Review

Platelet function in anaphylaxis

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Summary. Human platelets, following immunological or nonimmunological activation, are capable of releasing a variety of biologically active mediators and are able to actively participate in hypersensitivity reactions, including anaphylaxis. These cells constitutively express functional receptors for the Fc fragment of IgE, both the low affinity receptor (FcεRII) and the high affinity receptor (FcεRI), and could be activated via IgE. Alterations in platelet function have been demonstrated in patients with allergy and nonallergic hypersensitivity, including hypersensitivity to acetylsalicylic acid. Moreover, activated platelets may be responsible for anaphylactic transfusion reactions. Various haemostatic disturbances, particularly a drop in platelet number, were observed during anaphylactic shock. The current review summarises the data from human and experimental studies on platelet function in anaphylactic reactions.

Key words: anaphylaxis, platelet function

Resumen. Las plaquetas humanas tras activación inmunológica o no inmunológica tienen la capacidad de liberar varios mediadores biológicamente activos y son capaces de participar de forma activa en las reacciones de hipersensibilidad, incluida la anafilaxia. Estas células expresan constitutivamente receptores funcionales del fragmento Fc de la IgE, tanto el receptor de baja afinidad (Fcε RII) como el receptor de alta afinidad (FcεRI), y pueden activarse mediante la IgE. Se han observado alteraciones de la función plaquetaria en pacientes con alergia e hipersensibilidad no alérgica, incluida la hipersensibilidad al ácido acetilsalicílico. Además, las plaquetas activadas pueden ser las responsables de las reacciones transfusionales anafilácticas. Se observaron varios trastornos hemostáticos, especialmente una reducción de la cifra de plaquetas durante un shock anafiláctico. El presente artículo resume los datos de estudios experimentales y en humanos sobre la función plaquetaria en las reacciones anafilácticas.

Palabras clave: Anafilaxia, función plaquetaria.

Anaphylaxis is a life-threatening, generalized or systemic hypersensitivity reaction, which is immunological or non-immunological in nature, and is triggered by many agents, including allergens [1]. Besides predominant mast cells, other inflammatory cells may be actively involved in hypersensitivity reactions. It has been hypothesised that hyperimmunization of patients with allergies might block IgE-mast cell-mediated symptoms but promote activation of an alternative anaphylaxis pathway. This consideration is consistent with the observation that not all humans experiencing anaphylaxis present evidence of mast cell degranulation [2].

Platelets, following stimulation by immunological and other stimuli, may modulate immuno-inflammatory reactions, including early- and late-phase allergic response. Many investigators reported allergen-induced changes in platelet activity in experimental animals and patients with atopic diseases [for review 3, 4]. Platelets can play a compensatory role in the development of immediate allergic responses in skeletal muscles in the absence of mast cells in mast cell-deficient mice. It seems that platelets may mediate both allergen-induced vascular permeability and leukocyte recruitment in the absence of mast cells. These data, in part, may explain the phenomenon of anaphylactic shock observed in mast cell-deficient mice [5].

It has been demonstrated that human platelets constitutively express functional FcεRI [6, 7] and FcεRII [8, 9], the receptors for IgE and that these cells may be capable of releasing different inflammatory mediators following antigen-specific activation through these receptors. Human platelets, incubated with the serum from patients with schistosomiasis or allergic asthma, became activated and cytotoxic in an allergen-specific mechanism

associated with the interaction of specific IgE bound to the platelet surface with the relevant antigen [10]. Flow cytofluorometric analysis revealed that 20% of platelets express FcεRII receptor and that the percentage of which increase up to 50% in patients with IgE-dependent allergic disorders or parasitic infections accompanied by high levels of circulating IgE [8, 9]. In allergic asthma and in patients with *Hymenoptera* venom hypersensitivity, IgE-dependent platelet activation expressed by the release of cytocidial mediators can be specifically triggered by the corresponding allergen [11]. In addition, it has been shown that activation of human platelets via the FcεRI induced release of platelet-derived mediators, such as serotonin and chemokine-like RANTES [7]. However, no significant differences were detected in the levels of FcεRI expression or this receptor-mediated serotonin release from platelets obtained from healthy individuals and atopic subjects [7].

