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REFERENCES

1. Loss G, Apprich S, Waser M, Kneifel W, Genuneit J, Buchele G, et al. The protective effect of farm milk consumption on childhood asthma and atopy: the GABRIELA study. J Allergy Clin Immunol 2011;128:766-73.e4.
2. Loss G, Depner M, Ulfman LH, van Neerven RJ, Hose AJ, Genuneit J, et al. Consumption of unprocessed cow's milk protects infants from common respiratory infections. J Allergy Clin Immunol 2015;135:56-62.
3. Kosaka N, Izumi H, Sekine K, Ochiya T. microRNA as a new immune-regulatory agent in breast milk. Silence 2010;1:7.
4. Xue L, Barrow A, Fleming VM, Hunter MG, Ogg G, Klenerman P, et al. Leukotriene E4 activates human Th2 cells for exaggerated proinflammatory cytokine production in response to prostaglandin D2. J Immunol 2012;188:694-702.
5. Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G, et al. ω-3 Fatty acids contribute to the asthma-protective effect of unprocessed cow's milk. J Allergy Clin Immunol 2016;137:1699-706.e1-13.
6. Litonjua AA, Tantisira KG, Lake S, Lazarus R, Richter BG, Gabriel S, et al. Polymorphisms in signal transducer and activator of transcription 3 and lung function in asthma. Respir Res 2005;6:52.
7. Vercelli D. Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol 2008;8:169-82.
8. Kumar M, Ahmad T, Sharma A, Mabalirajan U, Kulshreshtha A, Agrawal A, et al. Let-7 microRNA-mediated regulation of IL-13 and allergic airway inflammation. J Allergy Clin Immunol 2011;128:1077-85, e1-10.
9. Bosco A, Ehteshami S, Stern DA, Martinez FD. Decreased activation of inflammatory networks during acute asthma exacerbations is associated with chronic airflow obstruction. Mucosal Immunol 2010;3:399-409.
10. Baier SR, Nguyen C, Xie F, Wood J, Zempleni J. MicroRNAs are absorbed in biologically meaningful amounts from nutritionally relevant doses of cow milk and affect gene expression in peripheral blood mononuclear cells, HEK-293 kidney cell cultures and mouse livers. J Nutr 2014;144:1495-500.

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Food allergies can persist after myeloablative hematopoietic stem cell transplantation in dedicator of cytokinesis 8–deficient patients

To the Editor:

Dedicator of cytokinesis 8 (DOCK8) deficiency is a highly morbid combined immunodeficiency that features recurrent sinopulmonary infections, viral skin infections, and severe food allergies.[1,2] Hematopoietic stem cell transplantation (HSCT) cures infection susceptibility in patients with DOCK8 deficiency.[3-7] Whether HSCT also cures food allergy has not been systematically examined in human subjects.[8] To gain insight into the etiopathogenesis of food allergy and its potential treatment, we studied food allergy in 12 DOCK8-deficient patients who underwent HSCT at the National Institutes of Health (NIH) Clinical Center.

First, we retrospectively evaluated 6 patients who had received either matched related or unrelated donor cells after myeloablative conditioning (patients 1-6 in Table I and see the Methods section in this article's Online Repository at www.jacionline.org).[7] Of these, patients 2 and 4 reported histories of food-induced anaphylaxis before transplantation, and patient 5 reported a new food allergy after transplantation. After transplantation, skin prick testing to 8 common food allergens and specific IgE by using ImmunoCAP (Phadia, Uppsala, Sweden) confirmed sensitization to foods precipitating the reactions. Food challenges were not performed. A fourth patient (patient 1) reported oral pruritus to lentils before transplantation and again when re-exposed more than 1 year after transplantation. Donors in these cases were confirmed to have no history of food allergy.

Our observations of persisting or new food allergies were unexpected given anecdotal reports suggesting that HSCT cured food allergies and could have reflected a selection bias.[4,5,9] Thus we prospectively studied food allergies in the next 6 DOCK8-deficient patients undergoing transplantation at the NIH (patients 7-12 in Table I). This second group included 2 patients (patients 9 and 12) who had undergone related donor haploidentical transplantations and had systemic allergic reactions to foods to which they were already allergic before transplantation. Donors were confirmed to have no history of food allergy. Patient 9 was more than 8 months after HSCT and more than 2 months off tacrolimus when she had acute oral and facial angioedema, diffuse urticaria, vomiting, and difficulty breathing within minutes of eating oatmeal fortified with egg and milk. Her symptoms resolved after receiving epinephrine, diphenhydramine, and methylprednisolone. Before transplantation, she had had anaphylactic reactions to egg and milk. However, 2 months before her last reaction, her skin prick test responses were positive to egg but not milk, suggesting egg as the culprit (see Table E1 in this article's Online Repository at www.jacionline.org). Similarly, patient 12 was 45 days out after HSCT when she had oral and periorbital angioedema and diffuse urticaria and pruritus within 10 minutes of eating a kiwi fruit, with sensitization confirmed by means of skin prick testing (Table I and see Table E1). Years before transplantation, she too had had oral pruritus and lip angioedema after eating kiwi and had subsequently avoided it entirely.

