



Platelets as Inflammatory Cells in Atherosclerosis

Musa Abdulkarim Abdullahi^{1,2}, Cuiping Wang, Zakari Shaibu
2,3, Isah Adamu Danbala^{2,4}

1. Department of cardiology, affiliated hospital of Jiangsu university, Zhenjiang 212000, china

2. Overseas Education College, Jiangsu University, No 301 Xuefu Road Zhenjiang, Jiangsu, PRC.

3. Department of Gastrointestinal Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu 212002, PRC.

4. Department of Gastrointestinal Surgery, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu PRC.

Submitted: 01-05-2021

Revised: 10-05-2021

Accepted: 12-05-2021

ABSTRACT: Atherosclerosis is an incessant inflammatory ailment of veins. Lately, it has been found that platelets have an impact in the inflammatory reaction of the vein divider through various components, and go through the whole event and advancement of atherosclerosis.

Platelets are enacted by interfacing with leukocytes, endothelial cells, and ancestor cells in the course, starting inflammation of the vessel divider and the atherosclerotic course.

This article portrays the fundamental sub-atomic instruments that platelet starts and enhances the inflammatory reaction of the vein divider, which prompts the event and advancement of atherosclerosis.

Key words: platelets; inflammation; atherosclerosis; inflammatory cells; endothelial progenitor cells.

I. INTRODUCTION

Platelets are most popular as the cell go between of apoplexy. There is currently a developing recognition about the significant insusceptible and incendiary functions of PLTs in both health and sickness. Various investigations have shown that PLTs sway provocative cycles running from atherosclerosis to irresistible illnesses, which makes PLTs in the majority of various flowing cell kind carrying a safe capacity. PLTs associate with white blood cells and vascular epithelial tissue cells both legitimately by contact-subordinate systems and by implication via emitted immune go between driven systems (Aukrust et al., 2010). PLTs invulnerable impacts are consequently noted both locally at destinations of PLT enactment and foundationally at areas removed from PLT actuation itself. Platelet collaborations with provocative cells may intervene pro inflammatory results, however these cooperation have likely

developed to be valuable in restricting disease (Ruggeri, 2002). For instance, with a break in the skin there is presentation to microorganisms, and by joining thrombotic and resistant enrollment capacities, PLT might assist to center hemostasis and immune reactions in response of expected irresistible infections to forestall microbe attack. Notwithstanding, proceeded or constant PLT associations with white cells or endothelial cells can prompt unfavorable impacts from over the top immune incitement and inflammatory affront.

Atherosclerosis is the fundamental purpose behind practically all reasons for coronary heart diseases and peripheral blood arterial illness and numerous instances of stroke. Atherosclerosis as described by (Badimon et al., 2012) is a foundational incendiary cycle described by the collection of lipids and macrophages/white blood cells inside the intima of arteries. The testimony of these blood related materials and the resulting thickening of the wall regularly altogether bargain the leftover lumen prompting ischemic occasions distal to the blood vessel stenosis. Be that as it may, these underlying greasy streak injuries may likewise advance into weak plaques vulnerable to burst or disintegration (Weber and Noels, 2011). Plaque disturbance starts both PLT grip and total on the uncovered arterial surface and the initiation of the coagulating course prompting the supposed atherothrombotic measure. However, platelets have additionally been demonstrated to be carriers of administrative atoms (miniature RNA), to drive the provocative reaction and intercede atherosclerosis movement.

A few examinations recommend a significant part for platelets in atherogenesis, as arbitrator of clots positioning, also in form of depraver of inflammatory responses. A few lines of proof show that inflammatory reactions in



neighboring cells, such as white blood cells and endothelial cells are prompt by platelets as they are strong incendiary cells. In a similar way, platelets might themselves act in response to inflammatory arbiters delivered by these adjacent cells (Srivastava et al., 2008). In both the initial and latent phase of the cycle; there is an addition by these platelet-intervened inflammatory passages to atherogenesis. The two way collaboration between the platelets and various cells might in the same way be associated with the nonresolving irritation describing atherosclerosis. In patients with atherosclerotic issues, platelet-intervened inflammation has all the earmarks of being working notwithstanding the wide utilization of platelet-hindering medications (Aukrust et al., 2010).

Platelet enactment can be found in the various periods of atherosclerosis. Fitzgerald et al. (1986) First announced the identification of actuated platelets as characterized by P-selectin surface articulation in peripheral blood of patients with flimsy atherosclerotic illness. These flowing enacted platelets are probably going to connect with thrombotic occasions. Coursing initiated platelets were likewise recognized in the blood of atherosclerotic bunnies (Nathan and Ding, 2010) and according to (Furman et al., 1998) patients with stable coronary infection. The presence of coursing enacted platelets going before huge thrombotic occasions, for example, myocardial localized necrosis or stroke might be applicable to the turn of events and movement of atherosclerosis. The molecular processes liable for platelet initiation in atherosclerosis are obscure. In a thrombotic occasion, platelet initiation starts with the authoritative of adherent receptors to their ligands on extracellular grid constituents. This cycle as explained by (Ruggeri, 2002) is additionally reinforced by motioning through a thrombin delivered on the film of invigorated platelets, adenosine diphosphate (ADP) created by vascular cells and affected platelets, epinephrine delivered because of stress, and thromboxane (TX) A₂ blended by affected platelets. In the beginning stage of atherosclerosis, initiation of PLTs might be ascribed to (a) receptive oxygen species created by hazard components of atherosclerosis, involving O₂⁻, hydroxyl revolutionary, and ONOO⁻; (b) decrease in properties of endothelial antithrombotic cells, for example, creation of NO, prostacyclin, and CD39, an ectoADPase which debases ADP; or (c) an expansion in prothrombotic and proinflammatory arbitrator, involving tissue factor along with chemokine in the flow or in

dysfunctional state on the endothelium. Moreover, following arrangement of sores on the vessel divider, PLT actuation might be started by ligation of GPIb with the epithelial tissue receptor P-selectin and epithelial tissue von Willebrand factor (VWF) during PLT tying on unblemished however useless endothelium. PLT initiation impacts the improvement of atherosclerosis. Restraint of platelet TX A₂ creation by ibuprofen (Cyrus et al., 2007) and indomethacin (Praticò et al., 2001) or TX receptors (Cayatte et al., 2000) by opponent can drastically reduce the arrangement of atherosclerotic sores. Some clashing information exist. For instance, a few discoveries didn't uphold a gainful impact of anti-inflammatory medicine in atherosclerosis (Cayatte et al., 2000). Additionally, the inhibitory impact of headache medicine in atherosclerosis might be accomplished by stifling platelet cyclooxygenase (COX) - 1, yet additionally COX-2 in macrophages and smooth muscle cells in the vessel divider (Weber and Noels, 2011).

The idea of platelets as significant parts during the time spent atherogenesis has gotten progressively acknowledged due to amassing trial and clinical proof (Palinski and Napoli, 2002). Notwithstanding the advancement in acknowledging the atomic subtleties of atherosclerosis, especially by utilizing creature samples, the incendiary and thrombotic functions of initiated platelets particularly in the human framework stay hard to analyze, as regularly just the entanglements of atherosclerosis, i.e., stroke and myocardial localized necrosis are determinable yet not the plaque trouble (Morrell et al., 2014). Notwithstanding the expanding information about the perplexing pathogenesis of atherosclerosis our restorative accomplishments have very little further advanced since the endorsement of statins. Different cell types and various arbiters have been distinguished to contribute in compounding or settling atherosclerotic injuries and are subsequently basically to be considered as expected targets (Srivastava et al., 2008). This review study centers around understanding the part of platelets in the advancement of atherosclerosis by looking into platelets as provocative cells, the collaboration of platelets with vascular intima, leukocytes and endothelial ancestor cell and how blood vessels, leukocytes and platelets all add to the movement of atherosclerosis. In the past investigations carried on the subject being talked about, the significance of platelets for atherogenesis, at any rate for the human framework, stays questionable and deficiently comprehended. The current survey will



attempt to fill the holes present in past investigations.

