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Role of Platelets in the Pathogenicity of Atherosclerosis and Thrombosis in Coronary Heart Diseases

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Summary

Atherosclerosis is a chronic inflammatory process that results in coronary artery disease, peripheral artery disease and in many cases of stroke. It is a disease that involves multiple inflammatory cytokine which is regarded as the primary underlying cause of cardiovascular diseases (CVD). CVD is the leading cause of death in the developed and developing countries like Nigeria. From pathological perspective, the chronic inflammatory condition of atherosclerosis occurs due to interplay between platelets, monocytes, macrophages. Physiologically platelets play a significant role in coagulation and repair of endothelial injury. Pathologically, studies have shown that activated platelets release multiple inflammatory cytokines and chemokines that serve as positive mediators of atherosclerosis. This chemokine is (RANTES, P-selectin and PF-4). Activated platelet release p-selectin that mediate platelet adhesion and rolling to injured endothelial cell, RANTES trigger the recruitment of monocytes into the sub- endothelium and PF4 promote the differentiation of monocytes into macrophages in the intimal layer of the endothelium which engulf ox-LDL to form FOAM cells. Thus, the aim of this review is to understand and describe the role of activated platelets in atherosclerosis as well as therapeutic target of these platelet inflammatory chemokines which is the major mediator of atherosclerosis in human.

Keywords: Atherosclerosis, Chronic inflammatory process, Cardiovascular diseases, Platelets, Chemokines, Monocytes, Macrophages.

Introduction

It is well known that atherosclerosis and cardiovascular disease occur due to imbalance of immune response and excessive LDL cholesterol (Fabrizio and Francois, 2009). Atherosclerosis is a chronic inflammatory disease that involve LDL cholesterol, monocytes and macrophages and other circulating factors within the blood vessel. Atherosclerotic lesion or injury is triggered by chronic or repeated exposure to certain systematic or local stimuli. LDL cholesterol and other plasma lipids exhibit a proatherogenic activity and are involved in the initiation and enhancement of lesions, leading to endothelial dysfunction, disorganization, thickening of the vascular wall and then preceedingly to deposition of intracellular and extracellular lipids, monocytes, macrophages and T-cells (Badimon *et al*., 2012). It can therefore be concluded that high level of low-density lipoprotein cholesterol (LDLc) is a greater risk with of cardiovascular damage and its related complications. Studies have shown that activated platelets play a relevant role in atherosclerosis formation. However, the mechanism via which the platelet does this is unknown, although, activated plate have been recognized to release inflammatory chemokines and cytokines. Thus, aim of this review is to understand and describe the role of P-SELECTIN, RANTES and PF-4 from activated platelets in atherosclerosis as well as therapeutic target of these platelet inflammatory chemokines which is the major mediator of atherosclerosis in human.

Pathogenesis of Atherosclerosis via LDL

The basic mechanism of atherosclerosis was first described by an American pathologist, Dr.

Russel Ross in the late 1970's. He proposed that atherosclerosis occur as a result of response to an endothelial damage or injury that leads to the dysfunction of the endothelium (Hamad *et al.,* 2020). Earlier, atherosclerosis was thought to be a degenerative disease of old age, but evidence from researches made in the last two decades shows that atherosclerosis is not a degenerative disease as earlier thought to be, but a chronic inflammatory disease. It was also shown that the pathogenicity of atherosclerosis can be well understood at metabolic level of lipoproteins where it was said to be due to imbalance between the lipids metabolism and misconducted immune response leading to chronic inflammation in the vascular wall (Bergheau *et al.,* 2017). However, according to Lara-Guzman *et al.,* (2018), the basic mechanisms involved in pathogenesis of atherosclerosis are determined by multiple factors, where inflammation, oxidation and genetic predisposition are found to be the most important.

Owing to the high circulating amount of LDL and lipoprotein molecules in the blood, LDL can be transmigrated into the intimal layer of the vascular endothelium. Also, other contributing factors for the transmigration of LDL and their retention within the intimal layer are said to include size of the lipoprotein, permeability of the endothelium, basement membrane and extracellular matrix synthesis (Flood *et al.,* 2004). A protein molecule name apolipoprotein-B100 is mainly involved in the transmigration and retention of LDL within the intimal layer (Peluso *et al.,* 2012). After the transmigration and retention of LDL, these LDL molecules are then modified to become aggregated by a process of oxidation through the action of enzymes such as lipooxygenases, myeloperoxidases and free radicals (Hamad *et al.,* 2020).

