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Outline of Platelet Physiology: Its Hemostatic and Nonhemostatic Part In Illness Pathogenesis

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Abstract: - *Platelets are little anucleate cell parts that course in blood assuming pivotal part in overseeing vascular uprightness and controlling hemostasis. Platelets are additionally engaged with the crucial organic procedure of ceaseless aggravation related with malady pathology. Platelet records like mean platelets volume (MPV), platelets disseminated width (PDW), and platelet crit (PCT) are valuable as shoddy noninvasive biomarkers for evaluating the infected states. Dynamic platelets bear unmistakable morphology, where α and thick granule are effectively engaged with emission of particles like GPIIb, IIIa, fibrinogen, vWf, catecholamine's, serotonin, calcium, ATP, ADP, et cetera, which are associated with conglomeration. Differential articulations of surface receptors like CD36, CD41, CD61 et cetera have additionally been amounts in a few maladies. Platelet clinical research faces challenges because of the powerless idea of platelet structure capacities and absence of exact measure methods. Be that as it may, late headway in stream cytometry inputs immense advance in the field of platelets think about. Platelets actuation and brokenness have been ensnared in diabetes, renal illnesses, tumor beginning, Alzheimer's, and CVD. Taking everything into account, this paper explains that platelets are not that honest as they continue appearing and consequently various novel platelet biomarkers are up and coming soon in the field of clinical research which can be vital for foreseeing and diagnosing ailment state.*

1. Introduction

Platelets were found by Giulio Bizzozero in 1882 [1], however for a long time the dynamic and multifunctional nature of platelets remained a field of intrigue just for researcher. Anucleate, discoid platelets are the littlest blood particles which disclose their dynamicity through theirmorphology. Essentially they are related with hemostasis, which is to start blood coagulation. Albeit extremely powerful, they more often than not like to stay in dormant state and get initiated just when a vein is harmed. In any case, hemostasis or blood coagulation isn't the sole capacity of platelets; rather it is utilized in a few multifunctional qualities observing the homeostasis of the body. Its high affectability to various malady states in the long run appointed it to be a standout amongst the most available markers. While keeping connections with leukocytes and endothelial cells, it reestablishes its conduct as a critical incendiary marker [2]. Platelet reactivity for various sickness pathogenesis is broadly reliant upon some organically dynamic markers like CD36, CD41, CD42a, CD42b, and CD61. These incorporate some dynamic surface receptors and platelet secretory items. Platelet has a tendency to change the articulation and motioning of these markers in various illness conclusion and guess, giving an enormous field to investigate malady movement. Principally, platelet movement is related with the start of coagulation falls. Harm in vein makes the sub endothelial surface the essential target site of platelet activity, where it sets up the hemostasis. Different proaggregatory jolts otherwise called platelet agonists advance the activity of platelet grip to the sub endothelial surfaces. Amid this procedure, platelet changes its shape, discharges its granule substance, and bit by bit frames totals by following with each other [3]. Accordingly its essential movement remains related with limiting blood misfortune. Be that as it may, as examined prior platelets are restricted in managing hemostasis and thrombosis, as well as assume numerous critical parts in sickness way physiology. Platelet association and cardiovascular sickness movement remain an unsolved question for a long time

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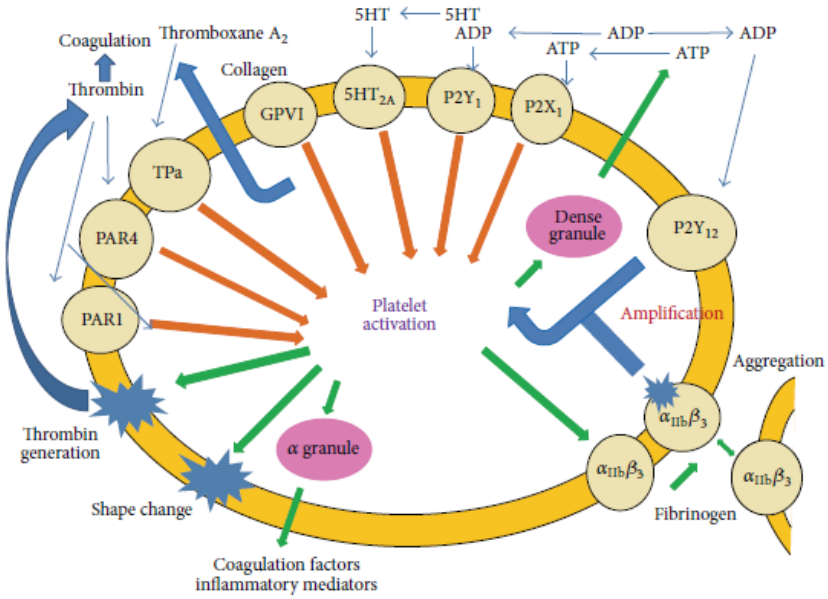