II. METHODOLOGY

Atherosclerosis is an incessant provocative vascular illness including ECs, vascular involuntary muscle cells and mononuclear cells. Atherosclerosis order as an incendiary ailment depends on the finding that insusceptible capable cells and favorable to inflammatory cytokines are profuse in atherosclerotic sores. It is portrayed by the development of an atheromatous plaque primarily made out of supportive of provocative oxidation low thickness lipoproteins and froth cells gathering in the intima of medium or enormous corridors, in high-shear pressure regions. It brings about vessel impediment initiating CVD beginning. The part of PLTs in early atherosclerosis have been proposed by pioneer contemplates.

To understand the role of platelets in the development of atherosclerosis, the current study reviewed articles dating from 2000-2020 from various databases. Keywords such as platelets, atherosclerosis, platelets and their inflammatory qualities, PLTs and leukocytes, interactions of PLTs with various cell types and tissues, PLTs and cardiovascular diseases, blood vessels and platelets relation to atherosclerosis, inflammatory response of platelets and atherosclerosis, role of platelets in early and late stages of atherosclerosis, and platelet mechanism in atherosclerosis and vascular inflammation were used to search and gather the data. Search engines such as Pubmed, Wiley library, frontiers in cardiovascular medicine, Augusta University, journal of thrombosis hemostasis, research gate, sage journals, Thieme, journal of clinical and experimental pharmacology and physiology, Springer Link, Ash publications, Elsevier, International journal of Molecular Sciences, Journal of Leukocyte biology, platelets journal, journal of expert review of cardiovascular therapy and Taylor and Francis online were utilized to gather the papers for reviewing. 100 papers were selected out of the 625 searched papers. An inclusion and exclusion criteria was established on the basis of direct relativity to the study subject, whereas articles which covered other cardiovascular diseases rather than atherosclerosis were excluded from the study. The selected 102 papers are reviewed in this study. Some of the papers dating back to 1990's are also reviewed.

Platelets are inflammatory cells

Surely, platelets are one of the preeminent huge processes of the intrinsic immune framework, and their basic parts in the spread of inflammation must be perceived. Both the platelet tally and the mean platelet volume (MPV) can determine illness seriousness. An expansion in size mirrors the endurance of a thrombotic or inflammatory milieu; along these lines, MPV has been suggested as a potential marker of platelet capacity and enactment (Kim et al., 2015). Platelets emit in excess of 300 dynamic substances from their intracellular granules, and granule proteins assume significant parts in both inflammation and clots development. For instance, α -granules contain numerous cytokines, favorable to and mitigating factors, and other bioactive particles that are fundamental controllers of clots development (Golebiewska and Poole, 2015). Recently, as evident by study of (Thomas and Storey, 2015) platelet serotonin in thick granules has been appeared to assume a noteworthy function in neutrophil advancing and bond to the endothelium. In different inflammatory conditions, platelets can increment vascular penetrability, bringing about edema, characterized as "a growing tumor", which is one of the principal indications of inflammation (Gros et al., 2014). Platelets may likewise cooperate with different cells (counting nearby platelets, leukocytes, and endothelial cells) not just through direct receptor-intervened cell-cell association yet additionally by official to fibrinogen by means of GpIIb/IIIa. Initiated platelets, communicating the high proclivity compliance of the GpIIb/IIIa integrin receptor, are equipped for authoritative to fibrinogen, essential crosslinking with neutrophils through their surface integrin receptor Mac-1 (Weber and Springer, 1997). Thusly, platelets not just carry leukocytes to a site where inflammation possibly prompts atherosclerosis yet additionally contain stores of proinflammatory go between, for example, thromboxanes and CD40 ligand (Phipps, 2000, Nijm et al., 2005). Notwithstanding filling in as a stage to which leukocytes can follow, platelets likewise can control the articulation and initiation of grip atoms on other cell types, such as endothelium and all white blood cells. Platelet-neutrophil and platelet-monocyte totals are observed in blood of patients accompanied with various infections and are recognized in the present time among the touchiest markers identified with platelet actuation (Mitsui et al., 2016, Pfluecke et al., 2016). A prothrombotic state might be emulated by them and hence, they are portrayed to



be connected with intense coronary disorder, neoplastic and immune system infections and inflammatory disorders. Platelets are not just engaged with vascular inflammation; study has likewise build up that they assume a key part in the improvement of vascular inflammation (Kastrati et al., 2006, Topol et al., 2001). Enacted platelets cooperate with cells in the vessel divider, for example, endothelial cells, neutrophils, and monocytes, through receptor-ligand or autocrine, paracrine pathways, and actuate each other to start a course response. A progression of cycles as evident from (Lindemann et al., 2001) prompts the expansion of the inflammatory reaction of the vein divider, inception and advancement of atherosclerotic plaque improvement, restenosis or thromboembolic events. Revisions in light of (Weber, 2005, Neumann et al., 1997, May et al., 1998, May et al., 1999, Langer et al., 2007a) have set up that inflammatory maladies, for example, flimsy angina pectoris, myocardial dead tissue, sepsis, inflammatory inside sickness, and rheumatoid joint pain, have variable degrees of platelet activation. Platelet actuation can likewise cause grave cardiovascular intricacies, for example, shaky angina pectoris, myocardial localized necrosis, or stent apoplexy, which can influence the anticipation of cardiovascular sickness. Subsequently, in accordance with (Massberg et al., 2006, Gawaz et al., 1997) hindrance of platelet capacity can decrease the rate of intense cardiovascular infection and extreme unfavorable occasions during the board. Even however platelets have no cores, they can in any case make proteins through interpretation (Bombeli et al., 1998).

These proteins control diverse organic functions of various cells through a succession of troublesome and sensitive systems, for example, cell endurance, esteem included, attachment, total, chemotaxis, and protein coagulation and hydrolysis, prompting the development of inflammation and cell accumulation. In the inflammatory state, platelets can likewise frame edifices with different cells in the blood, for example, leukocytes and ancestor cells, which are available in the blood or stick to the vessel divider (Springer, 1994, Pitsilos et al., 2003). Platelets are additionally known to cooperate with leukocytes in different manners. For instance, platelet enacting factor (PAF) is known to be fabricated by a decent variety of cells, especially those engaged with have assurance, for example, neutrophils, monocytes and endothelial cells. Once clung to the vein divider, platelets can likewise uphold the bond of

leukocytes and endothelial begetter cells through go between, for example, platelet initiating factor (PAF), macrophage inflammatory protein-1 α (MIP-1 α), RANTES or SDF-1 (Santoso et al., 2002, Diacovo et al., 1994) Therefore, advancing a chain of reactions, for example, endothelial cells, white blood cells and endothelial ancestor cells.