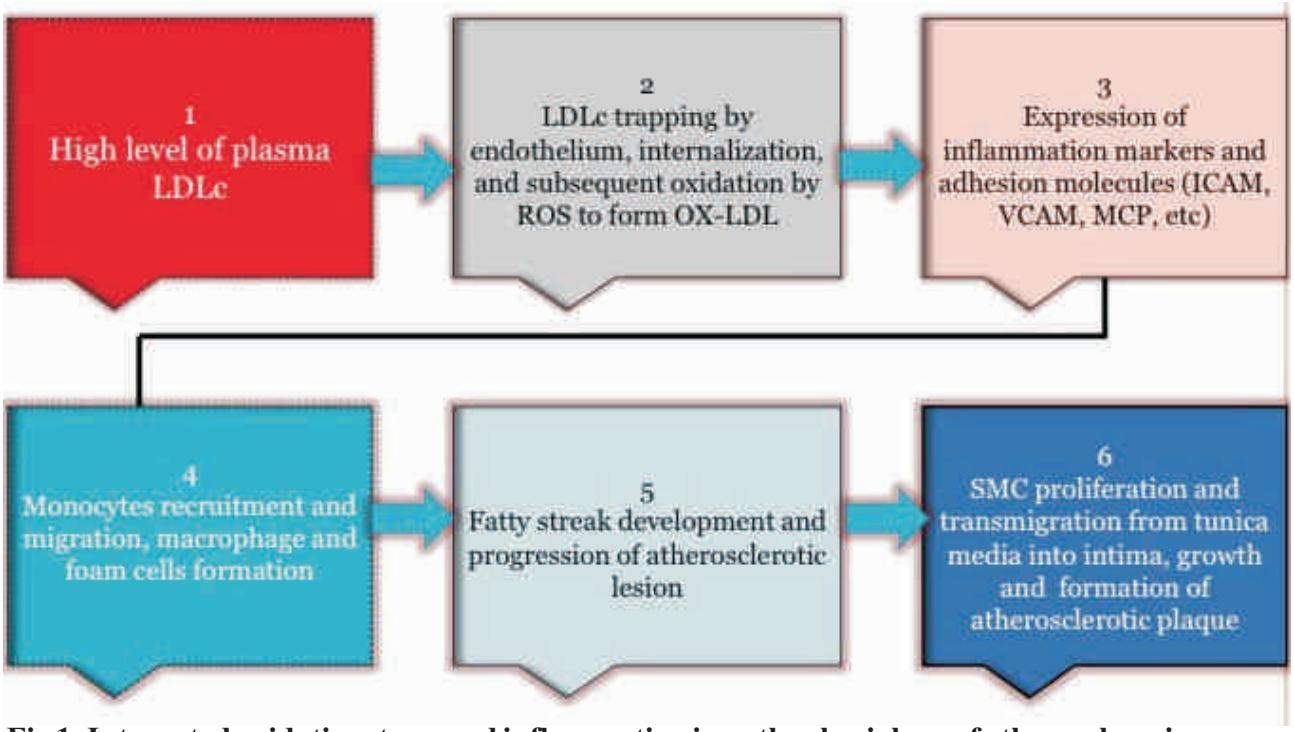

Fig 1: Integrated oxidative stress and inflammation in pathophysiology of atherosclerosis.

The endothelial cells act to the transmigration of LDL by releasing chemotactic substances. The released chemotactic substances and adhesion molecules are responsible for recruitment and adhesion of monocytes and other inflammatory cells on the endothelial wall. Adhesion molecules released by endothelial cells include integrins, selectins, vascular cell adhesion molecule-I (VCAM-I), intercellular adhesion molecule-I (ICAM-I), e.t.c. Chemo-attractants released on the other hand include platelet activating factor, chemokines like interleukin-8 (IL-8), monocytes chemo-attractant protein-1 (MCP) and so on (Hamad *et al.,* 2020). Adhered leukocytes are transmigrated into the intimal space of the endothelium. Following their transmigration, they can be transformed to macrophage by the influence of macrophage

colony stimulating factor and then express their own receptor known as the scavenger receptor (SR) for uptake of modified and oxidized LDL and then transform to foam cells (Tabas, 2009). Scavenger receptors expressed by macrophages include scavenger receptor class A (SRA)-I and SRA-II, CD-36, LOX-I, CXCL-16 and so on (Badimon *et al.,* 2012). In addition, transformed macrophages also release inflammatory mediators including cytokines (e.g IL-1β, IL-6, TNF-α) thereby accelerating the formation of atherosclerotic plaque (Hartman *et al.,* 2014 and Schieffer *et al.,* 2004).

LDL particles can also be cleaved by proteolytic, lipolytic and also hydrolytic enzymes in other to be incorporated with the immune cells (Badimon *et al.,* 2006; Napoli *et al.,* 1997). These modified and oxidized LDL in-turn, induces the endothelial cells to secrete chemotactic substances and at the same time express their adhesion molecules. However, oxidized LDL can play a role in fatty plaque progression by an oxidation production of chemo-attractant (lysophosphatidylcholine [LPC]) which not only induce monocytes and T-lymphocytes but also the endothelial cells in the expression of ICAM-1 and VCAM-1 (Hartman, 2014). LPC can also act as an enhancer of platelets derived growth factor and heparin binding epidermal growth factor in endothelial cells and smooth muscle cells. These growth factors serve also to promote the proliferation and transmigration of smooth muscle cells into the tunica intima of the vascular endothelium (Matsumoto *et al.,* 2007 and Ross, 1993). Interestingly, oxidized LDL can stimulate the induce metalloproteinase- 1 (MMP-1) and metalloproteinase-9 (MMP-9) in the vascular wall matrix thereby causing degradation of extracellular collagen and hence, formation of weak and unstable atherosclerotic plaque (Griendling, 2003).

