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Plaque, Platelets, and Plug – The Pathogenesis of Acute Coronary Syndrome

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1. Introduction

Acute coronary syndrome is a clinical condition of partial or total obstruction of blood flow in the coronary artery due to acute thrombus formation. Culprit vessel, coronary artery segment within which the site of origin of thrombus formation lies, is occupied by eroded or ruptured atherosclerotic plaque. Direct contact between circulating blood constituent and atherosclerotic plaque content owing to loss of endothelial cell barrier orchestrates the haemostasis events, i.e. thrombus formation and coagulation activation. Evolved within years of human life span, atherosclerotic undergoes three main steps: initiation, progression and finally complication (Libby, 2002).

Atherosclerotic plaque development involves cellular and molecular interactions as well as blood flow dynamic alterations in the affected area. Although these steps affect all individual, some gather the risk factors to develop progression and complication of coronary atherosclerotic lesion faster and more prominent than others. Given the dynamic nature of these steps, understanding several mechanisms engage in every step will provide insight into therapeutic approach. Here, we review the last two steps of coronary atherosclerotic plaque development, with the focus in the role of platelets, anucleated cells being the target for therapeutic advancement in atherosclerosis and acute coronary syndrome.

2. Formation of atherosclerotic plaque

The earliest event of atherosclerosis formation is the retention of apolipoprotein B-containing lipoproteins from circulation into subendothelial of the arterial wall (Tabas et al., 2007). This particular lipoprotein interacts with subendothelial proteoglycan through ionic affinity and hence instigates lipoprotein retention in the intimal layer, the innermost part of the arterial wall (Borén et al., 1998; Skalen et al., 2002). During this stage, the tendency of

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retention of lipoprotein depends greatly on sustained plasma level of apolipoprotein B-containing lipoproteins and, in the lesser degree, lipoprotein size, charge, and composition as well as endothelial permeability (Tabas et al., 2007). Three classes of lipoproteins have apolipoprotein B as integral constituent: very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and low density lipoproteins (LDL) (Sniderman et al., 1991). Among them, LDL has the biggest apolipoprotein B proportion and is the most likely to interact with subendothelial proteoglycan (Sniderman et al., 1991).

Modification of LDL apolipoprotein B entrapped in intimal layer by oxidative mechanism results in oxidative LDL (oxLDL) (Stocker & Keaney, 2004). Smooth muscle cells, endothelial cells and macrophages are capable to modify LDL via oxidative modification (Diaz et al., 1997). OxLDL is susceptible to scavenging macrophages and gives rise to the generation of cholesterol-laden foam cells (Stocker & Keaney, 2004). OxLDL continuously activates adjacent endothelial cells. Activated endothelial cells express adhesion molecules on their luminal surfaces which attract inflammatory cells from circulation, mainly monocytes and lymphocytes which transmigrate to intimal layer. The blend of inflammatory and resident vascular cells promotes the formation of atherosclerotic plaque. Arterial smooth muscle cells proliferate and migrate to the intimal layer in response to several growth factors releasing from chronic inflammation microenvironment in the intimal layer (Libby, 2002). Smooth muscle cells form a layer which envelopes the core of “inflammatory nidus” at the endothelial site, produce and release collagen and thus shape the so called fibrous cap. Below the cap, “inflammatory nidus” continuously attracts circulating LDL, modifies it and recognizes it as antigen which attracts more inflammatory cells.

Atherosclerotic plaque mainly composes of two constructions which undergo dynamic changes: fibrous cap and lipid-rich core. The theories of how plaque originated have been proposed. Response-to-injury theory proposes the initial step in atherogenesis is endothelial denudation due to injurious substance or forces leading to alteration of normal vascular homeostatic properties (Ross, 1993). Injury to endothelial cells enhances endothelial permeability and adhesiveness for leukocytes to attach and migrate into subendothelial. Here inflammation occurs and macrophage recruitment and platelet adhesion and aggregation take place, which promote procoagulant tendency of the plaque. Response-to-retention theory suggests LDL retention into subendothelial is the initial event and the prerequisite for plaque to form (Tabas et al., 2007). Endothelial injury does not play important role in this process, since plasma LDL is capable to cross normal endothelial cells through transcytosis mechanism and retains in subendothelial (Simionescu & Simionescu, 1993). Subsequent events are monocyte recruitment and lipid-laden macrophage formation which initiate subendothelial inflammation (Tabas et al., 2007). Oxidative modification theory indicates that to initiate plaque formation, subendothelial LDL should be modified chemically in order to attract macrophages’ scavenger receptor and be internalized to form foam cells (Stocker & Keaney, 2004). Native plasma LDL can enter subendothelial and is taken up by resident vascular cells via LDL receptor-mediated endocytosis. This native LDL does not initiate an inflammatory response and is not phagocytosed by monocytes, thus does not induce atherosclerosis (Torzewsky & Lackner, 2006).

As the plaque progress, fibrous cap is thinner and turn out to be fragile due to the imbalance of extracellular matrix metabolism, the infiltration of the fibrous cap by macrophages and foam cells, and the calcification process (Burnier et al., 2009). All of these contribute to fibrous cap weakening and lost its protective role. Once fibrous cap lose its integrity, it

exposes thrombogenic plaque to circulation. Platelets, around 150,000 until 450,000 per millilitre circulate in the blood without contacting endothelial cells, adhere to exposed site, are activated and initiate the event to seal the broken plaque surface. Unfortunately, this process gives rise to thrombus formation and acute coronary syndrome.

3. Activated platelet promotes progression of the plaque

Putative notion that platelets have role merely in the complicating stage of atherosclerosis has recently been challenged by several evidence indicating the wider involvement of platelets in both early and late atherosclerosis steps (Ruggeri, 2002; Gawaz et al., 2005). In histopathology study of human atherosclerosis, platelets were observed in the lesions, both in the free form and derivative form being phagocytosed by foam cells and macrophages (Sevitt, 1986). Platelet patrols the blood circulation ensuring the integrity of endothelial cells. Once this integrity disrupts, platelets expose to subendothelial component and rapidly undergo activation to form haemostasis thrombus; this is the case of plaque erosion or rupture in acute coronary syndrome. However, intact yet activated endothelial cells can also promote platelet activation, this is the case of progressed atherosclerosis plaque.

3.1 Role of platelet in progressed plaque dynamic

Advanced responses to modified apolipoprotein B-containing LDL through chronic and maladaptive inflammation, macrophage and foam cell apoptotic and plaque necrotic formation are representatives of progressed plaque (Tabas et al., 2007). Endothelial cells lining the plaque are continuously under activated state and express adhesion molecules and chemoattractant mediator in their surface. Monocytes and lymphocytes are attracted and adhere to these molecules and mediators, enter subendothelial and advance inflammatory state in the “inflammatory nidus” of the plaque (Lusis, 2000).

