Platelet Function in Cardiovascular Disease: Activation of Molecules and Activation by Molecules

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Abstract

Globally, one of the major causes of death is the cardiovascular disease (CVD), and platelets play an important role in thrombosis and atherosclerosis that led to death. Platelet activation can be done by different molecules, genes, pathways, and chemokines. Lipids activate platelets by inflammatory factors, and platelets are activated by receptors of peptide hormones, signaling and secreted proteins, microRNAs (miRNAs), and oxidative stress which also affect the platelet activation in older age. In addition, surface molecules on platelets can interact with other cells and chemokines in activated platelets and cause inflammation thrombosis events and CVD. However, these molecules activating platelets or being activated by platelets can be suggested as the markers to predict the clinical outcome of CVD and can be targeted to reduce thrombosis and atherosclerosis. However, hindering these molecules by other factors such as genes and receptors can reduce platelet activation and aggregation and targeting these molecules can control platelet interactions, thrombosis, and CVD. In addition, dual therapy with the receptor blockers and novel drugs results in better management of CVD patients. Overall, our review will emphasize on the molecules involved in the activation of platelets and on the molecules that are activated by platelets in CVD and discuss the molecules that can be blocked or targeted to reduce the thrombosis events and control CVD.

Keywords Platelet · Cardiovascular disease · Molecules · Activation

Introduction

Cardiovascular disease (CVD) is a cause of death in 17.3 million people per year, and the death rate increases day by day. Platelets are released from megakaryocytes and play an important role in hemostasis, thrombosis, and atherosclerosis [1–3]. Platelets have an important role in coronary thrombosis pathogenesis and atherogenesis. Studies have shown that platelet activity is different among different people in populations that can explain the variability of CVD [3, 4]. Platelets play an important role in the metabolism of lipids in CVD and lipids can activate platelets by inflammatory factors. Platelets have receptors for peptide hormones that can in turn activate them, resulting in thrombosis [3, 5].

Oxidative stress and reactive oxygen species (ROS) production can also activate platelets and have a role in the pathogenesis of CVD in older age. However, surface molecules interact with other cells and cause thrombosis when platelets are activated [1, 6]. Platelets secrete chemokines, which have a role in inflammation and hemostasis. These processes are induced by chemokines that are secreted from activated platelets and are stored in their granules (Table 1) (Fig. 1) [7]. Platelet activation is regulated by platelet signaling and secreted proteins, microRNAs (miRNAs), and molecular pathways in thrombosis. However, some small molecules can be targeted, inhibit chemokine heterodimerization, and control atherosclerosis progression [8–11]. In addition, some drugs used in CVD patients have shown beneficial effects in controlling thrombosis events [12]. Therefore, in this review article, we aimed to examine the molecules which activate platelets and molecules that are activated by platelets in CVD and molecules that can be targeted to better control thrombosis events and CVD.

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Table 1 Function and mechanism of platelets molecules involved in CVD