Moreover, it has been demonstrated that platelets can be activated through direct contact with T cells, and through the release of RANTES, a chemokine containing the C-C motif, secondarily recruiting more T cells that lead to further platelet activation [12], suggesting a link and positive feedback between platelets and T cells. Interestingly, in aspirin-induced asthma, a direct, non-IgE-dependent platelet activation by cyclooxygenase- inhibiting nonsteroidal anti-inflammatory drugs has been shown. Aspirin, indomethacin or flurbiprofen strikingly activated platelets from aspirin-sensitive asthmatics – characterised by the generation of cytocidial supernatants and a burst of chemiluminescence, but had no effect on platelets from healthy subjects. Sodium salicylate and salicylamide, which do not inhibit cyclooxygenase and are well tolerated by aspirin-sensitive patients, did not activate platelets from these patients to release of cytocidial factors [11, 13].

It is well known that the use of intravascular radiocontrast media may be associated with serious adverse reactions such as anaphylactic shock, and it is the most common iatrogenic cause of anaphylactic reactions. It has been demonstrated that some contrast media may be responsible for stimulation of platelet release reaction [14, 15]. Platelet degranulation *in vitro* induced by contrast media seems to be independent of their nonionic or ionic nature [14]. Using flow cytometry, it has been demonstrated that both ionic and nonionic contrast media degranulate blood platelets when mixtures of blood from normal donors and contrast media. The platelet degranulation does not significantly increase platelet function, as measured by flowing whole blood platelet aggregometry [14, 15]. The clinical implications of these findings are unclear and there is discrepancy between results obtained from *in vivo* and *in vitro* studies. However, it might be possible that changes in platelet activity induced by radiographic contrast media entail an increased risk of adverse reactions such as anaphylaxis, especially in atopic patients.

Interestingly, it is possible that activated platelets or platelet-derived microparticles are involved in anaphylactic transfusion reactions. Taking into consideration that anaphylactic reactions to platelets occur at a similar incidence per exposure as penicillin antibiotics, platelet-dependent reactions should be further investigated [16].

Platelets are a rich source of biologically active mediators, including chemokines which belong to C-C and C-X-C subfamilies, and these cells contain chemokine receptors. Chemokines, pro-inflammatory cytokines, are characterized by the presence of four conserved cysteine residues and are subdivided into 2 major subfamilies on the basis of positioning of these cysteine residues. The C-C subfamily has the first two cysteine residues adjacent to each other. The C-X-C subfamily is characterised by the separation of the first two cysteine residues by a variable amino acid [17]. The functionality of platelet-derived chemokines as well as the role of chemokine receptors has remained obscure. It has been suggested that chemokine receptors on platelets may be involved in inflammatory or allergic responses or in platelet activation in humans [18].

Beta-thromboglobulin (ß-TG) and platelet factor 4 (PF-4) belong to the C-X-C chemokines and are responsible for the accumulation and activation of leukocyte populations at the inflammatory sites [19]. These chemokines are closely similar in structure and immunologically specific for platelets and are established markers of platelet activation *in vivo* [20].

PAF (platelet-activating factor) is released by a variety of cells, including platelets, and it is an important mediator of inflammation and anaphylaxis [21]. It has been shown that PAF induces platelet aggregation [22] and release of their mediators including histamine, serotonin, PF-4 both *in vitro* and during anaphylaxis in the rabbit [23, 24]. It has been shown that PF-4 is implicated in histamine release from basophils [25] and mast cells [26]. Interestingly, it has been hypothesised that the release of histamine from human basophils by PF-4 may represent an important positive feedback mechanism in some immediate-hypersensitivity reactions. If IgE-dependent stimulation of basophils generates PAF that recruits platelets and induces the liberation of PF-4 [23], then PF-4 may be capable of augmenting and prolonging the hypersensitivity reaction by stimulating additional basophils, irrespective of their state of sensitization with IgE [25].

PAF may be a lethal mediator in anaphylactic shock; PAF antagonists and inhibitors are able to prevent PAF-induced death and death due to anaphylactic shock in animals [27, 28].