Figure 1: Platelet-activation mechanisms and role of the P2Y12 receptor. Platelet activation leads to dense-granule secretion of ADP, which activates P2Y12, inducing amplification of aggregation, procoagulant, and proinflammatory responses (adapted from Storey, 2008 [7]). With CVD remains another striking area to explore. Platelet hyperactivity in various diseases provokes adverse effects in some cases, especially in coronary artery disease where hyperaggregation obstructs blood circulation. Expression of platelet markers can be well studied by ELISA or Western blot. However, till date flow cytometry is the best standardized method to study platelet function [5, 6]. In this paper, we have tried to elucidate various aspects of platelets structure and function and their potential role in disease pathophysiology.

2. Versatility of Platelets: Its Structural and Functional Aspects

2.1. Ultra structure. Platelet ultra structure uncovers their behavioral peculiarities.Megakaryocytes of the bone marrow are site of platelet development. Breadth of develop platelet is 2-3 μm, which more often than not stays alive for 5– 9 days. Roughly 2/3 of the platelets course in the blood and 1/3 is put away in the spleen. The typical platelet check is (150– 400) × 103 for each microliter of blood. Every megakaryocyte can deliver 5000– 10000 platelets. A normal sound grown-up can create 1011 platelets for each day; old platelets are decimated by phagocytosis in the spleen and liver (Kupffer cells). Platelets are extraordinary in their auxiliary get together, however they are anucleate yet have particular mitochondria. Platelet plasma layer, made out of phospholipid bilayer, is the site of articulation of different surface receptors and lipid pontoons which helps in flagging and intracellular trafficking. These markers incorporate CD36, CD63, CD9, GPCR, IIbIIIa, and Overabundance 3. These surface receptors likewise trigger the arrival of α granules which assume a part in numerous capacities, in particular, coagulation, irritation, atherosclerosis, antimicrobial host guard, angiogenesis, wound repair, and tumorigenesis [9]. Among these surface receptors, GPCR has been accounted for to assume critical part in ADP discharge from thick granules which is its major secretory item [10]. Lopsidedly organized phospholipids (e.g., phosphatidylserine and phosphatidylinositol) exhibit in the internal layer of the plasma film keep up the steadiness of its surface amid nonprocoagulant state. Amid actuation (Figure 1) platelet surface bit by bit uncovered aminophospholipids by ATP-subordinate floppases and scramblases to start coagulation falls [11]. The open canalicular framework (OCS) is the "passage" framework display all through the platelet cell and stays associated with the plasma layer [12]. The significant part of OCS is to give section of outer components into the platelets and also to discharge its granule substance to the outside. Other than being a noteworthy stockpiling site for plasma layer glycoproteins, it encourages the development of filopodia amid platelet initiation [13]. Thick tubular arrangement of platelets is a shut station system of lingering endoplasmic reticulum and principally associated with calcium sequestration with the assistance of falls of responses including the initiation of G protein-coupled receptor Standard 1 [14, 15]. The

exceedingly specific cytoskeleton of platelets keeps up its discoid structures and in addition shields the cell from getting sheared in circulation system. It has threemajor segments: (1) the spectrinbased layer skeleton, (2) the actin cytoskeleton, and (3) the negligible microtubule curl. Platelets have two noteworthy stockpiling granules, to be specific, α and thick granules, whose capacity is to store organically dynamic atoms decisively engaged with start of coagulation and enlisting different cells amid irritation [16]. The more pervasive α granule contains proteins (e.g., GPIIbIIIa, fibrinogen, and vWf) which start the coagulation falls. Various film proteins fundamental to platelet work are additionally bundled into α granule which incorporates GPIIbIIIa, P-selectin (CD62P), and CD36. α granules likewise have the heft of cell P-selectin in their film. P-selectin by means of Pselectin glycoprotein ligand (PSGL1) has been accounted for to enlist neutrophils [17, 18]. Thick granules store an assortment of hemostatically dynamic particles which are discharged amid platelet enactment; these incorporate catecholamines, serotonin, calcium, adenosine 5□-diphosphate (ADP), and adenosine 5□-triphosphate (ATP).ADP is aweak platelet agonist, activating platelet shape change, granule discharge, and accumulation [19].