The communication of platelets and vascular intima

Under normal conditions, platelets don't stick to endothelial cells. In its place, platelets circle in veins without connecting to vessel dividers (Etulain and Schattner, 2014). Unblemished endothelial cells release arbiters that block platelet-endothelial communication through different components. The most basic of these endothelial cell go between are diphosphohydrolases (a successful platelet activator to bring down ADP), amino oxidases (that kill nearby vasoconstrictors), nitric oxide (NO, a neighborhood vasodilator) and prostacyclin (P gI_2), which assumes a fundamental function in the restraint of platelet grip and accumulation (Chen and López, 2005). By and by, underneath inflammatory issues, platelets can tie to endothelium reasonably since the physiological inhibitory components of endothelium are diminished and halfway because of the sign of some attachment atoms on the top of actuated PLTs and endothelial cells (Chen and López, 2005). After an endothelial physical issue, platelets stick to the sub-endothelial layer, are actuated, total, and in the long run structure a firm clots, deterring the harmed spot to hinder outpouring of intravascular blood into the extravasal area, in this manner performing barricade capacities. All stage depends on explicit surface receptors. Attachment underneath unusual shear is commonly intervened by the authoritative of GpIb/V/IX on PLTs to collagen-bound vWF, so improving the cooperation of GpVI with collagen. This GpVI-collagen cooperation can later bring about platelet enactment (Sarratt et al., 2005). Enacted platelets can actuate numerous different sorts of cells by delivering proinflammatory arbiters. Platelets can be initiated by EC bringing about proinflammatory bodies that predicament to sense organ on their surfaces (Weyrich et al., 2002). Additionally, through the accompanying strides of platelet-endothelial cell connections, PLTs become actuated by advancing over initiated epithelial tissue or sub endothelium. This invigorates endothelial cells to transform from an ontogeny inflammatory to a thrombotic taxonomy (Etulain et



al., 2014, Rondina et al., 2013). Lately, platelet serotonin in thick granules is presented to have a huge impact in neutrophil advancing and grip to the endothelium (Thomas and Storey, 2015). Presently vitro preliminaries have discovered that platelets can hold fast to enacted continually appropriated human monolayer endothelial cells. Platelets by and large go through platelet glycoprotein (GP) IIb,IIIa-subordinate extension systems, including communications with fibrinogen, fibronectin, and VWF Adhesion to enacted human umbilical vein endothelial cells (Zirlik et al., 2007, Chavakis et al., 2003).

Also, according to (Han et al., 2018) inflammation of ECs animates the indication of CD40 on their exterior membranes just as association of CD40 with CD40 ligand (CD40L) on PLTs, pointing in actuation of PLTs. CD40 minimizes NO creation and builds ROS creation by ECs, overpowering VEGF creation and forestalling angiogenesis, that finances to the pathological process of CVD (Urbich et al., 2002). Additionally, the actuation of PLTs tips to their authoritative with Mo (monophils) because of the association of PLTs p-selectin with Mo PSGL-1, that initiates Mo from flow in the direction of the vessel divider. Whereas, CD40-CD40L association builds the creation of Von Willebr and factor (VWF) from Weibel-Palade assortments of ECs, building up a reasonable foundation for monophils and T-cell separation on vessel divider and developing the level of inflammation (Popa et al., 2018). In option, research has likewise set up that endothelial cell surface receptors ICAM, $\alpha\beta 3$ integrin, and GPIb are additionally engaged with the attachment of initiated platelets to endothelial cells (Altieri et al., 1988). Vein inflammation is set off by communications between PLTs, white blood cells and endothelial cells that outcome in autocrine and paracrine initiation. This actuation is trailed by leukocyte enrollment into the vascular divider and animates an inflammatory response through the arrival of proinflammatory amalgamation (Gawaz et al., 2005). After platelet bond, a progression of inflammatory arbiters and mitogenic bodies are freed, bringing about changes in synthetic chemotaxis, attachment and proteolysis of nearby endothelial cells. For example, according to (Zarbock et al., 2007) the communication of GPIIb/IIIa and its receptor through platelet bond prompts the up-guideline of platelet CD62P and CD40L articulation, which prompts the enactment of CD40L-subordinate endothelial cells.

Regularly platelets don't interface legitimately with the unblemished vascular intima. Typical endometrium hinders platelet initiation by COX-2, PGI₂ or prostaglandins. When endothelial capacity is impeded, endothelial cells become inflammatory and platelets stick to the intima of veins.

Interaction between platelets and leukocytes

P-selectin on enacted PLTs starts their communications with white blood cells. According to the study of (Huo et al., 2003) amid the subtypes of white blood cells communicating with initiated PLTs, monocytes carry superiority over others in official enacted PLTs. The characteristic by which monocytes specially tie PLTs, a potential reason for the function of initiated PLTs in the improvement of atherosclerosis, is obscure. Commitment of PLTs with white blood cells brings about enactment of the white blood cells integrins Mac-1 and VLA-4. Thus, connections between initiated PLTs and white blood cells will be balanced out due to authoritative of WBCs integrins to PLTs intracellular grip atom 2 (ICAM-2) or glue plasma proteins adhered to enacted GPIIb/IIIa complex.

As of late, in accordance with the study of (McMurray and Stewart, 2000) it was indicated that GPIb is moreover a ligand for white blood cells Mac-1. The life expectancies and predeterminations of PLTs-WBCs totals are most certainly not very much characterized. In an investigation utilizing primates, according to the observation life range of PLT- monocyte totals was not identified with PLT P-selectin exuviation (Shaker et al., 2019). In the in vivo examination by (Huo et al., 2003), in a time period of 2-3 hours followed by an infusion of actuated PLTs, flowing PLTs-WBCs totals were not, at this point perceptible and "typical" WBCs subtype populaces were recouped. This time span is predictable with the time that circling enacted PLTs require for exuviation of their P-selectin, proposing that most PLT-WBC totals result in withdrawal (Gorbet and Sefton, 2004).

Notwithstanding, the likelihood that totals confiscates into outer membrane tissues or leukocyte phagocytosis PLTs adhere with their exterior membranes can't be avoided and requires to be researched. Change in macrophage work coming about because of PLT phagocytosis may fundamentally manage safe and inflammatory responses (Chirinos et al., 2005). PLTs authoritative to leukocytes direct monocyte



capacities. Initiated PLTs can up regulate proclivity and/ or on the other hand ardentness of WBCs integrins by means of P-selectin glycoprotein ligand-1 (PSGL-1) flagging or conveyance of PLT-inferred pro-inflammatory elements. Oxidization burst happens on WBCs because of PLT official. These fast PLT-intervened guidelines may assume a part in atherosclerosis by advancing monocyte enlistment. Actuated PLTs are moreover ready to cause an assortment of moderate responses. Resting monocytes don't communicate tissue factor, a protein associated with the inception of blood congealment and the development of atherosclerotic injuries. Nonetheless, actuation of CD142 record happens on collaboration with PLT P-selectin.

Thusly, CD142 mRNA, protein, and action are instigated more than a few hours (Schmitt et al., 2000), despite the fact that this was not affirmed in a later report (Huo and Ley, 2004). Various cytokines are instigated when WBCs tie PLT P-selectin through PSGL-1 and are prepared by a few distinctive synergistic activators. Introduction of monocytes to PLT P-selectin and PLT enacting factor prepares the record factor atomic factor- α and instigates articulation of tumor rot factor α (TNF α) and WBCs involving protein 1 (MCP-1). Monocytes presented to P-selectin and the PLT-inferred chemokine RANTES discharge an alternate arrangement of cytokines, involving lymphokine 8 (IL-8) and MCP-1. These responses fundamentally add to the inflammatory and proclamation reaction in vascular thrombotic malady (Dziedzic and Bijak, 2019). It isn't evident that rather these responses can be started in between of temporary cooperations among monocytes and PLTs. Hence, the significance of such responses in the advancement of atherosclerosis is obscure.

Platelets, leukocytes, and blood vessel walls can all play a role.

