P-Selectin is a Key Molecule Underlying the Pathophysiology of Aspirin-Exacerbated Respiratory Disease

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Abstract

Recently, the evidence for platelet association with allergic diseases has been established by many researches. Activated platelets contribute to airway hyperreactivity, bronchoconstriction, airway inflammation and airway remodeling in asthmatic patients. We aimed to clarify platelet activation and key molecules on platelets, which are mainly associated with the mechanism underlying aspirin-exacerbated respiratory disease.

Keywords: P-selectin; Adhesion; Aspirin-exacerbated respiratory disease; Asthma; Cysteinyl leukotriene; Platelet

Abbreviations

AERD: Aspirin-Exacerbated Respiratory Disease; COX: Cyclooxygenase; PAFL: Persistent Airflow Limitation; CysLT: Cysteinyl Leukotriene; LT: Leukotriene; uLTE4: Urinary Leukotriene E4; PGE2: Prostaglandin E2; EP2: E Prostanoid 2; AHR: Airway Hyperreactivity; ATA: Aspirin-Tolerant Asthma; PSGL-1: P-Selectin Glycoprotein Ligand 1; CD40L: CD40 Ligand; sP-selectin: Soluble P-selectin; sCD40L: Soluble CD40L; CEP: Idiopathic Chronic Eosinophilic Pneumonia; L-ASA: Lysine-Aspirin; LTC4S: LTC4 Synthase; 5-LO: 5-Lipoxygenase

Aspirin-exacerbated respiratory disease (AERD) is characterized by the triad of asthma, nasal polyposis, and hypersensitivity to aspirin and other cyclooxygenase (COX)-1 inhibitors [1]. Aspirin intolerance is one of the risk factors for severe asthma [1-3], particularly in patients with persistent airflow limitation (PAFL) [4]. The overproduction of cysteinyl leukotriene (cysLT) is the biochemical hallmark of AERD. Urinary leukotriene (LT) E4 (uLTE4) levels are 3-4 fold higher in AERD patients than in ATA patients, which further increase after aspirin-induced reaction in AERD patients [5]. Decreased levels of prostaglandin E2 (PGE2) were also a characteristic feature of AERD patients. Impaired E prostanoid 2 (EP2) expression and resistance to PGE2 were detected in nasal polyp fibroblasts from AERD patients [6]. However, the mechanism underlying the development of AERD has not been clarified in detail.

In addition to their role in hemostasis, platelets have the capacity to mediate immune responses during inflammation and to facilitate granulocyte recruitment into airways. Platelet activation has been detected in several allergic diseases, including asthma. Platelets play an important role in asthma, which contributes to airway hyper reactivity (AHR), bronchoconstriction, airway inflammation and airway remodeling [6,7]. Recently, Laidlaw and Boyce have demonstrated that platelet activity is strongly associated with the pathophysiology of AERD [7,8]. We have also hypothesized that platelets might be related to the pathogenesis of AERD because AERD patients can be caused respiratory reactions to aspirin and be desensitized with low-dose aspirin [8-12], which irreversibly inhibits COX-1 in platelets but not COX-2 in endothelial cells and leukocytes [12-14]. As circulating platelets lack a nucleus and ability of mRNA synthesis, it is generally assumed that thromboxane A2 synthesis is mainly dependent on COX-1 [14]. Refractory period to aspirin after an aspirin challenge test, which is almost equivalent to platelet lifespan, is also characteristic of such patients [15].

In this study, we recently assessed reported comparison of platelet activation in between patients with AERD and aspirin-tolerant asthma (ATA) under stable disease condition and during the aspirin challenge test [16]. Activated platelets bind to leukocytes via adhesion molecules, including P-selectin (CD62P)-selectin glycoprotein ligand 1 (PSGL-1), GPIIb/IIIa-Mac-1, and CD40 ligand (CD40L)-CD40 [17,18]. Considering this, we assessed platelet activation markers in AERD patients (n = 30) and ATA patients (n = 21) under stable disease condition, including the expression levels of P-selectin (CD62P), CD63, CD69, and GPIIb/IIIa (PAC-1) on peripheral platelets, the percentage of circulating platelet-adherent leukocytes, and the levels of soluble P-selectin (sP-selectin) and soluble CD40 ligand (sCD40L) in plasma. Ten idiopathic chronic eosinophilic pneumonia (CEP) patients (n = 10), who also showed airway eosinophilia and cysLT overproduction, and normal controls (n = 14) were also included in the study.