2.2. Platelet Receptors. Platelet surface receptors have been dependably a field of enthusiasm among researchers for a long time and platelets additionally can apply their granule substance amid infection guess. A rundown of platelet receptors, otherwise called platelet agonists, have been abridged in (Table 1) agreeing t their movement [20].

2.3. Platelet Endothelium Cooperation, Hemostasis, and Platelet Total. Platelets are totally not quite the same as endothelial cells and can interface in numerous ways when presented to endothelial surface (Table 2). These communications can be of traverse a separation otherwise called paracrine flagging by means of transient collaborations or through receptor interceded cell attachment. Platelets are likewise ready to discharge or exchange numerous substances as talked about before that additionally associate with endothelial cell [21]. In spite of the fact that platelets and endothelial cells are diverse from various perspectives, they do share some regular highlights, as both cell sorts are gotten from a typical bone marrow determined ancestor cell. Some of their transcriptional systems and quality articulation programs are additionally comparable like GATA-2, vWf,multimerin, and P-selectin. Them two store their bioactive materials in their cytoplasmic granules. From a transformative approach, endothelium can be considered as stationary in its way where platelets and megakaryocytes flow in bloodstream[22]. Endothelial cells with the assistance of COX-1, COX-2, and prostacyclin synthase can change over arachidonic corrosive into prostacyclin, which thusly hinders platelet work by the height of intracellular cyclic AMP levels [23]. Damage in the vessel divider actuates platelets to start coagulation, which is otherwise called hemostasis. Dynamic platelets promptly get actuated/repressed by a few endogenous and exogenous boosts. They start essential hemostasis by sticking themselves to the harmed vessel divider. GPIb-V-IX and GPIa-IIa receptors and subendothelial mixes like vWf and collagen collaborate with each other tomediate this system (Figure 6). Official of ligands to the GP receptors changes platelet shape and also triggers the arrival of its granule substance, which at last prompts the development of totals which are otherwise called "platelet attachments" or "white thrombi" (Figure 5). Platelet begins to change its shape by the development of pseudopods when intracellular Ca2+ fixation surpasses a particular edge. Amid shape change, platelet fibrinogen receptors (GPIIb/IIIa) are uncovered and enacted, and platelet-platelet collection is started. This is likewise known s essential collection which is reversible. In any case, resting platelets are not ready to tie fibrinogen. Arachidonic corrosive thromboxane pathway is a critical platelet actuation pathway (Figure 4). Ibuprofen, otherwise called acetylsalicylic corrosive, a medication broadly utilized as a part of CVD, hinders platelet collection through irreversible acetylation and inactivation of COX, bringing about blockage of TxA2 creation [24, 25]. Develop ordinary human platelets express just COX-1, as the anucleate platelet can't incorporate chemical once more. Accordingly the impact of headache medicine on them is changeless and cumulative.Thus, the cardioprotective impact of ibuprofen is applied through the irreversible and perpetual disability of thromboxane A2-subordinate platelet work, which decreases the advancement of intense blood vessel thrombosis [26]. ADP is another imperative platelet activator. P2Y12, an ADP particular receptor, is available on the platelet film and is coupled to inhibitory G-proteins and intervenes ADPinduced arrival of Ca2+, restraining adenylate cyclase and actuating the GPIIb/IIIa receptor which prompts platelet total. The thienopyridines, ticlopidine, and clopidogrel repress platelet activationviablockageof theP2Y12 receptor [27]. Thromboxane A2, ADP, and different substances, for example, serotonin, discharged from the enacted platelet, give critical positive input and fortify the platelet-rich cluster starting auxiliary conglomeration which is irreversible (Figure 3) [28].

