

The IgE-dependent pathway in allergic transfusion reactions: involvement of donor blood allergens other than plasma proteins

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Received: 22 January 2015 / Revised: 18 March 2015 / Accepted: 25 March 2015
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Abstract On transfusion, several plasma proteins can cause anaphylaxis in patients deficient in the corresponding plasma proteins. However, little is known about other allergens, which are encountered much more infrequently. Although it has been speculated that an allergen-independent pathway underlying allergic transfusion reactions (ATRs) is elicited by biological response modifiers accumulated in blood components during storage, the exact mechanisms remain unresolved. Furthermore, it is difficult even to determine whether ATRs are induced via allergen-dependent or allergen-independent pathways. To distinguish these two pathways in ATR cases, we established a basophil activation test, in which the basophil-activating ability of supernatants of residual transfused blood of ATR cases to whole blood basophils was assessed in the presence or absence of dasatinib, an inhibitor of IgE-mediated basophil activation. Three of 37 supernatants from the platelet concentrates with ATRs activated panel blood basophils in the absence, but not in the presence, of dasatinib. The basophil activation was inhibited by treatment of anti-fish collagen I MoAb in one case, suggesting that the involvement of fish allergens may have been present in donor plasma. We concluded that unknown non-plasma proteins, some of which had epitopes similar to fish antigens, in blood component may be involved in ATRs via an allergen/IgE-dependent pathway.

Keywords Allergic transfusion reactions · Basophil activation test · IgE-dependent pathway · Fish (mackerel) antigen

Introduction

Non-haemolytic transfusion reactions (NHTRs) comprise the most common type of transfusion reactions and include transfusion-related acute lung injuries, transfusion-associated circulatory overloads, allergic reactions, febrile reactions, post-transfusion purpura and graft versus host disease [1, 2]. Allergic transfusion reactions (ATRs) are the most common adverse events associated with the transfusion of plasma and particularly platelet concentrate (PC) and occur at a similar incidence as febrile reactions among patients receiving red blood cell transfusions [3–5]. ATRs most commonly manifest as urticaria, pruritus, erythematous rash, angioedema, bronchospasm and/or hypotension. These manifestations occur on a spectrum of severity and are most commonly mild and involve only localised pruritus and/or urticaria. More severe reactions involving angioedema, bronchospasm or hypotension occur in <1 % of all ATRs [4, 6, 7].

ATRs are mediated by mast cells and/or basophils. In general, the activation of mast cells/basophils and subsequent histamine release are mediated via 2 pathways, the allergen/IgE-dependent and independent pathways [5, 7]. The allergen/IgE-dependent pathway typically occurs after high-affinity FcεRI on the cell surface aggregates in response to the cell surface binding of IgE in complex with specific allergens [8–10]; but the only reported allergens in blood components are plasma proteins such as haptoglobin [11, 12], IgA [13, 14], and C4 [15, 16]. Transfusion recipients who are deficient in and possess antibodies against

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these plasma proteins may develop serious ATRs. However, plasma protein deficiencies and specific IgE levels are not always evaluated in ATR cases and even when such factors are evaluated, they are rarely identified [7, 17, 18]. The alternative allergen/IgE-independent pathway that underlies ATRs is largely unknown, and its activation via biological response modifiers (BRMs) such as accumulated inflammatory cytokines and chemokines in stored blood components has only been speculated [7, 19–23].

Recently, an interesting case report was published, suggesting that transfusion-related anaphylaxis occurred after the passive transfer of peanut allergens to a sensitised person [24]. In brief, the patient had a history of serious peanut allergy and his serum contained specific IgE antibodies against the major peanut allergen Ara h2. In addition, three-fifths of the blood donors recalled having eaten several handfuls of peanuts on the evening before they donated blood. Lingbao et al. also reported a case of ATR that was likely caused by the passive transfer of shrimp antigens to a shrimp-allergic patient [25]. However, these reports are limited by the lack of direct data to demonstrate that the food allergens were present in the blood components, although several other studies have shown that substantial amounts of food allergens are absorbed into the blood circulation in a digested form but retain certain molecular sizes and antigenicities [26, 27].

In the present study, we initially screened for PC transfusion-induced ATR cases in which the residual transfused blood supernatants exhibited basophil-activating abilities; subsequently assessed the basophilic activation pathway and finally, if the pathway was allergen/IgE-dependent, explored the possible involvement of antigen(s) present in donor blood other than plasma proteins. The PC supernatants of 3 anaphylactic shock cases activated basophils via the Fcε receptor in a basophil activation test (BAT). None of the patients in these 3 cases exhibited plasma protein deficiency or possessed antibodies against plasma proteins. In one case, in addition to the PC supernatant, the corresponding plasma collected at the same time as the PC revealed similar basophil activation activity. Furthermore, basophil activation could be inhibited via treatment with an anti-fish collagen I antibody. These results suggested that non-plasma protein antigen(s) present in the donor plasma, including food-derived antigens such as fish antigens, were possibly involved in ATRs.

