

Dominant, non-MHC genetic control of food allergy in an adjuvant-free mouse model

S. Parvataneni,* N. P. Birmingham,*† B. Gonipeta* & V. Gangur*†

Summary

Food allergy is a potentially fatal immune-mediated disorder with incompletely understood mechanisms. We studied the genetic control of food allergy using major histocompatibility complex-identical mice ($H2^s$) and an adjuvant-free method of sensitization. Whereas, transdermal exposure to hazelnut — a model allergenic food, elicited robust IgG1 response in both strains, an IgE response was evident only in A.SW mice. Following oral challenge, only A.SW but not SJL mice exhibited signs of systemic anaphylaxis and hypothermia. In addition, (A.SW $\times$ SJL) F1 hybrids exhibited IgE responsiveness, systemic anaphylaxis and hypothermia similar to A.SW, indicating dominant inheritance of these traits. Furthermore, whereas A.SW and F1 mice but not SJL elicited robust interleukin (IL)-4 response, all three strains elicited IL-5 and IL-13 responses by spleen cells. These data demonstrate for the first time, dominant non-MHC genetic control of food allergy and a critical role of IL-4 but not IL-5 or IL-13 in this model.

Introduction

Food allergy is an internationally growing, potentially fatal, immune-mediated disorder with mechanisms that are not completely understood (Sicherer & Sampson, 2006). Milk, egg, soy, wheat, tree nuts, peanuts, fish, shellfish, sesame, celery and mustard are considered as major allergenic foods of regulatory importance (Sicherer & Sampson, 2006). Peanuts, tree nuts and sesame in particular are often associated with potentially fatal systemic anaphylaxis (Sicherer & Sampson, 2006). It is estimated

that as many as 6–8% children and up to 4% adults are afflicted with food allergies (Sicherer & Sampson, 2006). Since food allergies start in childhood, and accidental ingestion can cause potentially fatal reactions, they represent a critical clinical problem at present (Sicherer & Sampson, 2006). However, the precise nature of factors underlying food allergy remains to be clearly defined.

Allergic disorders including food allergy are regarded as multifactorial with both genetics as well as environmental factors implicated in the disease development (Bjorksten, 2005; Dreskin, 2006). Although the rising prevalence of food allergy cannot be due to genetic factors alone, there is evidence that some food allergies such as peanut allergies have a strong genetic basis. Thus: (i) there is a higher rate of peanut allergy among siblings (7%) compared to the general population (0.5%) in the UK (Hourihane *et al.*, 1996); (ii) monozygotic twins are significantly more concordant for peanut allergy than dizygotic twins (Sicherer *et al.*, 2000); (iii) some studies, but not others, associated human leucocyte antigen (HLA) class II polymorphism with peanut allergy (Donovan *et al.*, 1996; Howell *et al.*, 1998; Shreffler *et al.*, 2006); and (iv) one study reported that polymorphism in the STAT6 gene encodes risk for nut allergy including peanut allergy in a population in UK (Amoli *et al.*, 2002). Thus, there is emerging evidence implicating a potential role for genetics in the development of food allergies. However, precise role of major histocompatibility complex (MHC)-linked genes versus non-MHC genes in food allergies remains to be clearly defined.

Mouse models have been widely used to elucidate the genetic basis of many complex human disorders including airways allergies and asthma (Venugopal *et al.*, 1995; Daser *et al.*, 1998; Ewart *et al.*, 2000). Because: (i) there is significant similarity in the allergic immune responses such as: the Th2 response to allergens leading to IgE induction, and the effector phase of an allergic response involving Fc ϵ R-I and mast cells; and (ii) availability of inbred strains of mice, MHC-identical strains etc., enables generation and linkage analysis of segregating populations including quantitative trait loci studies (Venugopal *et al.*, 1995; Daser *et al.*, 1998; Ewart *et al.*, 2000). However, the application of mouse models for genetic studies on food allergy has been very limited (Morafo *et al.*, 2003; Bjorksten, 2005).

* Food Allergy and Immunology Laboratory, Department of Food Science and Human Nutrition, and † National Food Safety and Toxicology Center, Michigan State University, East Lansing, MI 48824, USA

Received 12 September 2008; revised 3 April 2009; accepted 17 June 2009

Correspondence: Venu Gangur, Food Allergy and Immunology Laboratory, Department of Food Science and Human Nutrition, and National Food Safety and Toxicology Center, Michigan State University, East Lansing, MI 48824, USA. Tel: 517-355-8474x134; Fax: 517-353-8963; E-mail: gangur@msu.edu

We have previously reported an adjuvant-free mouse model of food allergy using hazelnut as a model allergenic food (Birmingham *et al.*, 2007). Using this adjuvant-free mouse model, and MHC-identical mice strains, here we studied the non-MHC genetic control of food allergy.

Materials and methods

The following materials were purchased from sources as indicated in the parenthesis. Hazelnut/filbert protein extract (Greer Labs, Lenoir, NC, USA); hazelnut extract was tested for protein content using a modified Lowry's method; LPS content of this material was tested and found to be < 0.5 pg/mg protein as measured by LAL assay (Cambrex Bio Science Walkersville, Inc., Walkersville, MD, USA); biotin-conjugated rat anti-mouse IgG1 and IgE antibodies; paired antibodies and recombinant standards for mouse interleukin (IL)-4, and IL-5 (BD PharMingen, San Diego, CA, USA); paired antibodies and recombinant standards for mouse IL-13 (R&D Systems, Minneapolis, MN, USA); p-nitrophenyl phosphate (Sigma, St Louis, MO, USA); and streptavidin alkaline phosphatase (Jackson ImmunoResearch, West Grove, PA, USA).