Platelet reaction is increased by means of substances discharged by platelet granules which select different platelets and platelets. The platelet connect at first shaped to essential hemostasis is generally unsteady. Coagulation course and arrangement of thrombin and fibrin drag out optional hemostasis. Amid platelet initiation, platelet film phospholipids turn out to be contrarily charged, which encourages coagulation enactment (e.g., FV, FVIIIa, FIXa, and FX). Official of the prothrombinase complex (FXa, FVa, Ca2+, and prothrombin) to the platelet film happens in this progression. Promote platelet enactment is started by the development of thrombin. These falls prompt the arrangement of "red thrombus" reinforcing the blood coagulation [29]. In place vascular endothelium discharges two noteworthy antiaggregants, prostacyclin (PGI2) and nitric oxide (NO), which keep the development of thrombus inside the vein [31].

3. Platelet Dysfunction in Disease Pathophysiology

Lately, platelets have risen to be importantmarkers for malady pathophysiology. They are multifunctional blood particles and essential clinical focuses for some illness pathophysiology (Figure 8). Being vital incendiary markers, they assume essential parts in atherosclerosis and cardiovascular issue which are associated with sort 2 diabetes. They have significant part in tumor science and unfavorably susceptible aggravation. Thrombin, an agonist discharged by platelets has significant part in aggravation [41– 44], angiogenesis [45] and embryonic advancement [46, 47].

4. Platelet Dysfunction in Cardiovascular Disorder (CVD) and Diabetes

Diabetes mellitus is heterogeneous, multifactorial, polygenic disease characterized by defect in insulin's secretion (the beta cell secretory defect) and action (insulin resistance) [48]. Type 2 which is themost prevalent formis basically a lifestyle disorder now becoming a major global threat. Obesity is the major cause of diabetes in the adults [49]. The most prevalent diabetic macrovascular complication is cardiovascular disorder [50]. BMI was significantly and linearly associated with systolic blood pressure, fasting glucose levels, plasma total cholesterol,VLDL cholesterol, and LDL cholesterol levels and was inversely and linearly associated with HDL cholesterol

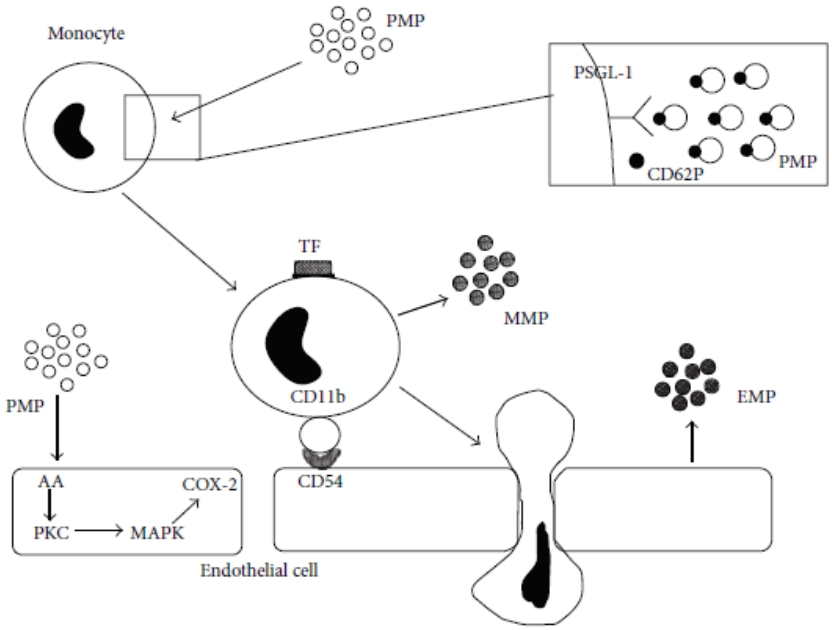

Figure 2: Mechanism of vascular changes by platelet-derived microparticles (PMPs). PMPs activate monocytes by a reaction between Pselectin and PSGL-1 (P-selectin glycoprotein ligand-1). Activated monocytes induce expression on the cell surface of tissue factor (TF) and CD11b.Activatedmonocytes also induce release ofmonocyte-derived microparticles(MMPs). PMPs induceCOX-2 production in endothelial cells. PMPs enhance expression of CD54 (ICAM-1) on the endothelial surface. Activated endothelial cells also induce release of endothelial cell-derived microparticles (EMPs), enhancing adhesion between endothelial cells and monocytes. Finally, monocytes induce migration of endothelial cells, resulting in vascular changes. Abbreviations: arachidonic acid (AA); protein kinase C (PKC); mitogen-activated protein kinase (MAPK) (adapted from Nomura, 2001 [8]).

level [51], having a direct correlation in developing T2DM. Obesity is a key feature ofmetabolic syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between body mass index (BMI) and increasing adiposity [52].