Materials and methods

PCs associated with or not associated with ATRs and their corresponding plasma collected at the same time as PCs

From July 2008 to September 2009, 37 cases of ATR caused by PC transfusion were reported to the Japanese Red Cross

Table 1 Summary of ATR cases

Symptoms	Number of cases		
	Total	BAT-positive	Allergic histories ^a
Anaphylactic shock	11	3	2
Anaphylaxis	1	0	0
Hypotension	7	0	0
Allergic	11	0	0
Others	7	0	2
Total	37	3	4

^a All histories were against drug and observed in patients of BAT-negative cases

Kinki Block Blood Center. All of these residual products were collected between 3 and 7 days of ATR occurrence, and the cell-free PC supernatants were separated from the platelets via centrifugation at $18,600\times g$ for 10 min at room temperature and stored at -40°C . The clinical symptoms of the 37 cases are summarised in Table 1. No antibodies against plasma proteins, including IgA, haptoglobin, C4, C9, α_2 -macroglobulin and ceruloplasmin, HLA class I, HLA class II or human platelet antigens (HPAs), were detected in the patients' sera. In addition, IgA, haptoglobin, C4, α_2 -macroglobulin and ceruloplasmin deficiencies were ruled out in all patients. Two patients with “anaphylactic shock” and another two patients with “other ATRs” had allergic histories to drug. In Japan, all PCs are collected via apheresis, and plasma is simultaneously collected and placed on an inventory hold for 6 months. This collection method allowed us to analyse the plasma products that corresponded with the ATR-associated PCs in some cases. PCs that were not released because of alanine aminotransferase levels >60 U/L were used as control PCs without ATRs. The PC supernatants of control PCs were also used in some experiments.

Preparation of peripheral whole blood

Heparinised peripheral whole blood was collected from our healthy laboratory personnel and used as a source of basophils for the *in vitro* basophil activation assay.

This research project was approved by the Ethics Committee of the Japanese Red Cross Society Blood Service Headquarters.

Reagents

Purified mouse anti-human IgE monoclonal antibody (MoAb) was obtained from Beckman Coulter (Fullerton, CA, USA). FITC-conjugated mouse anti-HLA-DR MoAb and PE-conjugated mouse anti-CD203c MoAb were also purchased from Beckman Coulter. PE-Cy5-conjugated

mouse anti-CD123 MoAb and FACS lysing solution were purchased from BD Biosciences (San Jose, CA, USA). Purified mouse anti-HLA class I MoAb (clone: W6/32) was purchased from Cedarlane (Hornby, ON, Canada). Anti-fish collagen I MoAb was purchased from Alpha Diagnostic International (San Antonio, TX, USA). Anti-fish collagen I polyclonal antibody was purchased from Acris Antibodies (San Diego, CA, USA). Mackerel extract was purchased from Torii Pharmaceutical (Tokyo, Japan). *N*-Formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP) and lipopolysaccharide (LPS) were obtained from Sigma-Aldrich (Deisenhofen, Germany). Recombinant human (rh) IL-3 and IL-33 were purchased from AbD Serotec (Oxford, UK) and R&D Systems (Minneapolis, MN, USA), respectively. Dasatinib was obtained from Trout Research Chemicals (Toronto, ON, Canada).

In vitro BAT

Aliquots of whole blood (100 µL) collected from healthy laboratory personnel were incubated with 5 µL of PC supernatants derived from PCs with or without ATRs at 37 °C for 30 min; the blood/sample ratio was 20:1 to mimic a clinical setting in which a patient with 5 L of blood receives 250 mL of PC. After the incubation, the mixtures were washed twice with phosphate-buffered saline (PBS) containing 0.5 % bovine serum albumin (BSA) and 10 mM ethylenediaminetetraacetic acid (EDTA; PBS/BSA/EDTA). The extent of CD203c expression on basophils from the whole blood samples was analysed via flow cytometry (FCM) as described below. In some experiments, whole blood was incubated with several concentrations of stimulatory agents such as anti-human IgE MoAb, anti-HLA class I MoAb, fMLP, LPS, rh IL-3 or rh IL-33 at 37 °C for 30 min. To inhibit IgE/IgE receptor-triggered basophil activation, whole blood was incubated in the presence or absence of dasatinib (1, 3 or 5 µM) at 37 °C for 30 min and subsequently, incubated with PC supernatants with or without ATRs, the corresponding plasma products of PCs with ATRs or several concentrations of stimulatory agents at 37 °C for an additional 30 min. To confirm the involvement of mackerel protein as an allergen, the anti-fish collagen I MoAb or polyclonal Ab was used. Each Ab was pre-incubated with the ATR-associated PC-SNs at 37 °C for 60 min and subsequently incubated with whole blood at 37 °C for an additional 30 min.

FCM

Following agent-mediated activation as described above, the whole blood samples were incubated on ice for 15 min with 10 µL of FITC-conjugated anti-HLA-DR MoAb, PE-conjugated anti-CD203c MoAb and PE-Cy5-conjugated

anti-CD123 MoAb. After washing with PBS/BSA/EDTA, the cells were treated with FACS lysing solution and subjected to FCM. HLA-DR-negative and CD123-positive cells in the FSC versus SSC blast cell window were identified as basophils. CD203c was used as a basophil activation marker.