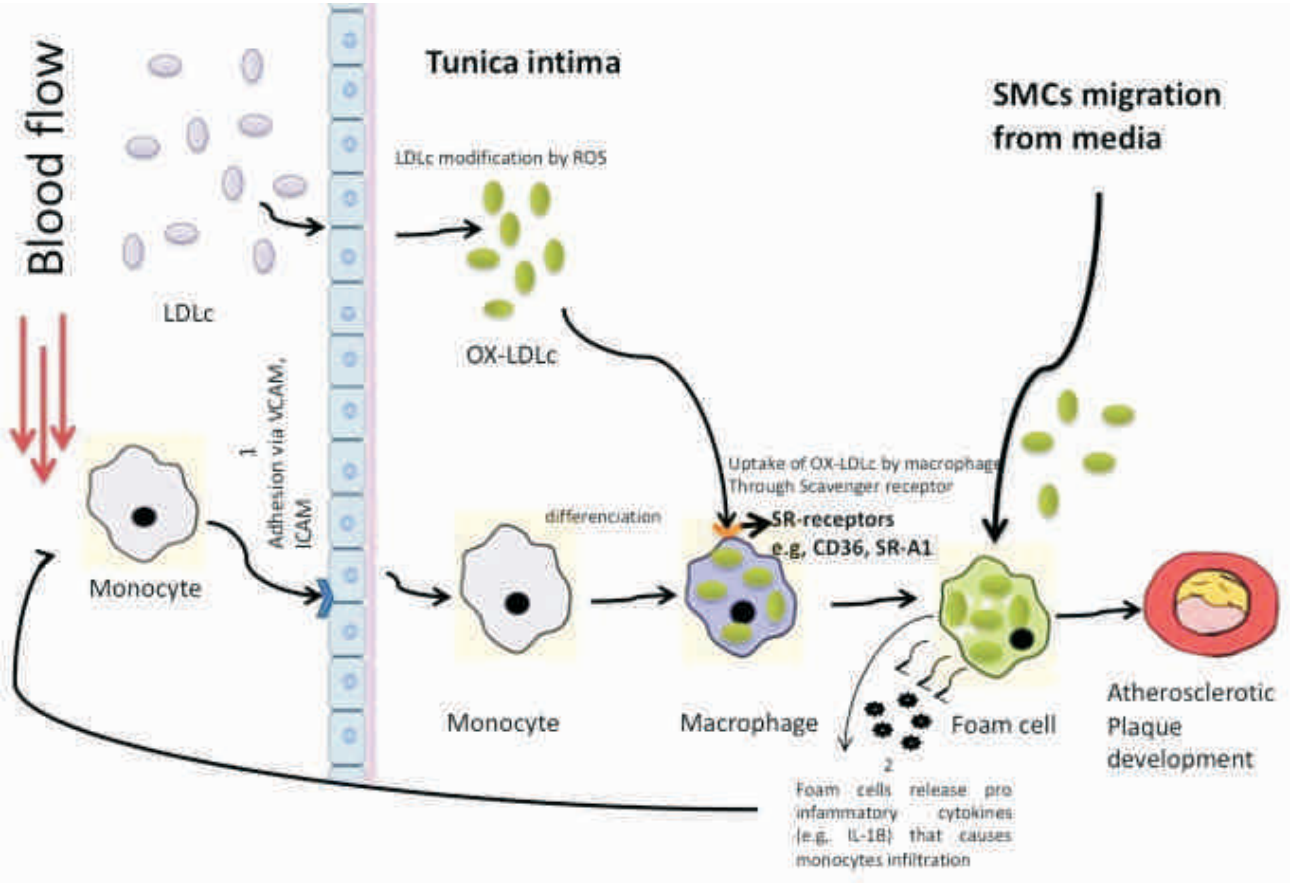

Fig 2: Mechanism of LDL cholesterol internalization, oxidation in the pathogenicity of atherosclerosis

Researchers also revealed that the internalization and subsequent transformation of vascular smooth muscle cells to foam cells is also regulated through the expression of LRP-1 which in another way serve as a receptor to many ligands and participate in signaling process (Badimon *et al.,* 2012). Following the transmigration of smooth muscle cells, they then express variety of LDL- receptor family (including LDL-R, LRP, VLDL-R) and scavenger receptor family (including CD-36 type I and type II) for cholesterol uptake (Badimon, 2011). More so, circulating bone marrow progenitor cells and other progenitor cells in the tunica adventitia are also recruited into the intimal space and serve as a potent source of vascular smooth muscle (Han, 2011). LRP-5 that is involved in the transmigration of mononuclear cells is revealed to be upregulated by agLDL (Llorente *et al.,* 2007 and Borrell-Pages *et al.,* 2011).

Mechanism of Platelet Activation and Aggregation on Disrupted Plaques

According to Nityanand (1993), endothelial disruption is not only the requirement for activation and attachment of platelets to the wall of blood vessels. It was also revealed that the mechanism involved in platelet activation and attachment also influenced by decrease in antithrombotic activities in blood, generation of reactive oxygen species and also increase production of inflammatory mediators (Binder, 2020). Following the activation of ruptured endothelium, platelets express certain receptors (p-selectin and integrin) that are responsible for their growing and adhesion to the endothelium. This activation allowed platelet to roll on the endothelium even at high shear rate. Therefore, platelet rolling is mediated by p-selectin expression whereas platelet adhesion is mediated by integrin. It can finally be said that p-selectin and integrin expression serve an essential role in the endothelium and platelet interaction (Burger and Wagner, 2003; Manka *et al.,* 2001). In addition to p-selectin and integrin adhesion molecules of platelets, they also contain several other mediators within their granules that are essential in the formation of firm thrombus (Badimon *et al.,* 2012). It was also revealed that platelets can initiate another interaction mechanism by the expression of its glycoproteins such as glycoprotein Ibα and IIβ3 (GPIIB/IIIa) with exposed endothelial von Willebrand factor. In another form, it also ridges the exposed endothelial collagen through glycoproteins GP Ia/IIa and GP VI receptors (Binder, 2020). According to Singbartl *et al. (*2001). Platelet interaction with endothelial collagen through GP VI stimulates the activation of other adhesion receptors like GP Ia/IIb receptors which in-turn accelerates the formation of firm stable thrombus. Following the formation of firm and stable aggregates of platelets, platelets then tend to change their shape and exit its contained granule constituents to interact with other constituents of the erupted endothelial lesion to promote the formation of thrombus. Example of granules released include serotonin, histamines, thromboxane A2 (TXA2) and so on (Badimon *et al.,* 2012). In addition to the granules platelets contained, it was revealed that they also contain a considerable amount of RNA molecules known as the micro RNAs (miRNA) whose function is to regulate protein expression by degrading messenger RNAs and thereby retarding the process of protein synthesis. These miRNAs are also said to exhibit a haematopoietic function by committing a number of progenitor cells to megakaryocytes lineage (Landry *et al.,* 2009 and Bruchova *et al.,* 2008). Lastly, platelets activation plays an essential role by inducing a positive feedback response to the original stimuli which leads to subsequent formation of a conformational change in the ligand binding region at the extracellular position and tails of glycoprotein αIIBβ3, thereby resulting to a high affinity binding region for fibrinogen and von Willebrand factor, thus forming a stable and firm bridge between platelets. This bridge formed between activated platelets explains the formation of platelet aggregates, thus referred to as platelet aggregation (von Hundelshausen *et al.,* 2001). Conclusively, it can be said that platelets activation, adhesion and aggregation play a crucial role in promotion of thrombogenesis following the disruption of an atherogenic plaque.