Our research group previously found hyperglycemiainduced oxidative stress in structural functional alterations of hemoglobin and red blood cells [53, 54]. But there are limited reports to elucidate the altered behavior of platelets in different diseases, majorly focusing on diabetes and associated cardiovascular disorders which are major threats to society in recent times.

4.1. Hyperaggregation in Platelets. One of the most common changes in platelet behaviour in diseased condition, such as diabetes, is platelet hyperaggregation. In response to various agonists, hyperaggregation in platelets was reported in patients with both type 2 and type 1 diabetes mellitus [55, 56]. Hyperaggregation is associated with generating more 11- dehydro-thromboxane B2 which is the important end product of thromboxane pathway as discussed earlier (Figure 2). DM has been reported to increase the production of this product as well as prothrombin accelerating aggregation; this can increase the chances of CVD among diabetic patients, as hyperaggregated platelets have a tendency to block the blood vessels. By contrast, anticoagulant markers, such as activated protein C, protein C activation peptide, and soluble thrombomodulin (TM), were depressed in T2DM, further increasing the chances of CVD [57].

4.2. Alterations inThromboxane Production. Thromboxane is an important product which plays profound role in platelet aggregation. Studies showed that thromboxane production is enhanced in diabetes subjects compared to controls increasing platelet aggregation, indicating a higher risk of CVD [58–60]. To initiate aggregation, platelets from patients with T2DM can synthesize greater amount of TxB2 but it requires less arachidonate, the precursor of thromboxane pathway and collagen, than from normal nondiabetic controls [61]. TxA2 production has been positively correlated with fasting plasma glucose and HbA1c; higher blood glucose increases the production of TxA2 which is an important product in thromboxane pathway. Several studies showed reduced TxA2 production in improved glycaemic controls [58, 62, 63]. Data suggests that 8-iso-PGF2α, a marker involved in lipid and arachidonate peroxidation; is correlated with TxA2 biosynthesis which could be a link between glycaemic control, oxidative stress, and platelet activation [64]. Thus alteration in thromboxane pathway can be a link between platelet dysfunction and diabetes, obesity, and CVD.

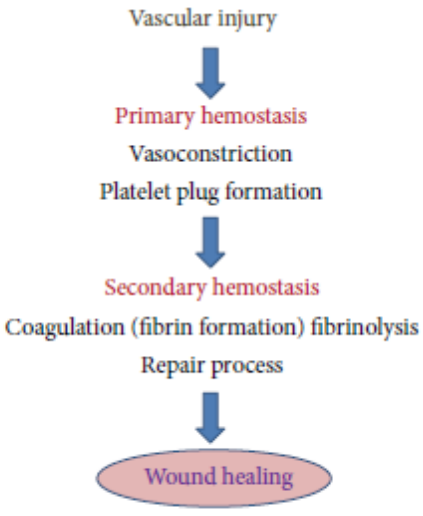

FIGURE 3: Pathway illustrating hemostasis.

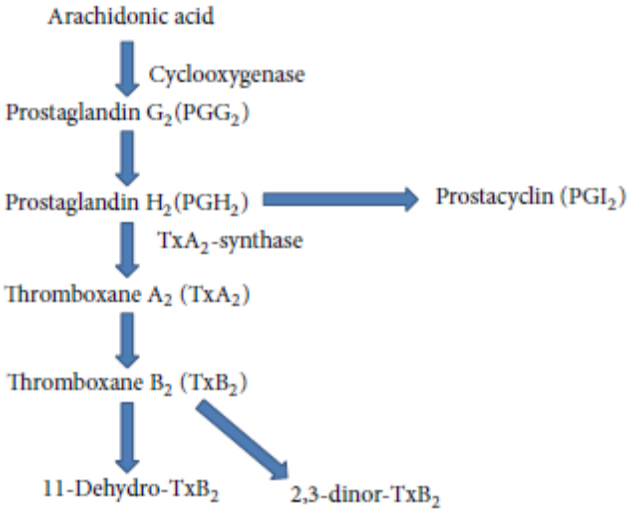

FIGURE 4: Thromboxane biosynthesis pathway.