To calculate the percentage of CD203c-positive basophils in each panel whole blood sample, a cursor was placed on the CD203c histograms at the point at which 5 % of the basophils were CD203c-positive without stimulation. When the percentage of CD203c-positive basophils following stimulation by each PC supernatant with ATR exceeded the mean $\pm$ 3 standard deviations (SDs) of 3 PC supernatants without ATRs and the percentage of CD203c-positive basophils exceeded 20 %, the specific PC supernatant with ATR was categorised as BAT-positive.

Allergen-specific IgE

Some whole blood collected from healthy laboratory personnel were tested for reactions against 85 food allergens via CAP RAST (Mitsubishi Diagnostic, Tokyo Japan). Only results exceeding 0.70 IU/mL were considered positive.

Statistical analysis

The Wilcoxon *t* test with the Bonferroni correction was used to determine any statistical significance in the data. A *p* value of <0.05 was considered statistically significant.

Results

Three PC supernatants from ATR cases activated basophils in vitro

Because patient blood was unavailable, 5 peripheral whole blood samples from healthy volunteers were used as sources of basophils for BAT. We first screened 37 PC-SNs with ATRs to determine whether they could activate whole blood panel basophils. Three PC supernatants with ATRs each activated the basophils from only 1 whole blood sample; particularly, the Case 1, Case 2 and Case 3 PC supernatants activated basophils from panel 3, panel 1 and panel 3 whole blood, respectively (Fig. 1). All 3 PCs were reported to have been associated with anaphylactic shock (Table 1). Plasma proteins, including IgA, haptoglobin, C4, α_2 -macroglobulin and ceruloplasmin, were detected in all 3 ATR patients, and no antibodies were detected against these representative plasma proteins, C9, HLA class I, HLA class II and HPA. None of the patients were recorded having allergy history including food allergy. However, this

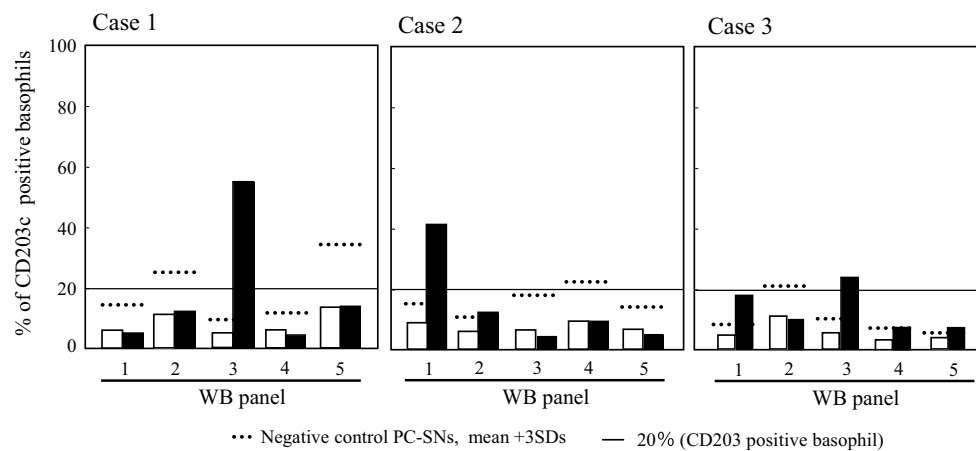


Fig. 1 The basophil activation ability of three PC supernatants of patients with ATR. The panels whole blood 1–5 show incubation with negative control PC supernatants from three control individuals (square) and PC supernatants (black square) of Case 1, Case 2 and Case 3 at 37 °C for 30 min. The whole blood samples were then stained with anti-HLA-DR, anti-CD123 and anti-CD203c MoAbs. HLA-DR-negative CD123-positive cells in the FSC versus SSC blast cell window were identified as basophils, and CD203c expression

was determined. The results are representative of two experiments. Bars show the mean percentage of CD203c-positive basophils. The percentage of CD203c-positive basophils after stimulation in each PC supernatant of patients with ATR exceeds the mean +3SDs of three control PC supernatants (dotted line), and the percentage of CD203c-positive basophils exceeds 20 % (solid line); the PC supernatants were categorised as BAT-positive

study was retrospective, and, hence, we only checked the records of reported by the doctors. Therefore, it is undeniable that their accurate allergic histories, especially food allergy, were largely unknown, although no allergic preposition was described with the patients in the records. None of the 34 remaining PC supernatants activated basophils from any of the 5 whole blood samples. These results suggested 2 possibilities; in the first, the 3 PC supernatants included unknown but specific allergens other than the above-described representative plasma proteins and in the second, BRMs that had possibly accumulated in PCs were involved in basophil activation. However, the latter possibility seemed unlikely because BRMs would have been able to activate basophils in most of the 5 panel bloods; furthermore, the basophils from panel 3 whole blood were activated not only by the Case 1 PC-SN but also by the corresponding plasma product from the Case 1 PC (data not shown). To explore the first possibility, we performed an inhibition experiment as described below.