The histomorphology of progressed plaque is characterized by the presence of large lipid-rich necrotic core, and a thin fibrous cap. Fibrous cap composes mainly of extracellular matrix produced by vascular smooth muscle cells (Lusis, 2000). Supportive function of fibrous cap relies on the integrity of this matrix which is maintained through fine balance between matrix production and degradation (Ross, 1993). In progressed plaque, the matrix degradation activity is increased in line with inflammatory activity in the “inflammatory nidus” of the plaque below the cap. Macrophage-derived proteases degrade extracellular matrix, thus weaken fibrous cap (Ross, 1993).

Necrotic core of progressed plaque is derived from foam cells that endure apoptosis and necrotic. Initially, necrosis core is an acellular lipid-rich core, which predominantly consist of deposited lipids, such as cholesterol esters and free cholesterol derived mostly from retained LDL particles (Lusis, 2000). High toxicity of LDL oxidation and formation of reactive oxygen species damage the surroundings vascular cells, including foam cells (Madamanchi et al., 2005). The death of foam cells discharges extracellular lipids and cell debris into adjacent environments, thus promotes necrotic core formation (Lusis, 2000). Necrotic core enlarges and, in addition to free cholesterol, composes of cholesterol crystals, hyalinized hemorrhage and foam cell necrotic remnants (Virmani et al., 2000). Intimal calcifications, resulting from advanced lipid oxidation and inflammatory cytokine reaction which modify osteogenic regulatory genes to promote osteogenesis, scatter in the base of necrotic core adjacent to the medial layer (Virmani et al., 2000; Abedin et al., 2004). Neovascularization in the intimal and

medial layer is another hallmark of progressed plaque (Fleiner et al., 2004). Hyperplastic network of vasa vasorum and ectopic neovascularization of the plaque are associated with intimal thickening, lipid contents and the degree of inflammation (Fleiner et al., 2004). The extent of these microvessels delivers a channel for entry of inflammatory cells into the plaque, boosting inflammation even more (Lusis, 2000). These blood vessel networks are fragile and prone to rupture and create an outward expansion of intraplaque hemorrhage that may overwhelm the integrity of the fibrous cap (Dickson & Gottlieb, 2003).

Thrombogenic property of lipid-rich necrotic core is determined by its collagen and tissue factor content. Two important direct platelet agonists dwell in the lipid-rich core, i.e. lysophosphatidic acid which mediates platelet shape change during thrombus formation and collagen which induces platelet adhesion and aggregation (Lusis, 2000). Tissue factor, another major thrombogenic substrate in the lipid-rich core, is released by endothelial cells, smooth muscle cells, monocytes and macrophages or foam cells (Moons et al., 2002). The most abundant tissue factor site is in the necrotic core (Moons et al., 2002). Tissue factor activates coagulation cascade and promotes thrombus stability through fibrin network formation. Platelets are also capable of releasing tissue factor which gives a hint of their role in supporting coagulation process (Zillmann et al., 2001).

3.2 Platelet-endothelial interaction promotes progressed plaque

Platelets have two storage granules, alpha and dense granules. Alpha granules contain adhesion molecules, chemokines, coagulation and fibrinolysis proteins, growth factors, and other proteins (Linden & Jackson, 2010). Dense granules contain molecules such as calcium, magnesium, phosphate and pyrophosphate, adenosine and guanosine triphosphate, adenosine and guanosine diphosphate and serotonin (Linden & Jackson, 2010). These granules develop in megakaryocytes, the progenitor cell of platelets. Platelets also contain lysosomes which have ubiquitous lysosomal membrane proteins: LAMP-1, LAMP-2, and CD63 (LAMP-3), acid hydrolases, cathepsins and other proteins (King & Reed, 2002).

In the alpha granules, platelet-specific proteins are synthesized only in megakaryocytes and delivered to platelets which undergo proteolysis upon platelet activation, which include platelet factor 4 (PF-4) and β -thromboglobulin (King & Reed, 2002). Platelet-selective proteins are synthesized principally by megakaryocytes but also in fewer numbers by few other cells and found in a larger concentration in platelets than plasma. These platelet-selective proteins include coagulation factor V, thrombospondin, P-selectin, and von Willebrand factor (King & Reed, 2002).

It is expected that platelets keep away from contact with vascular walls or other blood cellular components. Under steady laminar blood stream, platelets tend to flow away from endothelial cell surface area, avoiding connection with endothelial cells. Furthermore, intact and inactivated endothelial cells prevent platelets from adhering to their surface. Endothelial cells control platelet activity through inhibitory mechanisms involving cyclooxygenase 2 (Cox-2), prostacyclin or prostanoic synthetic systems (Gawaz, 2006). However, activated endothelial cells are capable of capturing platelets and activating them, even without any endothelial damage (intact endothelial cells). Activated platelets will express several molecules, release their granule contents and stimulate surrounding cells, thus promoting plaque progression.

3.2.1 Rolling and adhering of platelet to endothelial cell surface

During inflammation, endothelial cells are activated and change their phenotype becoming prone to be adhesive for platelets (Gawaz, 2006). In vitro experiment showed that platelets adhere to activated human umbilical vein endothelial cells (HUVEC) which is mediated by fibrinogen, fibronectin and von Willebrand factor bound to platelets and endothelial cell receptors, ICAM-1, integrin $\alpha v \beta 3$ and GPIb (Bombelli et al., 1998). In vivo experiment discloses that loose contact between platelets and activated endothelial cells precedes a tighter adhesion (Frenette et al., 1995). Rolling of platelets to activated endothelial cell is mediated by endothelial P-selectin and constitutively-expressed platelet P-selectin glycoprotein ligand 1 (PSGL-1) (Frenette et al., 1995; Frenette et al., 2002).

P-selectin is a type-1 membrane glycoprotein with a C-type lectin domain and is stored in the Weibel-Palade bodies of endothelial cells and alpha granules of platelets (Furie & Furie, 1995). It rapidly translocate to cell membrane upon endothelial cell or platelet activation (Frenette et al., 2002). PSGL-1 is an adhesion molecule primarily expressed in myeloid cells and T cells and functions as the main P-selectin ligand which mediates interactions between myeloid cells and endothelial cells as well as between myeloid cells and platelets (Vandendries et al., 2004). In the study of apoE-knock-out and the P-selectin gene deletion mice, atherosclerotic lesion development was significantly delayed, indicating the role of P-selectin as a key adhesion receptor in promoting advanced atherosclerosis (Dong et al., 2000). In early atherogenesis, it is likely that intact endothelial cells activate quiescent platelets through rolling mechanism via endothelial cell P-selectin and platelet PSGL-1 interaction. Endothelial cells coating atherosclerotic plaque are constantly under activated state, thus expressed P-selectin and attract platelets. P-selectin-expressed activated platelets bind to activated endothelial cells in a greater amount than non-activated platelets do.

