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Derleme / Review

Platelets in Preeclampsia: Function and Role in the Inflammation

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ÖZET

Preeklampside trombositlerin enflamasyondaki rolü ve etkileri

Preeklampsi tüm gebeliklerin %5-8' ini komplike eden gebeliğin hipertansif hastalığıdır. Preeklampsi patogenezinde kılcal damar yatağındaki inflamasyon önemli rol oynar. Preeklampside olduğu gibi dolaşımda serbest halde bulunan mikropartiküllerle trombositlerin karşılaşması sonucunda trombositler aktive olurlar. Aktive olan trombositler dolaşıma serbest moleküller salarlar ve hücre yüzeylerindeki adhezyon moleküllerinin artmasına neden olurlar. Serbest moleküller trombosit, lökosit ve endotel hücreleri arasındaki etkileşimleri düzenlerler. Adhezyon molekülleri de trombosit, lökosit ve endotel hücrelerinin birbirlerine bağlanmasına aracılık ederler. Oluşan trombosit-lökosit agregatları nötrofillerin inflamasyonun olduğu damarsal yapılara göçünün artmasına neden olur. Ayrıca, endotel hücrelerine bağlanan trombositler sitokinlerin yapımına ve inflamatuvar yanıtın artmasına neden olur. Bu derlemede, preeklamptik gebelerde trombosit fonksiyon bozuklukları ve trombositlerin preeklampsi patogenezindeki inflamatuvar rolünden bahsedeceğiz.
Anahtar sözcükler: Preeklampsi, trombosit aggregasyonu, trombosit aktivasyonu, inflamasyon

ABSTRACT

Platelets in preeclampsia: function and role in the inflammation

Preeclampsia is a hypertensive disease of pregnancy complicating 5-8% of all pregnancies. A growing body of evidence demonstrated that inflammation in microvasculature plays a major role in the pathogenesis of preeclampsia. Although circulating platelets are in rested state, when they are exposed to soluble mediators or microparticles in the inflamed vasculature as in preeclampsia, platelets are activated by engagement of the mediators on surface receptors. Upon activation, platelets degranulate some soluble and adhesion molecules. When soluble mediators released into the local microenvironment, they modulate the interactions between platelets, leukocytes and endothelial cells. Adhesion molecules expressed on the surface may initiate adherence between platelets, leukocytes and endothelial cells. Platelet-leukocyte aggregates promote the recruitment of neutrophils into the inflamed microvasculature. In addition to this, adherent platelets on endothelial cells induce production of inflammatory cytokines thus lead to amplification of inflammatory response. In this review, we mention platelet dysfunction in preeclamptic pregnancies and inflammatory role of platelets in the pathogenesis of preeclampsia.
Key words: Preeclampsia, platelet aggregation, platelet activation, inflammation

INTRODUCTION

Preeclampsia (PE) is a hypertensive disease of pregnancy complicating 5-8% of all pregnancies (1). Accumulating data indicated that inflammation in microvasculature is an important factor contributing to the pathogenesis of PE. Abnormal placentation is thought to be responsible from the release of microparticles and anti-angiogenic factors into the maternal systemic circulation. These soluble factors initiate activation of platelets, production of inflammatory cytokines, and vascular endothelial dysfunction (2). Although circulating platelets are in rested state, when they are exposed to soluble mediators or microparticles in the inflamed vasculature as in PE, platelets are activated by binding of the mediators on their surface receptors. Upon activation, platelets release various soluble and adhesion molecules such as CD40L, platelet endothelial cell adhesion molecule-1 (PECAM-1/CD 31). When soluble mediators release into the in the inflammatory milieu they trigger the interactions between platelets, leukocytes, and endothelial cells (ECs). The cross-talk between platelets and leukocytes stimulate the migration of neutrophils into the inflammatory site by forming platelet-leukocyte aggregates. Platelet-leukocyte association increases endothelium permeability and induce production of inflammatory cytokines thus leads to the amplification of morphological and molecular inflammatory response (3). Here we discuss the cross-talk between platelets, leukocytes and vascular cells and consequences of these interactions in PE.