Dasatinib inhibited the basophil activation elicited by ART PC supernatants

As the phosphorylation of tyrosines in several kinases comprises an early event in the IgE-dependent pathway [28–32], we utilised dasatinib [33–36], a multitargeted tyrosine kinase inhibitor, to inhibit IgE-mediated basophil activation [37]. To determine the dasatinib concentration that would provide suitable inhibition, we pretreated whole blood samples with different concentrations of dasatinib

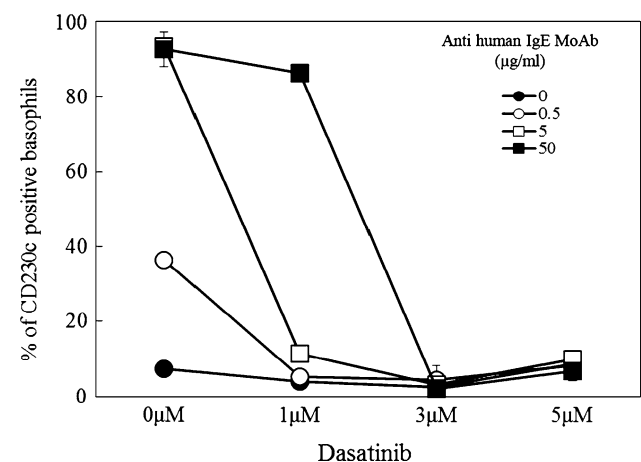


Fig. 2 Inhibitory effects of dasatinib on basophil activation via the IgE-dependent pathway. Five panels of whole blood show pretreatment with various concentrations of dasatinib (0, 1, 3 or 5 μM). Then the whole blood samples were stimulated with several concentrations of a mouse anti-human IgE MoAb (0, 0.5, 5 or 50 μg/mL). The percentage of CD203c-positive basophils was measured using FCM. The results show the average percentage of CD203c-positive basophils among five healthy volunteers. The results are representative of two experiments

and performed BAT using anti-IgE MoAb, which is known to activate basophils via the IgE-dependent pathway, as a positive control (Fig. 2). We found that a dasatinib concentration of $\geq 3 \mu\text{M}$ completely inhibited basophil activation at all concentrations of anti-IgE MoAb (Fig. 2). Several soluble bioactive molecules, including LPS, IL-3, fMLP,

Fig. 3 Selective inhibition of IgE-dependent basophil activation by dasatinib. Whole blood cells were pretreated with 3 μ M dasatinib (*black square*) or DMSO (*square*) at 37 °C for 30 min. Then, the cells were exposed to various concentrations of **a** IL-3 (0, 0.01, 0.1 or 1 μ g/mL) or **b** fMLP (0, 0.1, 1 or 10 μ M) at 37 °C for 30 min. The percentage of CD203c-positive basophils was measured using FCM. The results show the average percentage of CD203c-positive basophils among six healthy volunteers * $p < 0.05$. The results are representative of two experiments