In addition to platelet PSGL-1, platelet GPIb α is capable to interact with endothelial P-selectin and mediate platelet rolling (Gawaz et al., 2006). GPIb α is a component of GP Ib-IX-V complex which comprises four polypeptides: GP Ib α , GP Ib β , GP IX, and GP V (Romo et al., 1999). GP Ib-IX-V complex bind to subendothelial von Willebrand factor, exposed when endothelial cell disrupted and initiate thrombosis. GPIb α contains von Willebrand factor-binding site and molecular structure nearly similar to PSGL-1 (Romo et al., 1999). Consequently, during endothelial cell activation, in addition to P-selectin, von Willebrand factor are also released from Weibel Palade body to the surface cell membrane. Both endothelial cell P-selectin and von Willebrand factor become the target for platelet GPIb α (Theilmeier et al., 2002). A study using mice deficient of von Willebrand factor showed some level of protection from atherosclerosis thus elucidated the role of von Willebrand factor on plaque formation and progression in intact endothelial cells (Methia et al., 2001).

3.2.2 Tight adhesion of platelet to endothelial cell surface

P-selectin-mediated loose contact is subsequently changed by tighter connection involving endothelial cell integrin, $\alpha v \beta 3$ and platelet integrin, $\alpha IIb \beta 3$ (Langer & Gawaz, 2008). Ligation of platelet GPIb α to endothelial cell von Willebrand factor during platelet rolling lead to activation of platelet integrin (Kasirer-Friede et al., 2002). Integrins are ubiquitous transmembrane α/β heterodimers that mediate cell-matrix and cell-cell interactions (Bennet, 2005). Platelets express 3 members of the $\beta 1$ subfamily ($\alpha IIb \beta 1$, $\alpha v \beta 1$, and $\alpha v I \beta 1$) and 2 members of the $\beta 3$ subfamily ($\alpha v \beta 3$ and $\alpha IIb \beta 3$) (Bennet, 2005). An $\alpha IIb \beta 3$ is the most important integrin on platelets (Gawaz et al., 1991). In vitro and in vivo studies

show that platelet $\alpha\text{IIb}\beta 3$ and endothelial cell $\alpha v\beta 3$, mediate firm contact between platelets and activated endothelial cells (Bombeli et al., 1998; Maasberg et al., 1999). By forming a bridge to fibrinogen, $\alpha\text{IIb}\beta 3$ promotes arrest of platelets to adhesion molecules, intercellular adhesion molecule-1 (ICAM)-1, and to $\alpha v\beta 3$ on activated endothelial cells (Bombeli et al., 1998; von Hundelshausen & Weber, 2007). Fibrinogen links platelet fibrinogen receptor on the surface of $\alpha\text{IIb}\beta 3$ to the endothelial cell $\alpha v\beta 3$ and forms the firm platelet adhesion to activated endothelial cells (Gawaz et al., 1991).

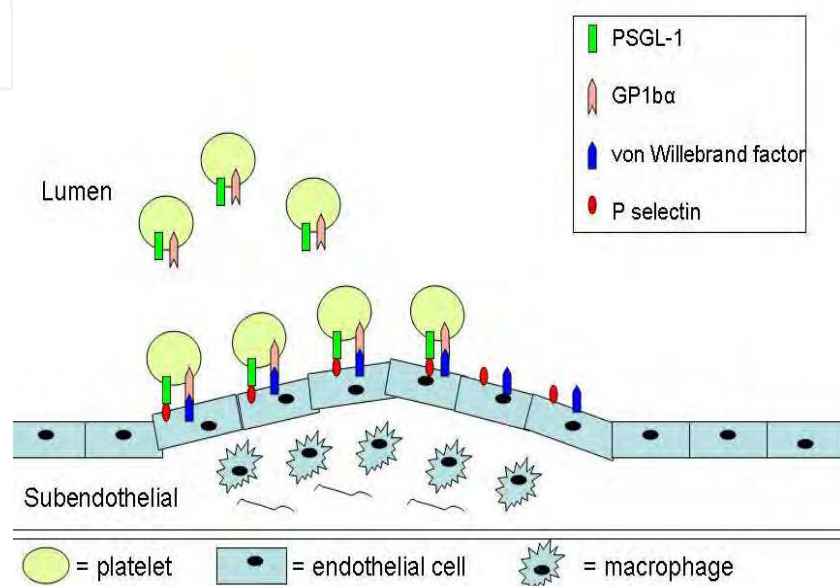


Fig. 1. Rolling of platelets to endothelial cells is mediated by platelet PSGL-1 and GP1b α bind to endothelial cell von Willebrand factor and P selectin.

It is worth mentioning that interaction between platelets and activated endothelial cells is not sufficient to promote thrombus formation. However, platelet adhesion to endothelial cells contributes to the progression of the plaque. Platelets mediate such effects through releasing products following adhesion and activation. The contents of storage granules are liberated upon platelet activation. It is estimated more than 300 proteins are secreted from activated platelets, which act in an autocrine or paracrine manner to modulate cell signaling and mediate the plaque progression (Coppinger et al., 2004).

Endothelial cell chemotactic, adhesion, and proteolytic capacities are altered by paracrine modulation of substances released by adherent activated platelets. Here are the lists of platelet contents released upon adhesion and activation : (1) adhesion proteins (e.g., P-selectin, vitronectin, fibrinogen, fibronectin, von Willebrand factor, thrombospondin and $\alpha\text{IIb}\beta 3$), (2) growth factors (e.g., PDGF, TGF- β , EGF and bFGF), (3) chemokines (e.g. RANTES, PF-4 and epithelial-neutrophil activating protein 78 (ENA-78)), (4) cytokine-like factors (e.g. IL-1 β , CD40 ligand and β -thromboglobulin) and (5) coagulation factors (e.g. factor V, factor XI, PAI-1, plasminogen and protein S) (Gawaz et al., 2005).

In vitro study revealed that activated platelets coincubated with cultured endothelial cells gave rise to a secretion of MCP-1 and surface expression of ICAM-1 and $\alpha v\beta 3$ on endothelial cells, which is mediated by an IL-1-dependent mechanism (Gawaz et al., 2000). MCP-1 is an effectual chemotactic factor for monocytes and ICAM-1 is an adhesion molecule which advocates monocyte and neutrophil recruitment to endothelial cells. This study emphasized

the important role of IL-1 β on mediating endothelial cell activity upon platelet activation. IL-1 is the prototypic cytokine released by inflammatory cells and three members of the IL-1 gene family have been identified: IL-1, IL-1 β , and IL-1 receptor antagonist (IL-1RA) (von Hundelshausen & Weber, 2007). Platelet activation induces rapid and persistent synthesis and release of IL1 β and converts endothelial cell phenotype to become more adhesive to circulating neutrophils (Lindemann et al., 2001). Inhibition of β 3 integrin attenuated the synthesis of platelet IL-1 β , indicating firm adhesion of platelet to endothelial cells is prerequisite for IL-1 β sustained secretion (Lindemann et al., 2001).