As a result, AERD patients showed higher expression levels of all surface markers, P-selectin, CD63, CD69, and PAC-1, on platelets, and higher levels of plasma sP-selectin and sCD40L than ATA patients. In the comparison between AERD patients and CEP patients, the expression levels of CD63 and CD69, and the level of plasma sCD40L in AERD patients were higher than those in CEP patients. Furthermore, the percentage of platelet-adherent eosinophils was significantly higher in AERD patients than in ATA patients and controls, although there was no difference between AERD patients and CEP patients.
We also assessed plasma levels of sP-selectin and sCD40L platelet activation markers in 24 AERD patients and 7 ATA patients during the aspirin challenge test. Blood samples were collected at 0-1, 1-3, 3-6, and 9-24 h after ingestion of lysine-aspirin (L-ASA) at a dose that produced a positive reaction in AERD patients or after ingestion of the last dose of L-ASA in ATA patients. The positive reaction was induced approximately 0.5-1 h after the ingestion of the last dose, and blood 0-1 h after the last dose was collected within 5-20 min from the occurrence of the reaction in AERD patients. Additionally, surface markers on platelets were also assessed at 0-1, 1-3, and 9-24 h in 8 AERD patients. Urine samples were also collected for measurements of LTE4 concentration at the following periods: 0-3, 3-6, 6-9, and 9-24 h.

There were no changes in the plasma levels of platelet activation markers and plasma markers, and the expression levels of the surface markers on platelets during the aspirin challenge test in both AERD and ATA patients. Other studies showed that platelets are activated after a mite challenge test in the early phase; however, the activation persisted until late phase after the allergen challenge test in some patients [19,20]. Our findings suggest that platelet activation did not occur in the early phase of aspirin-induced reaction. It is possible that platelets are activated in patients whose symptoms persistent for 9-24 h after aspirin-induced reaction.

When we considered the relationship of the markers with clinical characteristics, the levels of some of the platelet activation markers correlated with uLTE4 level and pulmonary function. In particular, the level of plasma sP-selectin well correlated with uLTE4 level and pre- and post-bronchodilator pulmonary function. Platelets lack 5-lipooxygenase (5-LO); however, adherent platelets contribute to the transcellular metabolism of LTs from leukocyte-derived LTA4 via LTC4 in platelets [21,22]. Laidlaw et al. demonstrated that almost 70% of the LTC4 activity in the granulocytes from AERD patients was platelet-derived, and uLTE4 concentration correlated strongly with the percentage of platelet-adherent leukocytes in peripheral blood [23].

Platelets in both mice and human subjects express the type 1 receptor for cysteinyl leukotrienes (cysLT1R) and cysLT2R, and can be stimulated by cysLT. The P2Y12 receptor was found as a novel receptor of LTE4, and mice lacking this receptor do not show allergic responses stimulated by cysLT. cysLT2R signaling by LTC4 subsequently causes an autocrine ADP-mediated response through the P2Y12 receptor, which induces the expression of P-selectin on the surface of murine platelets [24]. However, LTC4 cannot induce P-selectin expression on platelets from allergic patients [25]. It remains to be clarified whether platelets might be further activated by cysLT and serve in a positive feedback loop for inflammation in AERD patients.

Another study also indicated that P-selectin on the platelet surface is a key molecule in pulmonary eosinophil recruitment in patients with allergic asthma [26]. Platelet-adherent leukocytes, which highly express integrin, are recruited to airways by their firm adhesion to the bronchial endothelium [7]. In this study, AERD patients characteristically show severe eosinophil infiltration into the upper and lower airways and PAFL. Platelet adhesion to leukocytes particularly via P-selectin/PSGL-1 might mediate severe eosinophilia in airways of AERD patients.

In conclusion, P-selectin was found to be the key molecule related to cysteinyl leukotriene overproduction and PAFL in AERD patients. P-selectin might be a therapeutic target molecule in AERD patients. Furthermore, other antiplatelet therapies, blockade of the thromboxane A2 and P2Y12 receptors, would also be therapeutically useful in AERD patients.

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References