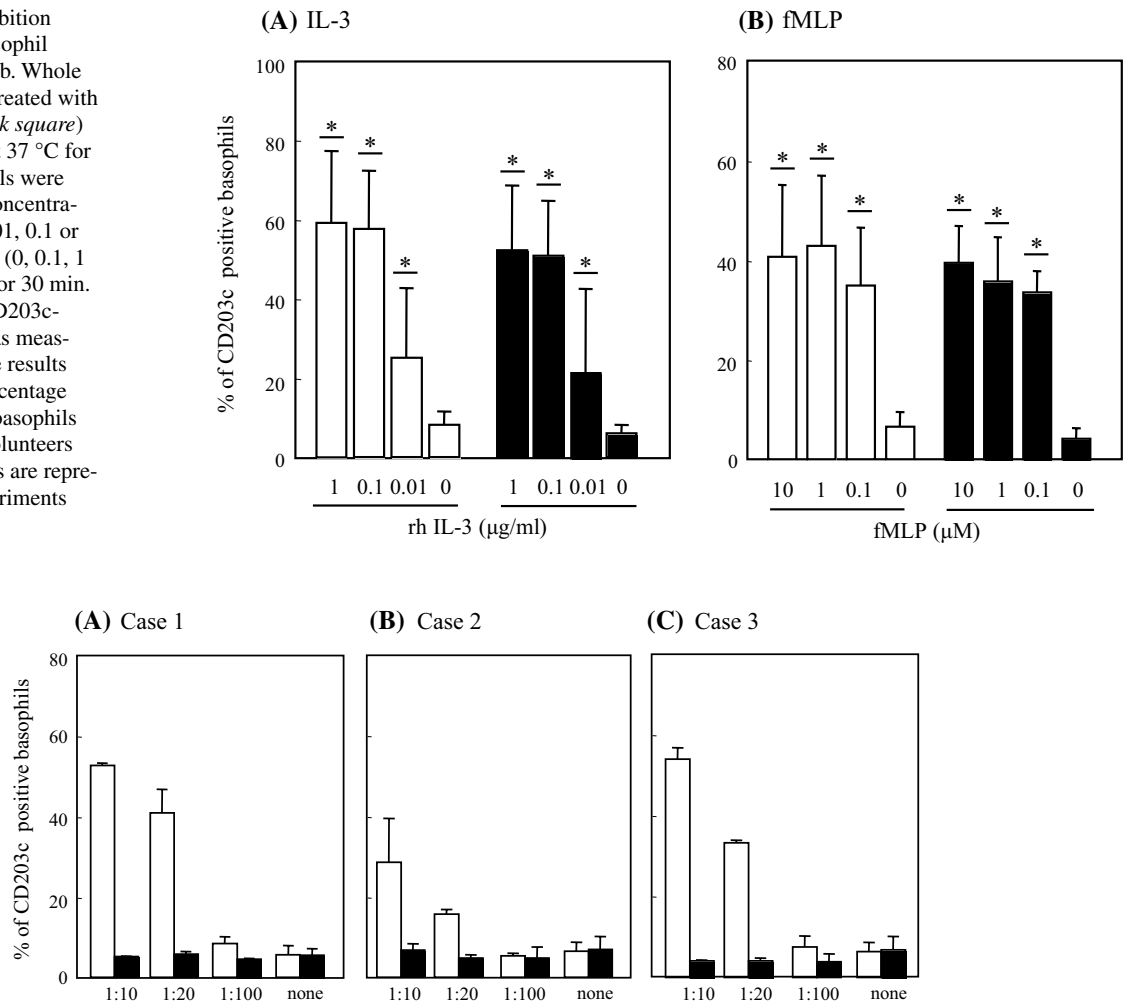


Fig. 4 Dasatinib inhibited the basophil activation elicited by PC supernatants of patients with ATRs. Whole blood cells were pretreated with 3 μ M dasatinib (*black square*) or DMSO (*square*), and then the cells were stimulated with PC supernatants of patients with ATR at several dilution ratios (1:10, 1:20 or 1:100). **a** Panel whole blood 3 stimulated with PC supernatants of Case 1, **b** panel whole

blood 1 stimulated with PC supernatant of Case 2 and **c** panel whole blood 3 stimulated with PC supernatant of Case 3. The percentage of CD203c-positive basophils was measured by means of FCM. The results show the percentage of CD203c-positive basophils and are representative of two experiments

IL-33 and anti-HLA class I antibody, activate basophils via the IgE-independent pathway [2, 5, 7]. Therefore, 3 μ M dasatinib failed to inhibit basophil activation in response to IL-3 and fMLP (Fig. 3). Dasatinib pretreatment also failed to inhibit basophil activation in response to LPS, IL-33 and anti-HLA class I antibody (data not shown).

Having confirmed that dasatinib inhibited only IgE-dependent basophil activation in our BAT system, we then determined which basophil activation was elicited by the PC supernatants. In the absence of dasatinib pretreatment, panel 3 whole blood basophil activation was observed upon stimulation with Case 1 PC supernatant at dilution rates of 1:10–1:100, but was completely inhibited by dasatinib pretreatment (Fig. 4a). Similar inhibition was observed when panel 1 and 3 whole blood were stimulated with Case 2 and

3 PC-SNs, respectively (Fig. 4b, c). These results indicated that PC supernatants from the 3 ATR cases activated basophils in the corresponding whole blood panels via the allergen/IgE-dependent pathway.

Allergen identification in the blood components from ATRs

Given the recent case of suggested passive peanut allergen transfer via transfusion [24], we investigated the possible involvement of food allergens in our 3 ATR cases. To explore this possibility, we first examined whether the panel 1 and 3 whole blood, from which basophils were activated by PC supernatants, contained specific IgE against food allergens using CAP RAST, which screens for IgE

