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PEAR1 polymorphisms as a prognostic factor in hemostasis and cardiovascular diseases

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Abstract
Platelet Endothelial Aggregation Receptor (PEAR1), as a platelet receptor, plays a vital role in hemostasis. This receptor, by its extracellular part, causes platelet adhesion and consequently initiates platelet aggregation. Dysfunction of PEAR1 can disrupt platelet aggregation in patients with cardiovascular diseases (CVDs). The content used in this paper has been taken from English language articles (2005–2020) retrieved from Pubmed database and Google scholar search engine using "Cardiovascular Disease", "PEAR1", "Polymorphism", and "Platelet Aggregation" keywords. Some PEAR1 polymorphisms can disrupt homeostasis and interfere with the function mechanism of cardiac drugs. Since polymorphisms in this gene affect platelet function and the platelet aggregation process, PEAR1 could be further studied in the future as an essential factor in controlling the treatment process of patients with cardiovascular diseases. PEAR1 polymorphisms through disruption of the platelet aggregation process can be a risk factor in patients with CVDs. Therefore, controlling patients through genetic testing and the evaluation of PEAR1 polymorphisms can help improve the treatment process of patients. According to the studies on the PEAR1 gene and the effect of different polymorphisms on some crucial issues in CVDs patients (changes in platelet activity), it is clear that if there is a significant relationship between polymorphisms and CVDs, they can be used as prognostic and diagnostic markers. This study aims to evaluate the prognosis and drug treatment of the PEAR1 gene in CVDs patients.

Keywords Cardiovascular diseases · PEAR1 · Polymorphism · Platelet aggregation · Hemostasis

Highlights

- PEAR1, as a platelet receptor, plays a significant role in platelet aggregation
- PEAR1 dysfunction has a close relationship with hemostasis disorders
- The presence of PEAR1 SNPs can interfere with the effect of cardiac medicines

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Introduction

Platelet aggregation is an essential step in the homeostasis system that begins following vascular injury and the secretion of stimulating molecules from platelet granules. According to studies, dysfunction at this stage of homeostasis is one of the crucial causes of CVDs [1–3]. Platelet aggregation is an essential mechanism in cardiac patients that is dependent upon several factors such as coagulation factors, platelet agonists, and coagulation receptors of platelets [4]. PEAR1, as a platelet aggregation stimulus, is secreted from alpha-platelet granules and phosphorylated as a Coagulation Receptor via the PI3K/AKT/PTEN pathway and its expression at the membrane surface is thereby implicated in the regulation of homeostasis [5, 6]. Disruption of the PEAR1 gene results in impaired platelet aggregation and single nucleotide polymorphisms (SNPs) in PEAR1 such as rs12566888 and rs12041331 can affect the progression and prognosis of CVDs. Some PEAR1 polymorphisms are also involved in the process of heart disease and its therapeutic mechanism, such as impaired cardiovascular drugs

[7–9]. Given the essential and undeniable role of PEAR1 in platelet aggregation, we can conclude that any impairment in the expression of this gene is likely to cause platelet dysfunction and disturb the hemostatic system. On the other hand, the essential role of hemostasis in the function of the cardiovascular system reveals that the dysfunction of the PEAR1 gene may play a role in the prognosis and treatment of CVDs and that laboratory and genetic tests can assess the presence or absence of polymorphisms in the PEAR1 gene and its impact on the disease. In this paper, we review and summarize previous studies on the PEAR1 gene and its polymorphisms concerning heart disease and the mechanism of drugs, as well as evaluating the PEAR1 signaling pathway and its role in platelet aggregation.

