S, Keane, C, Maguire, P, Wynne, K, Jenkinson, H. F, & Cox, D. (2007). Role of Streptococcus gordonii surface proteins SspA/SspB and Hsa in platelet function. *Infect Immun,* , 75, 5740-7.

[42] Krijgsveld, J, Zaat, S. A, Meeldijk, J, Van Veelen, P. A, Fang, G, Poolman, B, Brandt, E, Ehlert, J. E, Kuijpers, A. J, Engbers, G. H, Feijen, J, & Dankert, J. (2000). Thrombocidins, microbicidal proteins from human blood platelets, are C-terminal deletion products of CXC chemokines. *J Biol Chem,* , 275, 20374-81.

[43] Larsen, E, Celi, A, Gilbert, G. E, Furie, B. C, Erban, J. K, Bonfanti, R, Wagner, D. D, & Furie, B. (1989). Padgem protein: a receptor that mediates the interaction of activated platelets with neutrophils and monocytes. *Cell,* , 59, 305-12.

[44] Lindemann, S, Tolley, N. D, Dixon, D. A, Mcintyre, T. M, Prescott, S. M, Zimmerman, G. A, & Weyrich, A. S. (2001a). Activated platelets mediate inflammatory signaling by regulated interleukin 1beta synthesis. *J Cell Biol,* , 154, 485-90.

[45] Lindemann, S, Tolley, N. D, Eyre, J. R, Kraiss, L. W, Mahoney, T. M, & Weyrich, A. S. (2001b). Integrins regulate the intracellular distribution of eukaryotic initiation factor 4E in platelets. A checkpoint for translational control. *J Biol Chem,* , 276, 33947-51.

[46] Lotz, S, Starke, A, Ziemann, C, Morath, S, Hartung, T, Solbach, W, & Laskay, T. (2006). Beta-lactam antibiotic-induced release of lipoteichoic acid from Staphylococcus aureus leads to activation of neutrophil granulocytes. *Ann Clin Microbiol Antimicrob,* 5, 15.

[47] Loughman, A, Fitzgerald, J. R, Brennan, M. P, Higgins, J, Downer, R, Cox, D, & Foster, T. J. (2005). Roles for fibrinogen, immunoglobulin and complement in platelet activation promoted by Staphylococcus aureus clumping factor A. *Mol Microbiol,* , 57, 804-18.

[48] Mannaioni, P. F. Di Bello, M. G. & Masini, E. (1997). Platelets and inflammation: role of platelet-derived growth factor, adhesion molecules and histamine. *Inflamm Res,* , 46, 4-18.

[49] Mcintyre, T. M, Prescott, S. M, Weyrich, A. S, & Zimmerman, G. A. (2003). Cell-cell interactions: leukocyte-endothelial interactions. *Curr Opin Hematol,* , 10, 150-8.

[50] Meenan, N. A, Visai, L, Valtulina, V, Schwarz-linek, U, Norris, N. C, Gurusiddappa, S, Hook, M, Speziale, P, & Potts, J. R. (2007). The tandem beta-zipper model defines high affinity fibronectin-binding repeats within Staphylococcus aureus FnBPA. *J Biol Chem,* , 282, 25893-902.

[51] Mercier, R. C, Dietz, R. M, Mazzola, J. L, Bayer, A. S, & Yeaman, M. R. (2004). Beneficial influence of platelets on antibiotic efficacy in an in vitro model of Staphylococcus aureus-induced endocarditis. *Antimicrob Agents Chemother,* , 48, 2551-7.

[52] Miajlovic, H, Loughman, A, Brennan, M, Cox, D, & Foster, T. J. (2007). Both complement- and fibrinogen-dependent mechanisms contribute to platelet aggregation mediated by Staphylococcus aureus clumping factor B. *Infect Immun,* , 75, 3335-43.

[53] Miajlovic, H, Zapotoczna, M, Geoghegan, J. A, Kerrigan, S. W, Speziale, P, & Foster, T. J. (2010). Direct interaction of iron-regulated surface determinant IsdB of Staphylococcus aureus with the GPIIb/IIIa receptor on platelets. *Microbiology,* , 156, 920-8.

[54] Morath, S, Von Aulock, S, & Hartung, T. (2005). Structure/function relationships of lipoteichoic acids. *J Endotoxin Res,* , 11, 348-56.

[55] Moreillon, P, & Que, Y. A. (2004). Infective endocarditis. *Lancet,* , 363, 139-49.

[56] Murdoch, D. R, Corey, G. R, Hoen, B, Miro, J. M, & Fowler, V. G. Jr., Bayer, A. S., Karchmer, A. W., Olaison, L., Pappas, P. A., Moreillon, P., Chambers, S. T., Chu, V. H., Falco, V., Holland, D. J., Jones, P., Klein, J. L., Raymond, N. J., Read, K. M., Tripodi, M. F., Utili, R., Wang, A., Woods, C. W. & Cabell, C. H. (2009). Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med,* , 169, 463-73.