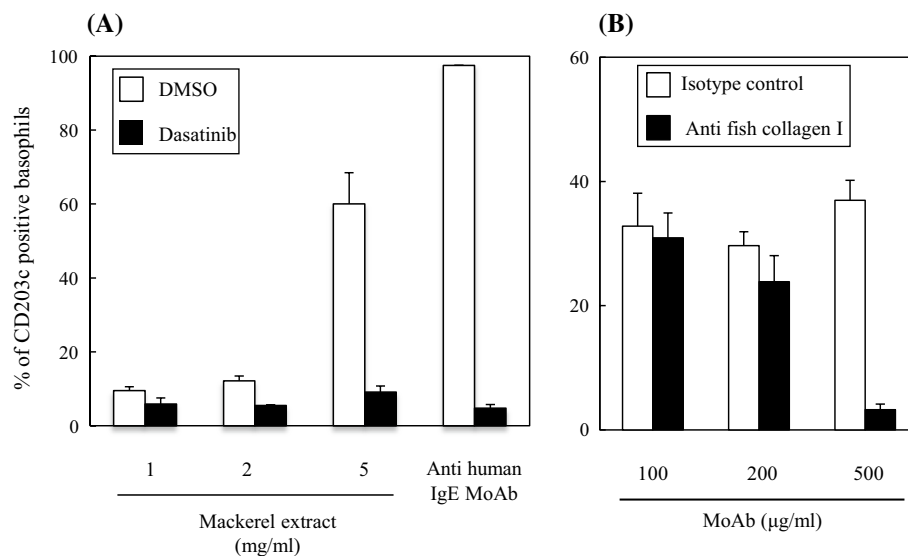


Fig. 5 Involvement of a fish antigen in basophil activation. **a** Panel whole blood 3 shows pretreatment with 3 µM dasatinib (black square) or DMSO (square) and then stimulation with either mackerel extract or vehicle at several concentrations (1, 2 or 5 mg/mL). **b** PC supernatant of Case 1 was pretreated with a mouse anti-fish collagen

polyclonal antibody (black square) or mouse IgG (square) at various concentrations (100, 200 or 500 µg/mL). Panel whole blood 3 shows stimulation with the pretreated PC supernatant of Case 1. The results show the percentage of CD203c-positive basophils and are representative of two experiments

antibodies against 85 food allergens. Specific anti-mackerel IgE was identified in the panel 3 whole blood, the basophils of which were activated by Case 1 and Case 3 PC supernatant. No specific IgE were detected in the panel 1 whole blood. Because the stimulation ability of Case 3 PC supernatant was low, we focused on the Case 1 PC supernatant in the following experiments.

Mackerel hypersensitivity has been extensively studied worldwide and a major allergen has been found to be collagen I [38], but no previous report has addressed the relationship between mackerel hypersensitivity and transfusion reaction. We then performed stimulation experiments to confirm the presence of mackerel-specific IgE in the panel 3 whole blood. First, we incubated panel 3 whole blood with mackerel extract and assessed the extent of basophil activation. The addition of mackerel extract elicited the activation of basophils from panel 3 whole blood, and this activation was completely inhibited by dasatinib (Fig. 5a). To test for the presence of mackerel allergens in Case 1 PC supernatant, we then incubated the panel 3 whole blood with Case 1 PC supernatant after pretreating the latter with an anti-fish collagen I antibody. Basophil activation was clearly inhibited by anti-fish collagen I antibody pretreatment in a dose-dependent manner, regardless of whether the antibody was polyclonal (data not shown) or monoclonal (Fig. 5b). Taken together, these results strongly suggested that Case 1 PC supernatant contained a fish allergen that activated the basophils in panel 3 whole blood, which contained specific anti-mackerel IgE. Because we could not

obtain patient blood in this case, in the future, another study involving patient blood from similar cases will be needed to assess whether fish allergen-containing PCs induce ATR in patients harbouring specific anti-mackerel IgE.

Discussion

In our previous study, we showed that BAT could be used as a functional test in the transfusion medicine field to examine whether observed transfusion reactions were allergic in nature [39]. However, we could not distinguish whether the allergen/IgE-dependent or independent pathway was involved in individual ATRs. In this study, in order to determine by which pathway ATRs were elicited, we used a healthy volunteer whole blood based BAT in combination with dasatinib pretreatment [33–37]. The screening of 37 ATR cases revealed 3 BAT-positive cases. In each case, the PC supernatant exhibited basophil-activating activity against only 1 of the 5 whole blood panels; particularly, Case 1 PC supernatant reacted with panel 3 whole blood, Case 2 PC supernatant with panel 1 whole blood and Case 3 PC supernatant with panel 3 whole blood. In all cases, basophil activation was inhibited by dasatinib, suggesting that the activation was mediated through the allergen/IgE-dependent pathway. No antibodies against representative plasma proteins or deficiencies in any representative plasma proteins were found in any of the patients. These results raised the possibility that the 3 PC supernatant

included unknown but specific allergens other than plasma proteins, and thus elicited basophil activation in an allergen/IgE-dependent manner. To screen for candidate allergens [24, 25], we first examined the panel whole blood that reacted with Cases 1 and 3 for food allergen-specific IgE via CAP RAST and found specific anti-mackerel IgE in the panel 3 whole blood. Subsequently, we demonstrated that panel 3 whole blood basophil activation by Case 1 PC supernatant was inhibited by pretreating the PC supernatant with anti-fish collagen I antibodies (Fig. 5b). Taken together, these results indicate the possible involvement of non-plasma protein antigens, some of which may have been fish (mackerel) allergens, in our ATR cases.

However, this study has several limitations. First, although we considered fish antigen as a candidate allergen that was present in the transfused PC and induced ATR in 1 case, we could not clearly demonstrate its presence. In addition, we could not identify a candidate allergen in the other 2 cases. In a future study, the allergen present in transfused blood should be unambiguously identified via more definitive methods.