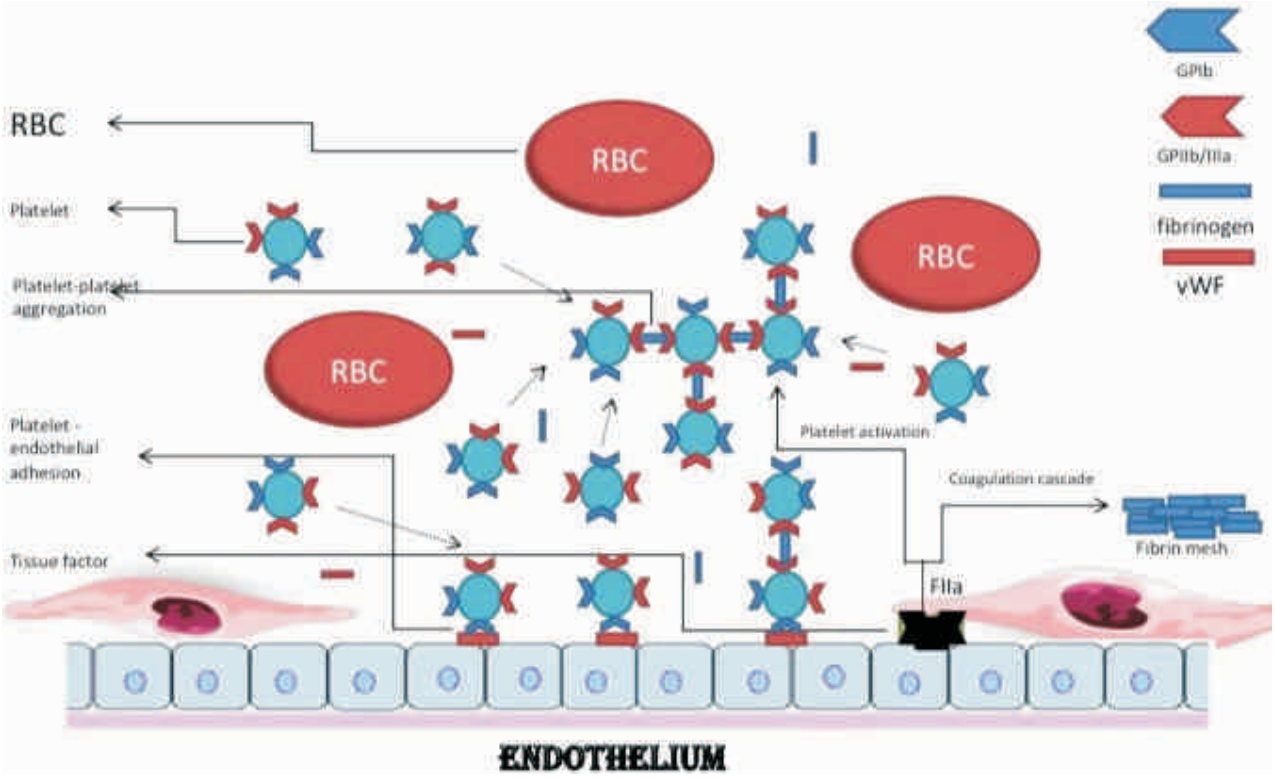

Fig 4: Vessel-related mechanisms involved in platelet adhesion, activation and further aggregation.

Platelet Activation and Inflammatory Chemokines in Atherosclerosis

The initial binding of platelet to the injured endothelium is through unique glycoprotein receptors (GPIb/Va/IXa) that are expressed by platelets. Von-Willebrand factor serve as a ligand for the binding of these glycoproteins to the injured endothelium. However, defect in the von Willebrand factor or one of these glycoproteins causes a defect in the formation of primary platelet plug and coagulation which are essential in stopping blood loss. Also, several other glycoproteins are found on platelets (notably GPVI and GBIa) that plays a role in platelet adhesion and rolling on the injured endothelium. Following the adhesion of platelet with the injured endothelium, certain autocrine and paracrine mediators (ADP, thrombin, epinephrine and thromboxane A2) are released by the adhered platelet that initiate the recruitment of circulating platelets from the flowing blood to form a primary hemostatic plug. These agonists of platelet recruitment results to the final expression of platelet integrin glycoprotein IIb/IIIa which is the main receptor used by platelets for adhesion and aggregation (Davi and Patrono, 2007). Studies revealed that platelet activation increases the rate of plaque formation by the acceleration of atherogenesis by COX-1–dependent thromboxane in low-density lipoprotein (LDL)–receptor −/− mice. These activated platelets also release inflammatory substances into the microenvironment that primarily alters the chemotactic, adhesive, and proteolytic function of the endothelium However, activated platelets are also capable of time-dependent synthesis of protein mediators, such as tissue factor and interleukin-1β. Interleukin-1β function as a major mediator of platelet-induced activation of endothelial cells, causing enhanced chemokine release and up-regulation of endothelial adhesion molecules to promote the adhesion of neutrophils and monocytes to the endothelium (Davi and Patrono, 2007). According to Fabrizio and Francois (2009), early deposition of lipids within the intimal space is said to be the prerequisite in the formation of rupture prone atherosclerotic plaque. Following the modification and oxidation of LDL, its retention

within the intimal, certain adhesion molecules are released by the endothelium that favor the recruitment and adherence of leukocytes (monocytes, macrophages and T-cells). CD40 ligand that is present in the cytoplasm of resting platelets is immediately presented on the surface after platelet activation. This CD40 ligand is cleaved to generate a soluble, functional fragment (soluble CD40 ligand) and then released into the extracellular environment, inducing inflammatory responses in the endothelium by binding CD40 on endothelial cells (Davi and Patrono, 2007). P-selectin is also released from platelet granules and binds to the P-selectin glycoprotein ligand 1 (PSGL-1) receptor on monocytes thereby promoting the adhesion of the monocytes to vascular-cell adhesion molecule-1 (VCAM-1) (Davi and Patrono, 2007). Bavendiek *et al.* (2002) explains the mechanism of leucocytes recruitment through the deposition of regulated on activation normal T-cell expressed and secreted (RANTES) and platelet factor (PF)-4 by platelets which work by causing the activation of integrins and endothelial nuclear factor-B (NFKB) which thus, triggers the transduction and translation of genes (such as MCP-1, avβ3, ICAM-1, VCAM-1) that are essential for monocytes attachment and transmigration. Platelets interaction with leukocytes is modulated through several cytokines and growth factors such as NFKB, tumor necrosis factor (TNF) α, granulocytes macrophage colony stimulating factors (GM-CSF), macrophage colony stimulating factors (M-CSF) and several other interleukins (example, IL-4) (Fabrizio and Francois, 2009). Platelet–leukocyte interactions also occur via P-selectin/P-selectin glycoprotein (PSGL)-1 or integrin Mac-1/GPIb and/or fibrinogenαIIbβ3 binding. Such interactions facilitate the formation of firm leukocyte-endothelial-adhered platelets complex or directly leukocytes-endothelium adhesion, thereby facilitating plaque formation (Badimon, 2012). Recruited monocytes however transform to macrophages following their transmigration, uptake the oxidized LDL using their expressed scavenger receptors and then differentiate to different type of inflammatory cells (foam cells, dendritic cells, osteoclasts, osteoblast-like cells) (Fabrizio and Francois, 2009). It was also revealed that platelets contain abundant amount of stromal derived factor (SDF-1) which serve as a potent chemokine against other progenitor cells and thereby responsible for their recruitment and same time regulation of their differentiation into foam cells or endothelial cells depending on the conditions (Badimon, 2011). Finally, atherosclerosis can be described as a pathologic process involving a cyclic interaction of platelets, chemotactic substances, endothelial cells, monocytes, macrophages, T-cells and other inflammatory cells.