Veins are additionally made out of various cells, for example, involuntary muscle and endothelial cells. The last are situated in the lumen of arteriole, have straight contact with cells circling in blood, and standardize pulse just as WBC running (Goveia et al., 2014). In a few infections (counting CVD), the physiological capacity of veins is interfered with as a result of inflammatory responses, oxidative pressure, and anomalous appearance of certain particles on the outside of ECs (Siti et al., 2015). Also, ongoing sign recommends that the utilization of medications in treatment of CVD can regulate inflammatory

reactions and diminish the creation of receptive aerobic species (Mo et al., 2018). Platelets are a nucleated cell pieces of megakaryocytes that hinder unnecessary blood misfortune upon arteriole injury by a cycle named hemostasis. Under physiologic conditions, the idle endothelium routinely delivers NO and PGI₂ into the flow to have PLTs in a relaxing state (Jackson, 2011). In case of endothelial harm, proteins of the sub endothelial lattice are all the way open into the lumen, bringing about authoritative and initiation of platelets, which then representative more platelets, total and seal the injury. Vein inflammation is brought about by connections between PLTs, WBCs and endothelial cells that outcome in autocrine and paracrine actuation. This actuation is trailed by leukocyte enrollment into the vascular divider and initiates an inflammatory response through the arrival of proinflammatory mixes (Gawaz et al., 2005).

ECs build up a layer among blood and extracellular cells and are dependable for keeping up the formation and directing the capacity of veins (Gevaert et al., 2017). Likewise, according to (Vorobiev et al., 2004) endothelial cells produce a progression of dilators, (for example, bradykinin and nitric oxide) and constrictors (like endothelin), repressing PLTs total and framing blood clump notwithstanding controlling the vascular tone. Nevertheless, platelets excessively become initiated during inflammatory states, prompting platelet connections with endothelial cells and leukocytes. Furthermore, proof creates the impression that platelets subsequently additionally satisfy significant parts in invulnerability and tweak physiologic and pathologic reactions all through inflammation and disease. Upon enactment, as stated by (Schrottmaier et al., 2015) platelets rapidly collaborate with inborn resistant cells and apply immunomodulatory impacts straightforwardly through cell-cell contact or in a roundabout way through the arrival of chemokines and cytokines. Platelet-leukocyte collaborations bring about leukocyte enlistment, actuation, extravasation, phenotype switch and changes in effector capacities (Kral et al., 2016). Plaque break brings about the introduction of firmly proclamation sub-endothelial framework, involving TF, and the ensuing enrollment and initiation of PLTs and WBCs prompts perilous blood vessel thrombosis. According to studies of (Jackson, 2011, Mackman, 2008, Badimon and Vilahur, 2014) over the most recent couple of years, the effect of invulnerable cells has progressed into center as for their association in apoplexy, and



various investigations have demonstrated that certain types of white blood cells add to the pathogenesis of atherosclerosis and apoplexy.

At first, platelets can frame totals with leukocytes, and invigorate the accumulation of leukocytes into the intima by actuating leukocyte attachment receptors or going about as scaffold cells. For example, platelet-monocyte totals can act through platelet-internal attachment to the vein divider. Likewise, platelets can chemo at white platelets and require a clingy surface to advance the accumulation of white platelets to the vein divider after bond to the intima. During this cycle, platelets, leukocytes, and vascular endothelial cells are actuated through an autocrine, paracrine, or bond receptor course. A few clinical perceptions recommend that, other than these traditional players, eosinophil may likewise assume a function in atherosclerosis and blood vessel apoplexy. A few lines of proof connection eosinophil to cardiovascular occasions, yet it isn't known which explicit part of the pathophysiology they put up and either they interface with PLTs as basic components of these cycles. In atherosclerosis, raised blood levels of the eosinophil cytotoxic effector protein ECP connect with the seriousness of blood vessel stenosis and estimate atherosclerotic weight (Xia et al., 2016, Niccoli et al., 2010). At the point when platelets are followed or enacted, P-selectin quickly moves from alpha particles to the plasma film, collaborates with PSGL-1 on the outside of leukocyte layers, and afterward monocytes or polymorphonuclear leukocytes hold fast carefully to the surface by means of Mac-1 (Schmidt et al., 2006)

The communication of PLTs with white blood cells is of most elevated essentialness in the guideline of both inflammatory and hemostatic cycles. After actuation, PLTs express P-selectin on their cell surface, that can associate with the selectin receptor PSGL-1 communicated on WBCs. In an inflammatory setting, platelets impact leukocyte departure by catching leukocytes at exact extravasation locales, hence encouraging tissue invasion in a PSGL-1/P-selectin-subordinate way, fairly clearing the way to extravasation (Zuchtriegel et al., 2016). For sure, neutrophils effectively look for actuated platelets to take part in a PSGL-1-intervened flagging occasion (Sreeramkumar et al., 2014). The association of PSGL-1 and P-selectin can likewise start the interpretation of some administrative proteins, for example, urokinase-type receptors (uPAR), a key cell surface protease receptor that manages

integrin-interceded leukocyte bond in vivo (Rauscher et al., 2003, Vasa et al., 2001, Heeschen et al., 2004, Hu et al., 2004, Daub et al., 2006).

Interaction between platelets and endothelial progenitor cell

PLTs are perceived to impact EPC enlistment and to advance their separation. It is settled that follower PLTs select flowing ancestor cells ex vivo and in vivo and incite depiction of EPCs into epithelial tissue epithelium (Langer and Gawaz, 2008). Circulating epithelial tissue forebear cell (EPCs) add to recovery and fix of the artery divider. Under physiological or obsessive conditions, numerous variables can influence the count and capacity of endothelial forebear cells in the course, for example, work out, statin use, age, smoking, diabetes, ceaseless cardiovascular deficiency, and intense coronary disorder (Schuh et al., 2008, Zhang, 2008). Besides, epithelial cells are thought to have a key part in the upkeep of artery unwavering quality and to go about as "fix" cells in light of epithelium tissue injury (Langer et al., 2007b, Langer et al., 2006, Wang et al., 2014, Hamilos et al., 2018). Enrollment of EPCs with respect to vascular sores has been seen as a basic introductory advance in atherosclerosis and a consequence of the activities of different CV danger factors. Late figures propose that a lessening in coursing epithelial cells leads not exclusively to diminished angiogenesis, yet additionally to the advancement of atherosclerosis (Xu, 2006). Furthermore, patients in danger for coronary supply route malady have a diminished number of circling EPCs with debilitated movement (Schmidt-Lucke et al., 2005, Heiss et al., 2005). Consequently, there is expanding sign that bone marrow-determined forebear cells have a genuine influence in vascular fix instruments at the site of vascular injuries.

In ordinary conditions, no attachment atoms or chromogenic factors are communicated on the outside of epithelial cells; nonetheless, when veins are harmed, vascular epithelium tissue development factor and stromal-inferred factor 1 (SDF-1) are emitted via them, that bring about preparation of epithelial tissue begetter cells. Epithelial cells are bone marrow (BM)-inferred cells engaged with the development of veins, and their expansion and separation can prompt ontogenesis and development of arterial framework (Del Papa and Pignataro, 2018). Actuated PLTs and endothelial cells select these invulnerable cells, which, in case of plaque burst, advance blood clot



arrangement and adjustment by TF conveyance and arrangement of WBCs extra-cell traps (NETs). At present, endothelial begetter cells are an examination problem area in atherosclerosis. Despite the fact that the function of foundational microorganisms in atherosclerosis isn't clear, existing investigations for the most part accept that bone marrow-determined CD34 or CD133-positive ancestor cells can separate into endothelial cells and fix harmed veins, assume a significant function in solidifying (Massberg et al., 2003, Stellos et al., 2008, Stellos et al., 2010). Numerous elements can assemble the arrival of endothelial ancestor cells in the bone marrow, for example, SDF-1, arterial endothelial development factor, erythropoietin, angiogenesis factor, granulocyte settlement development factor (CSF), and estrogen. Late examinations show that PLTs invigorate the chemo taxis and movement of EPC through the P-selectin glycoprotein ligand-1 (PSGL-1) and b1-cytoplasmic membrane (Langer et al., 2006, Lev et al., 2006). It gives the idea that the enlistment of CD34+ forebear cells is intervened by PSGL-1 just as by b1-and b2- cytoplasmic membranes. Homing isn't the main begetter cell measure that can be influenced by PLTs as the last can likewise animate the separation of CD34+ forebear cells into develop froth cells and epithelial tissue cells (Daub et al., 2006).