Mice

The following MHC identical strains were used in the study: A.SW- $H2^s$ $H2-T18^b$ /SnJ (type: congenic, major histocompatibility congenic; mutant strain; background strain: A/WySn; donar strain: non-inbred Swiss; $H2$ haplotype: $H2^s$ including $H2-T18^b$); and SJL/J- $H2^s$ (type: inbred strain; $H2$ haplotype: $H2^s$) mice (The Jackson Laboratory, Bar Harbor, ME, USA); (A.SWXSJL) F1 mice were produced in the animal facility of the Michigan State University as described before (Venugopal *et al.*, 1995). Only adult animals (6–8 weeks age) were used in the study. All animal procedures used were in accordance with the Michigan State University policies.

Transdermal sensitization and bleeding

Transdermal exposure experiments were performed using the method described by us before (Navuluri *et al.*, 2006; Birmingham *et al.*, 2007). Groups of mice were exposed to saline or hazelnut protein extract (500 µg/100 µL in saline per mouse per application); each mouse had the reagent applied to the skin of the back that had the hair clipped-off and covered with nonlatex nonocclusive bandage for 3 days. Mice were rested for 4 days. Then the cycle of exposure to saline or hazelnut was continued for 6 weeks. Blood samples were collected by the saphenous vein, and plasma was used in the antibody analysis.

Measurement of hazelnut-specific IgG1 and IgE antibodies in the plasma

Previously described enzyme-linked immunosorbent assay (ELISA) for hazelnut-specific IgG1 and IgE antibody analyses was used in this study (Birmingham *et al.*, 2003).

Induction of systemic anaphylaxis, clinical scoring and measurement of rectal temperature

Groups of hazelnut-sensitized versus saline-exposed mice were orally challenged with hazelnut protein (13 mg/mouse) or saline 500 µL per mouse on day 10 following sixth exposure using mouse feeding needles (22 gauge, Popper and Sons Inc., New Hyde Park, NY, USA). Mice were observed for signs of systemic anaphylaxis during the next 60 min. Clinical scoring (on a scale of 0 to 5) was performed by two to four individuals according to the method described previously (Li *et al.*, 2000). Score of 0, no symptoms; 1, scratching and rubbing around the nose and head; 2, puffiness around the eyes and mouth, diarrhoea, pilar erecti, reduced activity, and/or decreased activity with increased respiratory rate; 3, wheezing, laboured respiration, cyanosis around the mouth and the tail; 4, no activity after prodding, or tremor and convulsion; and 5, death. Rectal temperature was measured using a temperature probe (Yellow Springs Instrument Co., Yellow Springs, OH, USA; Physitemp Instruments, Inc., Clifton, NJ, USA) before and at 30 min after oral challenge.

Spleen cell culture and cytokine analyses

Spleen cells were harvested and standard cell cultures were setup essentially as described (Birmingham *et al.*, 2007). Briefly, spleen cells were cultured (7.5 million/mL) in the absence and presence of hazelnut protein extract (100 and 500 µg/mL). Cell culture in presence of medium alone served as a negative control. Cell culture supernatants were harvested at various time points over a 5-day culture for use in cytokine analyses. Pre-optimized ultrasensitive ELISA was used in cytokine measurement (typical assay sensitivity: IL-4, 1.5 pg/mL; IL-5: 7.5 pg/mL; IL-13: 15 pg/mL).

Statistical analysis

One-way ANOVA test was used to evaluate significance using GraphPad INSTAT software program (GraphPad software, San Diego, CA, USA). The statistical significance level was set at 0.05.

Results and discussion

Although elegant mouse models have been developed over the past several years to study mechanisms underlying food allergy development (Li *et al.*, 2000; Navuluri *et al.*, 2006; Birmingham *et al.*, 2007), it has not been widely exploited as yet to study the genetic control of food allergy. Therefore, here we sought to examine the potential use of MHC-identical mice strains to study the non-MHC genetic control of food allergy.

As evident, transdermal exposures to the hazelnut protein resulted in robust IgE antibody responses in A.SW but not SJL mice (Fig. 1a–d). In contrast, both strains exhibited elevated IgG1 antibody responses (Fig. 1e–h).

