Multipotent role of platelets in inflammatory bowel diseases: A clinical approach

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Abstract

There is evidence that inflammatory bowel diseases (IBD) combine both inflammation and coagulation in their pathogenesis and clinical manifestations. Although platelets (PLT) are well known for their role in hemostasis, there are a rising number of studies supporting their considerable role as inflammatory amplifiers in chronic inflammatory conditions. IBD are associated with several alterations of PLT, including number, shape, and function, and these abnormalities are mainly attributed to the highly activated state of circulating PLT in IBD patients. When PLT activate, they increase in size, release a great variety of bio-active inflammatory and procoagulant molecules/particles, and express a variety of inflammatory receptors. These inflammatory products may represent a part of the missing link between coagulation and inflammation, and can be considered as possible IBD pathogenesis instigators. In clinical practice, thrombocytosis is associated both with disease activity and iron deficiency anemia. Controlling inflammation and iron replacement in anemic patients usually leads to a normalization of PLT count. The aim of this review is to update the role of PLT in IBD and present recent data revealing the possible therapeutic implications of anti-PLT agents in future IBD remedies.

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Key words: Anemia; Crohn’s disease; Platelets; Thrombocytosis; Ulcerative colitis

Core tip: Many platelets (PLT) changes have been described in IBD, including morphological alterations (mean PLT volume, PLT distribution width, plateletcrit, and augmented granular content), count increase, microparticles release, over-excretion of granular content, and increased formation of PLT-PLT and PLT-leukocyte aggregates, which are all linked to PLT activation induced by inflammatory agonists. In this review article, we present the multipotent role of PLT in human biological paths and emphasize on how PLT participate in the chronic intestinal inflammation process in IBD.

INTRODUCTION

Inflammatory bowel diseases (IBD), namely Crohn’s disease (CD) and ulcerative colitis (UC), are disorders that primarily affect the gastrointestinal tract. The immune system, with its active components, dominates IBD pathogenesis, but many genetic and environmental factors have been also implicated. A growing number of
studies are highlighting the importance of non-immune cells like endothelial, mesenchymal, and nerve cells, as well as platelets (PLT), as key players in the IBD inflammatory cascade[1].

PLT dysfunction is considered as participating in IBD pathogenesis, although the existing evidence is rather weak. On the other hand, there is solid evidence supporting PLT having functions of potent proinflammatory cells in addition to their role in hemostasis. Several studies have shown that PLT constitute a crucial link between inflammation and coagulation in both UC and CD, creating a vicious circle in which participating parameters conserve and propagate each other[8].

Many PLT changes have been described in IBD, including morphological alterations [mean PLT volume (MPV)], PLT distribution width (PDW), plateletcrit (PCT), augmented granular content, count increase, microparticles (MPS) release, over excretion of granular content, and increased formation of PLT-PLT and PLT-leukocyte aggregates (PLA), which are all linked to PLT activation induced by inflammatory agonists (Table 1). In the following sections, we will present the multipotent role of PLT in human biological paths and emphasize how PLT participate in the chronic intestinal inflammation process in IBD.

### Pleiotropic Function of PLT

PLT are small anuclear fragments (1-6 μm) derived from bone marrow megakaryocytes, with a 5-9 d lifespan in humans. Their primary role is hemostatic; surveying endothelial barrier and interfering when vessel integrity is threatened[9]. A significant decrease of PLT (<20000/mm³) in septic models resulted in the disruption of the endothelial barrier in clinical studies[9]. Collagen from the exposed subendothelial layer at the injured vessel site binds to plasma von Willebrand factor and recruits circulating PLT to form a glycoprotein (GP) Ib-IX-V complex. PLT adhesion to the site of injury initiates a cascade of signaling transduction through GP VI and integrin family surface receptors. PLT become activated and transform into high affinity platforms which are suitable for participating in inflammatory reactions, lipid bond, and clot formation promotion[10]. In addition, PLT participate in wound repair and tissue regeneration by interacting with components of extracellular matrix and endothelium[11].

It has been demonstrated that PLT present innate immunological properties. They express Toll-like receptors which can bind to lipopolysaccharides on the outer membrane of gram(-) bacteria[12]. In vitro and in vivo studies have also demonstrated that PLT can internalize pathogens resistant to clearance such as *Staphylococcus aureus* or HIV virus, promoting further PLT activation changes[9]. Moreover, PLT stimulate the formation of extracellular DNA nets by neutrophils that trap and kill gram(-) microbes, via the lipopolysaccharides - Toll-like receptor 4 interaction in septic models[11,13].