Biology and signaling of PEAR1

PEAR1 is a type 1 receptor of the EGF (Epidermal Growth Factor) family, which is expressed on the surface of endothelial cells, platelets, and megakaryocytes [10] and it is also present on inactive platelets as well as their α-granules [5]. PEAR1 gene is located on a 1q23 chromosome, causing platelet aggregation and regulating platelet function via stabilizing αIIbβ3 (fibrinogen receptor) [11]. FcεRIα (IgE receptor) is a PEAR1 ligand that stimulates platelet aggregation and degranulation by binding PEAR1 [12]. PEAR1 gene has 23 exons and 22 introns, some polymorphisms of this gene increase platelet aggregation and impair platelet function [11, 13]. This receptor has fifteen extracellular domains of the EGF family and five intracellular domains rich in proline [10]. PEAR1 is a type of receptor tyrosine kinase (RTK) causing platelet- platelet adhesion via the EMI domain (EMILIN Family Domain) in its extracellular part and triggering PI3K/AKT/PTEN signaling, which leads to PEAR1-mediated stimulation of megakaryopoiesis and neoangiogenesis [5, 14]. Given that this receptor has tyrosine kinase property, both its inner and outer regions can bind phosphotyrosine to be phosphorylated [7]. Through PEAR1 binding to its ligands such as EMI domain, ADP or FcεRIα, Tyr-925, and Ser- 953/1029 amino acids in the cytoplasmic region are phosphorylated through Src Family Kinase (SFK) including c-Src, Fyn and Syk, which is dependent on c_Src and Fyn but independent of Syk. Afterward, by triggering PI3K/AKT/PTEN signaling, αII bβ3, which is a crucial factor in aggregation, is activated, and its stability increased at the platelet surface [5, 15–17]. The PEAR1, c-Src, Fyn, and PI3K (phosphatidylinositol 3-kinase) complex activates αIIbβ3 and stimulates aggregation [14]. PI3K/AKT/PTEN signaling is inhibited by SFK inhibitors (PP1) and PI3K Inhibitors (LY29400) (Fig. 1). As an antiplatelet drug andαII bβ3 antagonist, eptifibatide blocks PI3K/AKT/PTEN signaling and inhibits platelet aggregation [5, 18].

According to the above statements, we can assume that PEAR1 polymorphisms are likely to deactivate PI3K/AKT/PTEN, followed byαII bβ3 inactivation that disrupts platelet aggregation as well as the effect of coagulation drugs in patients with CVDs. As a result, platelet aggregation may be controlled using PEAR1 signaling inhibitors in patients with polymorphisms impairing this gene.

PEAR1 as an essential receptor in hemostasis

Platelet aggregation is a critical process in cardiac patients that is regulated by balancing the aggregation stimulators (ADP, collagen, epinephrine) and inhibitors (nitric oxide and prostacyclin). The stimulators increase PEAR1 expression on the platelet surface. According to studies, several polymorphisms in PEAR1 gene such as rs3737224, rs41299597, rs41273215, rs822442, rs11264579 enhance the expression of PEAR1. Moreover, rs3737224 and rs11264579 polymorphisms increase the binding of fibrinogen to αIIbβ3, which results in increased platelet aggregation as a result of these two functions [19–21]. On the other hand, rs12566888, which is an intron polymorphism with TT allele, decreases platelet aggregation induced by ADP or Epinephrine [21]. rs56260937, CC allele in rs2768759, TT allele in rs11264579 and rs56260937 augment platelet aggregation in the presence of platelet agonists such as collagen and epinephrine, which can increase the risk of CVDs [21, 22] (Table 1). According to investigations, Dextran Sulfate (DxS) (synthetic polysaccharide) and polyclonal antibodies lead to the phosphorylation of PEAR1 and initiate platelet aggregation [13, 23]. DxS and PEAR1 can stimulate αIIbβ3 and platelet aggregation through the PI3K/signaling pathway [15]. DxS activates αIIbβ3 by both Syk-dependent and Syk-dependent pathways [24]. In the former pathway, DxS binds to C-type lectin-like receptor-2 (CLEC-2) on the platelet surface, phosphorylating it by Syk, Fyn, and c-Src. In this way, phospholipase Cg2 (PLCg2) is phosphorylated and activated. Consequently, αIIbβ3 will be activated and platelet aggregation begins [15, 25, 26]. In the latter non-Syk-dependent pathway, platelet aggregation is regulated by PEAR1 phosphorylation and activation of the PI3K/AKT/PTEN pathway [5] (Fig. 1). Since the regulation of platelet aggregation in cardiac patients is a critical and hereditary issue, that some PEAR1 polymorphisms also affect this, these polymorphisms can be assessed to control platelet aggregation in patients with CVDs and to predict the hemostasis response to antiplatelet drugs to choose an effective strategy for the treatment of these patients.