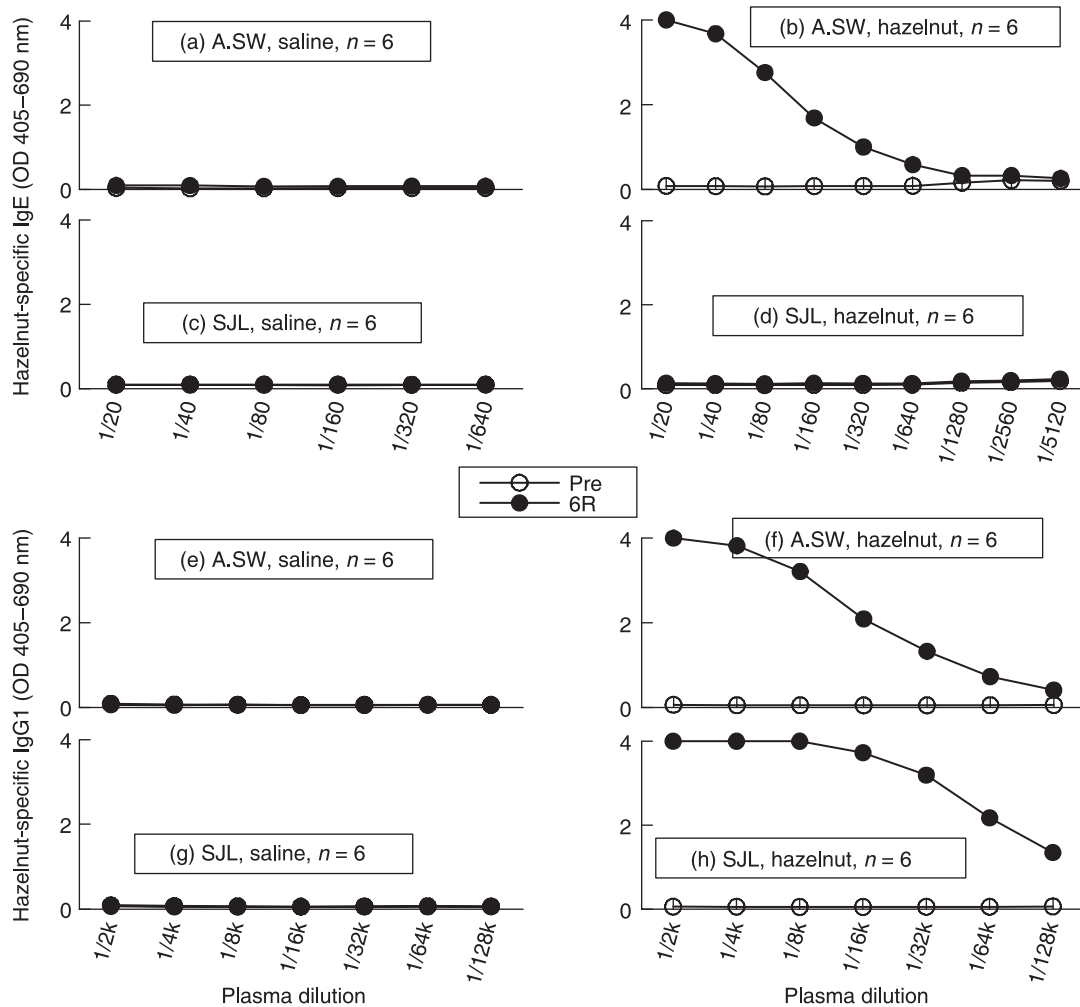


Figure 1. (a–h): Major histocompatibility complex-identical A.SW and SJL mice differ qualitatively in IgE but not IgG1 antibody response to transdermal hazelnut exposure. Groups of mice ($n = 6$ /group/strain) were transdermally exposed to hazelnut protein (500 μ g/mouse, HN) or saline. Specific IgE and IgG1 antibody levels in the plasma were measured before (pre) allergen exposure and after sixth exposure (6R). (a–d) IgE antibody levels in the plasma were titrated over a six to eight twofold dilutions starting from 1/20. (OD mean $\pm$ standard error). (e–h) IgG1 antibody levels in the plasma were titrated over a six to eight twofold dilutions starting from 1/2000.

None of the saline-exposed control mice had detectable antibodies of either type. These experiments were repeated, and differential allergic antibody response to hazelnut in these two MHC identical mice strains ($n = 12$ mice per strain) was confirmed.

We then examined the susceptibility of these mice to systemic anaphylaxis following oral hazelnut challenge. As evident, A.SW but not SJL mice exhibited significant clinical symptoms of systemic anaphylaxis during the 1 h post-oral challenge (Fig. 2a). Similarly, a significant drop in rectal temperature (a physiological quantifiable marker of systemic anaphylaxis) was evident only in A.SW but not in SJL mice (Fig. 2b). In the follow-up experiments, we also found that these strains differ in anaphylaxis following intraperitoneal challenge with the allergen as well ($n = 12$ mice per strain).

We studied the inheritance of immune and clinical readouts using (A.SW $\times$ SJL) F1 hybrid mice. All F1 mice

(both male and female) exhibited IgE responses to transdermal hazelnut exposure as well as clinical signs of systemic anaphylaxis and hypothermia following oral challenge similar to the A.SW parent (Fig. 3a–f). Female F1 mice exhibited relatively higher IgE responses compared to male F1 hybrids; however, there was no significant difference between the gender in either clinical symptoms or hypothermia.