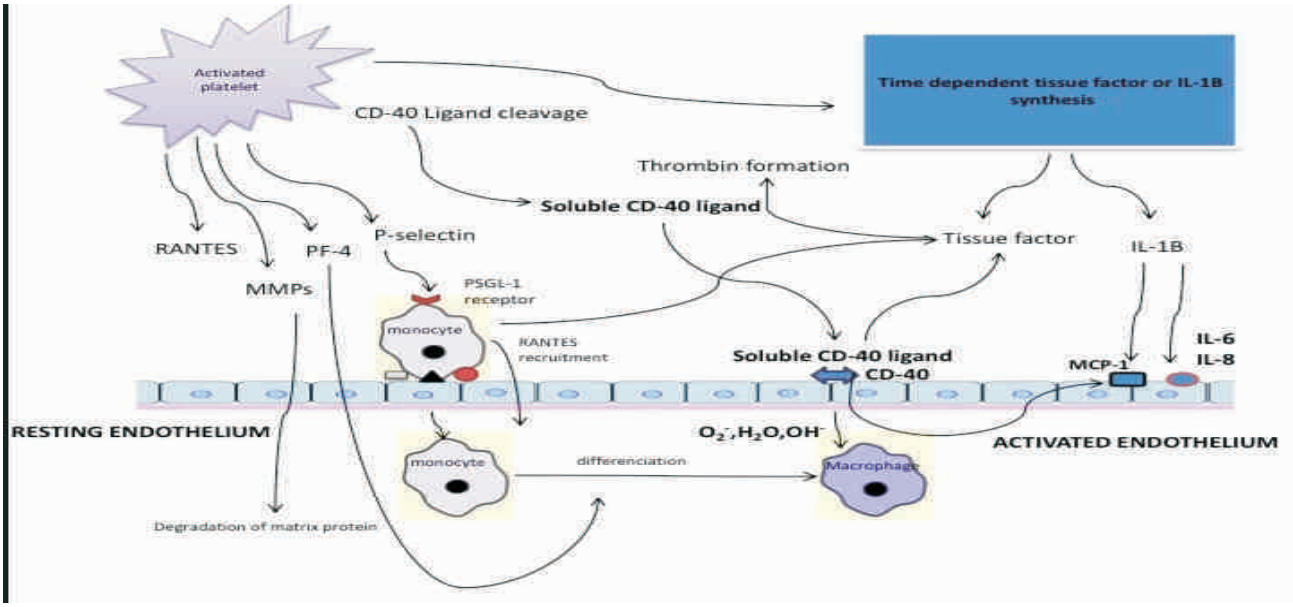

Fig 5: mechanism of platelet activation, chemokines release, monocyte recruitment, macrophage formation in atherosclerosis.

Activation of Coagulation Cascade in Thrombogenesis

Following the disruption of lipid rich plaque, coagulation pathway is activated when the tissue factor expressed by vascular smooth muscle cells, adventitial fibroblasts, endothelial cells and so on, are exposed to plasma, thus the formation of a complex by the binding of coagulation factor (F) VII/VIIa and the cellular surface. Series of these factors are activated which finally leads to the formation of thrombin. A second pathway is activated also by the activation of factor IX by tissue factor-factor VIIa complex which also leads to another series of events that again generates thrombin. The first activated pathway is referred to as the extrinsic pathway while the second activated pathway is referred to as the intrinsic pathway (Jerjes-Sanchez, 2005).

Activation of coagulation cascades also serve as a trigger for platelets activation. Following the activation of platelets, these activated platelets expose their phospholipid layer to the plasma membrane and thereby allows the binding of several other coagulation factors. These factors are found circulating in the plasma in their inactive zymogen forms where they become activated on binding with platelets (Badimon, 2012). Thrombin generated by coagulation cascade also activates platelet by cleaving a receptor on the platelets surface called protease-activated receptor 4 and then cause them to release their molecules [such as adenosine diphosphatase (ADP), serotonin, thromboxane A2 (TXA_2)]. These released agonists work by activating other platelets and therefore facilitate thrombus formation (Gurbel and Tantry, 2014).

Upon the activation of the coagulation cascade and subsequent formation of clot, circulating fibrinogen in then converted to fibrin and the fibrin clot is further stabilized through by crosslinking with factor XIIIa, forming a binding surface. Plasminogen found in the circulating plasma also gets activated to its active plasmin form and then binds to the binding surface that was formed by fibrin and factor XIIa. Plasminogen conversion to plasmin takes place by the action of tissue-type or urokinase-type plasminogen activator (tPA/uPA), where tissue-type plasminogen conversion to plasminogen is found to be the most abundant. Fibrinolysis can also be regulated by the anti-fibrinolytic proteins (example, α2-aantiplasmin, plasminogen activator inhibitor (PAI)-1 and -2, thrombin-activatable fibrinolysis inhibitor (TAFI) (Binder *et al.,* 2020 and Bouma and Mosnier, 2006).

Conclusively, both pathways of coagulation cascade lead to the formation of thrombin which function is to stabilize clots by activating factor XIII and then convert fibrinogen to stable active fibrin monomers and then subsequently, a stable clot formation.

Plaque Disruption and Platelet Activation

More than a few plaques liable to rupture at any moment. However, when they ruptured, they can precipitate and expose patients to chance of suffering from thrombotic complications. However, the susceptibility of a plaque to rupture depends not only on the content that is formed, but also on factors that include Lipid rich core, thin fibrous cap, inflammatory process within the fibrous cap, reduced collagen and vascular smooth muscle cells and neovascularization (Badimon *et al.,* 2012). Disruption of the formed plaque leads to the formation of thrombus. There are two (2) mechanisms that are involved in plaque disruption as demonstrated by researchers.

a) Plaque rupture: This is characterized by the disruption of thin fibrous cap which allows the lipid rich core to come in contact with the circulating blood (White *et al.,* 2016; Shah, 2003).
b) Plaque erosion: Plaque erosion on the other hand is characterized by superficial injury to plaques as seen in 22-44% of patients with fatal thrombi (White *et al.,* 2016; Shah, 2003).