From one viewpoint, platelets can make endothelial forebear cells separate into endothelial phenotypes and express some trademark receptors. Then again, co-culture of CD34 + forebear cells with PLTs for 5-10 days can prompt CD34 + cell macrophages and froth cell-like changes (Weyrich et al., 1996, Mahoney et al., 2001). The morphology of over 30% of cells expanded around multiple times (around 25 µm in measurement), the cells got round, and the granularity expanded. This separation cycle is identified with platelet phagocytosis inside the initial 24 hours, and LDL bound to the platelet surface may likewise assume a significant function in this cycle (May et al., 2000, May et al., 1998). Yet, these are in vitro perceptions. It is as yet hazy under what conditions platelets start the change of CD34 + endothelial forebear cells to endothelial cells, macrophages or froth cells, or how platelets control CD34 + endothelial ancestor cells to take an interest in vascular fix and injury.

III. CONCLUSION

Three decades after (Ross and Glomset, 1976) presented the contribution of PLTs in

atherosclerosis, direct proof presently bolsters the conclusion that enacted PLTs really assume a significant function in the improvement of atherosclerosis. Components with respect to the investment of platelets in atherosclerosis, albeit halfway recommended in essential examinations, have not been completely analyzed at this point. Examination of these systems may prompt new ways to deal with control the turn of events and movement of atherosclerosis. With the proceeded revelation of energizing new relationship among PLTs and inflammatory illness, PLTs will keep on getting better comprehended and acknowledged as an invulnerable cell. PLTs numbers, the assorted variety of PLT-inferred inflammatory arbitrator, and the potential for various cooperation among PLT and different cells, both legitimately and in a roundabout way, increment the effect of PLTs on inflammatory conditions, notwithstanding their little nucleate status. To better comprehend the invulnerable administrative elements of PLTs, their advanced role and function further research is required.

IV. ACKNOWLEDGMENT

Funding

This project was supported by the Health Committee fund of Jiangsu Province (H2018004), the National Natural Science Foundation of China(No.81400269) and the provincial key medical talents training fund (No: QNRC2016837).

Disclosure of Potential Conflict of Interest:

Declared by the authors of the study, no conflict took place during the study. The study was carried out in a pleasant manner by taking in consideration the views of all involved authors.

Informed Consent

No human studies were carried out by the authors for this article.

No animal studies were carried out by the authors for this article.

REFERENCES

- [1]. ALTIERI, D. C., BADER, R., MANNUCCI, P. M. & EDGINGTON, T. S. 1988. Oligospecificity of the cellular adhesion receptor Mac-1 encompasses an inducible recognition specificity for fibrinogen. *J Cell Biol*, 107, 1893-900.
- [2]. AUKRUST, P., HALVORSEN, B., UELAND, T., MICHELSEN, A. E., SKJELLAND, M., GULLESTAD, L., YNDESTAD, A. & OTTERDAL, K. 2010. Activated platelets and atherosclerosis.



- Expert review of cardiovascular therapy, 8, 1297-1307.
- [3]. 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.
- [4]. BADIMON, L. & VILAHUR, G. J. J. O. I. M. 2014. Thrombosis formation on atherosclerotic lesions and plaque rupture. 276, 618-632.
- [5]. BOMBELI, T., SCHWARTZ, B. R. & HARLAN, J. M. J. T. J. O. E. M. 1998. Adhesion of activated platelets to endothelial cells: evidence for a GPIIb/IIIa-dependent bridging mechanism and novel roles for endothelial intercellular adhesion molecule 1 (ICAM-1), $\alpha v\beta 3$ integrin, and GPIIb. 187, 329-339.
- [6]. CAYATTE, A. J., DU, Y., OLIVER-KRASINSKI, J., LAVIELLE, G., VERBEUREN, T. J. & COHEN, R. A. 2000. The thromboxane receptor antagonist S18886 but not aspirin inhibits atherogenesis in apo E-deficient mice: evidence that eicosanoids other than thromboxane contribute to atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology*, 20, 1724-1728.
- [7]. CHAVAKIS, T., SANTOSO, S., CLEMETSON, K. J., SACHS, U. J., ISORDIA-SALAS, I., PIXLEY, R. A., NAWROTH, P. P., COLMAN, R. W. & PREISSNER, K. T. 2003. High molecular weight kininogen regulates platelet-leukocyte interactions by bridging Mac-1 and glycoprotein Ib. *J Biol Chem*, 278, 45375-81.
- [8]. CHEN, J. & LÓPEZ, J. A. 2005. Interactions of platelets with subendothelium and endothelium. *Microcirculation*, 12, 235-46.
- [9]. CHIRINOS, J. A., HERESI, G. A., VELASQUEZ, H., JY, W., JIMENEZ, J. J., AHN, E., HORSTMAN, L. L., SORIANO, A. O., ZAMBRANO, J. P. & AHN, Y. S. 2005. Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. *Journal of the American College of Cardiology*, 45, 1467-1471.
- [10]. CYRUS, T., YAO, Y., DING, T., DOGNÉ, J. M. & PRATICÒ, D. 2007. A novel thromboxane receptor antagonist and synthase inhibitor, BM-573, reduces development and progression of atherosclerosis in LDL receptor deficient mice. *European journal of pharmacology*, 561, 105-111.
- [11]. DAUB, K., LANGER, H., SEIZER, P., STELLOS, K., MAY, A. E., GOYAL, P., BIGALKE, B., SCHÖNBERGER, T., GEISLER, T., SIEGEL-AXEL, D., OOSTENDORP, R. A., LINDEMANN, S. & GAWAZ, M. 2006. Platelets induce differentiation of human CD34+ progenitor cells into foam cells and endothelial cells. *Faseb j*, 20, 2559-61.
- [12]. DEL PAPA, N. & PIGNATARO, F. J. F. I. I. 2018. The role of endothelial progenitors in the repair of vascular damage in systemic sclerosis. 9, 1383.
- [13]. DIACOVO, T. G., DEFOUGEROLLES, A. R., BAINTON, D. F. & SPRINGER, T. A. 1994. A functional integrin ligand on the surface of platelets: intercellular adhesion molecule-2. *J Clin Invest*, 94, 1243-51.
- [14]. DZIEDZIC, A. & BIJAK, M. 2019. Interactions between platelets and leukocytes in pathogenesis of multiple sclerosis. *Adv. Clin. Exp. Med*, 28, 277-285.
- [15]. ETULAIN, J., NEGROTTO, S. & SCHATTNER, M. J. C. A. 2014. Role of platelets in angiogenesis in health and disease. 3, 48-57.
- [16]. ETULAIN, J. & SCHATTNER, M. J. G. 2014. Glycobiology of platelet-endothelial cell interactions. 24, 1252-1259.
- [17]. FITZGERALD, D. J., ROY, L., CATELLA, F. & FITZGERALD, G. A. 1986. Platelet activation in unstable coronary disease. *New England Journal of Medicine*, 315, 983-989.
- [18]. FURMAN, M. I., BENOIT, S. E., BARNARD, M. R., VALERI, C. R., BORBONE, M. L., BECKER, R. C., HECHTMAN, H. B. & MICHELSON, A. D. 1998. Increased platelet reactivity and circulating monocyte-platelet aggregates in patients with stable coronary artery disease. *Journal of the American College of Cardiology*, 31, 352-358.
- [19]. GAWAZ, M., LANGER, H. & MAY, A. E. 2005. Platelets in inflammation and atherogenesis. *J Clin Invest*, 115, 3378-84.
- [20]. GAWAZ, M., NEUMANN, F. J., DICKFELD, T., REININGER, A., ADELSBERGER, H., GEBHARDT, A. & SCHÖMIG, A. 1997. Vitronectin receptor