In order to understand the mechanism of genetic control, we studied the allergen-driven cytokine responses by spleen cells. As evident, robust allergen-driven IL-4 responses were evident in A.SW but not in SJL mice (Fig. 4a,b). Robust IL-5 responses were noted in both strains of mice with higher responses by A.SW mice (Fig. 4c,d). Significant and comparable IL-13 responses were noted in both strains (Fig. 4e,f). Furthermore, IL-4 responses in F1 hybrids were remarkably similar to the A.SW parent (Fig. 4a,b). In contrast, whereas IL-5

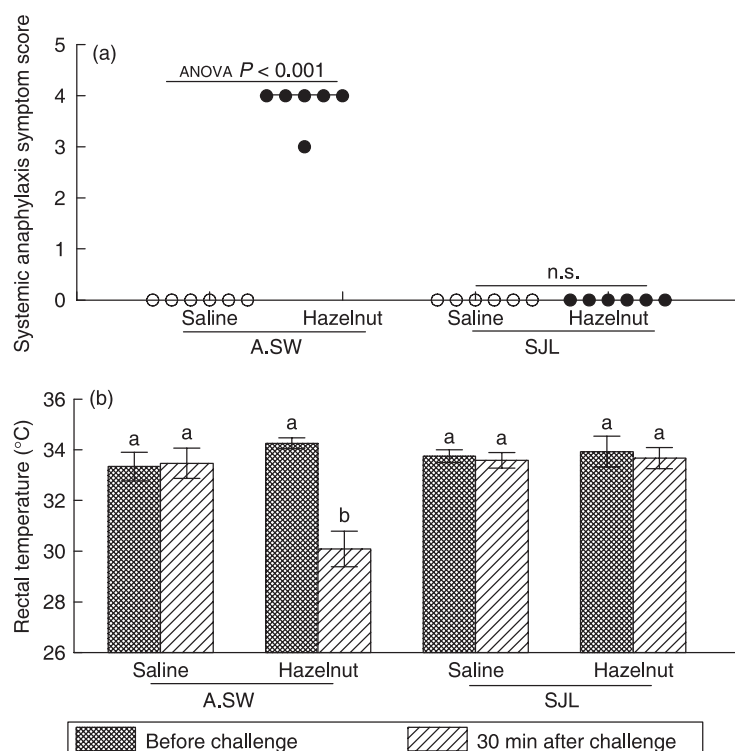


Figure 2. A.SW but not SJL mice exhibits systemic anaphylaxis and hypothermia following oral hazelnut challenge. Groups of mice ($n = 6$ /group/strain) were transdermally exposed to hazelnut protein (500 μ g/mouse, HN) or saline as described in materials and methods. After the sixth exposure, IgE induction was confirmed and then orally challenged with hazelnut (13 mg/mouse) or saline and examined for indicators of systemic anaphylaxis. Clinical symptoms are shown in (a) as a scatter plot with each symbol representing one mouse. Changes in rectal temperature before and at 30 min after oral challenge are shown in (b). Data (b) shown are mean $\pm$ standard error. Bars with different letters are significantly different (ANOVA, $P < 0.05$).

response of F1 mice was similar to the SJL parent (Fig. 4c,d), their IL-13 responses were much stronger than both the parents (Fig. 4e,f).

We are not aware of any previous study examining the genetic control of food allergy using MHC-identical strains of mice or F1 hybrids. One previous study compared peanut and cow's milk allergy phenotypes in C3H/HeJ and BALB/c mice using cholera toxin as adjuvant and reported that whereas C3H/HeJ is susceptible, the BALB/c mice are resistant (Morafo *et al.*, 2003); however, a subsequent study using cholera toxin adjuvant reported that BALB/c mice develop allergic responses to peanut and milk proteins (Adel-Patient *et al.*, 2005). Whereas our approach used MHC-identical mice strains and adjuvant-free method for sensitization, the previous study employed MHC-discordant mice strains and cholera toxin adjuvant-based method for sensitization. In contrast to the previous study, we not only compared two MHC-identical mice strains, but also studied the inheritance of various food allergy phenotypes by F1 hybrids generated using food allergy discordant parent mice strains.

It is noteworthy that the allergy-resistant versus-susceptible phenotype of these mice is unlikely to be specific to hazelnut *per se*. Because SJL mice are known to exhibit a low or no IgE response to many different allergens including ovalbumin, grass, birch, mite and hapten/parasite infestation (Watanabe *et al.*, 1976; Venugopal *et al.*, 1995). Similarly A.SW mice are known to exhibit a robust IgE response to above antigens although clinical

readouts were not studied (Watanabe *et al.*, 1976; Venugopal *et al.*, 1995). Therefore, we hypothesize that food allergy-resistant versus-susceptible phenotype of SJL versus A.SW mice might be secondary due to a general differential ability to generate an IgE response.

The precise reason why A.SW mice are susceptible while SJL mice are resistant to food allergy is not completely clear at this point although our data implicate IgE and IL-4 but not IgG1, IL-5 or IL-13 as major players in this phenotype discordance. One previous study reported that inability to generate an IgE response to anti-IgD antibody injection in SJL mice was associated with deficiency of NK 1.1 cells that promptly produce IL-4 (Yoshimoto *et al.*, 1995). However, one later study reported that NK1.1 cells do appear in the liver of SJL mice as they age, suggesting that NK1.1 cell deficiency in SJL mice is developmentally regulated (Murakami & Paul, 1998). Furthermore, CD1 knockout mice that are also deficient in NK1.1 cells can elicit IgE response to anti-IgD injection, suggesting that inability to generate an IgE response in SJL mice is unlikely due to NK1.1 cell deficiency *per se* (Smiley *et al.*, 1997). The lack of expression of NK 1.1 and the lack of IL-4 production in SJL were also reported to be independently controlled by distinct recessive genes (Beutner *et al.*, 1997). Thus, the relative deficiency in NK1.1 cell and defect in IgE production in SJL mice are only associated with one another and defect in NK1.1 cell is not the likely cause of defective IgE production.