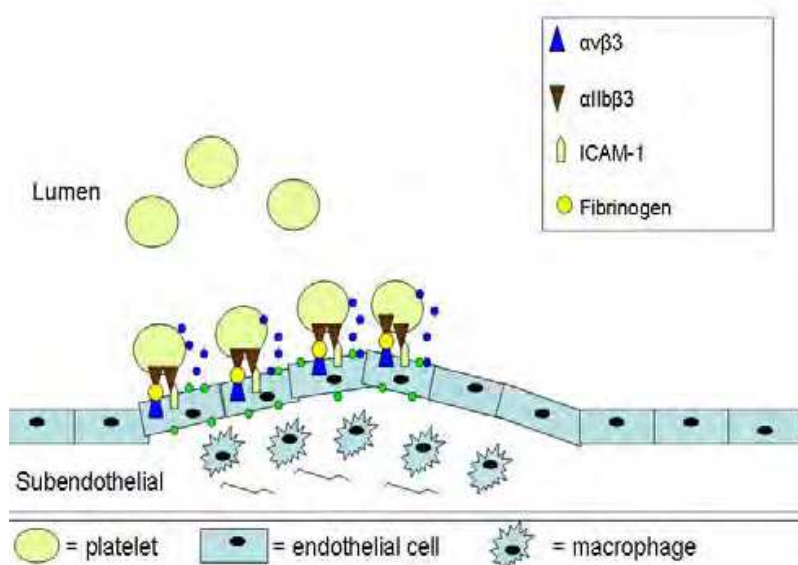


Fig. 2. Tight adhesion of platelets to endothelial cells is mediated by platelet α IIb β 3 bind to endothelial cell α v β 3, bridged by fibrinogen, and ICAM-1. This results in release of platelet contents (blue dots) which mediates endothelial activated molecules (green dots) expression,

Upon activation, platelet expresses CD40 ligand (CD40L) which ligates CD40 expressed by activated endothelial cells (Henn et al., 1998). Platelet CD40L and endothelial cell CD40 interaction amplifies the release of IL-8 and MCP-1 from endothelial cells and enhances the expression of endothelial cell adhesion receptors including E-selectin, VCAM-1, and ICAM-1 (Henn et al., 1998). In vivo study using mice deficient of platelet CD40L shows that platelet CD40L accelerate plaque formation and progression, mainly due to prevention of leukocyte recruitment (Lievens et al., 2010). This study implicates that platelet CD40L is important for recruitment of monocytes, neutrophils and lymphocytes during plaque intitution and progression. Ligation of CD40L on endothelial cells promotes endothelial cell tissue factor expression, thus enhances a procoagulant phenotype on endothelial cells (Slupsky et al., 1998). Furthermore, it implicates in both the generation and secretion of matrix metalloproteinase-9 (MMP-9) and protease receptor urokinase-type plasminogen activator receptor (uPAR), thus promotes proteolytic activity on endothelial cells (May et al., 2002). Tight adhesion of platelet to endothelial cell via α IIb β 3 binding enhances platelet CD40L upregulation and matrix degradation (May et al., 2002). This endothelial-mediated matrix degradation is important in digestion of fibrous cap, thus promotes imbalance of matrix production and degradation and subsequently weakens the cap. This contributes to loss of cap protection and threatens plaque in rupture-prone condition.

PF-4, stored in platelet alpha granules, is the most abundant protein secreted by activated platelets. In histopathological study on human carotid atherosclerotic, PF-4 accumulates within macrophages of the plaque in the early lesion and continues to accumulate in foam cells and neovascular endothelial cells as lesion progressed (Pitsilos et al., 2003). PF-4 is deposited on the endothelial cell surface and retained by subendothelial proteoglycan (Aidoudi & Bikfalvi, 2010). PF-4 can activate endothelial cells by stimulating E-selectin expression (Yu et al., 2005). In vitro study indicates that PF-4 inhibits apolipoprotein B-containing LDL catabolism and facilitates retention of LDL on cell surface (Sachais et al., 2002). PF-4 blocks LDL uptake by LDL receptor expressed by vascular wall cells, thus increases its retention and prolongs its residence time in the vascular space which allows apolipoprotein-B to be modified and increases ox-LDL deposition (Nassar et al., 2002).

RANTES, secreted by activated platelets, triggers monocyte arrest and recruitment under flow conditions in vitro and in perfused carotid arteries (von Hundelshausen et al., 2001). Platelet P-selectin is important mediator of RANTES upregulation, indicates that RANTES is secreted during platelet rolling to endothelial cells (Schober et al., 2002). In atherosclerotic lesions and injury of apolipoprotein-E deficient mice, RANTES is expressed on endothelial cells (von Hundelshausen et al., 2001). Endothelial cells should have been modified by IL-1 β , in order to receive the deposition of RANTES (Weyrich et al., 2002). Taken together, platelet-generated RANTES involves in atherosclerosis early in the beginning and more prominently in the plaque progression by modulating intimal hyperplasia and monocyte recruitment (Schober et al., 2002). Initial knowledge of ENA-78 activity is that this CXC chemokine superfamily member is synthesized and secreted by activated endothelial cells which give a proadhesive activity for neutrophils (Walz et al., 1997). Activated platelet expresses ENA-78 which attract leukocyte to adhere the endothelial cells (Schober et al., 2002). Furthermore, activated platelet-induced IL-1 β action can stimulate endothelial cells to secrete ENA-78 which encourage endothelial cell adhesiveness (Weyrich et al., 2002).

3.3 Platelet-leukocyte interaction enhances progressed plaque

Migration and recruitment of leukocytes into atherosclerotic plaque are essential steps of atherosclerosis progression. Leukocytes are captured and begin rolling on P-selectin expressing-endothelial cells. Leukocytes express PSGL-1 which engages in leukocyte rolling and attachment to P-selectin. Similar to that of platelet, P-selectin-mediated leukocyte binding to endothelial cells is a loose contact. This connection mediates rolling of leukocytes on the endothelial surface without firm attachment.

In addition to direct contact between leukocytes and endothelial cells, activated platelets interact with leukocyte as well. Among leukocytes, monocytes and lymphocytes are the first to be involved in atherogenesis and plaque progression.