- (alpha(v)beta3) mediates platelet adhesion to the luminal aspect of endothelial cells: implications for reperfusion in acute myocardial infarction. *Circulation*, 96, 1809-18.
- [21]. GEVAERT, A. B., LEMMENS, K., VRINTS, C. J., VAN CRAENENBROECK, E. M. J. O. M. & LONGEVITY, C. 2017. Targeting endothelial function to treat heart failure with preserved ejection fraction: the promise of exercise training. 2017.
- [22]. GOLEBIEWSKA, E. M. & POOLE, A. W. 2015. Platelet secretion: From haemostasis to wound healing and beyond. *Blood Rev*, 29, 153-62.
- [23]. GORBET, M. B. & SEFTON, M. V. 2004. Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes. *Biomaterials*, 25, 5681-5703.
- [24]. GOVEIA, J., STAPOR, P. & CARMELIET, P. J. E. M. M. 2014. Principles of targeting endothelial cell metabolism to treat angiogenesis and endothelial cell dysfunction in disease. 6, 1105-1120.
- [25]. GROS, A., OLLIVIER, V. & HO-TIN-NOÉ, B. 2014. Platelets in inflammation: regulation of leukocyte activities and vascular repair. *Front Immunol*, 5, 678.
- [26]. HAMILOS, M., PETOUSIS, S., PARTHENAKIS, F. J. C. D. & THERAPY 2018. Interaction between platelets and endothelium: from pathophysiology to new therapeutic options. 8, 568.
- [27]. HAN, L., DAI, L., ZHAO, Y.-F., LI, H.-Y., LIU, O., LAN, F., JIANG, W.-J. & ZHANG, H.-J. J. A. 2018. CD40L promotes development of acute aortic dissection via induction of inflammation and impairment of endothelial cell function. 10, 371.
- [28]. HEESCHEN, C., LEHMANN, R., HONOLD, J., ASSMUS, B., AICHER, A., WALTER, D. H., MARTIN, H., ZEIHNER, A. M. & DIMMELER, S. 2004. Profoundly reduced neovascularization capacity of bone marrow mononuclear cells derived from patients with chronic ischemic heart disease. *Circulation*, 109, 1615-22.
- [29]. HEISS, C., KEYMEL, S., NIESLER, U., ZIEMANN, J., KELM, M. & KALKA, C. 2005. Impaired progenitor cell activity in age-related endothelial dysfunction. *J Am Coll Cardiol*, 45, 1441-8.
- [30]. HU, Y., ZHANG, Z., TORSNEY, E., AFZAL, A. R., DAVISON, F., METZLER, B. & XU, Q. 2004. Abundant progenitor cells in the adventitia contribute to atherosclerosis of vein grafts in ApoE-deficient mice. *J Clin Invest*, 113, 1258-65.
- [31]. HUO, Y. & LEY, K. F. 2004. Role of platelets in the development of atherosclerosis. *Trends in cardiovascular medicine*, 14, 18-22.
- [32]. HUO, Y., SCHOBER, A., FORLOW, S. B., SMITH, D. F., HYMAN, M. C., JUNG, S., LITTMAN, D. R., WEBER, C. & LEY, K. 2003. Circulating activated platelets exacerbate atherosclerosis in mice deficient in apolipoprotein E. *Nature medicine*, 9, 61-67.
- [33]. JACKSON, S. P. J. N. M. 2011. Arterial thrombosis—insidious, unpredictable and deadly. 17, 1423-1436.
- [34]. KASTRATI, A., MEHILLI, J., NEUMANN, F. J., DOTZER, F., TEN BERG, J., BOLLWEIN, H., GRAF, I., IBRAHIM, M., PACHE, J., SEYFARTH, M., SCHÜHLEN, H., DIRSCHINGER, J., BERGER, P. B. & SCHÖMIG, A. 2006. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *Jama*, 295, 1531-8.
- [35]. KIM, C. H., KIM, S. J., LEE, M. J., KWON, Y. E., KIM, Y. L., PARK, K. S., RYU, H. J., PARK, J. T., HAN, S. H., YOO, T. H., KANG, S. W. & OH, H. J. 2015. An increase in mean platelet volume from baseline is associated with mortality in patients with severe sepsis or septic shock. *PLoS One*, 10, e0119437.
- [36]. KRAL, J. B., SCHROTTMAIER, W. C., SALZMANN, M., ASSINGER, A. J. T. M. & HEMOTHERAPY 2016. Platelet interaction with innate immune cells. 43, 78-88.
- [37]. LANGER, H., MAY, A. E., DAUB, K., HEINZMANN, U., LANG, P., SCHUMM, M., VESTWEBER, D., MASSBERG, S., SCHÖNBERGER, T. & PFISTERER, I. J. C. R. 2006. Adherent platelets recruit and induce differentiation of murine embryonic endothelial progenitor cells to mature endothelial cells in vitro. 98, e2-e10.
- [38]. LANGER, H. F., DAUB, K., BRAUN, G., SCHÖNBERGER, T., MAY, A. E., SCHALLER, M., STEIN, G. M., STELLOS,