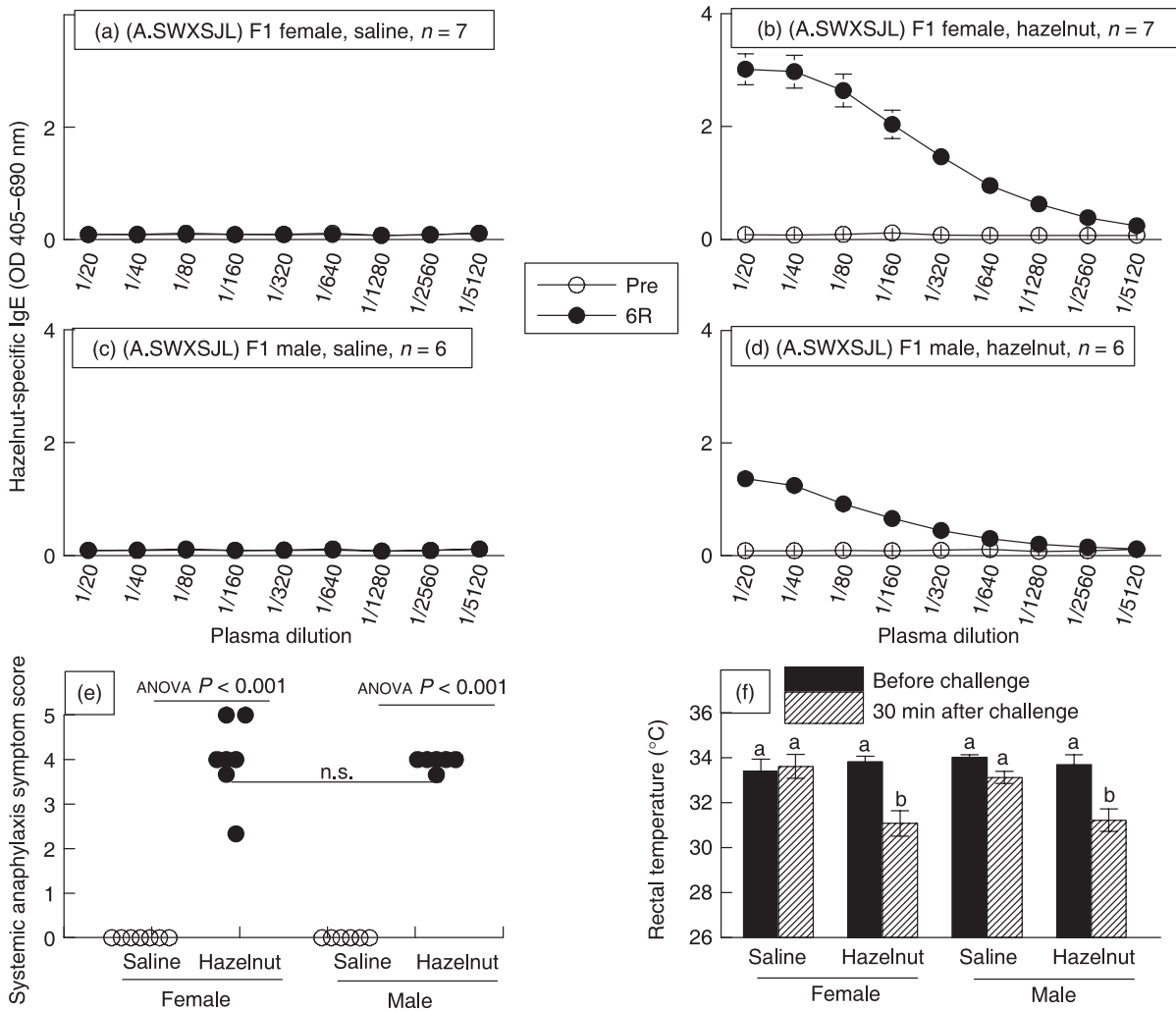


Figure 3. Dominant inheritance of allergic response, systemic anaphylaxis and hypothermia in both female and male (A.SW X SJL) F1 mice. Groups of mice ($n = 6$ to 7 /group/gender) were transdermally exposed to hazelnut protein ($500 \mu\text{g}/\text{mouse}$, HN) or saline (Sal) as described in materials and methods. Hazelnut-specific IgE (a–d) antibody levels in the plasma before (pre) and after the sixth exposure (6R) were measured by ELISA. Mice were then orally challenged with hazelnut ($13 \text{ mg}/\text{mouse}$) and examined for systemic anaphylaxis. Clinical symptoms are shown in (e) as a scatter plot with each symbol representing one mouse. Changes in rectal temperature are shown in (f). Data (f) shown are mean $\pm$ standard error; bars with different letters are statistically significant (ANOVA, $P < 0.05$).