Molecule	Function	Mechanism	References
LDL	Platelet activation molecule	Increase ROS formation Platelet activation Prothrombinase complex thrombin and thrombosis formation	[4, 13, 14]
WDR1	Platelet activation molecule	Increase ADF-cofilin Actin disassembling Decrease actin cytoskeleton and thrombin activation	[21–23]
Leptin	Platelet activation molecule	Increase PDE3A Decrease cAMP	[5, 26]
Adiponectin	Platelet activation molecule	Insulin resistance Hypoadiponectinemia	[27–30]
ROS	Platelet activation molecule	8-isoPGF2α increase Platelets aggregation Drugs' non-responsiveness	[31–35]
ADP	Platelet activation molecule	Increase platelet activation Activate leucocytes, endothelial cells, and SMCs	[37–39]
Fractalkine	Platelet activation molecule	Increase platelet activation Inducing P-selectin Platelet adhesion to fibrinogen and collagen	[40, 41]
GPVI	Platelet activation molecule	Platelet aggregation Initiate signaling cascades with Src family kinases (SFKs)	[43, 44]
integrin αIIbβ3	Platelet activation molecule	Platelet aggregation Initiate signaling cascades with Src family kinases (SFKs)	[43, 44]
talin	Platelet activation molecule	Bind and regulate αIIbβ3	[43, 44]
ILK	Platelet activation molecule	Integrin activation α-granule secretion and platelet activation	[45–47]
MPs	Platelet activation molecule	Induce angiogenesis and revascularization improvement	[49–51]
SPARC	Platelet activation molecule	Angiogenesis formation Cardiac integrity Platelet reorganization	[49–51]
MiRNA-223	Platelet activation molecule	Regulate EPB41L3 gene ACS formation and vascular dysfunction	[11]
MiRNA-126	Platelet activation molecule	Regulate VCAM-1 gene ACS formation and vascular dysfunction	[11]
ACC	Molecule activation by platelet	Fatty acid metabolism in platelets	[60, 61]
AMPK	Molecule activation by platelet	Changes in platelet shape and secrete the granules	[60, 61]
MLCs	Molecule activation by platelet	Changes in platelet shape and secrete the granules	[60, 61]
Cofilin	Molecule activation by platelet	Changes in platelet shape and secrete the granules	[60, 61]
Thrombin	Molecule activation by platelet	AMPK activation in platelets and phosphorylation of MLCs and cofilin	[60, 61]
CXCL7	Molecule activation by platelet	Most expression in platelet Role in CVD	[7]
CXCL4	Molecule activation by platelet	Increased atherosclerosis Heterodimer with CCL5 Bind to monocytes Modulate signaling pathways in the cells	[62–64]
CCL5	Molecule activation by platelet	Increase the monocytes and T-lymphocytes adhesion by ICAM-1 and VCAM-1 Increase angiogenesis	[65]
CXCL1	Molecule activation by platelet	Bind to CXCR2 Induce monocyte activation to atherosclerotic lesions	[66]
CXCL12	Molecule activation by platelet	Atherosclerotic lesions formation Activate platelets via CXCR4 Secrete by macrophages and increase the atherosclerosis	[67, 68]
CCL2	Molecule activation by platelet	Trigger atherosclerotic lesions formation	[7, 69]
CCL3	Molecule activation by platelet	Express in atherosclerosis Bind to CCR1 and CCR5	[7, 69]

LDL low-density lipoproteins, *WDR1* WD repeat domain 1, *ADP* adenosine diphosphate, *PDE3A* platelet phosphodiesterase 3A, *cAMP* cyclic adenosine monophosphate, *ROS* reactive oxygen species, *8-isoPGF2α* 8 isoprostaglandin F2 alpha, *SMCs* smooth muscle cells, *ACC* acetyl-CoA carboxylase, *AMPK* AMP-activated protein kinase, *MLCs* myosin light chains, *CVD* cardiovascular disease, *ILK* integrin-linked protein kinase, *MPs* microparticles, *SPARC* secreted protein acidic and cysteine rich
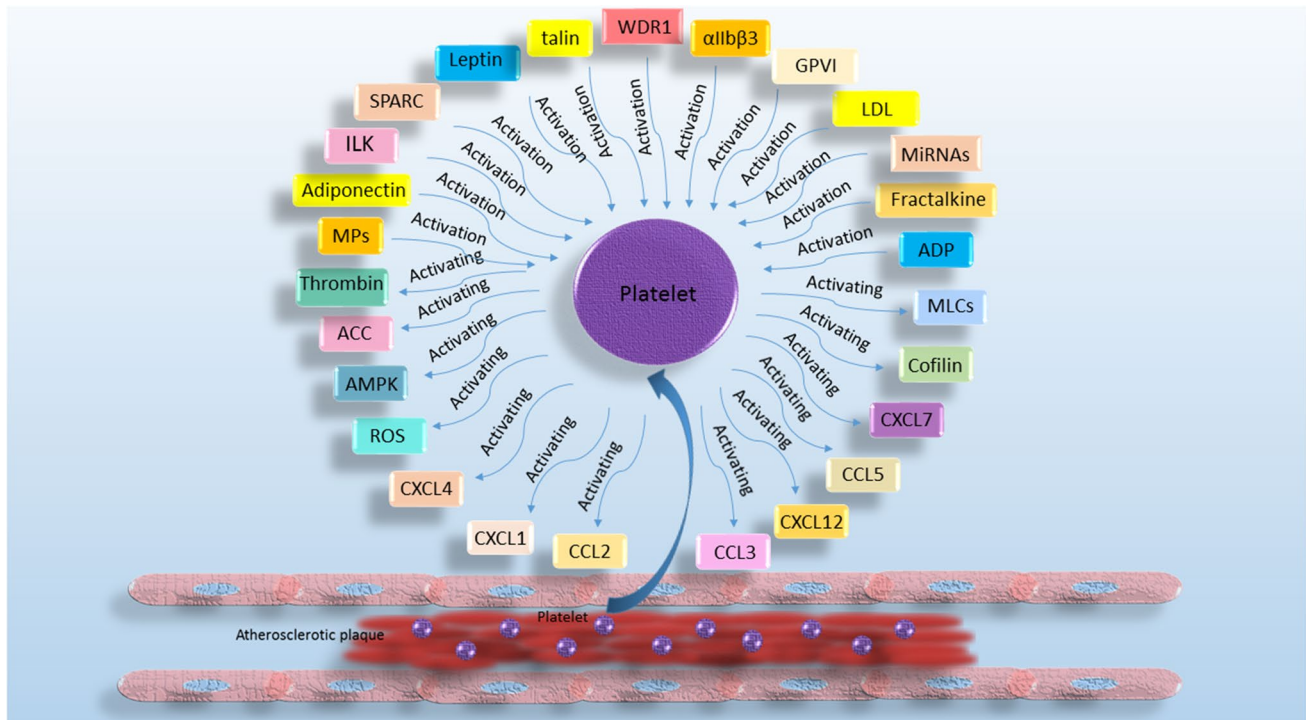
Fig. 1 Platelet activation by molecules and molecules activated by platelets in atherosclerosis formation. The molecules that activate platelet can effect platelet aggregation and adhesion to other cells and molecules which result in atherosclerotic plaques in circulation and CVD. On the other hand, molecules that are activated by platelets cause platelet interaction by other cells and atherosclerosis. *LDL* low-density lipoproteins, *WDR1* WD repeat domain 1, *ADP* adenosine diphosphate, *ROS* reactive oxygen species, *ACC* acetyl-CoA carboxylase, *AMPK* AMP-activated protein kinase, *MLCs* myosin light chains, *ILK* integrin-linked protein kinase, *MPs* microparticles, *SPARC* secreted protein acidic and cysteine rich