3.3.1 Activated platelets bind and promote monocyte activation and transmigration

Monocytes are predominant leukocytes lodge in atherosclerotic plaque. Adherent platelets efficiently mediate monocyte rolling and arrest, even at high shear rate. Monocyte rolling is mediated by P-selectin on activated platelets and PSGL-1, constitutively expressed on monocytes (Kuijper et al., 1998). CD15, expressed by monocytes, has also been shown to bind platelet P-selectin (Larsen et al., 1990).

The initial connection between platelet P-selectin and monocyte PSGL-1 and CD15 is a loose attachment, and within rapid period it leads to elevated expression of the monocyte

integrin $\alpha\text{M}\beta 2$ (membrane-activated complex 1 (Mac-1)) and makes tighter adhesion which support binding to platelet (Neumann et al., 1999). Monocyte Mac-1 has several counter-receptors expressed on activated platelet, such as GP1b, JAM-3 and ICAM-2 (Simon et al., 2000; Santoso et al., 2002; Diacovo et al., 1994).

Platelet junctional adhesion molecule (JAM) supports platelet chemokine deposition and promotes monocyte recruitment (von Hundelshausen & Weber, 2007). JAM-3 is identified as a counter-receptor on platelets for the monocyte Mac-1 and mediates platelet-monocytes interactions (Santoso et al., 2002). Mac-1 is also able to bind indirectly to platelet $\alpha\text{IIb}\beta 3$ linked by soluble fibrinogen bridge (Gawaz et al., 1991). Furthermore, several protein-receptor complexes mediate platelet-monocyte adhesion, such as thrombospondin which form a bridging of the CD36-CD36 interaction in both monocytes and platelets, CD40L on the platelet which attach to monocyte CD40 and monocyte triggering receptor expressed on myeloid cell 1 (TREM-1) to platelet-expressed TREM-1 ligand (Van Gils et al., 2009).

The attachment of activated adherent platelets to monocytes induces monocyte activation through shedding, expressing and releasing functional proteins. Interaction between platelets and monocytes increases the expression and activity of chemotaxis (MCP-1 and MIP-1 α), proteolysis (uPAR and MMP), thrombosis (tissue factors), activation (TNF- α and IL-8) and adhesion (Mac-1 and VLA-4) factors on monocytes as well as potentiates monocyte to macrophage differentiation (Gawaz et al., 2005). In this respect, platelet-monocyte interaction provides an atherogenic environment at the vascular wall that supports plaque formation and regression (Gawaz et al., 2005). Similar to adherent platelets, activated platelets circulating in blood stream can affect endothelial cell and leukocyte phenotype (Huo et al., 2003). Circulating activated platelets are detected in the blood of patients with atherosclerotic conditions, such as acute coronary syndromes (Sarma et al., 2002), stable coronary disease (Furman et al., 1998), and diabetes mellitus (Broijersen et al., 1998).

In vitro study shows that platelet P-selectin increases monocytoid cell adhesion to endothelial cells (Theilmeier et al., 1999). In vivo study using apoE-knock-out mice reveals that circulating activated platelets, through platelet P-selectin, promote monocyte recruitment to atherosclerotic plaque and accelerate the formation of atherosclerotic lesions (Huo et al., 2002). Platelet P-selectin-mediated interactions lead to deposition of platelet-derived proinflammatory factors, RANTES and PF-4, to the vessel wall and monocytes, resulting in activation of monocyte integrins, increased monocyte recruitment and accelerate atherosclerosis (Huo et al., 2002). Inversely, at low levels, activated endothelial cells express PSGL-1 and bind P-selectin on platelets and monocytes, thus mediating monocyte tethering and platelet recruitment to the endothelial cells (Da Costa Martins, 2007).

Not only do adherent platelets form tight binding to monocyte, but also circulating activated platelets attach to monocyte and form platelet monocyte complex (PMC). PMC reflected great capacity of platelet activation and in lesser extent, monocyte activation (Van Gils et al., 2009). Activated platelets bind via P-selectin to its receptor on monocytes, PSGL-1, and form complexes (Van Gils et al., 2009). PMCs mediate monocyte tethering and adhering to endothelial cell surface, making adherent monocyte-PMC cluster and promoting monocyte, and probably platelet, transmigration into subendothelial plaque lesion (Da Costa Martins et al., 2004). PMC high adhesive capability to activated endothelial cell is due to increasing integrin activation on monocyte and subsequently, increasing cell adhesion to fibronectin, VCAM-1 and ICAM-1 (Da Costa Martins, 2006). Monocytes transmigrate into

the atherosclerotic plaque, and change phenotype, becoming macrophages which express scavenger receptors and digest oxLDL to become foam cells (Libby & Aikawa, 2001).

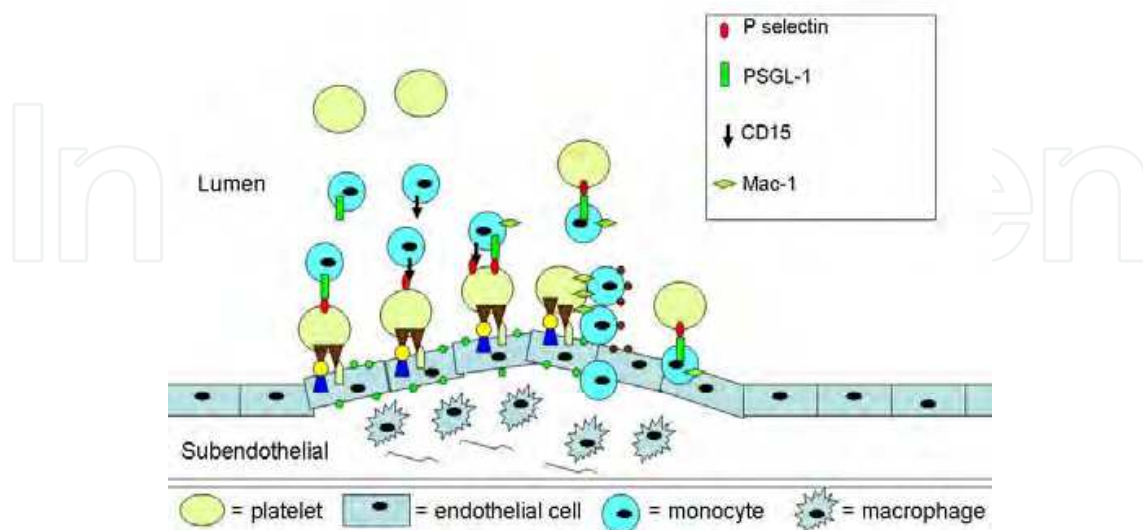


Fig. 3. Activated platelets recruit monocytes via platelet P selectin binding to monocyte PSGL-1 and CD15, subsequently stabilized by monocyte Mac-1 bind to counter receptors in platelets thus promoting monocyte adhesion and transmigration into subendothelial.