While some studies including our present study show that SJL mice produce very little IL-4 response by spleen cells, other studies reported that SJL mice produce significantly greater amounts of IL-4 in response to ovalbumin by spleen cells than the A.SW strain (Yoshimoto *et al.*, 1995; Beutner *et al.*, 1997; Fan *et al.*, 1997; Yang *et al.*, 1998). Another report showed that high titre and persistent anti-hapten IgE production can be obtained in SJL mice using appropriate immunization and radiation protocols (Watanabe *et al.*, 1976). Yet another study, reported that IgE responsiveness is not linked to either IL-4, interferon (IFN)- γ or TCRVB8 (that also contains NK1.1) genes in ASW and SJL mice *per se* (Venugopal *et al.*, 1995). Taken together, these studies suggest that: (i) SJL can produce IgE and IL-4 under some but not under other circumstances; and (ii) there is no evidence for a primary defect in the

IL-4, IFN- γ or TCRVB8 loci as the cause of defective IgE response in SJL. In light of these earlier studies, our finding that differential IgE and IL-4 response is associated with food allergy suggest that the non-MHC genetic control underlying the food allergy phenotypes in our model may involve the genetic regulation of IL-4 gene expression rather than due to a primary genetic defect in the IL-4 gene itself.

In this model we found no evidence for a role for IL-5 or IL-13 in hazelnut allergy. This is interesting because: IL-5 along with eotaxin has been shown to be very important player in a mouse model of ovalbumin-induced eosinophilic allergic gastritis (Hogan *et al.*, 2001). However, in that model eosinophilic gastritis was the disease phenotype in contrast to systemic anaphylaxis in our model. This suggests the possibility that IL-5 might be a

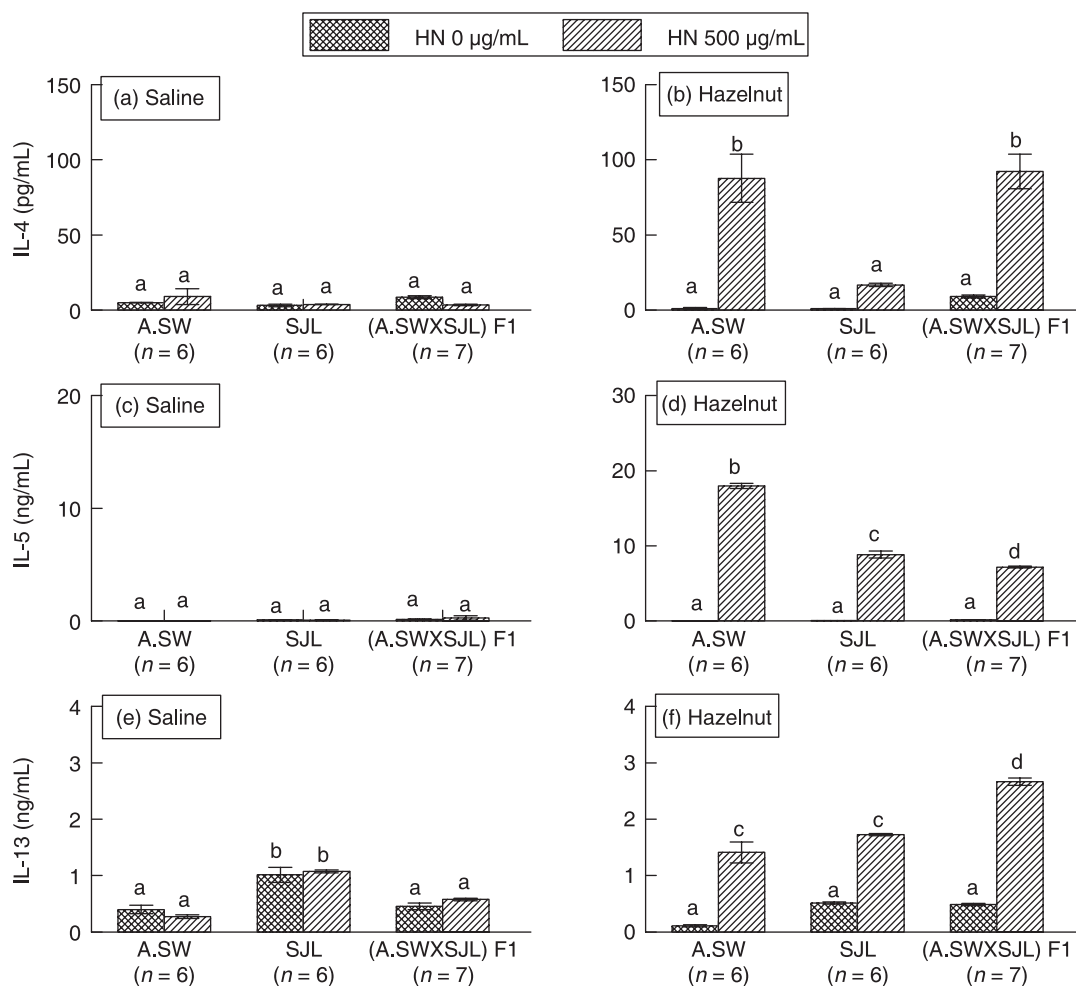


Figure 4. Hazelnut allergen-driven type-2 cytokine responses in MHC-identical A.SW, SJL and (A.SW X SJL) F1 mice: association of food allergy with interleukin (IL)-4 but not IL-5 or IL-13 responses. Spleen cells were isolated from groups of mice transdermally sensitized to hazelnut over a 6-week exposure protocol ($n = 6-7$ /group) and cultured with hazelnut protein (HN, 500 µg/mL) or culture medium (CM) alone. Cell culture supernatants were harvested on day 5 and analysed for IL-4 (a,b), IL-5 (c,d) and IL-13 (e,f) cytokines using optimized ELISA. Data shown are average $\pm$ standard error of duplicate analyses of culture supernatants. Bars with different letters are significantly different (ANOVA, $P < 0.05$).

key player in eosinophil-mediated food allergies but not in food allergies with systemic anaphylaxis which is dependent primarily on mast cells (Finkelman, 2007). In mice, the role of IL-13 in allergic disease is more complicated with reports, suggesting a key role for IL-13 in airways allergies and asthma (Wills-Karp, 2004); although contribution of IL-13 in IgE synthesis *in vivo* in mice is not completely clear (Zurawski & de Vries, 1994; Burd *et al.*, 1995). Our data clearly show that food allergy phenotypes including IgE response are not associated with IL-13 in this model.