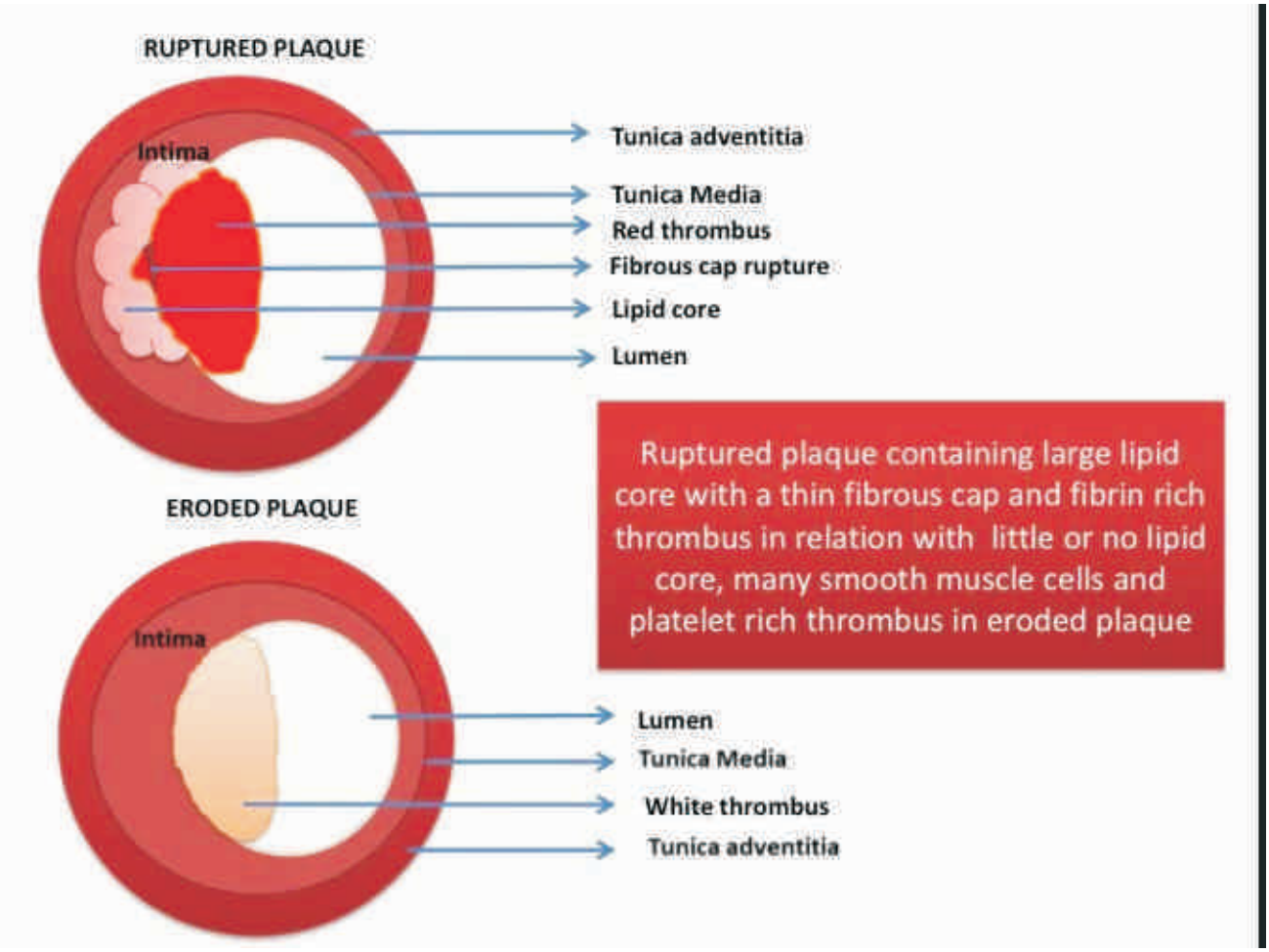

Fig 3: Illustration of the difference between eroded plaque and ruptured plaque

Plaques susceptible to disrupt by erosion are found to be rich in smooth muscle cells and abundant proteoglycans, versican and hyaluronan in the matrix in relative to small or absent necrotic lipid core and little inflammatory cells (White *et al.,* 2016; Shah, 2003).

Onset of Cardiovascular Events

Thrombus formation following the disruption of plaques is a critical process in the onset of acute cardiovascular events. However, according to Falk *et al. (*1995), thrombus does not always lead to complete occlusion of vessels with subsequent acute symptomatic events. Based on considerable number of researches carried out, it is observed that the underlying mechanism of thrombotic occlusion at sites of plaque disruption is very critical to the onset of cardiovascular events. However, certain mechanisms are said to be contributable factors in the occlusion of vascular blood flow by thrombus (Yujiro *et al.,* 2020).

I. Change in blood flow
II. Thrombus mediated vasoconstriction
III. Factor XI role in propagation of thrombus

1. Change in Blood Flow

Change in blood flow is said to be a major contributor to the development of thrombus. Blood flow disturbance induced by vascular narrowing or luminal surface distortion in arteries and subsequent atherosclerosis are thought to induce the activation of platelets and coagulation factors (Hathcock, 2006). A research carried out shows that Decreased ADAMTS- 13 activity under disturbed flow is said to increase platelet aggregation. Also, plaque disruption and coronary intervention can induce distal micro embolisms and microvascular constriction which then reduce coronary blood flow at sites of plaque disruption. Decreased ADAMTS- 13 activity under disturbed flow is said to increase platelet aggregation (Shida *et al.,* 2008).

Also, plaque disruption and coronary intervention can induce distal micro embolisms and microvascular constriction which then reduce coronary blood flow at sites of plaque disruption (Heusch *et al.,* 2009 and Marzilli *et al.,* 2000). Reduced blood flow facilitated thrombus propagation and thrombotic occlusion at plaque disruption sites in our animal models (Yamashita *et al.,* 2004). Reduced blood flow therefore facilitates thrombus propagation and thrombotic occlusion at plaque disruption sites.

2. **Thrombus Mediated Vasoconstriction**
Vascular constriction plays a crucial role in thrombotic occlusion. However, thrombus that arise following the disruption of a plaque may not be occlusive. Therefore, additional contribution of vasoconstriction can intervene and lead to vascular occlusion. Mural thrombi release many vasoactive agents which include 5-HT, ADP, ATP, thromboxane A2 and coagulation factors. Vasoconstriction induced by ADP and ATP is likely elicited in atherosclerotic vessels due to decreased NTPDase-1 activity, and FXa and thrombi increase the degree of vascular smooth muscle tone via PAR (Yujiro *et al.,* 2020).

3. **Factor X1 Role in Propagation of Thrombus**
Factor XI (FXI) is factor in the intrinsic pathway of coagulation and the zymogen of a trypsin-like serine protease which is activated by FXIIa, thrombin and FXIa (Grant and Aird, 2013). This FXI function as an amplification factor that further generates thrombin in the coagulation cascade pathway and also promotes clot resistance to fibrinolysis by action of thrombin activatable fibrinolysis inhibitor (TAFI). Therefore, this FXI is said to play a significant role in thrombus stabilization and propagation (von dem Borne, 1997). However, FXI is also considered less valuable in normal hemostasis, because it was found that factor XI deficiency usually does not lead to spontaneous bleeding (Bolton-Maggs, 2000). Studies revealed that high levels of plasma factor XI usually comprise an independent risk factor for deep venous thrombosis and ischemic stroke (Meijers 2000 and Yang 2006). Whereas, its deficiency is said to be associated with lower risk for these diseases (Preis *et al.,* 2017; Salomon *et al.,* 2001).