PLT can also act as mediators between innate and adaptive immune systems. When activated at inflammatory sites, they secrete large amounts of pro-inflammatory substances located in their intracellular granules[12] by which they crosstalk, recruit, and activate leukocytes, endothelial, and immune-like cells even at distant sites. A typical example of the remote PLT actions is the ability of PLT-derived CD40 ligand (CD40L) to activate dendritic cells in the injured tissue[13] and to stimulate immunoglobulin production by B-cell compartment[14].

PLT ability to interact with a large variety of cells is also implicated in the generation of vascular inflammation. Endothelium dysfunction triggers PLT activation processes and possibly renders PLT as the first in line to initiate atherosclerotic immune responses. Therefore production and release of PLT highly inflammatory cargo at the injured vessel wall induces and propagates the recruitment of leukocytes and the further construction of atherosclerotic lesions.

### Table 1 Platelet abnormalities in inflammatory bowel disease

| Number and morphological changes | Loss of discoid shape |
|----------------------------------|-----------------------|
| Acquisition of pseudopodia       | Size increase         |
| Count increase (reactive thrombocytosis) | Density increase     |
| Granular content augmentation    | MPV value decrease    |
| PDW value increase               | PCT value increase    |

Other abnormalities

- Overproduction and excretion of granular content products
- Increased incorporation of receptors in PLT membrane
- Overproduction of PLT-derived microparticles
- PLT-PLT aggregates formation
- Increased PLT-leukocytes formation

β-TG: β-thromboglobulin; GP: Glycoprotein; IBD: Inflammatory bowel disease; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; PF-4: Platelet factor-4; PLT: Platelets; vWF: Von Willebrand factor.

### Quantitative and Qualitative Platelet Changes in IBD

Elevation in PLT count (>450000 × 10³/L), defined as reactive thrombocytosis (RT), may frequently occur in certain conditions like hypo- or asplenism, blood loss, acute or chronic inflammatory disorders, malignancies, and iron deficiency. The first study reporting IBD RT in 1968 by Morowitz et al.[15] noted markedly-elevated concentration of circulating PLT during a period of increased clinical activity in a case series of IBD patients. This effect is the result of aberrant bone marrow throm-
bopoiesis under the influence of inflammatory mediators and the aftermath of reduced PLT lifespan due to accelerated activation and consumption of thrombocytes at the sites of inflammation.

Thrombopoiesis is mainly regulated by plasma thrombopoietin (TPO). Plasma TPO binds to C-Mpl receptors on the PLT surface, and the remaining fraction promotes thrombopoiesis by binding to the same receptors on progenitor megakaryocytes in bone marrow. Thus, in normal conditions thrombopoiesis is controlled by a negative feedback mechanism based on PLT mass in blood[16,17]. Cytokines and other inflammatory agents, especially interleukin 6 (IL-6), promote hepatic TPO production[19], which is considered an acute phase reactant[19]. Heits et al[19] have shown that IBD patients with thrombocytosis have elevated plasma TPO and IL-6 levels. However, the existing data are vague, as other studies display a lack of correlation between PLT number and TPO concentration, indicating other possible regulating factors in IBD RT[21]. Although PLT count is correlated to IBD disease activity[22], it is not considered an independent risk factor for the increased risk of thromboembolic (TE) events observed in IB patients as it is for cancer[23]. Properly designed and adequately powered clinical studies evaluating predictive laboratory indices for TE events in IBD are still lacking.

Moreover, some conflicting data have emerged over the last decade about the role of preoperative RT in the occurrence of chronic pouchitis in patients undergoing ileal pouch-anal anastomosis. Two studies from the Surgery Department Division of Colon and Rectal Surgery in California have pointed out that the presence of elevated PLT count before surgery was associated with an increased risk for chronic pouchitis postoperatively[24,25]; a severe complication that can result in the removal or diversion of the pouch. In discontinuity with these studies, Lian et al[26] failed to predict the occurrence of inflammatory pouch disorders based on pre-colectomy laboratory tests, including PLT count. Larger prospectively well-designed series with patients requiring ileal pouch-anal anastomosis are needed in order to verify possible implication of PLT in this subject.