Platelet Activation Molecules in CVD

Lipid and Inflammatory Factor Expressions as a Marker of Prognosis in CVD

Low-density lipoprotein (LDL) as an oxidized lipid metabolite can activate platelets and thrombosis by induction of tissue factors and inflammation factors in thrombosis. Platelets' LDL is correlated with CXCR7 surface expression. LDL induces ROS generation which increases the intraplatelet oxidative conversion of it into lipid peroxides. Oxidized metabolites associated with increased membrane phospholipids (PLs) in CVD patients showing the platelet lipidome alteration of triacylglycerols, cholesteryl esters, ceramides, sphingomyelin, and acylcarnitines [4, 13]. In addition, CXCL12 increases LDL uptake and pro-oxidative and prothrombotic platelet functions with CXCR4–CXCR7 which are induced by LDL [4]. Platelet lipidome is modulated by the CXCL12/CXCR4–CXCR7 axis which may have a pathophysiological role in CVD patients. Sphingomyelin increased levels upregulate sphingolipid catabolism in CVD patients and cause platelet hyper-reactivity. Platelet activation is associated with increased ceramide

and sphingosine-1-phosphate that alters sphingolipid levels in the blood [14]. Oxidized PLs cause inflammation, endothelial dysfunction, differentiation of monocyte and macrophage, plaque formation, and ischemic conditions which activate pro-inflammatory genes and thrombosis by scavenger receptor CD36 and platelet-activating factor receptor (PAFR), tissue factor (TF), and tissue factor pathway inhibitor (TFPI) [14, 15]. In patients with CVD, LDL binding increases the platelet receptors such as CD36 which result in the formation of ROS and platelet activation [13, 15]. LDL can activate platelets which, in turn, cause apoptosis and inflammatory responses in monocytes with CXCL12, through CXCR4–CXCR7 axis which results in atherogenesis [16]. Chemokines (such as CXCL12) which are secreted from platelets can effect inflammation and activate autocrine and paracrine responses and thrombosis. Platelet lipids (such as triacylglycerols and ceramides) are induced and increased by CXCL12/CXCR4–CXCR7 axis which results in CVD [17, 18]. LDL on platelets has a correlation with platelet numbers, which show that plasma lipids can effect platelet activation, prothrombinase complex accumulation, thrombin formation, and thrombosis [4]. Studies have shown that the expression of CXCL12 and CXCR4-CXCR7 on platelets

have effects on CVD prognosis and severity [19]. Plasma levels of LDL in CVD patients are significantly increased which serve as a prognostic marker for CVD. Increased expression of CXCR7 and CXCL12 in patients with CVD relates to the recovery and good prognosis (Table 1) (Fig. 1) [20, 21]. Therefore, targeting these receptors on platelets can suggest a new strategy to manage CVD for better treatment.