Previous studies have elegantly demonstrated that there are two types of IgG1 in mice: (i) anaphylactogenic IgG1 that is IL-4 dependent and (ii) non-anaphylactogenic IgG1 that is IL-4 independent (Faquim-Mauro *et al.*, 1999; Faquim-Mauro & Macedo, 2000; Finkelman, 2007; Tsujimura *et al.*, 2008). These reports together with our findings that SJL mice produce robust amounts of

IgG1 to hazelnut in the absence of a marked IL-4 response and that SJL mice are resistant to food allergy suggest that IgG1 response observed in this model belongs to the IL-4 independent non-anaphylactogenic IgG1 category.

MHC-linked HLA class II genes have been shown to play an important role in allergic immune responses in humans (Donovan *et al.*, 1996; Howell *et al.*, 1998; Sicherer *et al.*, 2000; Shreffler *et al.*, 2006). Our data demonstrate that it is possible to use this mouse model to study the non-MHC genetics in food allergy disease. Future studies using a segregating backcross and F2 mice colony should pave the way for detailed studies on the segregation of food allergy disease phenotypes, evaluation of candidate genes and eventually map the gene(s) for food allergy in this adjuvant-free mouse model.

In summary, these data demonstrate for the first time dominant non-MHC genetic control of food allergy and a critical role of IL-4 but not IL-5 or IL-13 in this model.

Acknowledgements

This work was supported by funding from the United States Environmental Protection Agency (STAR grant # R833133), the Michigan Agricultural Experiment Station and the Michigan State University, East Lansing, Michigan, USA.