Second, we utilised whole blood from healthy volunteers rather than the patients as the basophil source. This study was retrospective, and hence, patient whole blood was not available. However, patient blood would be indispensable for drawing a definitive conclusion. Considering that fresh whole blood is required to perform BAT, we would need to establish close communications with hospitals in order to obtain patient whole blood. However, fresh patient whole blood may not be always available. In this regard, it is less difficult to obtain patient serum/plasma than fresh whole blood. Therefore, it could be useful to set up a passive anaphylaxis reaction system in which patient serum/plasma is used as the patient IgE source, residual transfused blood as the allergen source and cultured basophils or mast cells as the responder cell source.

Third, we used only a 5-panel whole blood, although we successfully observed allergen-dependent pathway activation in 3 ATR cases, and the possible involvement of fish antigen in 1 case. Despite considering the high prevalence of IgE Abs among healthy volunteers [4], the number of panel whole blood that we used was too low to screen for all candidate allergens in the transfused blood. Therefore, it is conceivable that we may have overlooked some allergen-dependent ATR cases in this study. We have 3 options to overcome this limitation. First is to increase the number of panel whole blood; however, this is impractical. Second is to use patient whole blood instead of panel whole blood. Third is to use a passive anaphylaxis reaction system. As mentioned earlier, we should select the second and third options.

Fourth, we previously reported that 3 of 9 PC supernatants with ATRs could activate basophils in at least 1 of 5 whole blood from healthy laboratory personnel [39]. One

of the biggest differences in the 2 studies was that in the previous study, 1 PC supernatant elicited basophil activation in all panel whole blood, suggesting the involvement of an allergen-independent pathway. In contrast, there were no such cases in the present study. The reason for this discrepancy is currently unknown. However, it is possible that some allergen-independent but BRM-dependent cases were included in this study. However, given that the PCs used in this study were collected between 3 and 7 days from the ATR occurrence versus the collection within 24 h in the previous study, the potential BRMs, particularly cytokines and active lipids, in the PCs from this study may have lost their activity. Again, close communication and cooperation with medical institutions will be very important.

Acknowledgments The author thanks Dr. Yoriko Irie, Dr. Kanae Nishizawa and Dr. Yangsook Koh for the critical review of the manuscript.

Conflict of interest All authors have no conflicts of interest.

References

- Hedde NM, Klama L, Singer J, Richards C, Fedak P, Walker I, et al. The role of the plasma from platelet concentrates in transfusion reactions. *N Engl J Med*. 1994;331:625–8.
- Hirayama F. Recent advances in laboratory assays for nonhemolytic transfusion reactions. *Transfusion*. 2010;50:252–63.
- Geiger TL, Howard SC. Acetaminophen and diphenhydramine premedication for allergic and febrile nonhemolytic transfusion reactions: good prophylaxis or bad practice? *Transfus Med Rev*. 2007;21:1–12.
- Savage WJ, Tobian AAR, Savage JH, Hamilton RG, Ness PM. Atopic predisposition of recipients in allergic transfusion reactions to apheresis platelets. *Transfusion*. 2011;51:2337–42.
- Savage WJ, Tobian AAR, Savage JH, Wood RA, Schroeder JT, Ness PM. Scratching the surface of allergic transfusion reactions. *Transfusion*. 2013;53:1361–71.
- Domen RE, Hoeltge GA. Allergic transfusion reactions: an evaluation of 273 consecutive reactions. *Arch Pathol Lab Med*. 2003;127:316–20.
- Hirayama F. Current understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. *Br J Haematol*. 2013;160:434–44.
- Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. *J Allergy Clin Immunol*. 2009;124:639–48.
- Gilfillan AM, Peavy RD, Metcalfe DD. Amplification mechanisms for the enhancement of antigen-mediated mast cell activation. *Immuno Res*. 2009;43:15–24.
- Turner H, Kinet JP. Signalling through the high-affinity IgE receptor Fc epsilonR1. *Nature*. 1999;402:B24–30.
- Koda Y, Watanabe Y, Soejima M, Shimada E, Nishimura M, Morishita K, et al. Simple PCR detection of haptoglobin gene deletion in anaphylactoid patients with anti-haptoglobin antibody that causes anaphylactic transfusion reactions. *Blood*. 2000;95:1138–43.
- Shimada E, Tadokoro K, Watanabe Y. Anaphylactic transfusion reactions in haptoglobin-deficient patients with IgE and IgG haptoglobin antibodies. *Transfusion*. 2002;42:766–73.