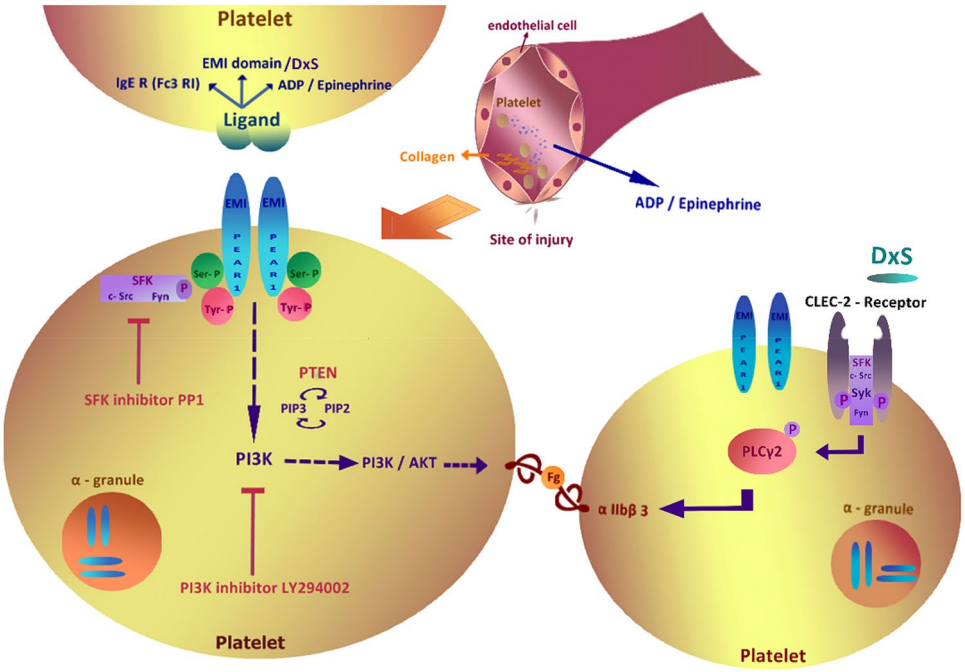

Fig. 1 Platelet aggregation can be done from two signaling pathways: the Syk path and the non-Syk path. The Syk pathway is performed by attaching dextran sulfate to CLEC-2 on the platelet surface, which causes the CLEC-2 to be phosphorylated by SFK (Syk, Fyn, c-Src), thereby activating the PLCg2 phosphorylation and It increases the expression of αIIbβ3 on the platelet surface. The non-Syk pathway is performed through PEAR1 phosphorylation, after vascular damage and secretion of platelet aggregation agonists (ADP, Collagen, Epinephrine,), PEAR1 secretes from platelet alpha granules and comes to the surface, then by binding to one of its ligands such as DxS, EMI Domain, and ADP, is activated by SFK (Fyn, C-Src), triggering a PI3K/AKT/PTEN signaling pathway and increasing the expression of αIIbβ3. The pathway associated with Syk is inhibited by PP1 (SFK inhibitor) and LY294002 (PI3K inhibitor)