Chronic inflammatory disorders are connected to several morphological changes in PLT indices calculated in whole blood count, such as MPV, PDW, and PCT. The most widely-studied PLT parameter in humans is MPV. PLT volume decreases when an inflammatory process is present, which is mainly attributed to thrombopoiesis abnormalities and increased PLT consumption. Inflammatory mediators stimulate bone marrow precursors to enhance PLT generation at the cost of maturation time, delivering smaller PLT in circulation, while at the same time larger and more active PLT are consumed at inflammatory sites, as is proposed in the intestinal microvasculature of IBD patients[27].

MPV changes are correlated to inflammatory disorders like myocardial infarction, stroke, diabetes mellitus, acute appendicitis, rheumatoid arthritis, chronic hepatic failure, and chronic pulmonary diseases[28-31]. Moreover, MPV could serve as a reliable predictor of high risk patients for portal venous thromboembolism[32], acute coronary syndromes[33], and stroke in patients with atrial fibrillation. MPV has also been proposed as a useful biomarker for early gastric, pancreatic, and hepatocellular carcinoma diagnosis[34], dietary compliance to celiac disease and exacerbation of chronic obstructive pulmonary disease[35].

In IBD patient studies a MPV value decrease has long been observed[36] which has been inversely correlated with endoscopic and disease activity indices, such as C-reactive protein and erythrocyte sedimentation rate[40,44]. This MPV reduction can be attributed to the decreased circulating reticulated PLT number that was found in patients with active UC compared to inactive and healthy control subjects[44]. In line, studies have reported an inverse relationship between extent of intestinal inflammation and MPV in IBD patients[40,41]. Öztürk et al[40] suggested that all PLT parameters (PDW, PCT, MPV) can prove to be useful surrogate markers for IBD follow-up, as they reveal strong relationship with activity indices. We observed that MPV, PCT, and PDW were correlated with certain iron deficiency markers (solute transferrin receptors, hemoglobin) but not with activity indices such as C-reactive protein, Crohn’s disease activity index score, or simple clinical colitis activity index score in IBD patients. This observation reflects a possible role of iron capacity as a regulator of megakaryopoiesis and PLT morphology[46]. Literature reports about MPV correlations with clinical and laboratory parameters in IBD patients are presented in Table 2.

**ASSOCIATION OF PLT WITH IRON DEFICIENCY IN IBD**

Anemia is the most frequent extra-intestinal manifestation of IBD, affecting approximately one third of patients[47,48]. The most prevailing type of IBD-associated anemia is iron deficiency anemia (IDA)[46,49]. Iron deficiency is related both with up-and downregulation in PLT count, with RT reported more frequently[50].

Several mechanisms related to iron deficiency have been implicated in PLT overproduction. Iron scarcity could trigger an increase influx of progenitor cells to the megakaryocyte cell compartment, a diminution of PLT maturation time[51], and the generation of high ploidy megakaryocytes. Megakaryocytes can proliferate through a procedure called endomitosis, and augment DNA ploidy and cytoplasmic volume and further abandon mitosis before cytokinesis take place[52]. Iron deficiency may lead to the production of larger polyploid megakaryocytes capable of generating numerically more PLT, as it is observed in an iron deficient rat model[53]. Moreover, striking amino-acid sequence homology between erythropoietin (key hormone controlling erythropoiesis) and TPO, both being members of the same hematopoietic growth
Reduced MPV in UC patients compared to HC

Reduced MPV in IBD patients compared to HC

Reduced MPV in IBD compared to HC

Correlation between MPV and disease activity indices

Reduced MPV in UC compared to HC

MPV decreases after remission in UC

MPV increases after remission in CD

Correlation between MPV and disease activity indices

Correlation between MPV and disease activity indices

Reduced MPV in CD patients compared to HC

MPV value did not correlate to disease activity

CD: Crohn’s disease; Hb: Hemoglobin; HC: Healthy controls; IBD: Inflammatory bowel diseases; MPV: Mean platelet volume; sTfR: Soluble transferrin receptor; UC: Ulcerative colitis.