Inflammatory Role of Platelet Activation in PE

It is well known that hypercoagulable state and platelet abnormalities that occur in normal pregnancy are accentuated in preeclamptic women. Particularly, thrombocytopenia in severe PE, increased platelet activation and decreased in vitro platelet aggregation to agonists in preeclamptic women has been demonstrated in previous studies (4-6). Activated platelets link hemostasis and inflammation through interaction with leukocytes and ECs (3).

Under normal physiological conditions, circulating platelets are in quiescent state. Healthy vascular endothelium secrete some mediators such as nitric oxide (NO), and adenosine which inhibit platelet activation thus, adhesion to the endothelium (7). However, inflammation in endothelium results in diminished production of these protective mediators (8). On the contrary, NO metabolites and adenosine levels are increased in preeclamptic patients in parallel to significant platelet activation in comparison with normotensive pregnants (9-11). Lyall et al. demonstrated that NO concentrations are increased in the feto-placental circulation in PE. Also, they suggested that elevated levels of NO compansate further platelet activation in preeclamptic women (9).

Circulating platelets are exposed to the soluble factors such as lipid mediators, cytokines and chemokines released by activated leukocytes and ECs as they course through inflamed vasculature (2,12,13). Accumulation of these mediators elicits an activation response that is characterized by the degranulation of platelet granules (8). Platelets contain three different types of granules (α-granules, dense core granules, lysosomes) (3). Dense granules store small non-protein molecules such as ADP, ATP and calcium. α-granules contain adhesion molecules e.g. P-selectin (CD62P), PECAM-1/CD31, glycoprotein IIb/IIIa (GPIIb/IIIa (CD41/CD61), von Willebrand factor (vWF), mitogenic factors (e.g. platelet-derived growth factor (PDGF)), vascular endothelial growth factor (VEGF), transforming growth factor-ß (TGF-ß)) and the factors relevant for coagulation and fibrinolysis. Upon activation, dense and α-granules are degranulated to play significant roles in platelet aggregation and platelet interactions with leukocytes and ECs. Thereafter, platelet-leukocyte aggregates and platelet-endothelial interaction induce production of inflammatory cytokines and amplify the inflammatory response. Platelet interaction between ECs and leukocytes is shown in Figure 1.