Interference of PEAR1 polymorphisms with anti-platelets drugs mechanism

SNPs can play a role in disease progression, the effect of medication, and response to treatment [27, 28]. The association of PEAR1 polymorphisms with the action mechanism of cardiovascular drugs and the treatment process of patients is a prime example of the impact of genetic disorders on CVDs patients [29]. The presence of PEAR1 polymorphisms results in unexpected and adverse effects in the treatment process of cardiac patients treated with antiplatelet drugs [22]. Research has shown that patients who have high platelet aggregation along with aspirin consumption are at increased risk of developing CVDs and the likelihood of non-response to antiplatelet drugs [30, 31]. Dual antiplatelet therapy (clopidogrel and aspirin) is an essential approach for the treatment of cardiac diseases that can be affected by the presence of PEAR1 polymorphisms [21, 32, 33]. PEAR1 polymorphisms damage platelet function both under normal conditions (without the presence of cardiac drugs) and after consumption of antiplatelet drugs. Aspirin inhibits platelet aggregation by irreversibly inhibiting cyclooxygenase (COX) and reducing the conversion of arachidonic acid to thromboxane A2 [31]. Ticagrelor, prasugrel, and clopidogrel are antiplatelet drugs that inhibit platelet aggregation via inhibiting P2Y12, which is a type of platelet receptor [34]. therefore, different responses of platelets to aspirin and other antiplatelet drugs may be affected by genetic changes [35]. Responses to drugs such as aspirin and clopidogrel have been reported to be significantly associated with rs12041331, which is one of the most prominent PEAR1 polymorphisms [36]. More than 15% of platelet function changes and abnormalities are due to rs12041331. There is a direct relationship between the number of G alleles present in rs12041331 and the expression of PEAR1 on the surface of endothelial cells and platelets. The GG allele of rs12041331 is highly correlated with the TT allele of rs12566888, which are related to the function of platelets [7, 37, 38]. In comparison with the AA allele, the presence of the GG allele of rs12041331 induces platelet aggregation and increases PEAR1 expression on the platelet surface, which is associated with reduced mortality in these patients [8] (Table 1). The CC allele of rs57731889 reduces platelet reactivity after taking prasugrel. On the other hand, the AA allele of rs822441 and TT allele of rs56260937 decrease the platelet response to prasugrel and aspirin [8, 39, 40]. Besides, rs11264580 and rs41273215

Table 1 The most important PEAR1 SNPs in CVDs

SNPs	Allele genotype	Expression of PEAR1	Function in hemostasis	Platelet response to cardiac drugs	Outcome	Refs
rs12041331	GG	Up	Stimulate platelet aggregation	The response to aspirin is increased	Reduce mortality	[7, 32]
	GA	Moderate	Moderate	Moderate	Moderate	
	AA	Down	Decreased platelet aggregation	The response to aspirin is reduced	Increase mortality	
rs2768759	AA	NR	–	–	–	[31, 39]
	AC	NR	–	–	–	
	CC	Up	Stimulate platelet aggregation	The response to aspirin is reduced	NR	
rs41299597	CC	Up	Stimulate Platelet Aggregation	NR	NR	[31, 39]
	CG					
	GG					
rs12566888	GG	NR	–	–	–	[48]
	GT	NR	–	–	–	
	TT	Down	Decreased platelet aggregation	–	–	
rs56260937	CC	NR	–	–	Increase risk of ischemic events	[8, 22]
	CT	NR	–	–		
	TT	Up	Stimulate platelet aggregation	The response to aspirin and prasugrel is reduced		
rs3737224	CC	Up	NR	The response to prasugrel is increased	–	[31]
	CT		NR		–	
	TT		Stimulate platelet aggregation		–	
rs11264579	CC	Up	Stimulate Platelet Aggregation	NR	Reduce risk of ischemic events	[39]
	CT					
	TT					
rs822442	CC	Up	Decreased ADP induced platelet aggregation	NR	–	[8, 39]
	CA			NR	–	
	AA			The response to aspirin is reduced	Increase mortality	

SNP single nucleotide polymorphism, *NR* not reported, *Up* upregulation, *Down* downregulation, *CVDs* cardio vascular diseases