WDR1 Gene's Role in Platelet Formation and the Risk of CVD

During the activation of platelet with an agonist such as thrombin, the calcium concentration will be increased, resulting in cytoskeletal rearrangement promotion and integrin activation, leading to platelet adhesion and aggregation. Adhesion as a platelet function is done by adhesive ligands, receptors, and actin cytoskeleton modulation [3]. WD Repeat Domain 1 (WDR1) is necessary for megakaryopoiesis and platelet production and is an important cofactor for an actin-depolymerizing factor (ADF)/-cofilin-F-actin that can increase the activity of ADF-cofilin resulting in the disassembling of actin [22, 23]. Increased expression of WDR1 decreases the adhesion and content of F-actin, calcium concentration, actin cytoskeleton, and thrombin activation. Lack of WDR1 causes inflammation and macrothrombocytopenia and decreases the ADF-cofilin which results in decreased platelet formation and depolymerization [3, 24]. Reducing the actin depolymerization by WDR1, increases the F-actin stabilization, leads to the activation and binding of WDR1 to the collagen matrix and increasing platelet adhesion. This event increases the platelet size without increasing the platelet production. These platelets get more activated and exert more prothrombotic activity which increase the risk of CVD (Table 1) (Fig. 1) [25, 26]. Understanding the genes which increase the platelet activity can help identify the therapeutic targets for these genes to control CVD.

Hormones as a Link Between Platelet Activation and CVD

Receptors of peptide hormones are presented on platelets and hormones such as leptin and can activate platelets and increase thrombosis. Studies have shown that leptin activates a platelet signaling cascade including the long form of the leptin receptor (LEPRL), Janus kinase 2 (JAK2), phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB), insulin receptor substrate-1 (IRS-1), and phosphodiesterase 3A (PDE3A). Activation of this cascade results in the increase of platelet phosphodiesterase 3A (PDE3A) and decreases the inhibitory role of cyclic adenosine monophosphate (cAMP) in platelets [5, 27]. Adiponectin is secreted from adipose tissue and has anti-atherosclerotic and anti-inflammatory effects on circulation [28]. Inhibition of activated platelets can inhibit atherosclerosis. Platelet activation relates to insulin resistance [28, 29]. Following the relationship between adiponectin and insulin resistance, a link between the activation of platelets with hypoadiponectinemia can be considered. Studies have shown that leukocyte–platelet aggregation is presented with hypoadiponectinemia and atherosclerosis (Table 1) (Fig. 1) [30]. Other factors such as body mass index, blood pressure, and lipid levels cause platelet activation [31]. Platelet activation relates to insulin resistance and hypoadiponectinemia and platelet–leukocyte aggregations can predict atherosclerosis in CVD patients [29].

Oxidative Stress and Hemostasis Imbalance in Older Age and CVD

Platelets have a role in thrombosis, hemostasis, and inflammation and in older age with the imbalance in these functions can result in CVD [32]. Oxidative stress is created due to the imbalance between ROS production and antioxidants. During platelet activation, ROS production including superoxide anion (O_2^-), hydroxyl radicals (OH), and hydrogen peroxide (H_2O_2) is done by calcium mobilization, nitric oxide inactivation, and interaction with arachidonic acid for isoprostanes formation [33]. ROS is generated in platelets by NADPH oxidase, cyclooxygenases, uncoupled endothelial nitric oxide synthase (eNOS), xanthine oxidase (XO), and mitochondrial respiration. However, the role of NADPH oxidase is vital for $O_2\%$ production [34]. Platelet phospholipids increase in older age and ROS production is presented in platelets, which have a role in the pathogenesis of CVD [35]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is essential for ROS production. Increased levels of 8-isoprostaglandin F2 alpha (8-isoPGF2α) are presented in CVD by platelet activation (Table 1) (Fig. 1) [36]. In older age, poor response to antiplatelet treatments and activation of platelets cause oxidative stress and aggregation of platelets that trigger non-responsiveness of drugs in CVD patients [37, 38]. Thus, oxidative stress and its pathways can be suggested as a target to control platelet activation in older age.