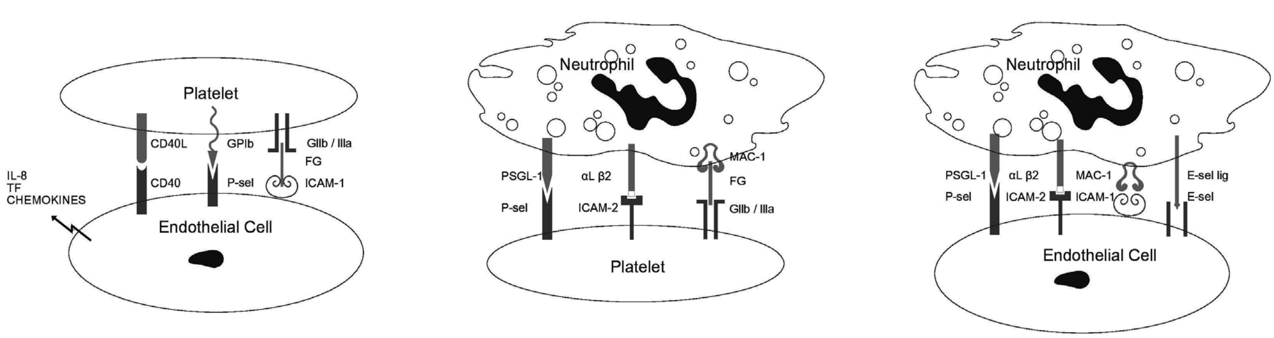

Figure 1: Interactions between platelet, neutrophil and endothelial cell in PE. Platelet adhesion to inflamed endothelial cells is mediated by CD40L, GPIb and GIIb/GIIIa with their counter-receptors CD40, P-selectin and ICAM-1 respectively. Binding of platelets to endothelium triggers secretion of IL-8, chemokines and tissue factor (TF) and followed by recruitment of leukocytes. Leukocyte recruitment leads to interaction with platelets. Firstly, platelet-neutrophil crosstalk is launched by P-selectin and PSGL-1. Thereafter, firm adhesion is formed by Mac-1/GIIb/IIIa and αLβ2/ICAM-2 ligand pairs. Also, activated neutrophiles can directly bind to endothelium through PSGL-1/P-selectin, αLβ2/ICAM-2, Mac-1/ICAM-1 and E-selectin ligand/E-selectin engagement. Mac-1, macrophage antigen-1; E-sel, E-selectin; E-sel lig, E-selectin ligand, ICAM, intracellular adhesion molecule; P-sel, P-selectin; PSGL1, P-selectin glycoprotein ligand 1; FG, fibrinogen; TF, tissue factor; αLβ2, lymphocyte function-associated antigen.

Platelet aggregation ability to different agonists has been widely studied previously in PE. Most of them have shown that PE was accompanied by a reduction in platelet aggregation in response to collagen, ADP, adrenalin and arachidonic acid compared with normal pregnancy in the third trimester (14-17). However, the platelet aggregation ability induced by the agonist, platelet-activating factor (PAF) has revealed conflicting results. Peraçoli et al. demonstrated that PE was associated with a decrease in the PAF-mediated platelet aggregation (18). On the contrary, other studies reported an increase in platelet aggregation in response to PAF (6,19). Ahlawat et al. indicated the presence of both activated (hyperaggregable) as well as exhausted (hypoaggregable) platelets in circulation of patients with PE (19). Reticuloendothelial system clears out excessive activated platelets from the circulation. Thus, remaining exhausted platelets in circulation lead to lesser aggragating ability in vivo in preeclamptic women (16). Although, studies regarding platelet aggregation abnormalities documented variable results, only one study reported that platelet aggregability might predict PE in early gestation. This study claimed that hyperaggregation response to collagen in early pregnancy had a 100% positive predictive value of subsequent PE (20). However, monitoring platelet aggregation in early pregnancy seems inadequate in predicting preeclampsia.

A growing body of evidence suggests that platelet activation demonstrated by a variety of increased soluble markers and adhesion molecules plays a central role in pathogenesis of PE. Beta-thromboglobulin (beta-TG) and Platelet Factor 4 (PF4), secreted products of activated platelets, have been shown to be increased in PE (21,22). Compared with normal pregnant or non- pregnant women, those with PE have an increased expression of activation markers such as CD62P (P-selectin), CD63, CD61 (fibrinogen receptor), CD42a (von Willebrand factor receptor), CD31 (PECAM-1) on resting platelet or in response to agonists (5, 23-25). P-selectin on activated platelet surface binds P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils, monocytes and leads to formation of platelet-leukocyte aggregates (26). This reaction initiates activation of polymorphonuclear cells (27,28). Besides, activated platelets bound on inflamed endothelium induce interactions with neutrophils first, followed by endothelial-neutrophil interactions through P-selectin-PSGL-1 receptor binding (29). Soluble P-selectin (sP-selectin), cleavage product of P-selectin released by activated platelets and ECs, has been demonstrated to increase in the plasma of preeclamptic women (30-33). These studies claimed that higher levels of sP-selectin may confirm the presence of platelet and endothelial cell activation in preeclamptic women. In addition, Chavvaria et al. reported that sP-selectin levels increased previously at mid-gestation in patients who developed subsequent PE in comparison with normal pregnants. They claimed that early enhanced activation of ECs, platelets and leukocytes seem to be present in preeclamptic patients, especially in those that develop severe PE (33). Bosio et al. also demonstrated that sP-selectin concentrations were significantly elevated by 10-14 weeks in women who later developed PE (34). On the contrary, Robb et al. found that P-selectin and sP-selectin concentrations increased with gestation compared to non-pregnant women. They argued that systemic platelet activation is a feature of pregnancy but this is not affected by established PE (35).