References

- Adel-Patient, K., Bernard, H., Ah-Leung, S., Creminon, C. & Wal, J.M. (2005) Peanut- and cow's milk-specific IgE, Th2 cells and local anaphylactic reaction are induced in Balb/c mice orally sensitized with cholera toxin. *Allergy*, **60**, 658.
- Amoli, M.M., Hand, S., Hajeer, A.H., Jones, K.P., Rolf, S., Sting, C., Davies, B.H. & Ollier, W.E. (2002) Polymorphism in the STAT6 gene encodes risk for nut allergy. *Genes and Immunity*, **3**, 220.
- Beutner, U., Launois, P., Ohteki, T., Louis, J.A. & MacDonald, H.R. (1997) Natural killer-like T cells develop in SJL mice despite genetically distinct defects in NK1.1 expression and in inducible interleukin-4 production. *European Journal of Immunology*, **27**, 928.
- Birmingham, N., Payankulam, S., Thanavorakul, S., Stefura, B., HayGlass, K. & Gangur, V. (2003) An ELISA-based method for measurement of food-specific IgE antibody in mouse serum: an alternative to the passive cutaneous anaphylaxis assay. *Journal of Immunological Methods*, **275**, 89.
- Birmingham, N.P., Parvataneni, S., Hassan, H.M., Harkema, J., Samineni, S., Navuluri, L., Kelly, C.J. & Gangur, V. (2007) An adjuvant-free mouse model of tree nut allergy using hazelnut as a model tree nut. *International Archives of Allergy and Immunology*, **144**, 203.
- Bjorksten, B. (2005) Genetic and environmental risk factors for the development of food allergy. *Current Opinion in Allergy and Clinical Immunology*, **5**, 249.
- Burd, P.R., Thompson, W.C., Max, E.E. & Mills, F.C. (1995) Activated mast cells produce interleukin 13. *Journal of Experimental Medicine*, **181**, 1373.
- Daser, A., Batjer, N., Kolsch, U., Kotz, K., Schmeling, H., Schou, C. & Renz, H. (1998) Quantitative assessment of immediate cutaneous hypersensitivity in a model of genetic predisposition to atopy. *International Archives of Allergy and Immunology*, **117**, 239.
- Donovan, G.R., Manolios, N., Weiner, J.M., Grennan, D., Huang, Q., Dunckley, H. & Baldo, B.A. (1996) A family study of allergy: segregation with HLA but not with T-cell receptor genes. *Journal of Allergy and Clinical Immunology*, **97**, 712.
- Dreskin, S.C. (2006) Do HLA genes play a role in the genetics of peanut allergy? *Annals of Allergy, Asthma and Immunology*, **96**, 766.
- Ewart, S.L., Kuperman, D., Schadt, E., Tankersley, C., Grupe, A., Shubitowski, D.M., Peltz, G. & Wills-Karp, M. (2000) Quantitative trait loci controlling allergen-induced airway hyperresponsiveness in inbred mice. *American Journal of Respiratory Cell and Molecular Biology*, **23**, 537.
- Fan, T., Yang, M., Halayko, A., Mohapatra, S.S. & Stephens, N.L. (1997) Airway responsiveness in two inbred strains of mouse disparate in IgE and IL-4 production. *American Journal of Respiratory Cell and Molecular Biology*, **17**, 156.
- Faquim-Mauro, E.L. & Macedo, M.S. (2000) Induction of IL-4-dependent, anaphylactic-type and IL-4-independent, non-anaphylactic-type IgG1 antibodies is modulated by adjuvants. *International Immunology*, **12**, 1733.
- Faquim-Mauro, E.L., Coffman, R.L., Abrahamsohn, I.A. & Macedo, M.S. (1999) Cutting edge: Mouse igg1 antibodies comprise two functionally distinct types that are differentially regulated by IL-4 and IL-12. *Journal of Immunology*, **163**, 3572.
- Finkelman, F.D. (2007) Anaphylaxis: lessons from mouse models. *Journal of Allergy and Clinical Immunology*, **120**, 506; quiz 516–7.
- Hogan, S.P., Mishra, A., Brandt, E.B., Royalty, M.P., Pope, S.M., Zimmermann, N., Foster, P.S. & Rothenberg, M.E. (2001) A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nature Immunology*, **2**, 353.
- Hourihane, J.O., Dean, T.P. & Warner, J.O. (1996) Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *Bmj*, **313**, 518.
- Howell, W.M., Turner, S.J., Hourihane, J.O., Dean, T.P. & Warner, J.O. (1998) HLA class II DRB1, DQB1 and DPB1 genotypic associations with peanut allergy: evidence from a family-based and case-control study. *Clinical and Experimental Allergy*, **28**, 156.
- Li, X.M., Serebrisky, D., Lee, S.Y., Huang, C.K., Bardina, L., Schofield, B.H., Stanley, J.S., Burks, A.W., Bannon, G.A. & Sampson, H.A. (2000) A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses. *Journal of Allergy and Clinical Immunology*, **106**, 150.
- Morafo, V., Srivastava, K., Huang, C.K., Kleiner, G., Lee, S.Y., Sampson, H.A. & Li, A.M. (2003) Genetic susceptibility to food allergy is linked to differential TH2-TH1 responses in C3H/HeJ and BALB/c mice. *Journal of Allergy and Clinical Immunology*, **111**, 1122.
- Murakami, M. & Paul, W.E. (1998) Age-dependent appearance of NK1.1+ T cells in the livers of beta2-microglobulin knockout and SJL mice. *Journal of Immunology*, **160**, 2649.
- Navuluri, L., Parvataneni, S., Hassan, H., Birmingham, N.P., Kelly, C. & Gangur, V. (2006) Allergic and anaphylactic response to sesame seeds in mice: Identification of Ses i 3 and basic subunit of 11s globulins as allergens. *International Archives of Allergy and Immunology*, **140**, 270.
- Shreffler, W.G., Charlop-Powers, Z. & Sicherer, S.H. (2006) Lack of association of HLA class II alleles with peanut allergy. *Annals of Allergy, Asthma and Immunology*, **96**, 865.
- Sicherer, S.H. & Sampson, H.A. (2006) 9. Food allergy. *Journal of Allergy and Clinical Immunology*, **117**, S470.
- Sicherer, S.H., Furlong, T.J., Maes, H.H., Desnick, R.J., Sampson, H.A. & Gelb, B.D. (2000) Genetics of peanut allergy: a twin study. *Journal of Allergy and Clinical Immunology*, **106**, 53.
- Smiley, S.T., Kaplan, M.H. & Grusby, M.J. (1997) Immunoglobulin E production in the absence of interleukin-4-secreting CD1-dependent cells. *Science*, **275**, 977.
- Tsujimura, Y., Obata, K., Mukai, K., Shindou, H., Yoshida, M., Nishikado, H., Kawano, Y., Minegishi, Y., Shimizu, T. & Karasuyama, H. (2008) Basophils play a pivotal role in immunoglobulin-G-mediated but not immunoglobulin-E-mediated systemic anaphylaxis. *Immunity*, **28**, 581.
- Venugopal, G., Yang, M., Luo, Z., Salo, D., Cheang, M. & Mohapatra, S.S. (1995) Analysis of Tcrvb8, II4, and Ifg as genetic predisposition factors for atopic IgE response in a murine model. *Journal of Immunology*, **155**, 5463.
- Watanabe, N., Kojima, S. & Ovary, Z. (1976) Suppression of IgE antibody production in SJL mice. I. Nonspecific suppressor T cells. *Journal of Experimental Medicine*, **143**, 833.
- Wills-Karp, M. (2004) Interleukin-13 in asthma pathogenesis. *Current Allergy and Asthma Reports*, **4**, 123.
- Yang, M., Cao, Y. & Mohapatra, S.S. (1998) Cd8+ T cells inhibit immunoglobulin E synthesis in low responder SJL/J mice. *Immunology*, **93**, 230.
- Yoshimoto, T., Bendelac, A., Hu-Li, J. & Paul, W.E. (1995) Defective IgE production by SJL mice is linked to the absence of CD4+, NK1.1+ T cells that promptly produce interleukin 4. *Proceedings of the National Academy of Sciences of the United States of America*, **92**, 11931.
- Zurawski, G. & de Vries, J.E. (1994) Interleukin 13, an interleukin 4-like cytokine that acts on monocytes and B cells, but not on T cells. *Immunology Today*, **15**, 19.