[57] Netzer, R. O, Altwegg, S. C, Zollinger, E, Tauber, M, Carrel, T, & Seiler, C. (2002). Infective endocarditis: determinants of long term outcome. *Heart,* , 88, 61-6.

[58] Nieswandt, B, Varga-szabo, D, & Elvers, M. (2009). Integrins in platelet activation. *J Thromb Haemost,* 7 Suppl , 1, 206-9.

[59] Brien, O, Kerrigan, L, Kaw, S. W, Hogan, G, Penades, M, Litt, J, Fitzgerald, D, Foster, D. J, & Cox, T. J. D. (2002). Multiple mechanisms for the activation of human platelet aggregation by Staphylococcus aureus: roles for the clumping factors ClfA and ClfB, the serine-aspartate repeat protein SdrE and protein A. *Mol Microbiol,* , 44, 1033-44.

[60] Seaghdha, O, Van Schooten, M, Kerrigan, C. J, Emsley, S. W, Silverman, J, Cox, G. J, Lenting, D, & Foster, P. J. T. J. (2006). Staphylococcus aureus protein A binding to von Willebrand factor A1 domain is mediated by conserved IgG binding regions. *FEBS J,* , 273, 4831-41.

[61] Olaison, L, & Pettersson, G. (2003). Current best practices and guidelines. Indications for surgical intervention in infective endocarditis. *Cardiol Clin,* vii., 21, 235-51.

[62] Patrono, C, & Patrignani, P. Garcia Rodriguez, L. A. (2001). Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J Clin Invest,* , 108, 7-13.

[63] Patti, J. M, Allen, B. L, Mcgavin, M. J, & Hook, M. (1994). MSCRAMM-mediated adherence of microorganisms to host tissues. *Annu Rev Microbiol,* , 48, 585-617.

[64] Pawar, P, Shin, P. K, Mousa, S. A, Ross, J. M, & Konstantopoulos, K. (2004). Fluid shear regulates the kinetics and receptor specificity of Staphylococcus aureus binding to activated platelets. *J Immunol,* , 173, 1258-65.

[65] Plummer, C, Wu, H, Kerrigan, S. W, Meade, G, & Cox, D. Ian Douglas, C. W. (2005). A serine-rich glycoprotein of Streptococcus sanguis mediates adhesion to platelets via GPIb. *Br J Haematol,* , 129, 101-9.

[66] Prendergast, B. D, & Tornos, P. (2010). Surgery for infective endocarditis: who and when? *Circulation,* , 121, 1141-52.

[67] Raibaud, S, Schwarz-linek, U, Kim, J. H, Jenkins, H. T, Baines, E. R, Gurusiddappa, S, Hook, M, & Potts, J. R. (2005). Borrelia burgdorferi binds fibronectin through a tandem beta-zipper, a common mechanism of fibronectin binding in staphylococci, streptococci, and spirochetes. *J Biol Chem,* , 280, 18803-9.

[68] Rasmussen, R. V, Host, U, Arpi, M, Hassager, C, Johansen, H. K, Korup, E, Schonheyder, H. C, Berning, J, Gill, S, Rosenvinge, F. S, & Fowler, V. G. Jr., Moller, J. E., Skov, R. L., Larsen, C. T., Hansen, T. F., Mard, S., Smit, J., Andersen, P. S. & Bruun, N. E. (2011). Prevalence of infective endocarditis in patients with Staphylococcus aureus bacteraemia: the value of screening with echocardiography. *Eur J Echocardiogr,* , 12, 414-20.

[69] Remadi, J. P, Habib, G, Nadji, G, Brahim, A, Thuny, F, Casalta, J. P, Peltier, M, & Tribouilloy, C. (2007). Predictors of death and impact of surgery in Staphylococcus aureus infective endocarditis. *Ann Thorac Surg,* , 83, 1295-302.

[70] Rendu, F, & Brohard-bohn, B. (2001). The platelet release reaction: granules' constituents, secretion and functions. *Platelets,* , 12, 261-73.

[71] Ruggeri, Z. M. (1999). Structure and function of von Willebrand factor. *Thromb Haemost,* , 82, 576-84.

[72] Ruggeri, Z. M. (2009). Platelet adhesion under flow. *Microcirculation,* , 16, 58-83.

[73] Ruggeri, Z. M, & Mendolicchio, G. L. (2007). Adhesion mechanisms in platelet function. *Circ Res,* , 100, 1673-85.

[74] Ruggeri, Z. M, Orje, J. N, Habermann, R, Federici, A. B, & Reininger, A. J. (2006). Activation-independent platelet adhesion and aggregation under elevated shear stress. *Blood,* , 108, 1903-10.

[75] Santoro, S. A, & Zutter, M. M. (1995). The alpha 2 beta 1 integrin: a collagen receptor on platelets and other cells. *Thromb Haemost,* , 74, 813-21.

[76] Savage, B, Almus-jacobs, F, & Ruggeri, Z. M. (1998). Specific synergy of multiple substrate-receptor interactions in platelet thrombus formation under flow. *Cell,* , 94, 657-66.

