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Role of platelets in allergic airway inflammation

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Increasing evidence suggests an important role for platelets and their products (eg, platelet factor 4, β-thromboglobulin, RANTES, thromboxane, or serotonin) in the pathogenesis of allergic diseases. A variety of changes in platelet function have been observed in patients with asthma, such as alterations in platelet secretion, expression of surface molecules, aggregation, and adhesion. Moreover, platelets have been found to actively contribute to most of the characteristic features of asthma, including bronchial hyperresponsiveness, bronchoconstriction, airway inflammation, and airway remodeling. This review brings together the current available data from both experimental and clinical studies that have investigated the role of platelets in allergic airway inflammation and asthma. It is anticipated that a better understanding of the role of platelets in the pathogenesis of asthma might lead to novel promising therapeutic approaches in the treatment of allergic airway diseases. (J Allergy Clin Immunol 2015;135:1416-23.)

Key words: *Platelets, asthma pathophysiology, leukocyte recruitment, dendritic cells, T_H2 sensitization, airway remodeling*

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Abbreviations used
ADP: Adenosine diphosphate
BHR: Bronchial hyperresponsiveness
CD40L: CD40 ligand
DC: Dendritic cell
5-HT: 5-Hydroxytryptamine
TLR: Toll-like receptor

Platelets are anucleated blood elements that are involved in hemostasis and thrombosis. However, it has also been recognized for some time that platelets can have a range of other functions that are relevant to the pathogenesis of allergic airway diseases, such as asthma. Intriguingly, it is now understood that platelets can act as inflammatory cells and contribute to host defense against infection, performing many functions normally associated with leukocytes. For example, platelets can undergo phagocytosis[1] and chemotaxis[2,3] and release a wide variety of inflammatory mediators that coordinate inflammatory cell activation (release potent defensive products that are active against pathogens). They can also be activated by certain inflammatory mediators themselves.[4-6] It is now clear that platelets are a necessary component of host defense exemplified by recent observations that platelet depletion leads to a reduced ability of animals to resist infections by microorganisms.[1,7,8] This involvement of platelets is probably through an ability to optimize the recruitment of leukocytes into tissues because platelet depletion has now been reported to lead to a reduction of leukocytes infiltrating a number of tissues (including the lung) in response to both nonallergic (eg, bacterial LPS and zymosan[3]) and allergic stimuli.[2] Given that many inflammatory diseases are the result of inappropriate activation of pathways normally reserved for host defense, it is plausible that inappropriate platelet activation might also contribute to the pathogenesis of inflammatory diseases.

In the present review we provide evidence for platelet activation in patients with asthma and other allergic diseases, including recent evidence of platelet involvement during sensitization to allergens, along with our current understanding of the mechanisms whereby platelets can contribute to many of the features of allergic airways disease, including acute bronchoconstriction, leukocyte infiltration, airway remodeling, and bronchial hyperresponsiveness (BHR; summarized in Fig 1).[9]

EVIDENCE FOR PLATELET ACTIVATION IN PATIENTS WITH ALLERGIC INFLAMMATION AND ASTHMA

Of particular relevance to allergic inflammation is the observation that platelets express ***IgE receptors*** on their surfaces.[10] Human platelets have been shown to express both high-affinity[10] and low-affinity[11] IgE receptors, although the level of expression of these receptors is variable and they are not found on all platelets from a given donor. Nonetheless, the expression of IgE receptors on platelet surfaces is clearly important for optimal host defense against parasitic infections because, based on the seminal work of Capron and Joseph[11] in the 1980s, we know that platelets expressing IgE receptors play an essential role in killing certain types of parasites. Therefore it is not surprising that platelets from patients with allergic disease can also respond to common airborne allergens, such as those derived from house dust mite.[2,12]

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Terms in boldface and italics are defined in the glossary on page 1417.

However, it is important to recognize that allergen-induced platelet activation is distinct from the classical aggregation and secretion induced by thrombotic stimuli.[10,13] Moreover, platelets obtained from allergic donors undergo chemotaxis *in vitro* when exposed to the allergen to which the patient is sensitized. This direct activation of platelets to migrate in response to allergens might help explain the observation that platelets have been found extravascularly in the lung tissue of allergic mice at early time points after allergen exposure.[2] These observations of platelet migration into the lung are consistent with other reports that platelets have been found extravascularly in other settings, such as in synovial fluid of patients with arthritis.[14,15]