Studies have also identified a correlation between PLT count, red blood cell parameters, and anemic indices in otherwise healthy IDA patients \[^{45}\]. In a recent study we observed a mutual relationship between PLT count and iron deficiency parameters. Inflammatory indices (C-reactive protein, Crohn’s disease activity index score, and simple clinical colitis activity index score) and iron deficiency markers (ferritin, soluble transferrin receptors, and index) were correlated to PLT count in 198 consecutive IBD patients, indicating that RT is probably a multifactorial event in which iron deficiency and inflammation hold a major role. Moreover, taking into account the low inflammatory indices in our patients’ cohort, we assumed that iron deficiency could be the main factor affecting PLT count in IBD \[^{46}\].

**PLT AS ACTIVE INFLAMMATORY COMPONENTS**

PLT circulate at a highly-activated state in IBD, as it is demonstrated by an increased concentration of circulating PLT activation markers in the systemic circulation of patients \[^{49}\]. This activation possibly takes place in the mesenteric microcirculation, where PLT are exposed to several inflammatory mediators \[^{49}\]. Molecules in the site of injury like subendothelial collagen, cytokines from activated leukocytes, and endothelial cells, increased local adenosine diphosphate (ADP) concentration due to reduced capillary blood flow, substances released from neighboring cells, arachidonic acid, PLT activating factor (PAF), and thrombin generation augment PLT accumulation and activation in the intestinal microvasculature in IBD \[^{49}\]. During activation, PLT lose their normal discoid shape, obtain projecting forms called pseudopodia, release an increased amount of microparticles (PDMPs), and grow in size and density. Numerous metabolic reactions happen within their cytoplasm, where various inflammatory mediators are being produced \[^{49}\].

**Table 2 Mean platelet volume correlations with clinical and laboratory parameters in inflammatory bowel disease patients**

| Ref.         | Disease (n) | HC (n) | MPV correlations                                                                 |
|--------------|-------------|--------|----------------------------------------------------------------------------------|
| Yüksel et al \[^{43}\] | UC (61)     | 27     | Reduced MPV in UC compared to HC                                                  |
| Jüremo et al \[^{49}\] | UC (18), CD (9) | 12     | Inverse correlation between MPV and disease activity                             |
| Güçlü et al \[^{45}\] | UC (41), CD (107) | (-)    | Inverse correlation between MPV and disease activity                             |
| Voudoukis et al \[^{46}\] | UC (91), CD (107) | 102    | Reduced MPV in active compared to non-active disease                              |
| Öztürk et al \[^{46}\] | UC (103), CD (72) | 40     | Reduced MPV in IBD patients compared to HC                                        |
| Kaporitakis et al \[^{46}\] | UC (93), CD (66) | 38     | Correlation of MPV with Hb and sTfR                                              |
| Kayahan et al \[^{46}\] | UC (37)     | 20     | Correlation between MPV and disease activity indices                              |
| Liu et al \[^{46}\] | CD (61)     | 50     | Reduced MPV in CD patients compared to HC                                        |

\[^{43}\] In a Kulnigg-Dabsc et al \[^{43}\] study that didn’t observe any alteration in PLT production with the concomitant use of erythropoietin combined to iron replacement therapy in IBD patients with RT.

A special interest in IDA associated RT has arisen over the last few years in IBD \[^{45,46}\]. In a Kulnigg-Dabsc et al \[^{40}\] study, iron replacement was associated with dose-dependent normalization of PLT count which remained within normal range after therapy, highlighting a regulatory rather than a toxic effect of iron on PLT. Patients presented with mildly elevated or within-normal range inflammatory indices at baseline and during treatment, demonstrating that RT could be mainly attributed to IDA rather than systemic inflammatory response \[^{43}\]. In another study, iron replacement was not only associated with PLT count decrease, but also to a significant decrease in PLT activation markers, such as P-selectin and PLT-aggregation, suggesting that iron management may express anti-thromboembolic properties in IBD patients with increased risk for TE events. However, the small number of participants and the need for study protocol modification during the active phase does not allow us to make safe conclusions \[^{46}\].