- K., BUELTMANN, A., SIEGEL-AXEL, D., WENDEL, H. P., AEBERT, H., ROECKEN, M., SEIZER, P., SANTOSO, S., WESSELBORG, S., BROSSART, P. & GAWAZ, M. 2007a. Platelets recruit human dendritic cells via Mac-1/JAM-C interaction and modulate dendritic cell function in vitro. *Arterioscler Thromb Vasc Biol*, 27, 1463-70.
- [39]. LANGER, H. F. & GAWAZ, M. 2008. Platelets in regenerative medicine. *Basic Res Cardiol*, 103, 299-307.
- [40]. LANGER, H. F., MAY, A. E., VESTWEBER, D., DE BOER, H. C., HATZOPOULOS, A. K. & GAWAZ, M. 2007b. Platelet-induced differentiation of endothelial progenitor cells. *Semin Thromb Hemost*, 33, 136-43.
- [41]. LEV, E. I., ESTROV, Z., ABOUFATOVA, K., HARRIS, D., GRANADA, J. F., ALVIAR, C., KLEIMAN, N. S. & DONG, J. F. 2006. Potential role of activated platelets in homing of human endothelial progenitor cells to subendothelial matrix. *Thromb Haemost*, 96, 498-504.
- [42]. LINDEMANN, S., TOLLEY, N. D., DIXON, D. A., MCINTYRE, T. M., PRESCOTT, S. M., ZIMMERMAN, G. A. & WEYRICH, A. S. J. T. J. O. C. B. 2001. Activated platelets mediate inflammatory signaling by regulated interleukin 1 β synthesis. 154, 485-490.
- [43]. MACKMAN, N. J. N. 2008. Triggers, targets and treatments for thrombosis. 451, 914-918.
- [44]. MAHONEY, T. S., WEYRICH, A. S., DIXON, D. A., MCINTYRE, T., PRESCOTT, S. M. & ZIMMERMAN, G. A. 2001. Cell adhesion regulates gene expression at translational checkpoints in human myeloid leukocytes. *Proc Natl Acad Sci U S A*, 98, 10284-9.
- [45]. MASSBERG, S., GAWAZ, M., GRÜNER, S., SCHULTE, V., KONRAD, I., ZOHLNHÖFER, D., HEINZMANN, U. & NIESWANDT, B. 2003. A crucial role of glycoprotein VI for platelet recruitment to the injured arterial wall in vivo. *J Exp Med*, 197, 41-9.
- [46]. MASSBERG, S., KONRAD, I., SCHÜRZINGER, K., LORENZ, M., SCHNEIDER, S., ZOHLNHÖFER, D., HOPPE, K., SCHIEMANN, M., KENNERKNECHT, E. & SAUER, S. J. T. J. O. E. M. 2006. Platelets secrete stromal cell-derived factor 1 α and recruit bone marrow-derived progenitor cells to arterial thrombi in vivo. 203, 1221-1233.
- [47]. MAY, A. E., KANSE, S. M., LUND, L. R., GISLER, R. H., IMHOF, B. A. & PREISSNER, K. T. 1998. Urokinase receptor (CD87) regulates leukocyte recruitment via beta 2 integrins in vivo. *J Exp Med*, 188, 1029-37.
- [48]. MAY, A. E., NEUMANN, F.-J., PREISSNER, K. T. J. T. & HAEMOSTASIS 1999. The relevance of blood cell-vessel wall adhesive interactions for vascular thrombotic disease. 82, 962-970.
- [49]. MAY, A. E., NEUMANN, F.-J., SCHÖMIG, A. & PREISSNER, K. T. J. B., THE JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY 2000. VLA-4 ($\alpha 4\beta 1$) engagement defines a novel activation pathway for $\beta 2$ integrin-dependent leukocyte adhesion involving the urokinase receptor. 96, 506-513.
- [50]. MCMURRAY, J. J. & STEWART, S. 2000. Epidemiology, aetiology, and prognosis of heart failure. *Heart*, 83, 596-602.
- [51]. MITSUI, C., KAJIWARA, K., HAYASHI, H., ITO, J., MITA, H., ONO, E., HIGASHI, N., FUKUTOMI, Y., SEKIYA, K., TSUBURAI, T., AKIYAMA, K., YAMAMOTO, K. & TANIGUCHI, M. 2016. Platelet activation markers overexpressed specifically in patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol*, 137, 400-11.
- [52]. MO, J., YANG, R., LI, F., ZHANG, X., HE, B., ZHANG, Y., CHEN, P. & SHEN, Z. J. P. 2018. Scutellarin protects against vascular endothelial dysfunction and prevents atherosclerosis via antioxidation. 42, 66-74.
- [53]. MORRELL, C. N., AGGREY, A. A., CHAPMAN, L. M. & MODJESKI, K. L. 2014. Emerging roles for platelets as immune and inflammatory cells. *Blood*, The Journal of the American Society of Hematology, 123, 2759-2767.
- [54]. NATHAN, C. & DING, A. 2010. "Nonresolving inflammation." *Cell* 140: 871-882.
- [55]. NEUMANN, F. J., MARX, N., GAWAZ, M., BRAND, K., OTT, I., ROKITTA, C., STICHERLING, C., MEINL, C., MAY, A. & SCHÖMIG, A. 1997. Induction of



- cytokine expression in leukocytes by binding of thrombin-stimulated platelets. *Circulation*, 95, 2387-94.
- [56]. NICCOLI, G., FERRANTE, G., COSENTINO, N., CONTE, M., BELLONI, F., MARINO, M., BACÀ, M., MONTONE, R. A., SABATO, V. & SCHIAVINO, D. J. A. 2010. Eosinophil cationic protein: A new biomarker of coronary atherosclerosis. 211, 606-611.
- [57]. NIJM, J., WIKBY, A., TOMPA, A., OLSSON, A. G. & JONASSON, L. J. T. A. J. O. C. 2005. Circulating levels of proinflammatory cytokines and neutrophil-platelet aggregates in patients with coronary artery disease. 95, 452-456.
- [58]. PALINSKI, W. & NAPOLI, C. 2002. The fetal origins of atherosclerosis: maternal hypercholesterolemia, and cholesterol-lowering or antioxidant treatment during pregnancy influence in utero programming and postnatal susceptibility to atherogenesis. *The FASEB Journal*, 16, 1348-1360.
- [59]. PFLUECKE, C., BERNDT, K., WYDRA, S., TARNOWSKI, D., BARTHEL, P., QUICK, S., ULBRICH, S., CHRISTOPH, M., WAESSNIG, N., SPEISER, U. J. T. & HAEMOSTASIS 2016. Atrial fibrillation is associated with high levels of monocyte-platelet-aggregates and increased CD11b expression in patients with aortic stenosis. 116, 993-1000.
- [60]. PHIPPS, R. P. J. P. O. T. N. A. O. S. 2000. Atherosclerosis: the emerging role of inflammation and the CD40-CD40 ligand system. 97, 6930-6932.
- [61]. PITSILOS, S., HUNT, J., MOHLER, E. R., PRABHAKAR, A. M., PONCZ, M., DAWICKI, J., KHALAPYAN, T. Z., WOLFE, M. L., FAIRMAN, R., MITCHELL, M., CARPENTER, J., GOLDEN, M. A., CINES, D. B. & SACHAIS, B. S. 2003. Platelet factor 4 localization in carotid atherosclerotic plaques: correlation with clinical parameters. *Thromb Haemost*, 90, 1112-20.
- [62]. POPA, M., TAHIR, S., ELROD, J., KIM, S. H., LEUSCHNER, F., KESSLER, T., BUGERT, P., POHL, U., WAGNER, A. H. & HECKER, M. J. P. O. T. N. A. O. S. 2018. Role of CD40 and ADAMTS13 in von Willebrand factor-mediated endothelial cell-platelet-monocyte interaction. 115, E5556-E5565.
- [63]. PRATICÒ, D., TILLMANN, C., ZHANG, Z.-B., LI, H. & FITZGERALD, G. A. 2001. Acceleration of atherogenesis by COX-1-dependent prostanoid formation in low density lipoprotein receptor knockout mice. *Proceedings of the National Academy of Sciences*, 98, 3358-3363.
- [64]. RAUSCHER, F. M., GOLDSCHMIDT-CLERMONT, P. J., DAVIS, B. H., WANG, T., GREGG, D., RAMASWAMI, P., PIPPEN, A. M., ANNEX, B. H., DONG, C. & TAYLOR, D. A. 2003. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation*, 108, 457-63.
- [65]. RONDINA, M. T., WEYRICH, A. S. & ZIMMERMAN, G. A. J. C. R. 2013. Platelets as cellular effectors of inflammation in vascular diseases. 112, 1506-1519.
- [66]. ROSS, R. & GLOMSET, J. A. 1976. The pathogenesis of atherosclerosis. *New England journal of medicine*, 295, 369-377.
- [67]. RUGGERI, Z. M. 2002. Platelets in atherothrombosis. *Nature medicine*, 8, 1227-1234.
- [68]. SANTOSO, S., SACHS, U. J., KROLL, H., LINDER, M., RUF, A., PREISSNER, K. T. & CHAVAKIS, T. 2002. The junctional adhesion molecule 3 (JAM-3) on human platelets is a counterreceptor for the leukocyte integrin Mac-1. *J Exp Med*, 196, 679-91.
- [69]. SARRATT, K. L., CHEN, H., ZUTTER, M. M., SANTORO, S. A., HAMMER, D. A. & KAHN, M. L. 2005. GPVI and alpha2beta1 play independent critical roles during platelet adhesion and aggregate formation to collagen under flow. *Blood*, 106, 1268-77.
- [70]. SCHMIDT-LUCKE, C., RÖSSIG, L., FICHTLSCHERER, S., VASA, M., BRITTEN, M., KÄMPER, U., DIMMELER, S. & ZEIHNER, A. M. 2005. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation*, 111, 2981-7.
- [71]. SCHMIDT, R., REDECKE, V., BREITFELD, Y., WANTIA, N., MIETHKE, T., MASSBERG, S., FISCHEL, S., NEUMANN, F.-J., SCHÖMIG, A., MAY, A. E. J. T. & HAEMOSTASIS 2006.