5. Platelet Dysfunction in Other Diseases

5.1. Heart Disease. Not only diabetes related cardiovascular disorder but also platelet dysfunction has been reported in other heart diseases. It has been reported in many cases that patients with congestive heart failure (CHF) have increased risk of venous thromboembolism, stroke, and sudden death J. Mehta and P. Mehta first reported that patients with CHF have significantly higher number of circulating platelet aggregates than the normal subjects [In one study, patients with left ventricular dysfunction have shown increased number of fibrin D-dimer, fibrinogen and vWf levels compared to healthy controls Patients with acute decompensated heart failure (AHF) show more abnormalities of platelet activation than stable CHF patients and healthy controls In heart failure, endothelial nitric oxide (NO) production is much lower where oxidative stress and NO degradation rate are much higher. Platelet has been shown to produce less bioactive NO in patients with heart failure, mainly due to the defect in the the platelet l-arginine/NO/guanylyl cyclase pathway .[Thus altered platelet activity can givemajor insights into heart disease and can be an interesting field to explore.

5.2. Renal Disease. Complex hemostatic disorders have been found in patients with end stage renal disease (ESRD) that may be in form of bleeding diatheses. Platelet dysfunctions result due to the presence of toxic products in the circulating blood. Dialysis improves this complication; however, it does not eliminate the risk of hemorrhage. Some common pathological features include thrombocytopenia, glomerular thrombosis, and thrombi in small arteries and glomerular capillaries both intrinsic platelet abnormalities and impaired platelet-vessel wall interaction can contribute to platelet dysfunction In renal failure, the normal activation process of the platelets to form aggregates is impaired.

5.3. Cancer and Tumorigenesis. Platelet plays versatile role in cancer progression. The procoagulant environment provided by platelets can secure the coagulation of cancer cells, protecting them from immune system, thus prompting the formation of tumors Platelets facilitate tumor cell migration and invasiveness, prompting metastasis. It has been reported in both breast and ovarian cancer that platelets increase the invasiveness of cancer cells which can induce the further progression of the disease Moreover; tumor cells also have the ability to aggregate platelets further increasing the chance of inducing metastasis. Activation of platelets and regulation of other cells have been controlled by thrombin by means of G protein-coupled protease-activated receptors (PARs) Researchers have shown that thrombin signaling also contributes hugely to the progression of tumorigenesis and angiogenesis

5.4. Alzheimer's Disease. Platelet dysfunction has been also implicated in Alzheimer's disease (AD), which is the most common form of dementia. Platelet can store a huge amount of amyloid precursor protein (APP**)**; recent finding shows that platelet APP metabolism may accumulate Aβ in the brain and its vasculature through the blood brain barrier Platelet □-granules store RANTES, an inflammatory signaling molecule whose secretion from PBMC

has been reported to increase in AD The fluidity of the hydrocarbon region of platelet membranes from the AD patients is significantly higher than that of control group Platelet secretases activities and COX enzyme activity (which is also a component in APP secretion pathway) have been impaired in platelets of AD patients, thus making this blood particle a suitable marker of this disease

6. Conclusion

Biomarkers are currently rising with gigantic logical and clinical incentive through the entire adventure of the infection procedure. Before analysis, markers can be utilized for forecast, screening, and hazard appraisal. Amid finding, markers can decide arranging, evaluating, and determination of introductory medication treatment. Amid treatment, markers are utilized to screen the forecast of treatment or to choose extra treatment required. Platelet lists demonstrating differential brokenness, hyper enactment, conglomeration, or attachment are fit for communicating the characters of malady pathogenesis. Precise assurance of platelet files is financially savvy and their impeded capacity can be corresponded with the aggravation associated with sick state. Hence, an endeavor to recognize diverse platelet biomarkers is of critical effect on the worldwide scene of clinical application and improvement.

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