Studies have also identified a correlation between PLT count, red blood cell parameters, and anemic indices in otherwise healthy IDA patients \[^{45-48}\]. In a recent study we observed a mutual relationship between PLT count and iron deficiency parameters. Inflammatory indices (C-reactive protein, Crohn’s disease activity index score, and simple clinical colitis activity index score) and iron deficiency markers (ferritin, soluble transferrin receptors, and index) were correlated to PLT count in 198 consecutive IBD patients, indicating that RT is probably a multifactorial event in which iron deficiency and inflammation hold a major role. Moreover, taking into account the low inflammatory indices in our patients’ cohort, we assumed that iron deficiency could be the main factor affecting PLT count in IBD \[^{46}\].
PLT granular products, such as P-selectin, GP IIb/IIIa, CD40L, and GP53, are incorporated into the cytoplasmic membrane, giving them a more adhesive and interacting phenotype. Moreover, PLT during activation develop receptors for chemokines, cytokines, and complement components, enabling them to participate in various inflammatory cascades in IBD\(^1\) (Figure 2). Molecules released from the activated PLT induce an inflammatory phenotype in endothelial cells and leukocytes. Polymorphonuclear cells enhance their superoxide, PAF, and leukotriene production, and endothelial cells stimulated by certain PLT factors (PAF, histamine, and RANTES) increase vascular permeability\(^3\). CD40L(+) PLT of IBD patients induce I- and V-cell adhesion molecules (CAM) and IL-8 overexpression when co-cultured with human intestinal microvascular endothelial cells in an experimental colitis model\(^62\).

P selectin is a member of the CAMs family mainly produced in PLT. A soluble fraction of P-selectin is also detected in patients with inflammatory disorders, including IBD, and possibly serves as selectin binding inhibitor\(^63\). The lectin containing N-terminal domain of P-selectin binds to P-selectin glycoprotein ligand (PSGL-1) found in leukocytes (mainly polymorphonuclears) mediating recruitment and rolling of infiltrating leukocytes in the gut mucosa, and initiating activation processes like chemokines production by monocytes and CD4(+) T-cells, as well as superoxide overexcretion by neutrophils\(^1\). P-selectin ligation to PSGL-1 also serves in PLT-PLT aggregation and PLA formation\(^5\), induces tissue factor (TF) generation, and stimulates the release of PDMPs bearing TF by leukocytes\(^64\). The above mentioned findings highlight the significant role of P-selectin in IBD pathogenesis.

CD40L (CD 154) is a protein, strongly related to tumor necrosis factor (TNF) and expressed on the surface of activated PLT and immune system cells. CD40L has the ability to bind CD40 located on the surface of most immune, endothelial, and other mesenchymal cells\(^65\). There are three CD40 family members encountered in humans: CD40, CD40L, and the soluble form of CD40L (sCD40L) derived by enzymatic fragmentation of CD40L in serum\(^66\). The latter is believed to be produced and released only by activated PLT in IBD patients\(^67\). Increased levels of CD40L(+) PLT and sCD40L are demonstrated in disorders combining inflammation and thrombosis, such as unstable angina, myocardial infarction\(^68\), and IBD\(^67,69\).

CD40L interactions have a significant role in immune mediated activation of inflammation and thrombosis. They induce TF expression by endothelial cells and monocytes\(^65\). SCD40L is able to bind onto GP IIb/IIIa to promote arterial thrombosis stabilization, as was demonstrated in CD40L deficient mice\(^69\). Pro-inflammatory responses of CD40L/CD40 result in chemokines, ILs, and CAMs (V-CAMs, I-CAMs, P/E-Selectin) upregulation in PLT and other immune cells\(^65\). CD40L can stimulate PAF production, thus inducing PLT activation, propagating immune mediated angiogenesis in IBD in both human and murine models\(^70\), and provoking cytokine overexcretion by human intestinal microvascular endothelial cells such as IL-8, which constitutes a ma-
Intestinal microvascular inflammation

↑ thrombin
↑ ADP
↑ arachidonic acid
Proinflammatory cytokines
Subendothelial collagen exposure

PLT activation
Increased production
Activated PLT

PLT: Platelets; ADP: Adenosine diphosphate; PDMP: Platelet-derived microparticles; PDGF: Platelet-derived growth factor; EGF: Epidermal growth factor; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; PF-4: Platelet factor-4; IL: Interleukin.

Figure 2 Factors affecting platelet function and platelet products in inflammatory bowel disease. PLT: Platelets; ADP: Adenosine diphosphate; PDMP: Platelet-derived microparticles; PDGF: Platelet-derived growth factor; EGF: Epidermal growth factor; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; PF-4: Platelet factor-4; IL: Interleukin.

POTENTIAL ROLE OF PLT IN THROMBOSIS IN IBD

PLT spontaneous aggregation is a unique feature found in the blood of IBD patients that is not encountered in other inflammatory conditions. Aggregation is believed to be primarily accomplished in the mesenteric microcirculation where PLT come into close contact with increased inflammatory mediators. PLT aggregates are independent of disease activity, as their existence has been noted in colonic biopsies of IBD patients in remission, but not in healthy controls.