13. Arnold P, Schmidt MD, Howard F, Taswell MD, Gerald J, Gleich MD. Anaphylactic transfusion reactions associated with anti-IgA antibody. *N Engl J Med*. 1969;280:188–93.
14. Sander SG, Mallory D, Malamut D, Eckrich R. IgA anaphylactic transfusion reactions. *Transfus Med Rev*. 1995;1:1–8.
15. Lambin P, Le Pennec PY, Hauptmann G, Desaint O, Habibi B, Salmon C. Adverse transfusion reactions associated with a precipitating anti-C4 antibody of anti-Rodger specificity. *Vox Sang*. 1984;47:242–9.
16. Westhoff CM, Sipherd BD, Wylie DE, Toalson LD. Severe anaphylactic reactions following transfusions of platelets to a patient with anti-Ch. *Transfusion*. 1992;32:576–9.
17. Sandler SG. How I manage patients suspected of having had an IgA anaphylactic transfusion reaction. *Transfusion*. 2006;46:10–3.
18. Sandler SG, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion is not evidence based. *Transfusion*. 2015;55:199–204.
19. Wadhwa M, Seghatchian MJ, Lubenko A, Contreras M, Dilger P, Bird C, et al. Cytokine levels in platelet concentrates: quantitation by bioassays and immunoassays. *Br J Haematol*. 1996;93:225–34.
20. Edvardsen L, Taaning E, Mynster T, Hvolris J, Drachman O, Nielsen HJ. Bioactive substances in buffy-coat-derived platelet pools stored in platelet-additive solutions. *Br J Haematol*. 1998;103:445–8.
21. Phipps RP, Kaufmann J, Blumberg N. Platelet derived CD154 (CD40 ligand) and febrile responses to transfusion. *Lancet*. 2001;357:2023–4.
22. Wakamoto S, Fujihara M, Kuzuma K, Sato S, Kato T, Naohara T, et al. Biologic activity of RANTES in apheresis PLT concentrates and its involvement in nonhemolytic transfusion reactions. *Transfusion*. 2003;43:1038–46.
23. Garraud O, Hamzeh-Cognasse H, Cognasse F. Platelets and cytokines: how and why? *Transfusion Clin Biol*. 2012;19:104–8.
24. Jacobs JF, Baumert JL, Brons PP, Joosten I, Koppelman SJ, van Pampus EC. Anaphylaxis from passive transfer of peanut allergen in a blood product. *N Engl J Med*. 2011;364:1981–2.
25. Gao L, Sha Y, Yuan K, Ling L, Ai D, Ying H, et al. Allergic transfusion reaction caused by the shrimp allergen of donor blood: a case report. *Transf Apheres Sci*. 2014;50:68–70.
26. Aihara Y, Kotoyori T, Takahashi Y, Osuna H, Ohnuma S, Ikezawa Z. The necessity for dual food intake to provoke food-dependent exercise induced anaphylaxis (FEIA): a case report of FEIA with simultaneous intake of wheat and umeboshi. *J Allergy Clin Immunol*. 2001;107:1100–5.
27. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: implications for future treatment. *J Allergy Clin Immunol*. 2008;121:1344–50.
28. Benhamou M, Feuillard J, Lortholary O, Bourgeois C, Michel L, LeGoff L, et al. Protein tyrosine kinases in activation signal of human basophils through the immunoglobulin E receptor type 1. *J Leukoc Biol*. 1996;59:461–70.
29. Eiseman E, Bolen JB. Engagement of the high-affinity IgE receptor activates src protein-related tyrosine kinases. *Nature*. 1992;355:78–80.
30. Costello PS, Turner M, Walters AE, Cunningham CN, Bauer PH, Downward J, et al. Critical role for the tyrosine kinase Syk in signaling through the high affinity IgE receptor of mast cells. *Oncogene*. 1996;13:2595–605.
31. Kepley CK, Wilson BS, Oliver JM. Identification of the Fc epsilonR1-activated tyrosine kinases Lyn, Syk, and Zap-70 in human basophils. *J Allergy Clin Immunol*. 1998;102:304–15.
32. Miura K, MacGlashan DW. Phosphatidylinositol-3 kinase regulates p21 ras activation during IgE-mediated stimulation of human basophils. *Blood*. 2000;96:2199–205.
33. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers VL. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science*. 2004;305:399–401.
34. Lombardo LJ, Lee FY, Chen P, Norris D, Barrish JC, Behnia K, et al. Discovery of N-(2-chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino) thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem*. 2004;47:6658–61.
35. Doggrel SA. BMS-354825: a novel drug with potential for the treatment of imatinib-resistant chronic myeloid leukaemia. *Expert Opin Investig Drugs*. 2005;14:89–91.
36. Gambacorti-Passerini C, Gasser M, Ahmed S, Assouline S, Scapozza L. Abl inhibitor BMS354825 binding mode in Abelson kinase revealed by molecular docking studies. *Leukemia*. 2005;19:1267–9.
37. Kneidinger M, Schmidt U, Rix U, Gleixner KV, Vales A, Baumgartner C, et al. The effects of dasatinib on IgE receptor-dependent activation and histamine release in human basophils. *Blood*. 2008;111:3097–107.
38. Sakaguchi M, Toda M, Ebihara T, Irie S, Hori H, Imai A, et al. IgE antibody to fish gelatin (type 1 collagen) in patients with fish allergy. *J Allergy Clin Immunol*. 2000;106:579–84.
39. Matsuyama N, Hirayama F, Wakamoto S, Yasui K, Furuta RA, Kimura T, et al. Application of the basophil activation test in the analysis of allergic transfusion reactions. *Transfus Med*. 2009;19:274–7.