Molecules in Immune Functions of Platelets

The immune system plays an essential role in atherosclerosis formation as an inflammatory disease. Platelets are first activated on vascular damage and secrete cytokines from the α-granules [39]. The platelets then express the P-selectin receptors, integrins such as glycoprotein (GP) IIb/IIIa, and Toll-like receptors expression for immunological activities. Platelets can also activate leukocytes, endothelial cells, and smooth muscle cells (SMCs) with different receptors and secretion of mediators such as adenosine diphosphate (ADP), thromboxane A2 (TXA2), cytokines such as IL-1b

and TGF-β, and chemokines such as CCL5 and CXCL12 [40–42]. Platelets also express the fractalkine receptor on their surface when being activated. Fractalkine reduces the vascular NO by increasing the ROS formation in the vessel wall leading to NO scavenging through the activation of NADPH oxidases. In addition, fractalkine induces the chemotactic, vasoconstrictive properties and platelet activation by its receptor CX3CR1 on its surface which supports the adhesion of platelets by GP Ib and increases the adhesion of leukocyte to endothelium under flow conditions [43, 44]. Studies have shown that agonists such as ADP can increase platelet activation besides fractalkine [45]. Increased expression of fractalkine correlates with platelet activation in patients with CVD when they are treated with drugs such as clopidogrel. Experimental studies on CVD patients have shown that activation of CX3CR1 by fractalkine inhibits adenylyl cyclase release in the endothelium which is associated with increased platelet reactivation to ADP and better response to P2Y12 inhibition by clopidogrel [46, 47]. In addition, platelets can be activated by fractalkine which induces P-selectin adhesion of platelets to fibrinogen and collagen (Table 1) (Fig. 1) [47]. Thus, the molecules of immune functions of platelets can be suggested as a target to control CVD.

Platelet Signaling Proteins: Functional Role in Thrombosis and CVD

Platelet activation along with specific interactions induces signaling pathways that result in intracellular phosphorylation, reorganization of cytoskeleton, and secretion of granules which finally leads to platelet adhesion, aggregation, and thrombosis [48]. The main platelet receptors such as GPVI and the integrin αIIbβ3 have a role in platelet aggregation that initiate their signaling cascades with Src family kinases (SFKs). Also, the talin protein can bind to β3 by a phosphotyrosine binding domain (PTB) and regulate αIIbβ3 [49, 50]. Integrin-linked protein kinase (ILK) in platelets has a central role in integrin activation by complex formation of Cys-His protein (PINCH) and parvin leading to α-granule secretion and platelet activation. Studies have shown the new N-terminal proteolytic fragments of ILK with PINCH binding domain have an important role in platelet activation by integrin αIIbβ3 [10, 51–53]. Therefore, signaling proteins have a major role in thrombosis, and targeting these proteins can be suggested for better control and management of CVD.

Platelet Secreted Proteins: Potential Role in Preventing CVD

In platelet activation, the release of proteins is a critical step. Studies have shown that several secretory proteins increase during platelet activation as microparticles (MPs) in patients with acute coronary syndrome (ACS) [54]. MPs can induce angiogenesis and revascularization improvement in ischemic patients. Also, glycoprotein secretes from α-granules during platelet activation and is presented in MPs. Studies have shown that secreted protein acidic and cysteine rich (SPARC) has a role in angiogenesis formation and maintenance of cardiac integrity after myocardial infarction (MI) [55–57]. In addition, SPARC regulates platelet reorganization by ILK modulation and can be secreted in activated platelets of ACS patients [58]. Thus, MPs and SPARC protein may have a therapeutic application to prevent CVD and dysfunction improvement after MI.