PLT aggregation in IBD seems to represent the initial response of PLT leading to an increased risk for TE. The reported prevalence of TE events (arterial or venous thrombosis) in IBD is between 1.3% and 6.0%, with a 1.5-3.6 fold increased risk compared to the general population and other inflammatory disorders. The development of TE in IBD seems to be multifactorial, with interaction of genetic and acquired factors (e.g., inflammation, hospitalization, and operations). TE events in IBD indicate a higher predilection towards younger age compared to non-IBD subjects. Thromboembolism is considered a negative prognostic outcome and represents one of the four leading causes of death in these patients. Thrombosis may correlate with disease activity, but it is interesting to note that one third of the events happen during clinical remission, indicating a continuous activated state of PLT and coagulation systems in IBD.

Moreover, the increased concentration of PLA in circulation is also considered as an aftermath of leukocyte sequestration in mesenteric circulation, where they bind to activated PLT. This interaction is mainly guided by PLT(+) P-selectin ligation to leukocytes PSGL-1. After this initial step, further ligation of PLT GP IIb/IIIa to MAC-1 leukocyte membrane receptors, with fibrinogen serving as the bridging connector, intensifies binding and promotes PLA formation. PLA are major inflammatory agent carriers, more active than circulating leukocytes or activated PLT alone and exhibiting an enhanced ability to adhere to mucosal endothelium. Increased PLA formation is noted in many chronic inflammatory disorders like diabetes mellitus, cardiovascular and collagenous tissue diseases, asthma, systemic lupus, and rheumatoid arthritis. Therefore, PLA is indexed as a sensitive marker of inflammation and PLT activation though not in consistency with IBD activity in recent studies.

Platelet-derived microparticles and IBD

Eukaryotic cells are capable of budding small vesicles like exosomes (endosomal products), apoptotic bodies (byproducts of cell death), and MPs. Circulating MPs are a heterogeneous mixture of cellular membrane fragments that are derived from a great variety of cells, and

Other factors (protein S, ADP, calcium, chemokines, cytokines, complement components receptors, β-thromboglobulin)
recapitulate the functions of their cellular origin. They influence a diverse series of physiological and pathological functions, as they can transfer genetic material (m-RNA, micro-RNA, DNA), membrane receptors, and a series of parental molecules to target cells. MP formation is a well-regulated process consisting of local concentration changes in specific intracellular molecules, cytoskeleton disruption, and phosphatidylserine inversion in the outer membrane layer of ancestral cells.

Although MPs are detected in low concentrations in health, a great variety of cardiovascular diseases, inflammatory disorders, cancer, and diabetes are associated with increased MP production. They are considered major procoagulant factors, due to TF and phosphatidylserine exposure on their membrane. PDMPs represent the most abundant MP population in humans, approximately 70%-90% of cell-derived MPs. Among them a large amount of PDMPs originate from megakaryocytes. PDMP production is enhanced in vitro by PLT agonists like Ca²⁺, thrombin, ADP, collagen, fibrinogen, and high shear stress, confirming the statement that PDMPs are mainly derived by activated PLT.

PDMPs are increased in autoimmune disorders such as mixed connective tissue disease, systemic sclerosis, primary Sjögren’s syndrome, systemic lupus erythematosus, rheumatoid arthritis, Raynaud’s phenomenon, and psoriasis, as well as in cardiovascular diseases such as atherosclerosis, acute coronary syndrome, pulmonary embolism, and pulmonary arterial hypertension. Moreover, they can be used as antithrombotic indicators and side-effect markers following blood transfusion.

Several studies have been conducted in IBD patients. Andoh et al. showed increased PDMPs in active IBD patients compared to inactive ones and healthy controls. PDMPs correlated with clinical disease activity indices and PLT activity markers, and significantly reduced after remission achievement. However, this study included a small sample size for exporting safe conclusions and PDMPs were measured using ELISA and not flow cytometry, the latter being considered a more reliable method. Chamouard et al. demonstrated that infliximab therapy induced a significant decrease in circulating MPs, mainly of PLT origin, in CD but not in UC, implicating that PDMPs shedding is important in the IBD inflammatory response. Finally, Palkovits et al. noted that TF(+) MP and especially TF(+) PDMPs were significantly increased in IBD patients compared to healthy controls, although they didn’t correlate with markers of coagulation activity and inflammation. These results indicate that PDMPs may have an important role in IBD. Taking into account the high procoagulant and proinflammatory predisposition of PDMPs, they can be useful targets, or even vectors, of future IBD therapies.