Critique

The sourced articles talked about the extra cellular matrix components exposed to blood for platelet adhesion and aggregation which include von Willebrand factor, fibronectin, laminin, collagen. Also, they have discussed well on the markers released by activated platelets (including CD-8, CD-4, CD40L, IL-1β, IL-8, INF-α, Platelet Factor-4, Neutrophil activating Protein, RANTES, ENA-78) for the propagation of inflammatory processes. Having known these markers released by activated platelets, the inhibition of thrombocyte activation at the damaged coronary plaque is the target of the new therapeutic strategies in preventing atherosclerotic plaque development. Some of the therapeutic analogs used include eptifibatide, abciximab, the cyclooxygenase inhibitor (aspirin), heparin octa saccharide analog as well as aryl phosphoglyceride and bis-aryl phosphate antagonists.

However, evidence-based information is needed on how the inflammatory cytokines are related to the found factors (LDL and other plasma lipid level) said to be affected in the mechanism of atherosclerosis. Example, comparism of the rate at which LDL level is affected with other inflammatory markers in the blood, comparism of oxidative stress markers and inflammatory markers. This comparism will add more value in research by giving valuable information on the intensity of the inflammatory markers there by knowing the most significant marker in atherosclerotic patients with risk of cardiovascular events.

Conclusion

Atherosclerosis is a chronic inflammatory disease that involves the formation of an atherosclerotic plaque, disruption of the plaque, propagation and subsequent occlusion of the blood vessels. It is

explained as an imbalanced lipid metabolism integrated with misconducted immune response, leading to chronic inflammatory process in the blood vessel wall**.** Oxidation and modification of accumulated LDL contribute to multiple stages of atherosclerotic plaque development through production of inflammatory cytokines. However, thrombus does not always lead to complete occlusion of vessels with subsequent acute symptomatic events. It is observed that the underlying mechanism of thrombotic occlusion at sites of plaque disruption at sites of plaque disruption is very critical to the onset of cardiovascular events. However, certain mechanisms such as change in blood flow, thrombus mediated vasoconstriction, factor XI role in propagation of thrombus are also said to be contributable factors in the occlusion of vascular blood flow by thrombus.

References

Badimon, L., Martinez-Gonzalez, J., Llorente-Cortes, V. (2006). Cell biology and lipoproteins in atherosclerosis. *Current Molecular Medicine*; **6**: 439–456.

Badimon, L., Padró, T., Vilahur, G. (2012). Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *European Heart Journal, Acute Cardiovascular Care*; **(1):** 60–74.

Badimon, L., Storey, R. F. and Vilahur, G. (2011). Update on lipids, inflammation and atherothrombosis. *Thrombosis and Haemostasis*; **105 (1)**: S34–42.

Bavendiek, U., Libby, P., Kilbride, M. (2002). Induction of tissue factor expression in human endothelial cells by CD40 ligand is mediated via activator protein 1, nuclear factor kappa B, and Egr-1. Journal of *Biology and Chemistry*; 277: 25032–25039.

Bergheanu, S. C., Bodde, M. C., Jukema, J. W. (2017). Pathophysiology and treatment of atherosclerosis: current view and future perspective on lipoprotein modification treatment. *Netherland Heart Journal*; **25(4)**:231–242.

Binder, C. J., Jan Bor´enb, Alberico, C. I., Florian, K., Ziad, M. J., Simona, N., Katariina, O., Paolo, Raggih, K.J., Arnold von Eckardsteinf. (2020). The year 2020 in Atherosclerosis.

Bolton-Maggs, PH. (2000). Factor XI deficiency and its management. *Haemophilia;* **6**: 100–109.

Bouma, B.N., Mosnier, L.O. (2006). Thrombin activatable fibrinolysis inhibitor (TAFI)—how does thrombin regulate fibrinolysis? *Annals of. Medicine;* **38**: 378–388.

Borrell-Pages, M., Romero, J. C., Juan-Babot, O. (2011). Wnt pathway activation, cell migration, and lipid uptake is regulated by low-density lipoprotein receptor-related protein 5 in human macrophages. *European Heart Journal*; **32**: 2841–2850.

Bruchova, H., Merkerova, M. and Prchal, J. T. (2008). Aberrant expression of microRNA in polycythemia vera. *Haematologica*; **93**: 1009–1016.

Burger, P. C. and Wagner, D. D. (2003). Platelet P-selectin facilitates atherosclerotic lesion development. *Blood*; **101**: 2661–2666.

Davi, G. and Patrono, C. (2007). Mechanisms of Disease Platelet Activation and Atherothrombosis. *New England Journal of Medicine;* 357:24.

Falk, E., Shah, P. K., Fuster, V. (1995). Coronary plaque disruption. *Circulation;* **92**: 657–671.

Flood, C., Gustafsson, M., Pitas, R. E. (2004). Molecular mechanism for changes in proteoglycan binding on compositional changes of the core and the surface of low-density lipoprotein-containing human apolipoprotein B100. *Arteriosclerosis, Thrombosis and Vascular Biology;* **24**: 564–570.

Grant, M. A., Aird, W. C. (2013). Molecular evolution of the vertebrate blood coagulation system. In: Marder VJ, Arid WC, Bennett JS, Schulman S, White GC II, eds. Hemostasis and Thrombosis.

Griendling, K.K., FitzGerald, G.A. (2003). Oxidative stress and cardiovascular injury part I: basic mechanisms and in vivo monitoring of ROS. *Circulation*; **108(16)**:1912–1916.

Gurbel, P. A., Tantry, U. S. (2014). Antiplatelet and anticoagulant agents in heart failure. *Journal of American College of Cardiology*; **2**:1-14.

Hamad, A. H. A., Zenab, B., Hamad, M., and

Muhammad, B. I. (2020) Basic pathogenic mechanisms of atherosclerosis. *Egyptian Journal of Basic and Applied Sciences;* **7**: 116-125,

Han, C.I., Campbell, G.R., and Campbell, J.H. (2011). Circulating bone marrow cells can contribute to neointimal formation. *Journal of Vascular Research*; **38**: 113–119

Hartman, J., Frishman, W.H. (2014). Inflammation and atherosclerosis: A review of the role of interleukin-6 in the development of atherosclerosis and the potential for targeted drug therapy. *Cardiology Review;* **22(3)**:147–151.