Consistent with the presence of IgE receptors on platelets, platelet activation has been demonstrated to accompany allergen exposure in patients with allergic asthma. Thus allergen challenge is associated with a mild peripheral thrombocytopenia, presumably as a result of localized pulmonary recruitment[16] and the presence of platelet leukocyte complexes in the circulation.[12,17] Platelet activation has also been observed in patients with asthma, measured as an increase in the levels of a number of platelet-derived mediators, such as platelet factor 4, β-thromboglobulin (β-TG), RANTES, and thromboxane in peripheral blood or in bronchoalveolar lavage fluid, respectively.[13,18,19] It has long been known that platelets isolated from peripheral blood of patients with allergic disease have also been shown to have abnormal platelet aggregatory responses *in vitro* that correlate with IgE levels.[20,21] Such platelets are thought to represent an "exhausted platelet" phenotype as a result of the platelets having been continuously activated *in vivo*.[20,21] This altered platelet behavior manifests itself in allergic patients as a mild hemostatic defect associated with prolonged bleeding time.[20,21] Thus despite platelet activation in response to allergen exposure, the incidence of cardiovascular events in patients with asthma is no greater than in the general population, and indeed, there is some suggestion that they actually have less calcification of their arteries,[22,23] suggesting a specific dichotomy in platelet activation and function in allergic inflammation distinct from that involved in hemostasis and thrombosis (see below). It has also been reported that patients with allergic asthma have a shortened platelet survival time that can be corrected after treatment with glucocorticosteroids,[12,13] and an increase in the number of ***megakaryocytes*** found in the pulmonary circulation has also been demonstrated at autopsy of patients who have died of status asthmaticus.[24]

PLATELETS AND BRONCHOSPASM

One of the earliest observations that platelets might play a role in asthma was the ability of this cell to release ***spasmogens*** for airway smooth muscle[5] and that depletion of platelets from experimental animals led to the abolition of bronchospasm induced by substances that could activate platelets.[25,26] Indeed, more than 3 decades ago, platelet depletion was observed to inhibit allergen-induced bronchoconstriction in the rabbit,[26] observations subsequently confirmed[27] and extended to the bronchoconstriction induced by mediators known to be released by platelets such as platelet-activating factor.[25] It is now evident that platelets can release a number of spasmogens that can cause constriction of human airway smooth muscle,[5,12] including ***5-hydroxytryptamine (5-HT)***, which has been demonstrated to induce bronchoconstriction in asthmatic patients.[28] This is of interest because animals deficient in one of the enzymes involved in the synthesis of 5-HT have reduced allergen responses in the airways because of decreased platelet sequestration and subsequent release in the lungs.[29] Furthermore, we have recently demonstrated that platelet depletion can reduce the ability of bradykinin and capsaicin to induce bronchoconstriction in guinea pigs but is not able to influence bronchoconstriction induced by the direct-acting spasmogens methacholine and histamine.[13]

PLATELETS AND BHR

Platelet depletion has also been reported to reduce allergen-induced BHR in allergic rabbits[27] associated with a reduction in eosinophil infiltration into the lung. Recently, Lommatzsch et al[30] have suggested that platelets can cause airways obstruction and BHR through an effect involving nerve growth factor, and others have suggested the release of "platelet-derived hyperreactivity factor"[13,30] might contribute to BHR. Interestingly, the platelet-derived mediator platelet

GLOSSARY

CD11B/CD18: Also known as complement receptor type 3 (CR3), which binds iC3. Deficiency of CD18 in patients with type I leukocyte adhesion deficiency results in a lack of β_2-integrin adhesion molecules.

CD40 LIGAND: A cell-surface molecule found on $CD4^+$ T lymphocytes. CD40 ligand interactions with CD40 are important for germinal center formation and terminal differentiation of B lymphocytes. CD40 ligand mutations are responsible for X-linked hyper-IgM syndrome.

5-HYDROXYTRYPTAMINE (5-HT): Also known as serotonin. Tryptophan is the precursor of serotonin. There are more than a dozen serotonin receptors. Ondansetron and sumatriptan bind to 5-HT receptors. Melatonin is synthesized from serotonin in the pineal gland. Most serotonin is found outside the central nervous system. Serotonin helps regulate cardiovascular function, bowel motility, and bladder control.

IgE RECEPTORS: The high-affinity receptor, known as FcεRI, has higher binding affinity for IgE than any other Fc receptor for its ligand. FcεRI is mainly expressed on mast cells and basophils. FcεRII, also known as CD23, is related to C-type lectins and has a constitutive form (CD23a) and a form induced by IL-4 (CD23b). FcεRII mediates endocytosis of IgE-coated particles.

LEUKOTRIENES: Lipids derived from arachidonic acid through the lipoxygenase pathway. Leukotriene (LT) C_4 is degraded into LTD_4 and LTE_4. Cysteinyl leukotrienes are powerful bronchoconstrictors. Cysteinyl leukotrienes also have the ability to affect blood vessels, mucociliary clearance, and eosinophilic inflammation.

MEGAKARYOCYTES: A cell derived from hematopoietic stem cells that reside primarily in the bone marrow. Mature megakaryocytes release roughly 2×10^{11} platelets into the bloodstream per day in healthy adults.

SPASMOGENS: A substance that produces smooth muscle contractions. Examples include histamine, serotonin, and bradykinin. Airway smooth muscle in asthmatic patients has been shown to have increased shortening velocity and maximal shortening.

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