Monocytes are the main source of tissue factor, an important determinant of thrombogenic plaque (Lindmark et al., 2000). Along with more monocyte recruitment, macrophage proliferation and tissue factor production intensify, filling the plaque with inflammatory and thrombogenic material which promote plaque progression.

3.3.2 Activated platelets bind and promote lymphocyte activation and transmigration

Lymphocyte transmigration from circulation to atherosclerotic plaque follows three steps: selectin-mediated rolling, integrin-modulated adhesion and transmigration. The transmigration of all lymphocyte populations, i.e. T cells, B cells, and natural killer cells, are enhanced by activated platelets (Li, 2008). Activated platelets interact with lymphocytes through binding between platelet P-selectin and lymphocyte PSGL-1 forming a loose contact, which subsequently induces clustering of α L integrin and enhances lymphocyte firm adhesion via ICAM-1 binding (Atarashi et al., 2005). Among lymphocytes, T cells have stronger adhesive capacity than B cells, indicates that T cells are selectively recruited in mediation of P-selectin expressing cells (Li, 2008). Enhancement of T cell adhesion on subendothelial matrix is mediated by activated platelets through formation of platelet-T cell conjugates and via ligations of P-selectin, CD40L and α IIB β 3 integrins (Li, 2008).

In progressed atherosclerotic plaque, T cells make up nearly 10% to 20% of the cell population and assemble at sites which are prone to rupture and cause fatal thrombosis (Hansson et al., 2002). Most of the T cells in atherosclerotic lesions is T helper (CD3+ and CD4+) and T-cell antigen receptor positive (TCR β +), which indicate a function of recognition of antigens presented by macrophages or dendritic cells (Hansson et al., 2002). They modulate cell mediated immunity through secretion of interferon (IFN- γ), IL-2, and IL-22 (Hansson et al., 2002). IFN- γ inhibits smooth muscle cell new collagen synthesis, which is essential in supporting fibrous caps, thus weakens fibrous cap and promotes rupture-prone

plaque (Libby et al., 2010). Smooth muscle cells in the rupture-prone plaque express HLA-DR which is susceptible to IFN- γ action (Libby & Aikawa, 2001). Furthermore, activated T cells induce production of MMP and tissue factor, mediated by CD40-CD40L binding, which enhances the thrombogenicity of the plaque lipid-rich core (Libby et al., 2010).

4. Activated platelet plays important role in coronary atherothrombosis

Arterial thrombosis is the acute complication that develops on the chronic atherosclerosis lesion, i.e. atherothrombosis, and in the coronary artery it causes acute coronary syndromes, during which blood flow through coronary segment is partially or totally obstructed. Platelets are prominent constituents of the thrombi that occlude the lumen of arteries. In this regard, atherothrombosis is a term that describes the combination of acute, a complication, and chronic, a progression, events of arterial disease (Ruggeri, 2002). Platelets are involved in both processes, through promoting plaque progression and participating in ruptured plaque-driven thrombus formation (Ruggeri, 2002).

Inducing event of acute coronary syndrome is plaque rupture or erosion. Rupture of fibrous cap lining the plaque is account for 60–65% of occlusive thrombi and erosion of endothelial cells lining the plaque is responsible for the rest 35–40% (Dickson & Gottlieb, 2003). In the rupture-prone atherosclerotic plaque, fibrous cap maintains protective role for the integrity of the plaque and provides a barrier between the thrombogenic material in the necrotic core and circulating blood components, mainly platelets and coagulation factors (Libby & Aikawa, 2001). As plaque progressed, leukocyte-driven inflammation is heightened in the intimal layer. Inflamed leukocytes can hinder biosynthesis of collagen from smooth muscle cells and can themselves overexpress collagen-degrading proteinases which in turn give the condition of the imbalance between collagen synthesis and degradation, thus weakening the fibrous caps and lead to plaque rupture (Libby & Aikawa, 2001). Furthermore, leukocytes participate in augmentation the production of the procoagulant factor, primarily tissue factor, in plaque lesion and give rise to the high thrombogenicity of the plaque's lipid core (Libby et al., 2010). In addition to intrinsic factor within plaque, vessel lumen shear stress contribution for rupture of the plaque is considerate as well, since lumen restricted-area surrounding the plaque causes a local rising in blood flow velocity. Wall shear rate may exceed considerably at the edge of a severe occlusion in a coronary artery. High shear stress may specifically enhance platelet reactivity to matrix extra cellular of plaque (Ruggeri, 2002). The main trigger for the formation of a thrombus is the loss of the endothelial cell barrier and exposure of thrombogenic subendothelial extracellular matrix components with circulating blood. The response of platelets to this event can be divided into three successive but closely integrated phases: adhesion, activation and aggregation (Ruggeri, 2002). Several indices of activated platelets in the circulating blood are increased in patients with coronary artery disease and acute coronary syndromes, such as platelet surface molecule expression, platelet-monocyte aggregates, platelet-neutrophil aggregates and soluble proteins releasing upon platelet activation, mainly soluble CD40L (sCD40L) (Linden et al., 2007; Setianto et al., 2010).

4.1 Platelet tethering and adhesion initiate atherothrombosis

Erosion or rupture of the plaque poses circulating platelets, some of them have already activated, with highly thrombogenic extra cellular matrix components of the lipid core

which contains several adhesive molecules such as collagen, von Willebrand factor, laminin, fibronectin and thrombospondin (Andrews & Berndt, 2004). These molecules, once exposed, provide ligands for various activated platelet surface receptors. Under low shear rate condition, such as in vein and large artery flow, the molecules bind to platelet receptors are collagen, fibronectin and laminin, whereas under higher shear rates, such as in small arteries and atherosclerotic vessel, collagen and von Willebrand factor are principal molecules to mediate platelet slackening, tethering and adhesion (Andrews & Berndt, 2004). The early step of atherothrombosis is tethering of platelets to the surface of rupture plaque and is accomplished through the interaction between platelet GPIb α and collagen-bound von Willebrand factor (Ruggeri, 2002) and platelet GPVI and collagen (Andrews & Berndt, 2004). GPIb α is the major ligand-binding subunit of GPIb-IX-V or von Willebrand factor receptor and, in addition to binding site for von Willebrand factor, contains partially overlapping binding sites for the leukocyte integrin Mac-1, α -thrombin, and P-selectin expressed on activated platelets or activated endothelial cells (Andrews & Berndt, 2004). GPVI is a collagen receptor of the immunoglobulin superfamily that forms a complex with the FcR γ -chain at the cell surface in human and mouse platelets (Andrews & Berndt, 2004).