Platelet-Endothelial Cell Interactions

Platelets can directly initiate inflammatory responses in blood vessel walls. This response involves the interactions of CD40 with CD40L (36). CD40L has been detected in platelets and translocated to surface of activated platelets (37). The interaction of CD40L on activated platelets with CD40 on ECs or monocytes induces the synthesis of adhesion molecules, proinflammatory cytokines (e.g. IL-8), chemokines, and tissue factor (38,39). Soluble CD40L (sCD40L), cleavage product of CD40L, induce an inflammatory or thrombotic response by causing further platelet activation (40). Previous studies demonstrated that platelet surface expression of CD40 and serum concentrations of sCD40L were significantly higher in women with PE compared with the normotensive pregnant women (41,42). This may contribute to link platelet activation to inflammation and in turn to potential endothelial damage in PE (43). Upon activation, platelets release RANTES (regulated on activation, normal T cell expressed and secreted), a chemokine inducing leukocyte chemotaxis, which promotes leukocyte activation and endothelial adhesion (44). Growth-regulated protein alpha (Gro-α) is another chemokine secreted by platelets (45).

Mellembakken et al. demonstrated that Rantes and Gro-α, secreted by platelets in inflamed endothelium, increased in preeclamptic patient compared with the normotensive pregnant women (41). These findings suggest that chemotactic factors and pro-inflammatory cytokines released by activated platelets induce both activation of leukocytes and interaction between leukocytes and ECs, thereby augmenting the inflammation in microvasculature. Additionally, several studies have shown that PE was associated with endothelial cell activation markers such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin whereas normal pregnant women did not show endothelial cell activation (32,46,47). These receptors engage with the ligands on leukocytes thereby augment the inflammatory response.

Platelet- leukocyte Interactions

Platelet-leukocyte interaction is mediated by binding of P-selectin on platelets with PSGL-1 on leukocytes (48). This initial binding leads to activation of Macrophage 1 antigen, CD11b/18 (Mac-1) on leukocyte surface. Then, firm adhesion of platelet-leukocytes is formed by binding of activated Mac-1 (49,50) to its platelet ligands including GPIb (51), ICAM-2 (52) and fibrinogen bound to platelet integrins GPIIb/IIIa (53). Also, binding takes place between platelets and monocytes through thrombospondin and glycoprotein IV (CD36, thrombospondin receptor) found both on surface of these cells. Several investigators reported that preeclampsia was associated with activation of neutrophils and monocytes (23,54-56). Barden et al. demonstrated an increase in basal neutrophil CD11b and CD18 expression in women with PE (56). Moreover, another study by Lukanov et al. demonstrated that platelet-monocytes aggregates significantly elevated in PE in comparison with normal pregnancy (57). Therefore, platelet-leukocyte interactions augment the inflammatory response seen in PE.

Prediction of PE

Although many activation markers of platelets were defined in PE, only several reports mentioned about the early prediction of PE based on the elevation of these markers before 20 weeks of gestation. Of these, increased first-trimester CD63 expression in combination with first-trimester antenatal diastolic blood pressure has been claimed to predict PE (58). Also, sP-selectin was shown to be elevated in early gestation of women who subsequently develop PE (33,59).

In conclusion, platelets may have a key role in the induction of inflammation in patients with PE through the interaction with leukocytes and endothelium. However, future studies are warranted to relate the intensity of platelet activation and severity of PE.

Conflict of Interest: All of the authors declare that there is no conflict of interest.

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