- EMMPRIN (CD 147) is a central activator of extracellular matrix degradation by Chlamydia pneumoniae-infected monocytes. 95, 151-158.
- [72]. SCHMITT, A., JOUAULT, H., GUICHARD, J., WENDLING, F., DROUIN, A. & CRAMER, E. M. 2000. Pathologic interaction between megakaryocytes and polymorphonuclear leukocytes in myelofibrosis. *Blood, The Journal of the American Society of Hematology*, 96, 1342-1347.
- [73]. SCHROTTMAIER, W. C., KRAL, J. B., BADRNYA, S. & ASSINGER, A. 2015. Aspirin and P2Y₁₂ Inhibitors in platelet-mediated activation of neutrophils and monocytes. *Thromb Haemost*, 114, 478-89.
- [74]. SCHUH, A., LIEHN, E. A., SASSE, A., HRISTOV, M., SOBOTA, R., KELM, M., MERX, M. W. & WEBER, C. 2008. Transplantation of endothelial progenitor cells improves neovascularization and left ventricular function after myocardial infarction in a rat model. *Basic Res Cardiol*, 103, 69-77.
- [75]. SHAKER, H., KHAN, M., MULDERINK, T., KOEHLER, T. J., SCUREK, R., TUBERGEN, T., PACKARD, L., SINGER, J., MAZARIS, P. & MIN, J. 2019. The role of CT perfusion in defining the clinically relevant core infarction to guide thrombectomy selection in patients with acute stroke. *Journal of Neuroimaging*, 29, 331-334.
- [76]. SITI, H. N., KAMISAH, Y. & KAMISIAH, J. J. V. P. 2015. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). 71, 40-56.
- [77]. SPRINGER, T. A. 1994. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell*, 76, 301-14.
- [78]. SREERAMKUMAR, V., ADROVER, J. M., BALLESTEROS, I., CUARTERO, M. I., ROSSAINT, J., BILBAO, I., NÁCHER, M., PITAVAL, C., RADOVANOVIC, I. & FUKUI, Y. J. S. 2014. Neutrophils scan for activated platelets to initiate inflammation. 346, 1234-1238.
- [79]. SRIVASTAVA, K., COCKBURN, I. A., SWAIM, A., THOMPSON, L. E., TRIPATHI, A., FLETCHER, C. A., SHIRK, E. M., SUN, H., KOWALSKA, M. A. & FOX-TALBOT, K. 2008. Platelet factor 4 mediates inflammation in experimental cerebral malaria. *Cell host & microbe*, 4, 179-187.
- [80]. STELLOS, K., LANGER, H., DAUB, K., SCHOENBERGER, T., GAUSS, A., GEISLER, T., BIGALKE, B., MUELLER, I., SCHUMM, M., SCHAEFER, I., SEIZER, P., KRAEMER, B. F., SIEGEL-AXEL, D., MAY, A. E., LINDEMANN, S. & GAWAZ, M. 2008. Platelet-derived stromal cell-derived factor-1 regulates adhesion and promotes differentiation of human CD34+ cells to endothelial progenitor cells. *Circulation*, 117, 206-15.
- [81]. STELLOS, K., SEIZER, P., BIGALKE, B., DAUB, K., GEISLER, T. & GAWAZ, M. 2010. Platelet aggregates-induced human CD34+ progenitor cell proliferation and differentiation to macrophages and foam cells is mediated by stromal cell derived factor 1 in vitro. *Semin Thromb Hemost*, 36, 139-45.
- [82]. THOMAS, M. R. & STOREY, R. F. 2015. The role of platelets in inflammation. *Thromb Haemost*, 114, 449-58.
- [83]. TOPOL, E. J., MOLITERNO, D. J., HERRMANN, H. C., POWERS, E. R., GRINES, C. L., COHEN, D. J., COHEN, E. A., BERTRAND, M., NEUMANN, F. J., STONE, G. W., DIBATTISTE, P. M. & DEMOPOULOS, L. 2001. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med*, 344, 1888-94.
- [84]. URBICH, C., DERNBACH, E., AICHER, A., ZEIHNER, A. M. & DIMMELER, S. J. C. 2002. CD40 ligand inhibits endothelial cell migration by increasing production of endothelial reactive oxygen species. 106, 981-986.
- [85]. VASA, M., FICHTLSCHERER, S., AICHER, A., ADLER, K., URBICH, C., MARTIN, H., ZEIHNER, A. M. & DIMMELER, S. 2001. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res*, 89, E1-7.
- [86]. VOROBIEV, G., ODARYUK, T., TSARKOV, P., TALALAKIN, A. & RYBAKOV, E. J. B. J. O. S. 2004. Resection of the rectum and total excision of



- the internal anal sphincter with smooth muscle plasty and colonic pouch for treatment of ultralow rectal carcinoma. 91, 1506-1512.
- [87]. WANG, Y., LI, Z. Y., WANG, W. J. J. O. C. & THERAPY 2014. Platelet-leukocyte interaction in atherosclerosis and atherothrombosis: what we have learnt from human studies and animal models. 1, 92-97.
- [88]. WEBER, C. 2005. Platelets and chemokines in atherosclerosis: partners in crime. *Circ Res*, 96, 612-6.
- [89]. WEBER, C. & NOELS, H. 2011. Atherosclerosis: current pathogenesis and therapeutic options. *Nature medicine*, 17, 1410-1422.
- [90]. WEBER, C. & SPRINGER, T. A. 1997. Neutrophil accumulation on activated, surface-adherent platelets in flow is mediated by interaction of Mac-1 with fibrinogen bound to alphaIIb beta3 and stimulated by platelet-activating factor. *J Clin Invest*, 100, 2085-93.
- [91]. WEYRICH, A. S., ELSTAD, M. R., MCEVER, R. P., MCINTYRE, T. M., MOORE, K. L., MORRISSEY, J. H., PRESCOTT, S. M. & ZIMMERMAN, G. A. 1996. Activated platelets signal chemokine synthesis by human monocytes. *J Clin Invest*, 97, 1525-34.
- [92]. WEYRICH, A. S., PRESCOTT, S. M. & ZIMMERMAN, G. A. 2002. Platelets, endothelial cells, inflammatory chemokines, and restenosis: complex signaling in the vascular play book. *Circulation*, 106, 1433-5.
- [93]. XIA, G.-L., WANG, Y.-K. & HUANG, Z.-Q. J. B. R. I. 2016. The correlation of serum myeloid-related protein-8/14 and eosinophil cationic protein in patients with coronary artery disease. 2016.
- [94]. XU, Q. 2006. The impact of progenitor cells in atherosclerosis. *Nat Clin Pract Cardiovasc Med*, 3, 94-101.
- [95]. ZARBOCK, A., POLANOWSKA-GRABOWSKA, R. K. & LEY, K. 2007. Platelet-neutrophil-interactions: linking hemostasis and inflammation. *Blood Rev*, 21, 99-111.
- [96]. ZHANG, C. 2008. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol*, 103, 398-406.
- [97]. ZIRLIK, A., MAIER, C., GERDES, N., MACFARLANE, L., SOOSAIRAJAH, J., BAVENDIEK, U., AHRENS, I., ERNST, S., BASSLER, N., MISSIOU, A., PATKO, Z., AIKAWA, M., SCHÖNBECK, U., BODE, C., LIBBY, P. & PETER, K. 2007. CD40 ligand mediates inflammation independently of CD40 by interaction with Mac-1. *Circulation*, 115, 1571-80.
- [98]. ZUCHTRIEGEL, G., UHL, B., PUHR-WESTERHEIDE, D., PÖRNBACHER, M., LAUBER, K., KROMBACH, F. & REICHEL, C. A. J. P. B. 2016. Platelets guide leukocytes to their sites of extravasation. 14, e1002459.