Platelet miRNAs in CVD

MicroRNAs (miRNAs) are a group of small (18–25 nucleotides) non-coding RNAs that regulate gene expression by targeting mRNA and its degradation, and post-translationally affecting mechanisms in proteins [59, 60]. The miRNAs have a significant role in inflammation and CVD. The miRNAs are present in platelets with regulatory functions and MPs include several miRNAs, which cause the communications of platelets with vascular cells that lead to inflammation and vascular homeostasis [61–63]. MiRNAs have a role in the pathogenesis of ACS and CVD by lipid metabolism regulation, inflammation, cell proliferation, angiogenesis, and platelet activation [64]. MiRNAs have a biological role in the regulation of different proteins by complex gene networks and different target genes [65]. Studies have shown the dysregulated expression of miRNAs in ACS and CVD, and miRNA-223 and miRNA-126 have shown the association with CVD target genes. The miRNA-223 can regulate EPB41L3 gene, and the miRNA-126 regulates VCAM-1 gene, and both have a role in ACS formation and vascular dysfunction [11]. Therefore, the miRNAs can be suggested as biomarkers for the diagnosis and as therapeutic targets for better treatment of CVD patients.

Molecules Activation by Platelets in CVD

Lipids Signaling Pathways in Activated Platelets

Lipids have an essential role in the regulation of platelet functions. Acetyl-CoA carboxylase (ACC) is the AMP-activated protein kinase (AMPK) substrate and has a central role in fatty acid metabolism in platelets. Thrombin stimulation can activate AMPK in platelets and phosphorylation of myosin light chains (MLCs), cofilin, and vasodilator-stimulated phosphoprotein (VASP). These proteins cause the changes in platelet shape and secrete the granules when the platelets are activated [66, 67]. Studies have shown that ACC phosphorylation by AMPK can regulate lipid content, but not lipid

oxidation of platelets and additional surface molecules that are involved in the interactions of platelets and thrombosis. AMPK-ACC signaling deficiency causes changes in platelet structure by increasing TXA2 and ADP secretion and results in thrombosis, which is collagen-specific (Table 1) (Fig. 1) [6]. The mitochondrial lipid oxidation mechanisms involve increased levels of arachidonic acid (AA), phosphatidyle-thanolamine plasmalogen (PEP) lipids, thromboxane A2 (TXA2), and granule secretion of platelets by collagen. These highlight a unique regulatory pathway in platelets that have an effect on thrombus formation by modulation of the specific PL content in platelet activation [6]. This finding shows the pathological progress of atherosclerosis. Therefore, lipids and their related signaling pathways such as AMPK-ACC can be a target to control thrombosis and atherosclerosis.

Chemokines Involved in Activated Platelets in CVD

Platelets have a role in inflammation and hemostasis. These processes are induced by chemokines that are secreted from activated platelets and are stored in their granules. CXCL7 is a chemokine that has the most expression in platelets and has a role in CVD [7]. The platelet CXCL4 expression is increased in atherosclerosis. In addition, CXCL4 can make a heterodimer with CCL5. This heterodimer can bind to mono-cytes, which by other chemokines can modulate signaling pathways in the cells [68, 69]. CXCL4 increases the differentiation of macrophages and inhibits monocyte cell death [70]. CCL5 forms activated platelets, increases the monocyte and T lymphocyte adhesion by ICAM-1 and VCAM-1 to the endothelium, and increases angiogenesis [71]. CXCL1 is secreted by activated platelets and binds to CXCR2 that induces monocyte activation to atherosclerotic lesions [72]. Other chemokines that are secreted by platelets are CXCL8, CXCL12, CCL2, CCL3, and CCL17. CXCL12 has a role in atherosclerotic lesion formation, activates platelets via CXCR4, secrets by macrophages and increases atherosclerosis [73, 74]. CCL2 is presented in atherosclerotic lesions, and induction of CCL2 in activated platelets can trigger atherogenesis plaque formation. CCL3 also is expressed in atherosclerosis, which can bind to CCR1 and CCR5 (Table 1) (Fig. 1) [7, 75]. Therefore, different chemokines and expressions of their pathways involved in activated platelets can be targeted to be decreased, suggesting the decrease in atherosclerotic plaque formation and CVD.

Discussion

The main question is that by which mechanisms the chemokines involved in platelets can be used as therapeutic targets. Studies have shown that some small molecules can