USE OF ANTI-PLATELET DRUGS IN IBD

Anti-PLT therapy is unanimously certified as evidence-based primary and secondary prevention therapy in high risk cardiovascular patients resulting in reduced mortality rate. Based on existing evidence, one can assume that PLT could be an ambitious target cell for IBD therapies, as it represents the critical crossroad between inflammation and coagulation.

Clopidogrel is a potent suppressor of PLT activation, PLA formation and production of PLT activation markers such as P-selectin. Clopidogrel significantly inhibited PLT inflammatory markers and resolved IBD symptoms in rats after a single intra-colonic administration of trinitrobenzenesulfonic acid and oxazolone. Moreover, salicylic compounds like 5-aminosalicylic acid regimens, which are broadly used in IBD, significantly reduced PLT activation markers in IBD patients. However, the use of aspirin even in a low dose in IBD is still uncertain, as it is associated with exacerbation symptoms and should be offered in patients with a strong indication for it. Larger randomized controlled studies evaluating its systematic anti-inflammatory effect in IBD are needed in order to verify possible benefits.

Azathioprine and 6-mercaptopurine are reported to inhibit collagen, ADP, and arachidonic acid-dependent PLT aggregation, as well as PLA aggregate formation. Other studies evaluating anti-PLT activation marker products in experimental colitis have also been conducted. CD40/CD40L pathway inhibitor (Trapidil) administration resulted in a significant reduction of colonic inflammation in wild type murine DSS induced colitis. Moreover, CD40L deficient mice exhibited a reduced infiltration of the parental molecules to target cells. MP formation is enhanced in vitro by PLT agonists like Ca²⁺, thrombin, ADP, collagen, fibrinogen, and high shear stress, confirming the statement that PDMPs are mainly derived by activated PLT.

FDTPs are increased in autoimmune disorders such as mixed connective tissue disease, systemic sclerosis, primary Sjögren’s syndrome, systemic lupus erythematosus, rheumatoid arthritis, Raynaud’s phenomenon, and psoriasis, as well as in cardiovascular diseases such as atherosclerosis, acute coronary syndrome, pulmonary embolism, and pulmonary arterial hypertension. Moreover, they can be used as antithrombotic indicators and side-effect markers following blood transfusion.

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In conclusion, there an increasing data suggesting that PLT are important key regulators in inflammatory disorders beyond hemostasis and thrombosis. Inflammation, wound repair, angiogenesis, atherosclerosis, and tumor metastasis are only some examples that reveal PLT multifactorial role. In IBD pathogenesis, PLT activation could be the missing link between inflammation and coagulation, two “independent” processes linked in such a way that each one activates and propagates the other.

Thrombocytosis has been associated with IBD mani-
festations such as disease activity, iron deficiency anemia, and development of pockiutis, whereas PLT parameters (PDW, PCT, and MPV) have been suggested as surrogate markers for IBD. PLT count increase cannot be attributed only to inflammation, as we believe that iron deficiency should be considered a major governor of thrombopoiesis. Until now, no study was designed in such a way as to discriminate to what extent inflammation and iron deficiencies are responsible for PLT increase. However, particular interest should be given to iron replacement in IBD patients, and especially those with thrombocytosis and low inflammatory indices or/and low hematocrit.

The possible association between iron replacement therapy and reduction of PLT activation markers raises new questions regarding the involvement of iron scarcity in the increased incidence of TE events in IBD patients, although the data are as yet inconclusive. Additionally, PLT parameters seem to display good predictive value regarding disease activity, and can be cautiously used as cost-effective follow-up biomarkers in IBD.

Despite the increasing number of studies revealing the dominant role of PLT in IBD, little has been clarified regarding the efficacy of anti-PLT drugs in IBD. Perhaps different existing pathways between PLT hemostasis and coagulation could explain the lack of potent anti-PLT drugs approved in IBD. Breaking this vicious cycle by altering the increased incidence of TE events in IBD patients, and especially those with thrombocytosis and low inflammatory indices or/and low hematocrit.

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