Using a murine model of penicillin V-induced systemic anaphylaxis, it has been demonstrated that induction of anaphylaxis causes a rapid increase in circulating PAF level [29]. Heuer et al. observed increased plasma level of PAF in patients with adverse anaphylactic reaction to intravenous analgetics [30]. However, the significance of PAF in anaphylaxis may vary between animals and humans.

It is known that different hemostatic disturbances occur during anaphylaxis, including alterations in platelet function. Sequestration and activation of platelets

accompany changes in platelet function during anaphylaxis. It has been shown that the number of circulating platelets decreases abruptly in the early phase of severe anaphylactic shock in rats. The aggregated platelets were removed from the circulation mostly by the spleen, and parts of them were accumulated in the lung and the small intestine. The loss of platelets was manifested by the prolongation of bleeding time [31]. It is of interest to note that prolonged bleeding time was also observed in subjects suffering from respiratory atopy [32, 33]. Pinckard et al. observed dynamic changes in circulating platelet number during IgE-induced anaphylactic shock, suggesting that IgE-induced platelet alterations, probably induced by PAF, play a major role in the pathogenesis of anaphylaxis in the rabbit [34]. In this study, intravascular aggregation and pulmonary sequestration of platelets were demonstrated within 30-60 sec after an i.v. antigen injection into animals making only IgE antibody against the antigen, which results in the development of a profound but transient thrombocytopenia. The number of platelets in the systemic circulation returned to normal, prechallenge level within 60 min, in part explaining the difficulties encountered in demonstrating these cells at inflammatory sites [34]. Interestingly, the platelets that returned to the circulation 1 hour after the anaphylaxis were shown to be unresponsive to the secretion-inducing activity of PAF as compared with platelets examined before antigen challenge. By contrast, platelet responsiveness to other stimuli such as collagen, thrombin and C3b was unchanged. The state of specific desensitization of platelets to PAF upon their subsequent return provides strong evidence for the action of this mediator on platelets *in vivo* during IgE-mediated anaphylaxis [35]. Specific depletion of circulating platelets significantly decreased the anaphylactic response, protected against the lethal consequences of the antigen provocation and markedly reduced other parameters of anaphylaxis in rabbits [34]. Using two murine models of PAF-induced death and active anaphylactic models, it has been demonstrated that human recombinant plasma-type PAF acetylhydrolase reduces mortality in a dose-dependent manner, suggesting that PAF is an important mediator in the lethality of anaphylaxis, and that PAF acetylhydrolase may be beneficial for treatment of anaphylactic shock [28].

Moreover, platelet function was investigated in humans with hypersensitivity to *Hymenoptera* venom (yellow-jacket or honey-bee venom), the allergic disorder that induces IgE-mediated systemic reactions. Significant modulation of IgE-dependent platelet reactivity during specific desensitization in patients with *Hymenoptera* hypersensitivity and a history of anaphylactic reactions was also observed [36].

It has been demonstrated that platelets from patients with a history of anaphylactic reaction (largely local and systemic), positive skin test and high values of specific IgE release cytocidial factors and generate specific platelet chemiluminescence after their *ex vivo* activation by venom antigen. The decrease in platelet reactivity towards specific *Hymenoptera* venom was observed in patients with a history of severe anaphylactic reactions after effective desensitization by the rush method [36, 37]. Interestingly, in two cases of polysensitized patients, after *Hymenoptera* venom desensitization alone, platelets not only lost their reactivity to venom but also towards the other allergen. In addition, the decrease in skin-test sensitivity after this therapy correlated with the decrease in platelet reactivity [37]. We observed a significant diminished platelet aggregation response in house dust mite-sensitive patients with persistent allergic rhinitis, which partially improved after specific allergen immunotherapy [38].

Conclusions

A growing body of evidence indicates that platelets are important cells in different-types of hypersensitivity reactions, in which these cells may participate as secondary cells stimulated by other inflammatory cells and as effector cells directly activated by antigens. Further studies should be performed, especially in humans, to clarify the significance of platelets in anaphylaxis.

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