Von Willebrand factor, stored both by alpha granules of platelets or Weibel-Palade body of endothelial cells, is an adhesive glycoprotein found in circulating blood or subendothelial matrix (Andrews & Berndt, 2004). Circulating von Willebrand factor, which amount is much higher than that in subendothelial matrix, can be immobilized in exposed collagen via collagen binding site and become the substrate for platelet GP1b α (Massberg et al., 2003). In addition to collagen-bound, circulating von Willebrand factor can also be immobilized by forming the multimeric connection to matrix-bound, platelet-bound or subendothelial von Willebrand factor (Ulrichs et al., 2005). Immobilized von Willebrand factor is capable to catch circulating platelets via binding with platelet GPIb α (Andrews & Berndt, 2004). Ligation of non-activated platelet GPIb α with collagen-bound von Willebrand factor is not stable enough and is intended mainly to slow down platelets and maintain them in the rupture site, where subsequently platelets will be activated through various receptors, mainly integrin, and stable adhesion is formed.

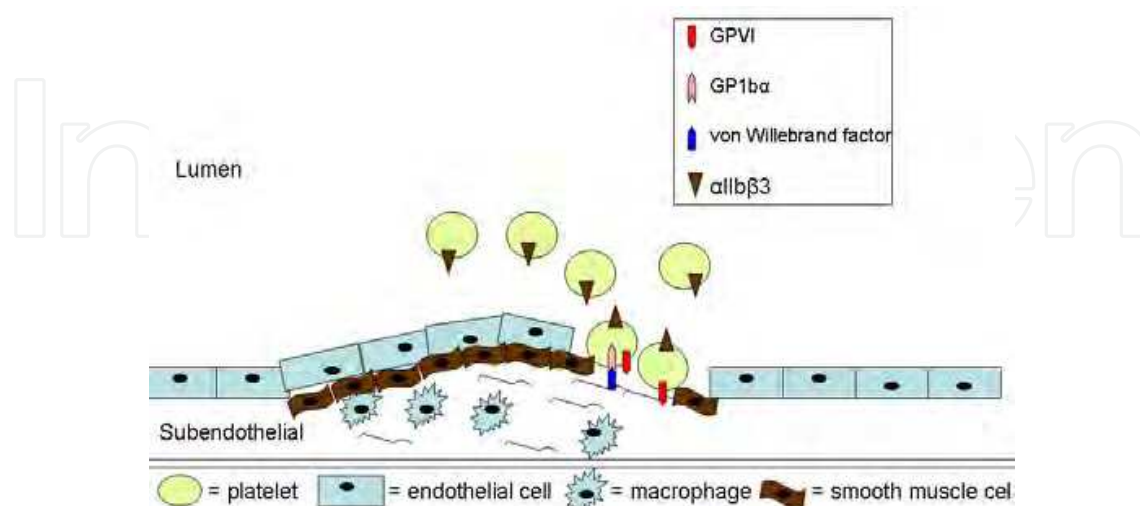


Fig. 4. Plaque rupture exposes platelets to thrombogenic collagen which attract them to adhere via platelet GPVI bind to collagen and GPIb α bind to collagen-bound von Willebrand factor, initiate thrombus formation.

In addition to collagen-bound von Willebrand factor, collagen itself can capture non-activated circulating platelets through platelet GPVI. However, GPVI has only a low affinity for collagen which makes GPVI, same as GPIb α , incapable to mediate stable platelet adhesion. Ligation of GPVI during the initial contact between platelets and subendothelial collagen provides an activation signal through platelet integrins, α IIb β 3 and α 2 β 1, which is essential for subsequent stable platelet adhesion and aggregation (Gawaz, 2004). Although not tightly adherent, this early adhesion of platelets is of adequate affinity to facilitate arrest at high shear rate, leading ultimately to much more stable integrin-mediated adhesion (Andrews & Berndt, 2004).

4.2 Platelet activation and aggregation enhance atherothrombosis

Platelet activation and aggregation are the ensuing steps that occur within minutes, marked by the accumulation of platelets into the haemostatic thrombus (Ruggeri, 2002). Collagen-bound von Willebrand factor and platelet GPIb α interaction convey signal activation of platelet integrin α IIb β 3 to undergo conformational changes which are compulsory for firm, irreversible platelet resting on the subendothelial matrix surface (Gawaz, 2004). Conformational changes of α IIb β 3 enable an exposure of fibrinogen binding site which form cross linking with α IIb β 3 on different platelets by fibrinogen bridge (Andrews & Berndt, 2004). Similarly, ligation of GPVI shifts platelet α IIb β 3 and α 2 β 1 from a low to a high affinity state and contributes to stable platelet adhesion (Gawaz, 2004). Until this step, stable adhesion of platelets is promoted by irreversible binding of platelet α IIb β 3 to collagen-bound von Willebrand factor and platelet α 2 β 1 to uncoated collagen. The integrin-dependent stable adhesion of platelets consequently leads to activation of adherent platelets. Activated platelets are receptive to wide range of agonists or stimulants and adhesive proteins. They express surface receptors, which, upon activation by agonists and adhesive proteins, stimulate internal signaling pathways that lead to further platelet activation, degranulation, and capacity enhancement to bind with other adhesive proteins or platelets. Transmembran receptors are the main agonist-stimulated receptor families and greatly activated during thrombus formation. The important platelet receptors in this class are thrombin receptors (protease activation receptor (PAR-1 and PAR-4), ADP receptors (P2Y1, and P2Y12) and integrins (mainly α IIb β 3) (Freedman, 2005).

Activation of platelets by thrombin through PAR-1 and PAR-4 receptors results in calcium flux, platelet shape change, and stimulation of a variety of platelet-signaling pathways (Freedman, 2005). Importantly, thrombin-PAR receptor interaction leads to activation of integrin α IIb β 3 receptor complex through inside-out signalling (Freedman, 2005).

In non-activated platelets, α IIb β 3, the most abundant platelet integrins, has a very low affinity for its ligands (Cosemans et al., 2008). However, platelet activation remarkably increases the capacity of α IIb β 3 to attach to its ligands, particularly fibrinogen, fibrin, fibronectin and von Willebrand factor (Cosemans et al., 2008). These soluble adhesive proteins are immobilized and are attached to activated α IIb β 3 on the surface of activated adherent platelets and become the substrate for more non-activated circulating platelet recruitment and aggregation (Ruggeri, 2002). The interaction of circulating platelets with adherent platelets carries on through activated α IIb β 3 cross linking between platelets bridged by soluble fibrinogen, thus form the platelet aggregates (Gawaz, 2004). Platelet activation increases the surface density of α IIb β 3, thus more soluble fibrinogen attach and bridge other platelets, makes cross linking and allows continuing platelet aggregation and

thrombus growth. The inhibition of interaction of platelet $\alpha\text{IIb}\beta_3$ - von Willebrand factor and $\alpha\text{IIb}\beta_3$ - fibrinogen by $\alpha\text{IIb}\beta_3$ antagonists, i.e. tirofiban, abciximab and eptifibatide, is of potentially benefit in acute settings of coronary atherothrombosis, due to inhibition of platelet aggregation, thrombus growth and stability.