Hathcock, J.J. (2006). Flow effects on coagulation and thrombosis. *Arteriosclerosis Thrombosis and Vascular Biology;* **26**: 1729–1737.

Heusch, G., Kleinbongard, P., Bo¨se, D. (2009). Coronary microembolization: From bedside to bench and back to bedside. *Circulation;* **120**: 1822–1836.

Jerjes Sanchez, C., (2016). Mechanism of Thrombosis. *Journal of Thrombosis and Thrombolysis*;**44(3)**:377-385.

Koskinen, J.S., Kyto, V., Juonala, M. (2020). Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study, *Atherosclerosis*; **293**:18–25.

Landry, P., Plante, I., Ouellet, D. L. (2009). Existence of a microRNA pathway in anucleate platelets. *Nat Nature Structural & Molecular Biology*; **16**: 961–966.

Lara-Guzmán, O. J., Gil-Izquierdo, Á., Medina, S. (2018). Oxidized LDL triggers changes in oxidative stress and inflammatory biomarkers in human macrophages. *Redox Biology*; **15**:1–11.

Leu, P., Soubeyrand, S., Hegele, R.A. (2020). Molecular mechanism linking a novel PCSK9 copy number variant to severe hypercholesterolemia, *Atherosclerosis;* **304**: 39–43.

Llorente-Cortes, V., Royo, T., Otero-Vinas, M. (2007). Sterol regulatory element binding proteins downregulate LDL receptor-related protein (LRP1) expression and LRP1-mediated aggregated LDL uptake by human macrophages. *Cardiovascular Research*; **74**: 526–536.

Manka, D., Collins, R. G., Ley, K. (2001). Absence of p-selectin, but not intercellular adhesion molecule-1, attenuates neointimal growth after arterial injury in apolipoprotein e-deficient mice. *Circulation*; **103**: 1000–1005.

Marzilli, M., Sambuceti, G., Fedele, S., L'Abbate, A. (2000). Coronary microcirculatory vasoconstriction during ischemia in patients with unstable angina. *American Journal of College of Cardiology;* **35**: 327–334.

Matsumoto, T., Kobayashi, T., Kamata, K. (2007). Role of lysophosphatidylcholine (LPC) in atherosclerosis. *Current Medical Chemistry*; **14 (30)**:3209–3220.

Meijers, J.C., Tekelenburg, W.L., Bouma, B.N., Bertina, R.M., Rosendaal, F.R. (2000). High levels of coagulation factor XI as a risk factor for venous thrombosis. *New England Journal of Medicine*; **342**: 696–701.

Montecucco, F., Mach, F. Atherosclerosis is an inflammatory disease. *Semin Immunopathology;* **31**: 1–3.

Napoli, C., D'Armiento, F.P., Mancini, F.P. (1997). Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low-density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *Journal of Clinical Investigation*; **100**: 2680–2690.

Nityanand, S., Pande, I., Bajpai, V.K. (1993). Platelets in essential hypertension. *Thrombosis Research;* **72**: 447–454.

Peluso, I., Morabito, G., Urban, L. (2012). Oxidative stress in atherosclerosis development: the central role of LDL and oxidative burst. *Endocrine Metabolism and Immune Disorders Drug Targets*; **12(4)**:351–360.

Preis, M., Hirsch, J., Kotler, A. (2017). Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood;* **129**: 1210–1215.

Ross, R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature;***362 (6423)**:801–809.

Salomon, O., Steinberg, D. M., Zucker, M.,

Varon, D., Zivelin, A., Seligsohn, U. (2011). Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. *Thrombosis and Haemostasis;* **105**: 269–273.

Schieffer, B., Selle, T., Hilfiker, A. (2004). Impact of interleukin-6 on plaque development and morphology in experimental atherosclerosis. *Circulation*; **110(22)**:3493–3500.

Shah, P. K. (2003). Mechanisms of plaque vulnerability and rupture. *Journal of American College of Cardiology;* **41**: 15S–22S.

Shida, Y., Nishio, K., Sugimoto, M. (2008). Functional imaging of shear-dependent activity of ADAMTS13 in regulating mural thrombus growth under whole blood flow conditions. *Blood;* **111**: 1295–1298.

Singbartl, K., Forlow, S. B. and Ley, K. (2001). Platelet, but not endothelial, P-selectin is critical for neutrophil-mediated acute postischemic renal failure. *Federation of American Societies for Experimental Biology Journal;* **15**: 2337–2344.

Tabas, I. (2009). Macrophage apoptosis in atherosclerosis: consequences on plaque progression and the role of endoplasmic reticulum stress. *Antioxidant Redox Signal;* **11**: 2333–2339.

von dem Borne, P.A.K., Bajzar, L., Meijers, J.C.M., Nesheim, M.E., Bouma, B.N. (1997). Thrombin-mediated activation of factor XI results in a thrombin activatable fibrinolysis inhibitor-dependent inhibition of fibrinolysis. *Journal of Clinical Investigation;* **99**: 2323–2327.

von Hundelshausen, P., Weber, K.S., Huo, Y. (2001). RANTES deposition by platelets triggers monocyte arrest on inflamed and atherosclerotic endothelium. *Circulation*; **103**: 1772–1777.

White, S.J., Newby, A.C., Johnson, T.W. (2016). Endothelial erosion of plaques as a substrate for coronary thrombosis. *Thrombosis and Haemostasis*; **115**: 509–519.

Yamashita, A., Matsuda, S., Matsumoto, T. (2009). Thrombin generation by intimal tissue factor contributes to thrombus formation on macrophage-rich neointima but not normal intima of hyperlipidemic rabbits. *Atherosclerosis;* **206**: 418–426.

Yamashita, A., Sumi, T., Goto, S. (2006). Detection of von Willebrand factor and tissue factor in platelets-fibrin rich coronary thrombi in acute myocardial infarction. *American Journal of Cardiology*; **97**: 26–28.

Yang, D.T., Flanders, M.M., Kim, H., Rodgers, G.M. (2006). Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. *American Journal of Clinical Pathology;* **126**: 411–415.

Yujiro, A., Atsushi, Y., Yuichiro, S., Kinta, H. (2020) Pathophysiology of atherothrombosis: Mechanisms of thrombus formation on disrupted atherosclerotic plaques. *Pathology International*; DOI: 10.1111/pin.12921

Zernecke, A., Shagdarsuren, E., Weber, C. (2008). Chemokines in atherosclerosis: an update. *Arteriosclerosis Thrombosis and Vascular Biology*; **28**:1897–190.

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