block heterodimerization of chemokines and control their pathological effects in arteriosclerosis [7]. Platelet activation and thrombosis are the complicated processes and several molecular pathways are involved in this event. Protein kinase C family (PKCs) has a dual role in both protection against thrombosis and pro-aggregation activities of factors involved in thrombosis [76, 77]. Studies have shown that PKCs have an important role in the proliferation of malignant megakaryocytopoiesis and the expression of PKCs is increased in myelofibrosis which correlates with the risk of thrombosis [78]. In addition, in patients with thrombosis and CVD, higher expression of PKC is detected compared to patients with no arterial complication. Therefore, PKCs can be targeted to reduce clinical complications in CVD patients [11]. Platelets have an immunomodulatory role in athero-sclerosis and interact with inflammatory cells by different receptor-ligand. Activated platelets interact with monocytes and transfer myeloid-related protein (MRP-14) to these cells and macrophages [79]. Also, platelets transfer CCL5 and PF4 chemokines to immune cells. MRP-14 increases the adhesive function of platelets by P-selectin expression which is independent of the aggregation process. P-selectin causes platelet–leukocyte interactions and atherosclerotic plaque formation. Studies have shown that the lack of MRP-14 decreases these interactions and MRP-14 can be used as a target in platelets to control atherosclerosis [80–82]. When platelets are activated, increased inflammation and fibrosis by angiotensin II (Ang II) that is induced by hypertension are observed. This happens in the early stage of infarc-tion by binding P-selectin, which has increased expression in plasma, to its receptor P-selectin glycoprotein ligand-1 (PSGL-1), which results in platelet–leukocyte interaction, inflammation, and cardiac remodeling [83]. Phosphatidyl-choline transfer protein (PCTP) is expressed in platelets and reduces the platelet aggregation in the presence of activated receptor 4 (PAR4) [84]. Runt-related transcription factor 1 (RUNX1) is a transcription factor that regulates genes in platelets. Studies have shown that PCTP is regulated by RUNX1 and is a target for it. Higher PCTP expression in blood as a marker can predict death and clinical outcome in CVD patients. Therefore, regulation of PCTP by RUNX1 can be used as a target to control CVD [85].

To control CVD, proteasome inhibitors have an impact on platelet function and hemostasis and can target plate-lets, which, Bortezomib (Velcade) as a proteasome inhibi-tor, causes thrombocytopenia and platelet death. However, proteasome inhibitors also have a role in platelet proteome activation and thrombosis [86–88]. Studies have shown that platelets have the ubiquitin/proteasome system, which can ubiquitinate their proteome and change their cytoskeleton by targeting Filamin A and Talin-1 proteins and proteasome proteolysis. Proteasome inhibitors affect platelet response to thrombotic stimulations and effectively cause delay in the

arterial thrombosis [89]. Following platelet activation, ADP from dense granules and thromboxane A2 are released by the activation of thromboxane synthase and cause platelet aggregation and thrombus formation with glycoprotein IIb/IIIa receptor activation by continuous ADP-P2Y12 receptor signaling [90]. The P2Y12 receptor blocker (clopidogrel) increases inhibition of coronary thrombosis and reduces CVD. Even low-dose FXa inhibitor with clopidogrel or acetylsalicylic acid (ASA) was beneficial for CVD patients. Moreover, dual antiplatelet therapy with thrombin and FXa inhibitor has also shown beneficial effects. This shows the combination use of platelet activation and thrombin formation drugs, which both modulate thrombosis [11, 91].

Dual antiplatelet therapy with ASA and clopidogrel has indicated good results for 12 months in ACS and coronary stenting patients [90]. However, dual therapy of clopidogrel with ASA was not effective compared to ASA monotherapy for the long-term outcome in patients with CVD [92]. In addition, dual ticagrelor with ASA therapy and PAR-1 with vorapaxar inhibits the effects of platelet thrombin, does not have an effect on coagulation, increases bleeding compared to ASA alone, and has no effect on CVD [12, 93]. On the other hand, rivaroxaban with clopidogrel or ASA has shown the best effect on thrombosis in recent studies [91].

Appropriate anticoagulant doses need balancing of the benefits and the risks in CVD patients. Therefore, the dual antiplatelet and anticoagulant therapy depends on the anticoagulant safety for decreasing serious bleeding in these patients [11].

Conclusion and Future Perspectives

Molecules that activate platelets and the molecules that are activated by platelets can be used as markers to predict the clinical outcome of CVD patients. In addition, these molecules or their signaling pathways can be targeted to control thrombosis events and atherosclerosis. Blocking and targeting these molecules by other molecules, genes, and receptors, which have a role in reducing the platelet activation, aggregation, and platelet interactions with other cells in thrombosis, can be suggested to control CVD. In addition, dual treatments of receptor blockers with new drugs together cause better treatment effects in CVD patients. Future studies are still needed to find the answer of questions and solve the challenges in this field.

Compliance with Ethical Standards

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