[77] Semple, J. W, & Freedman, J. (2010). Platelets and innate immunity. *Cell Mol Life Sci*, , 67, 499-511.

[78] Sheu, J. R, Hsiao, G, Lee, C, Chang, W, Lee, L. W, Su, C. H, & Lin, C. H. (2000a). Antiplatelet activity of Staphylococcus aureus lipoteichoic acid is mediated through a cyclic AMP pathway. *Thromb Res*, , 99, 249-58.

[79] Sheu, J. R, Lee, C. R, Lin, C. H, Hsiao, G, Ko, W. C, Chen, Y. C, & Yen, M. H. (2000b). Mechanisms involved in the antiplatelet activity of Staphylococcus aureus lipoteichoic acid in human platelets. *Thromb Haemost*, , 83, 777-84.

[80] Shiraki, R, Inoue, N, Kawasaki, S, Takei, A, Kadotani, M, Ohnishi, Y, Ejiri, J, Kobayashi, S, Hirata, K, Kawashima, S, & Yokoyama, M. (2004). Expression of Toll-like receptors on human platelets. *Thromb Res*, , 113, 379-85.

[81] Siboo, I. R, Chambers, H. F, & Sullam, P. M. (2005). Role of SraP, a Serine-Rich Surface Protein of Staphylococcus aureus, in binding to human platelets. *Infect Immun*, , 73, 2273-80.

[82] Siegel, I, & Cohen, S. (1964). Action of Staphylococcal Toxin on Human Platelets. *J Infect Dis*, , 114, 488-502.

[83] Tabuchi, A, & Kuebler, W. M. (2008). Endothelium-platelet interactions in inflammatory lung disease. *Vascul Pharmacol*, , 49, 141-50.

[84] Tang, Y. Q, Yeaman, M. R, & Selsted, M. E. (2002). Antimicrobial peptides from human platelets. *Infect Immun*, , 70, 6524-33.

[85] Thon, J. N, & Italiano, J. E. (2010). Platelet formation. *Semin Hematol*, , 47, 220-6.

[86] Thuny, F, Grisoli, D, Collart, F, Habib, G, & Raoult, D. (2012). Management of infective endocarditis: challenges and perspectives. *Lancet*, , 379, 965-75.

[87] Tzeng, D. Y, Deuel, T. F, Huang, J. S, & Baehner, R. L. (1985). Platelet-derived growth factor promotes human peripheral monocyte activation. *Blood*, , 66, 179-83.

[88] Varki, A. (1994). Selectin ligands. *Proc Natl Acad Sci U S A*, , 91, 7390-7.

[89] Wahl, S. M, Hunt, D. A, Wakefield, L. M, Mccartney-francis, N, Wahl, L. M, Roberts, A. B, & Sporn, M. B. (1987). Transforming growth factor type beta induces monocyte chemotaxis and growth factor production. *Proc Natl Acad Sci U S A*, , 84, 5788-92.

[90] Ward, J. R, Bingle, L, Judge, H. M, Brown, S. B, Storey, R. F, Whyte, M. K, Dower, S. K, Buttle, D. J, & Sabroe, I. (2005). Agonists of toll-like receptor (TLR)2 and TLR4 are unable to modulate platelet activation by adenosine diphosphate and platelet activating factor. *Thromb Haemost*, , 94, 831-8.

[91] Wilson, W, Taubert, K. A, Gewitz, M, Lockhart, P. B, Baddour, L. M, Levison, M, Bolger, A, Cabell, C. H, Takahashi, M, Baltimore, R. S, Newburger, J. W, Strom, B. L, Tani, L. Y, Gerber, M, Bonow, R. O, Pallasch, T, Shulman, S. T, Rowley, A. H, Burns, J. C, Ferrieri, P, Gardner, T, Goff, D, & Durack, D. T. (2007). Prevention of infective

endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *J Am Dent Assoc,* 138, 739-45, 747-60.

[92] Yeaman, M. R, Tang, Y. Q, Shen, A. J, Bayer, A. S, & Selsted, M. E. (1997). Purification and in vitro activities of rabbit platelet microbicidal proteins. *Infect Immun,* , 65, 1023-31.

[93] Youssefian, T, Drouin, A, Masse, J. M, Guichard, J, & Cramer, E. M. (2002). Host defense role of platelets: engulfment of HIV and Staphylococcus aureus occurs in a specific subcellular compartment and is enhanced by platelet activation. *Blood,* , 99, 4021-9.

[94] Zhang, G, Han, J, Welch, E. J, Ye, R. D, Voyno-yasenetskaya, T. A, Malik, A. B, Du, X, & Li, Z. (2009). Lipopolysaccharide stimulates platelet secretion and potentiates platelet aggregation via TLR4/MyD88 and the cGMP-dependent protein kinase pathway. *J Immunol,* , 182, 7997-8004.

IntechOpen

IntechOpen

IntechOpen