increase platelet responsiveness to prasugrel [21]. Notably, the TT allele of rs56260937 arises the risk of ischemia [22]. In patients undergoing percutaneous coronary intervention (PCI), rs12041331 increases the risk of cardiovascular disease and mortality rates [41]. Studies on patients with Kawasaki disease, which is a vascular disease, indicate that the presence of rs12041331 and rs12566888, although not involved in the pathology of this disease, are associated with increased risk of coronary artery aneurysm (CAA) in these patients [11]. In two studies investigating rs2768759 in PEAR1, different results have been obtained regarding the association of this polymorphism with mortality rates in patients with CVDs. Research has shown that in the presence of aspirin, the CC allele of rs2768759 induces platelet aggregation with high intensity. Therefore, the presence of this polymorphism reduces platelet response to aspirin and thereby increases the risk of heart attacks [31, 41] Compared to the T allele of rs4661012, the G allele boosts the inhibition of platelet aggregation (IPA) and decreases platelet aggregation in the presence of ticagrelor. Furthermore, the G allele decreases IPA in presence of ticagrelor and thus increases platelet aggregation in comparison with the T allele [8]. Remarkably, the presence of the T allele in rs11264579 reduces the incidence of ischemic diseases, and the presence of this allele can be considered as a protective factor against heart disease [39]. In other studies on a group of patients with CVDs, no association has been observed between PEAR1 polymorphisms and CVDs, and no conclusions about the role of this gene in the prognosis of patients have been reached. It has also been reported that PEAR1 polymorphisms do not affect the relationship between MPV and platelet counts [18, 41, 42]. Like other genetic effects, the impact of anticoagulants on heart disease is an inherited factor in which

PEAR1 polymorphisms are involved. Examining the polymorphisms in the PEAR1 gene and considering their effect on antiplatelet drugs can determine the treatment process of CVDs.

Discussion

CVDs can be caused by a disruption in several important factors such as dysfunction of the hemostatic system and genetic disorders. According to investigations, genetic variation has been identified in 40–60% of patients with CVDs [2, 43]. Dysfunction of the PEAR1 gene may be involved in the pathogenesis of CVDs [7]. The expression of PEAR1 is associated with the expression of genes such as ANG2, ACVRL1, and ENG that are involved in endothelial function [44]. PEAR1 plays a role in the regulation of platelet function, platelet aggregation, thrombopoiesis, and angiogenesis by expressing a transmembrane protein on the surface of platelets, endothelial cells, and megakaryocytes, the dysfunction of which may affect the prognosis of CVDs patients and their response to drugs [42, 45]. PEAR1 protein, a tyrosine kinase receptor, is secreted from α-granules upon platelet activation and phosphorylated through PI3K/AKT/PTEN signaling, binding the PEAR1 of the adjacent platelet through EMI domain in its extracellular domain that stabilizes and activates the fibrinogen receptor and regulates platelet aggregation [5, 23, 44]. The presence of PEAR1 polymorphisms can lead to platelet and coagulation problems in patients with CVDs through impairment of hemostasis, PEAR1 expression on the membrane surface, or platelet dysfunction (in the presence of antiplatelet drugs) [45]. Regulation of platelet aggregation process, platelet function, and the effect of antiplatelet drugs in cardiovascular patients are critical issues associated with PEAR1 polymorphisms [8, 32, 46]. It can be speculated that these polymorphisms affect PEAR1 signaling, disrupt platelet function and homeostasis, thereby regulating platelet responses to platelet agonists. Since the presence of PEAR1 polymorphisms interferes with the effect of certain cardiac drugs, the changes in treatment modality and the prescribed medication for patients with CVDs can improve the treatment course of CVDs patients. Decreased expression of PEAR1 and polymorphisms such as rs12041331 in this gene, boost the proliferation and migration of endothelial cells that can be investigated as prognostic factors in CVDs patients [44]. Given the critical role of PEAR1 in platelet aggregation, it can be concluded that the presence of PEAR1 polymorphisms disturbs platelet function and hemostasis [47]. The impact of PEAR1 polymorphisms on the occurrence of CVDs is controversial and the precise role of these polymorphisms in platelet function has not been fully elucidated (4). However, a more precise review of abnormalities in PEAR1 as a risk factor for CVDs and investigation of PEAR1 signaling can contribute to the treatment process of patients. It is also possible to study PEAR1 polymorphisms as a prognostic factor in patients with CVDs and thus provide a basis for further studies in the future.

Author contributionss

NS conceived the manuscript and revised it. NA, SN and SS wrote the manuscript and prepared tables and figures.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Informed consent For this type of study, informed consent is not required.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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