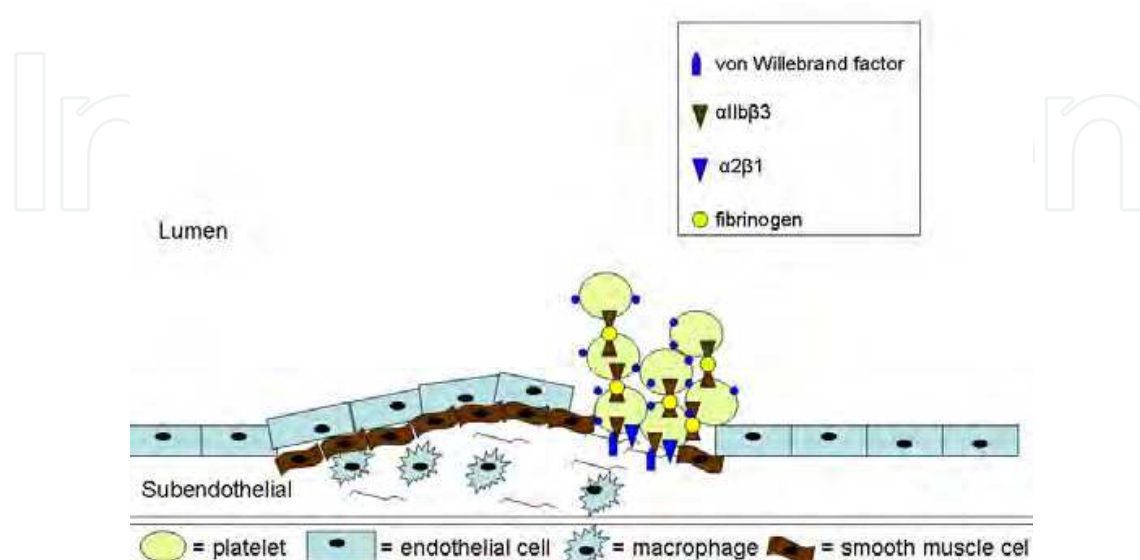


Fig. 5. Adhesion and activation of platelets form stable plug via platelet $\alpha\text{IIb}\beta_3$ bind to collagen-bound von Willebrand factor and platelet $\alpha_2\beta_1$ bind to collagen, thus stimulate release of platelet surface receptors (blue dots) receptive to agonists and adhesive proteins.

In addition to integrin activation, several means of activation responses of platelets include: mobilization of cytosolic calcium, secretion of ADP, shedding and secretion of CD40L, released of thromboxane A2 (TxA2) and formation of pseudopods which support an effective sealing of the denuded plaque area (Cossemans et al., 2008; Gawaz, 2004). ADP, secreted by dense granules of activated platelets, stimulates platelets in autocrine loop through its receptors, P2Y1 and P2Y12. P2Y1 activation mediates platelet shape change and initiates platelet aggregation by mobilization of intracellular calcium (Andre et al., 2003). P2Y12 activation by ADP signal mediates inhibition of adenylyl cyclase and stabilizes platelet aggregates as well as participates in the firm adhesion by activating $\alpha\text{IIb}\beta_3$ (Andre et al., 2003). Persistent signal to keep P2Y12 in active state is of paramount important to prevent platelet disaggregation and to maintain $\alpha\text{IIb}\beta_3$ in its active conformation (Cossemans et al., 2008). In addition to autocrine loop, ADP also works in paracrine mechanism by stimulating and recruiting non activated circulating platelets and inducing them to undergo aggregation with adherent platelets (Gawaz, 2004). Antagonist for P2Y12, i.e. ticlopidine and clopidogrel, has already been widely used in acute coronary syndrome.

CD40L, expressed and released by activated platelets, binds to activated $\alpha\text{IIb}\beta_3$ and contributes in supporting platelet aggregate stability (Andre et al., 2002). Upon platelet activation, the cytosolic CD40L protein is exocytosed to the platelet plasma membrane from where it is also shed and release into circulation in soluble form, sCD40L (Andre et al., 2002). These transmembran and soluble forms are detected to be elevated in patients with acute coronary syndrome (Aukrust et al., 1999; Garlichs et al., 2001; Setianto et al., 2010). Both transmembrane and soluble CD40L can form a cluster with platelet $\alpha\text{IIb}\beta_3$ and lead to more platelet activation and enhance thrombus formation and stabilization (Andre et al., 2002).

TxA₂ is made from arachidonic acid and is secreted by activated adherent platelets. It strengthens the activation process after the release into the extracellular space and creates platelet feedback activation by acting in an autocrine and paracrine manner on its thromboxane platelet receptor (Gawaz, 2004). TxA₂ has a vasoconstricting activity and thus favors formation of the thrombus by slowing down the blood flow (Gawaz, 2004). Aspirin induces a complete and permanent inhibition of platelet TxA₂ production through the inactivation of cyclooxygenase. In addition to $\alpha\text{IIb}\beta 3$ -mediated stability, several other adhesion and signaling receptors contribute to thrombus stability, such as PECAM-1, JAM-A, JAM-C, ESAM, CD226, and Eph kinases/ephrins, which enable the tight contact of one platelet with receptors on adjacent platelets (Brass et al., 2005).

5. Conclusion

Platelet is a key maker for progression of atherosclerotic plaque. Its ability to interact with activated endothelial cells and leukocytes, provides the milieu of inflammation and thrombus-prone environment in atherosclerotic plaque. Platelet, with a relatively similar pattern, captures monocyte and lymphocyte and grants them the path to transmigrate into atherosclerotic plaque. Platelet is a central player during coronary plaque rupture. It starts and nurtures coronary thrombus formation and stabilization. Platelet-based therapeutic modalities for atherosclerosis and acute coronary syndrome are still in progressed studies with some of them yielding beneficial effect while others inconclusive.

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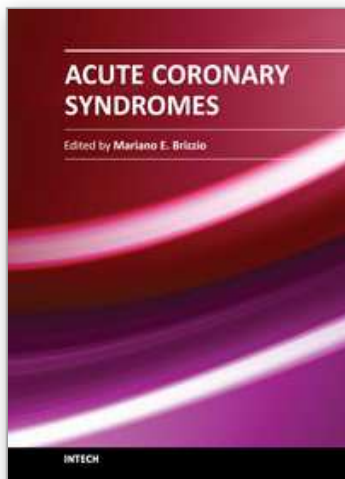
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This book has been written with the intention of providing an up-to-the minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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