Among the patients studied prospectively, a third patient who underwent matched unrelated donor transplantation reported that a previously resolved food allergy had returned. Patient 7 was 3 months out of HSCT when he had cramping abdominal pain, vomiting, diarrhea, and headache within 15 minutes of eating scrambled eggs. His symptoms occurred on 2 more occasions following concentrated egg ingestion but never when he ate baked goods that contained eggs. He had had similar symptoms in his early school age years but had been eating eggs freely for the decade before transplantation. Skin prick testing confirmed that he had reacquired reactivity to egg after transplantation (Table I and see Table E1). The donor was confirmed to have no history of food allergy. Patient 7 also had a history of anaphylaxis to walnut as recently as 3 years before HSCT. Because of persisting positive skin prick tests, he continued to strictly avoid tree nuts after transplantation.

TABLE I. Pre- and post-HSCT clinical food allergies, skin prick test responses, and total serum IgE levels in the studied DOCK8-deficient patients

	Patient no.	Age at HSCT (y)/sex	Months after HSCT at most recent allergy evaluation	Trans-plant type	GVHD prophylaxis type and duration of therapy after transplantation	Gut GVHD	Clinical food allergies			Skin prick testing		Total serum IgE (IU/mL)	
							Foods causing reaction before HSCT	Foods causing reaction after HSCT	Symptoms with most severe reaction before HSCT	Before HSCT, positive*	After HSCT, positive	Peak before HSCT	Most recent after HSCT
Patients studied retrospec-tively	1	18/F	18	MRD	Cyclosporine: 12 mo	Yes	Lentils	Lentils	Oral pruritus only	ND	ND	8,031	870
	2	10/F	23	MRD	Tacrolimus: 8.5 mo	No	Egg, milk, wheat, soy, sesame, tree nuts	Not challenged	Anaphylaxis	ND	Egg, milk, wheat, soy, cashew (ND: sesame)	6,690	1,058
	3	23/M	21	MRD	Tacrolimus: 14 mo	No	None	None	None	ND	ND	51,010	153
	4	27/M	37	URD	Tacrolimus: 11 mo	No	Peanut	Not challenged	Anaphylaxis	ND	Peanut	1,162	17.4
	5	25/F	24	URD	Tacrolimus: 3 wk then, cyclosporine: 14 mo	No	None	Shrimp	Gastrointestinal symptoms only	ND	Shrimp	38.5	6.1
	6	16/F	18	URD	Cyclosporine: 11 mo	No	None	None	None	ND	ND	180	9.4
Patients studied prospec-tively	7	19/M	12	URD	Tacrolimus: 9 mo	No	Egg: resolved in early childhood, tree nuts persisted	Egg, no tree nut exposure	Anaphylaxis	Walnut, cashew	Egg, walnut	6,398	1,224
	8†	21/M	Died	URD	Tacrolimus: ongoing	Yes	Milk, egg, peanut	Not challenged	Anaphylaxis	Milk, egg, peanut, shrimp	ND	31,403	627
	9	20/F	12	Haplo	Tacrolimus: 6 mo	No	Egg, milk, wheat, peanut, cashew	Egg/milk, no exposure to others	Anaphylaxis	Egg, wheat, peanut, cashew	Egg, wheat, peanut, cashew	6,905	67.8
	10	13/M	10	MRD	Tacrolimus: 7 mo	No	Egg, wheat, peanut, kiwi, banana	Not challenged	Anaphylaxis	Egg, wheat, peanut	Egg, wheat, peanut	>6,000	915
	11	9/F	6	URD	Tacrolimus: ongoing	Yes	None	None	None	None	None	2.0	2.9
	12	19/F	3	Haplo	Tacrolimus: ongoing	No	Kiwi, concentrated milk, concentrated egg	Kiwi, no exposure to others	Oral angioedema and pruritus	Milk, egg, cashew (kiwi not done)	Egg, kiwi	>6,000	594

F, Female; *GVHD*, graft-versus-host disease; *Haplo*, haploidentical; *M*, male; *MRD*, matched related donor; *ND*, not done; *URD*, unrelated donor.

*Skin prick tests were performed for the common food allergens milk, egg, soy, wheat, peanut, walnut, cashew, and shrimp for each patient before and after HSCT unless otherwise indicated. All positive results are listed.

†The patient died less than 3 months after transplantation; no follow-up skin prick tests were performed.

We observed that while total serum IgE levels plummeted after HSCT, they remained elevated in most patients (Fig 1). Food-specific IgE levels also remained high for months after transplantation in several patients, even at levels having greater than a 95% positive predictive value for clinical food reactivity for some (see Table E2 in this article's Online Repository at www.jacionline.org). Moreover, skin prick testing revealed persisting mast cell reactivity to food allergens, which seemed to correlate best with the anaphylactic episode described after transplantation in patient 9 (see Table E1). Persistence of allergen sensitization occurred regardless of donor type. The possibility of long-lived, host-derived, IgE-producing plasma cells in the bone marrow could explain allergy persistence. Indeed, we observed that bone marrow chimerism approached but did not reach 100% (see Table E3 in this article's Online Repository at www.jacionline.org).